Exploring bone mineral density changes in total knee arthroplasty revisions and the impact of conal implants

Submitted by Michael Gundry to the University of Exeter
as a thesis for the degree of
Doctor of Philosophy in Medical Studies
in September 2020

I certify that all material in this thesis which is not my own work has been identified and that no material has previously been submitted and approved for the award of a degree by this or
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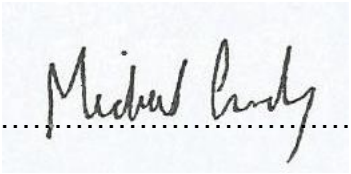
Signature: 

ABSTRACT

Introduction - The link between low bone mineral density (BMD) leading to greater fracture risk is well established in the literature; what is not fully understood is the impact of total knee revisions (rTKR) and cone implantation on BMD. This is important due to the increasing fracture risk associated with reductions in BMD. This feasibility study investigated a new type of Stryker cone for rTKR patients, and its impact on BMD utilising different imaging technologies and providing recommendations to be implemented for a full follow-up trial.

Method - A systematic review was conducted to investigate total knee replacement (TKR) and rTKR on BMD results to establish known reported BMD changes after surgery, and to highlight the knee regions investigated. A bovine study was then conducted in order to test the different setup imaging technologies and possible analysis of the cones. Additionally, a novel piece of 3D-SHAPER hip software was utilised to investigate bone changes in the hip across three groups (TKR, rTKR, and controls) which could then be compared to the main BMD changes or used as an alternative to the other imaging options. The main study involved recruiting 37 participants all undergoing rTKR to either a cone or non-cone group, with all participants undergoing a series of scans via: CT scans (only at six months), DXA and x-ray at intervals of pre-op, six weeks, three, six and 12 months. Additionally, all participants completed questionnaires on mental health, lower extremity functionality, and quality of life. In addition to BMD investigation, hip and knee alignment was also explored at pre and post-op intervals, as well as pixel density changes, both utilising long leg x-ray imaging.

Results – Systematic review results reported 2,431 papers, of which 27 studies were included, across all the studies BMD losses appeared greatest at 12 months. The bovine study helped develop the imaging and analysis required for the main study. The 3D-SHAPER ability to be applied to hip DXA imaging showed promise; which was reflected in the control, rTKR and TKR data. The development of different imaging technologies have potential in moving forward into a full trial. Recommendations would include: utilising DXA imaging as the main modality, given its gold standard for BMD changes and its consistency when using a standardised positioning protocol and ROI placement. Long leg x-

ray imaging to be used to investigate alignment and pixel density changes, as this imaging is convenient as part of routine follow-up care, although the inclusion of a step wedge within all long leg images would be required to allow pixel density standardisation for investigating in-growth. Finally, the CT imaging could not determine ingrowth in this feasibility study, and therefore should not be utilised in the full study. For the main feasibility study results, 35 participants attended pre-op, 26 attended six weeks and three months, at six months 25 attended, and 22 at 12 months. Results show rTKR is associated with lower BMD in the tibial and femoral stems, and in the medial tibial condyle, and associated with increases beyond the tibial and femoral stems, in both groups. The main difference is in lateral tibial condyle where there are associated increases in BMD in the cone group, and losses reported in the non-cone group. The questionnaire results show a favourable impact for rTKR, with reductions in depression, anxiety, and increases in functionality post-surgery, with the cone group reporting greater changes, although not statistically significant between groups. Alignment analysis shows little difference between.

LIST OF PUBLICATIONS AND CONFERENCES

Gundry M, Hourigan P, Hopkins S, Knapp K, Toms M. Cone and non-cone total knee revisions: bone mineral density changes in the ipsilateral and contralateral hips. Online (originally Liverpool) 1 December 2020. ROS conference proceedings.

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Gundry M, Hopkins S, Nunns M, Knapp K, Toms A. A systematic review to assess the impact total knee replacement/arthroplasty/revision on bone mineral density Liverpool 10-12 June 2019. UKIO conference proceedings.

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ABBREVIATIONS

aBMD ..... Areal Bone Mineral Density
AEC ..... Automatic Exposure Controls
AORI ..... Anderson Orthopaedic Research Institute
AP ..... Anteroposterior
ASIS ..... Anterior Superior Iliac Spine
BMC ..... Bone Mineral Content
BMD ..... Bone Mineral Density
BMI ..... Body Mass Index
CaP ..... Calcium phosphate
CC ..... Caudally to Cranially
CI ..... Confidence intervals
CKD ..... Chronic Kidney Disease
cm ..... Centimetres
COV ..... Coefficient of Variation
CT ..... Computed Tomography
DECT ..... Dual Energy Computed Tomography
DICOM ..... Digital Imaging and Communications in Medicine
DXA ..... Dual energy X-Ray Absorptiometry
ERT ..... Estrogen Replacement Therapy
EQ-5D-3L ..... Quality of Life
FOV ..... Field of View
g/cm^2 ..... Grams per centimetre squared
HADS ..... Hospital Anxiety Depression Scale
HKA ..... Hip Knee Angle
HRT ..... Hormone Replacement Therapy
JPN ..... Joint Space Narrowing
kVp ..... Kilovoltage peak
LDFA ..... Lateral Distal Femoral Angle
LEFS ..... Lower Extremity Functionality Score
LSC ..... Least Significant Change
LUT ..... Look Up Table
mPTA ..... Medial Proximal Tibial Angle
mg/cm^2 ..... Milligrams per centimetre squared
ML ..... Medially to Laterally

mm ..... millimetres
mPTA..... Medial Proximal Tibial Angle
MS ..... Microsoft
NHS..... National Health Service
OKS..... Oxford Knee Score
OP ..... Osteoporosis
OS ..... Osteoarthritis
PA..... Posterioanterior
PACS ..... Picture Archive and Communications System
PBM ..... Peak Bone Mass
PIS ..... Participant Information Sheet
PRISMA…….. Preferred Reporting Items for Systematic reviews and Meta-Analysis
PTH ..... Parathyroid Hormone
QA ..... Quality Assurance
QCT..... Quantitative Computed Tomography
QOL..... Quality of Life
RD&E ..... Royal Devon and Exeter Hospital
RHOA..... Radiographic Hip Osteoarthritis
ROI..... Region of Interest
rTKR..... Total Knee Revision
SD ..... Standard Deviation
SE ..... Standard Error
SERM..... Selective Estrogen Receptor Modulators
SID ..... Source to Image Distance
TBS ..... Trabecular Bone Score
THA..... Total Hip Arthroplasty
THR..... Total Hip Replacement
TKA ..... Total Knee Arthroplasty
TKR..... Total Knee Replacement
UK ..... United Kingdom
US ..... United States
WHO ..... World Health Organisation
WL..... Window Level
WW ..... Window Width

OVERVIEW OF THESIS

The primary goal was to conduct a feasibility study in order to investigate the impact of cone implantation in total knee revision patients has on bone mineral density (BMD), and compare them to their own baseline data, and against non-cone (control) participants. A collection of methods and techniques were utilised and tested to answer this question in order to hopefully provide information towards moving to a full trial.

Participants were recruited and randomly assigned into cone (those who received a cone implant as well as the knee revision), and non-cone groups (those who only received the knee revision) and monitored over a 12 month post operation recovery period. Bone mineral density changes were assessed from baseline against subsequent visits within the 12 month period, this was done utilising dual-energy x-ray absorptiometry (DXA) imaging of the; total body, lumbar spine, bilateral hips and bilateral knees. Furthermore, x-ray imaging was also used to investigate pixel density changes on long leg knee x-rays throughout the visits, with alignment angulation also explored using x-ray imaging. Computed Tomography (CT) was also utilised to investigate bone in-growth into the conal implants. Questionnaire data was also gathered on patient outcomes such as: depression and anxiety (Hospital Anxiety and Depression Scale (HADS)), functionality and pain (Lower Extremity Functional Scale (LEFS), Oxford Knee Score (OKS)), quality of life (EQ-5D-3L), and medical history (Bone health questionnaire), with these possibly contributing to bone changes and recovery.

The original aim of this study was to recruit 51 participants in total, followed up over a 12 month period. Due to attrition, illness, recruitment, and COVID-19 issues, only 37 participants consented, with 35 undergoing a DXA pre-op scan. For clarity a list of those who completed each method is in the table below:

Table 0.1. *Participant completion numbers*

Completed	**Pre-op**	**6 weeks**	**3 months**	**6 months**	**12 months**
DXA	35	26	26	25	22
X-ray	31	N/A	24	18	12
CT	N/A	N/A	N/A	13	N/A
LEFS	35	28	28	28	25
HADS	35	28	27	26	26
OKS	35	29	27	26	27
EQ-5D-3L	35	28	26	26	27
Bone health questionnaire	35	26	26	25	22

Over the coming chapters the background to the study, the development of the imaging methods and analysis involved, and the results gathered, will be discussed as well as the limitations and recommendations of this feasibility study.

CHAPTER 1 INTRODUCTION AND BACKGROUND

1.1 MOTIVATION FOR STUDY

Low bone mineral density (BMD) is referred to as osteopenia; in its most severe form it is called osteoporosis (OP). In the United Kingdom (UK) over three million people suffer from OP [1], with an estimated 75 million people in Europe, USA and Japan [2].

Low BMD is most commonly seen in women more than men, in the elderly population (60+ years), including the post-menopausal age group. With OP causing more than 8.9 million fractures per year, resulting in an OP fracture every three seconds [3]. The majority of these fractures occur in the hip, wrist or vertebrae [1]. Studies have shown that fractures in the low BMD groups can lead to severe pain, low quality of life, and death [4, 5]. This is due to these fractures being a major source of morbidity and mortality especially in the low BMD group.

1.1.1 BMD AND FRACTURE RISK

The link between low BMD and fracture risk has been investigated utilising several different testing methods, in which several studies have shown a link between low BMD and fracture risk. Legrand et al [6] investigated BMD and vertebral fractures in 200 men, reporting a relationship between fracture numbers against femoral BMD, spinal BMD, and age; concluding that low trochanter BMD and age were the best for predictors for vertebral fracture. Additionally, Marshall et al [7] conducted a meta-analysis on 229 studies on BMD and fracture risk in women, and concluded that low BMD measurements can identify people who are at increased fracture risk.

This link is supported by a study by De Laet et al involving 5814 men and women [8], concluding similar results, stating that fracture risk to the hip was determined by age and BMD. Cummings et al [9] research developed this idea further; stating that low hip BMD was a stronger predictor of fracture than BMD at other sites. They also reported that loss of BMD in the proximal femur was a major risk factor for hip fracture in the aged population [10].

A study by Melton et al [11] concurred with the research of Cummings et al and Legrande et al in demonstrating that the more the BMD decreased the greater the risk of a femoral neck and trochanteric fracture; concluding that hip fractures were uncommon in women with a femoral bone density above or equal to 1.0 grams per square centimetre (g/cm^2), and as BMD declined fracture frequency increased.

The link between low BMD with increased fracture risk is so strongly supported that several clinical trials have used patients' low BMD to make sure they have a sufficient number of patients having fractures during follow-up [12].

It is reported that older people with one or more long term condition such as OP account for 70 % of all National Health Service (NHS) spending [13], with £1.5 billion spent every year on hip fractures alone [13] (excluding the cost to social care), and accounting for 69,000 unplanned hospital admissions [14]. Furthermore, as well as the increased risk of fracture, the physical and social ramification on patients with OP must be noted, with 42 % of patients with OP feeling socially isolated by their disease [15], and 50 % of people giving up sport or exercise due to the impact of having an OP fracture [15]. Of those who have experienced an OP fracture 42 % are in long term pain they do not think will ever go away [15].

Due to low BMD being so strongly associated with fracture risk**,** the impact of life changing repercussions and the cost to the NHS, any intervention to reduce BMD loss is extremely important**.** One area of research where there is a possible intervention, and where BMD loss has been evidenced is in total knee replacements (TKR), total knee revisions (rTKR) and total knee arthroplasties (TKA)**.**

1.1.2 TKR/A OR rTKR AND BMD

Several studies have shown a loss of BMD post TKR (arthroplasty); Gazdzik et al [16] reported a decrease in BMD 12 months after TKR surgery with the most significant BMD decrease during the period of 5-12 weeks after the surgery at the periprosthetic region. Other research concurs with this, stating the greatest loss of periprosthetic BMD has been observed within the first three months (12

weeks) after surgery [17-19], with some research reporting a temporary BMD loss of 13 % at the proximal tibia [20].

This BMD loss is further supported by a study by Kim et al [21] who investigated 48 Korean patients (11 males, 37 females, mean age 63 years) post TKR, they reported a significant decrease in BMD at the trochanters and femoral neck in the first three months post-surgery, followed by a recovery of the BMD losses to -2.14 % at 12 months. A similar trend is seen across the research by Ishii et al [22], Hopkins et al [23] and Petersen et al [24] who all reported a decrease in total hip BMD during the first six months post-operative.

Other research investigated the effects of TKR 12 months post-operative; Beaupre et al [25] conducted a cohort study across 12 months and demonstrated BMD decreased significantly by 1.80 % at the total hip over that time. Soininvaara et al [26] measured the BMD of bilateral hips in 69 patients undergoing TKA (20 male, 49 female, mean age 67 years). They found a decrease in BMD at 12 month post-operative of up to 2.7 % per year in the ipsilateral hip and up to 1.18 % per year in the contralateral hip. This bone loss affecting the operated side more than the non-operated has been seen in other studies [27]. Mintzer et al [28] reported that within the first 12 months post-operative 68 % of patients had radiographic evidence of bone loss at the distal anterior femur. There are many more studies that have shown a correlation between TKR (arthroplasty) and BMD loss [24**,** 29, 30, 31, 32, 33, 34]. Although there are some studies that dispute this association and have shown no change in BMD post TKR/A [20, 35, 36], with some research actually showing a small increase [37].

One explanation for this decline in BMD is a reduction in mobility of the patient post-surgery leading to non-weight bearing and thus disuse related bone loss [28, 38], this potentially explains the trend of such significant BMD reductions in the first six months, and then levelling out at two years postoperative [22, 39, 40], although this in itself has been contested [20, 41].

1.1.3 TKR/A OR rTKR AND FRACTURE RISK

Due to the majority of research reporting a significant loss of BMD post TKR/A

or rTKR, the possible associated fracture risk must be investigated. A study by Meek et al [42] reported that women aged ≥70 years who had TKR were 1.6 times more likely to have a fracture than younger patients, and 2.3 times more likely to suffer a fracture than men. This is further supported by Toogood et al [43] who stated that the greater majority of annual periprosthetic fractures were more often elderly and female. Preliminary results from the Sahlgrenska Academy in Mölndal [44], analysed medical records from 1987 to 2002; concluding that individuals who had TKR had an increased risk for hip fracture by 4 %, with the risk for vertebral fracture increasing by 19 % compared to the population without TKR.

Prieto-Alhambra et al [45] research supports this increase in hip fracture post TKR, reporting that hip fracture rates were insignificantly reduced compared to controls before the operation, but within 12 months postoperative TKR patients had a higher rate of hip fracture than controls, with relative risk increasing significantly up to 1.58, and then declining to equal the controls by three years. Additional research [46] has also shown a relationship between TKA and fracture risk, reporting a 54 % increased risk of hip fracture, in particular among adult patients aged 71 years or older, with the increase risk of hip fracture greatest after the first few years. Research by Prieto-Alhambra et al has shown an even higher figure, reporting a 58 % increase in hip fracture in patients who had undergone TKR [45].

This increase in fracture risk during the first few years is time-dependent, and as such could be associated with the evidence that supports early BMD decline as an important predisposing factor contributing to fracture risk [47, 48, 49, 50, 51].

Although it must be acknowledged there are other reasons put forward for the increased fracture risk in patients undergoing TKR, with some reports stating there is a higher incidence of falls, thus a higher chance of fracture. Research by Matsumoto et al [52] reported that of 81 patients, who underwent TKA, the incidence of falls was 38 % in the first year post-operatively, compared to 24 % in non-TKA cohort. Additional research also shows a higher rate of falls indicating scores of between 23-43 % [53, 54, 55, 56]. Although some research

contradicts this and shows fall incidences were not significantly higher in the TKR group [23].

Due to an ageing population there is an increasing demand for TKR and rTKR, with a reported 79,000 primary TKR and 5,600 rTKR done in 2012 in the UK alone, this figure is estimated to increase to 117 % for primary TKR and 332 % for rTKR all by 2030 [57]. In addition to the increase in surgeries possibly resulting in more patients having low BMD following knee replacement or revision, there is the cost of the potential fractures associated. It is estimated in 2010 that 536,000 new fragility fractures were experienced. With an estimated 3.21 million people aged 50+ with OP; the economic burden of new and prior fractures stands at £3,496 million per year, and by 2025 this burden is estimated to increase by 24 % to £5,465 million [58]; therefore any intervention to reduce BMD loss should be considered.

There is research that shows that for an 8 % increase in BMD this will result in a risk reduction in vertebral fractures by 54 %, and for a 5 % increase in BMD there can be a hip fracture relative risk reduced by 50 % [12]. With a combination of an ageing population, increase in surgeries, patient impact and budgetary influence, ways to increase BMD or at least reduce its loss through intervention needs to be investigated. These reasons are the motivation for this research, if there is a way to maintain, increase, or slow the loss of BMD in TKR, TKA or rTKR patients then this could not only reduce fracture rates and improve patient lives, but also reduce the financial burden on the NHS.

This study addressed this by investigating how metaphyseal cone implants could potentially impact BMD changes. Currently there is no such type of cone study, but it is postulated this type of cone could help reduce BMD loss in patients having rTKR.

1.2 STRUCTURE OF BONE: AN OVERVIEW

The human adult skeletal consists of approximately 206 bones [59], of which 80 make up the axial skeleton [60] and 126 make up the appendicular skeleton [61, 60]. Bones provide a combination of different functions such as permitting

movement and locomotion, structural framework support [59, 61], protecting vital internal organs, and maintaining mineral homeostasis; especially calcium and phosphorus, storing up to 99 % of the body's calcium [59, 62]. Bones also provide the environment for haematopoiesis production; the creation of white blood cells, platelets and red blood cells [59, 63], as well as storing chemical energy in the form of yellow bone marrow [59].Each bone can be placed into one of five categories; long bones, short bones, flat bones, irregular and sesamoid bones [59].

LONG BONES

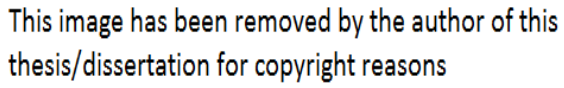


Figure 1.1 *An illustration of the anatomy of a long bone [64]*

A long bone (figure 1.1) is composed of three main subdivisions; the diaphysis which contains a long hollow shaft which promotes bone strength whilst minimising weight [59, 61], and also contains yellow bone marrow and blood vessels. The epiphysis which forms the proximal and distal large rounded ends of the long bones, and finally the metaphysis which is located between the epiphysis and diaphysis and permits bone to grow in length [59, 61]. Additional characteristics of a long bone include the articular cartilage; this is composed of elastic hyaline cartilage and covers the proximal and distal ends of the bones, providing shock absorption to the area of the joints [59, 65]. There is also the periosteum that covers the long bones and is made up of a tough connective tissue providing a blood supply [59, 65]. It can also serve as an attachment spot for ligaments and tendons, as well as helping nourish and repair bone during fracture recovery [59, 65].

Long bones are mainly composed of compact bone which is situated at the diaphysis, with spongy bone in the epiphysis [59]. Examples include the humerus, metacarpals, and femur.

SHORT BONES

Short bones are defined as being approximately equal in width as they are in length and have a primary function of providing stability and support whilst experiencing little movement [59]. They consist of only a thin layer of compact bone, with the majority being spongy bone on the inside along with relatively large amounts of bone marrow [59]. Examples include the trapezium, scaphoid, and lunate.

FLAT BONES

Flat bones are thin, strong, flat plates of bone with the main function of providing protection to the vital organs of the body whilst also providing a large area for muscle attachment [59]. They are made up of compact bone enclosing a layer of spongy bone [59]. Examples include the sternum, scapulae, and ribs.

IRREGULAR BONES

These are bones in the body which cannot be grouped into any other category due to their complex and irregular shape. They primarily consist of spongy bone, with a thin outer layer of compact bone, although this can vary depending on the type of bone [59]. Examples include the sacrum, vertebrae, and mandible.

SESAMOID BONES

Sesamoid bones are usually short and are embedded in a tendon where there is considerable friction [59]. Their main function is to protect the tendon from overuse improving the mechanical function of the joint [59]. Examples include the patella, and the pisiform.

1.2.1 COMPACT AND SPONGY BONE

As stated each of the five bone categories contains a combination of two different types of bone, these are: compact bone (also called cortical bone) and spongy bone (also referred to as cancellous or trabecular bone). Compact bone

makes up 80 % of the skeleton with 20 % being spongy bone [59].

COMPACT BONE

Compact bone is the strongest form of bone tissue, and is found underneath the periosteum of all bones, making up the majority of the diaphysis of the long bones [59]. Compact bone tissue provides support and protection whilst also withstanding the stresses produced by locomotion and weight bearing [59].

The basic structural units of compact bone are called osteons or Haversian systems (see figure 1.2). Each osteon has a central part called the central (Haversian) canal which contains blood vessels, lymphatic's and nerves, the canal is also surrounded by concentric rings called lamellae which are circular plates of mineralised salts (primarily calcium and phosphate giving bone its compression strength), and collagen fibres (giving bone its tensile strength [59]) resulting in a matrix. Between the rings of this matrix, are small spaces called lacunae in which osteocytes are located [59]. Extending in all directions from the lacunae are tiny canaliculi, these contain extracellular fluid and connect lacunae with one another as well as the central canals, forming an intricate system of interconnected canals throughout the bone. This system provides many routes for oxygen and nutrients to reach the osteocytes and facilitates the removal of waste products [66].

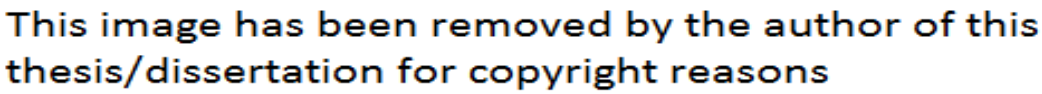


Figure 1.2. *An illustration of the anatomy of compact bone [67]*

SPONGY BONE

In contrast to compact bone tissue, spongy bone tissue, also known as cancellous or trabecular bone does not contain osteons; it is also lighter and less dense than compact bone which reduces the overall weight to the bone. Spongy bone (figure 1.3) also makes up the majority of interior bone tissue, it is

seen in the flat, short, sesamoid, and irregular bones, and it is also the core component of the epiphyses in long bones. Spongy bone is normally situated where the bone is not heavily stressed, or where stressors are applied from many directions, spongy bone is also always covered by a layer of compact bone to protect it.

Due to spongy bone not containing osteons, it instead consists of lamellae arranged into thin columns of bone called trabeculae [59], these columns contain lacunae, canaliculi and osteocytes, between these trabeculae there are macroscopic spaces which are filled with red bone marrow [59] in bones that produce blood cells (such as the clavicle, sternum, vertebrae [68]), and yellow bone marrow in other bones (such as the shaft of the femur) and is used in the storage of fats [68]. Additionally, both types of bone marrow contain a large amount of small blood vessels that provide sustenance to the osteocytes.

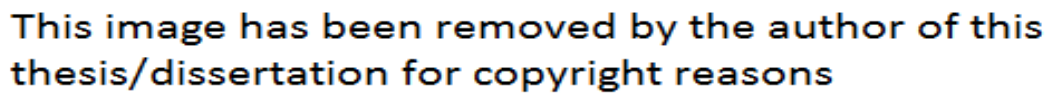


Figure 1.3. *An illustration of a crosssectional anatomy of spongy bone zoomed in [69]*

1.2.2 CHARACTERISTICS OF BONE

Both cortical and trabecular bone possess different properties, with the combination of these producing its mechanical qualities. Therefore, their geometric characteristics and architecture will be discussed, and the impact

these changes have in distribution of weight bearing loads and effect of fracture.

Both cortical and trabecular bone prefer to be aligned in the optimal orientation to tolerate longitudinal loading forces, of which frequent weight bearing is applied. If these loading forces are applied across differing degrees rather than longitudinally, then there is an increase in stress upon the bone when the same load is applied across the transverse plan, reporting a higher stress to the bone, increasing its fracture risk [70].

As this stress is applied the energy is dissipated across the geometric and density properties of the bone dissipating the stress applied. With structural weak bone this stress might allow holes or cracks to appear creating porosity within the bone [71]. Porosity in both trabecular and cortical bone is well known, and its link to increased fracture risk has been demonstrated [72].

Trabecular bone is designed for weight bearing and strength; it has a high surface to area and volume ratio allowing distribution of weight and helps in the remodelling process. The architectural factors that determine trabecular bone strength are interrelated with the greatest mechanical optimisation seen due to high trabecular number, higher trabecular thickness, and connectivity [73, 74]. This trabecular bone transfers weight bearing stressors to the cortical bone. Any bone loss in the trabeculae can lead to increased fracture risk which is associated with loss of trabecular number, reduced connectivity, and increase in porosity [75].

In cortical bone the surface to volume ratio in cortical bone is much lower than in trabecular bone [76], although cortical bone is denser than trabecula bone, with a reported porosity of 5-10 % (compared to approximately 50 % in trabeculae bone). Cortical bone also has a higher calcium and water content than trabecular bone [76]. Both trabecular and cortical bone are important to bone strength, and the relationships are complex [76].

1.2.3 BONE ANATOMY OF THE KNEE

This research will be investigating rTKR and therefore the anatomy of the knee must be stated. The knee joint (see figure 1.4) also referred to as the

tibiofemoral joint [59] is made up of four main bones:

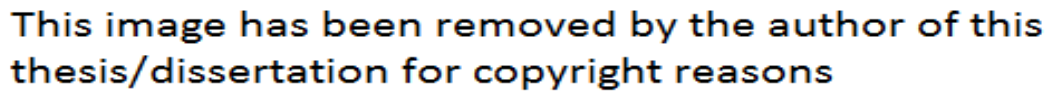


Figure 1.4. *An x-ray of a knee labelled (A) [77] and an illustrated structural view of the knee (B) [78].*

FEMUR

This is a long bone, and is the strongest, heaviest, and longest bone in the human body [59]. The distal part of the femur makes up the superior portion of the knee joint and is composed of the medial and lateral epicondyles (which participate in the knee joint via ligament attachments), this distal femoral end articulates with the tibia and patella creating the knee joint [59].

TIBIA

The tibia is the largest weight bearing medial bone of the lower leg and second longest bone in the body [78]. The proximal tibia makes up the inferior portion of the knee joint and is composed of the medial and lateral tibial condyles; these articulate with the medial and lateral condyles of the femur creating the knee joint. The tibia also contains the intercondylar eminence which is the attachment site for the cruciate knee ligaments [59], and inferior to that is the tibial tuberosity which protrudes outwards allowing the attachment of the patellar ligament.

FIBULA

The fibula is a thin bone which is parallel and lateral to the border of the tibia and connected via the interosseous membrane [59]. The head of the fibula

articulates with the tibia on its inferior surface on the lateral condyle. The fibula does not play a vital role in the knee joint as it does not articulate with the femur [59] and does not bear much the weight of the lower leg [59].

PATELLA

The patella is largest sesamoid bone, and it is positioned anteriorly at the knee and glides along the femoral condyles [78]. It gives mechanical advantage to the knee joint and relieves friction between the bone and muscles during movement [78].

In addition to the bones that create the knee joint there are also many articulations, tendons, and intracapsular components. The knee joint itself is the largest and most complex joint in the human body [59], and is classified as a modified hinge joint with three articulations [59]:

1. Laterally between the meniscus, and the tibial and femoral lateral condyles [59]
2. Medially between the meniscus, and the tibial and femoral medial condyles [59]
3. An intermediate joint between the femur surface and the patella [59].

As stated there are a large amount of structures that support and stabilise the knee joint such as: the patellar ligament, oblique popliteal ligament, arcuate popliteal ligament, tibial collateral ligament, fibular collateral ligament, intracapsular ligament, anterior cruciate ligament, poster cruciate ligament, medial meniscus, lateral meniscus, prepatellar bursa, infrapatellar bursa and suprapatella bursa. These mentioned either strengthen the joint (e.g. patellar ligament), limit hyperextension (e.g. anterior cruciate ligament), provide and circulate synovial fluid cushioning the joint (e.g. medial meniscus) or reduce friction in the joint (e.g. suprapatellar bursa).

1.2.4 BONE ANATOMY AND REGIONS OF THE HIP

This research will also be investigating rTKR impact on the proximal femur recorded as hip BMD, and the subset regions and features within the hip. The proximal femur (hip) areas of interest within the bone are shown in figure 1.5.

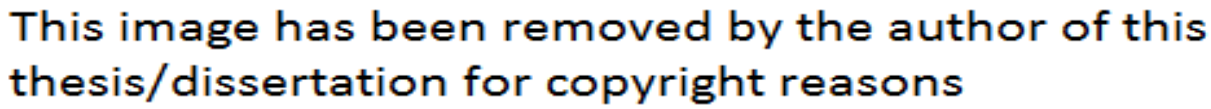


Figure 1.5. *A [79] shows a labelled left hip x-ray, and B shows a Dual-energy X-ray Absorptiometry (DXA) image of a left hip with the regions highlighted by the software labelled on the image.*

GREATER TROCHANTER

A feature of the proximal femur, which provides insertion points for muscles such as the gluteus and piriformis [80].

LESSER TROCHANTER

The lesser trochanter lies inferiorly between the neck and the shaft, projecting medially, this feature provides an insertion point for the ilio-psoas muscle [80].

FEMORAL NECK

Attaches the femoral shaft to the head of the femur, and lies at an average angle of 125° [80]. This the most common site for hip fracture [81] and is comprised of both cortical and trabecular bone [82].

FEMORAL SHAFT

Makes up the main body of the femur and contains several features such as lines, muscle attachments, and insertion points. It also attaches the femoral neck to the more distal part of the femur [80].

WARDS TRIANGLE

Is an abundant area of trabeculae bone that sits within the region of the neck of the femur [83], reporting the lowest BMD in the femoral neck it has been reported as a sensitive indicator of OP [84], but should not be utilised

independently from the total hip BMD for a diagnosis of OP [85].

1.2.5 BONE HISTOLOGY

As well as the structure and classification of bone, it must be recognised that all types of bone in the skeletal system must undergo continuous and dynamic bone remodelling. This is to help adapt to changing biomechanical forces and in removing old and damaged bone and replacing it with new, mechanically stronger bone, to build bone and preserve bone strength [61]. Therefore, the build-up of BMD, and the histology of bone creation, will now be described.

Bone contains extracellular matrix which is made up of 30 % collagen fibres, 15 % water, and 55 % crystallised mineral salts [59]. The most common mineral salt is calcium phosphate, in which it combines with calcium hydroxide to form crystals of hydroxyapatite [59].During the formation of these crystals they combine with several ions such as magnesium and potassium, and other salts like calcium carbonate and calcium hydroxide [59].

These mineral salts are then deposited into the spaces of the collagen fibres that form the skeletal framework, the minerals then crystallise, and the tissue hardens, this process is called calcification, this process is initiated by a type of cell called an osteoblast, which is one of three types of cell that contribute to bone homeostasis and building of BMD [59].

OSTEOBLASTS

Osteoblasts are bone forming cells [86], they synthesise and secrete collagen fibres and other extracellular components, they also initiate calcification during which they become imprisoned by the extracellular matrix and are converted into osteocytes [59, 87].

OSTEOCYTES

Osteocytes are formed from osteoblasts being trapped in the bone matrix [86], these are the most abundant bone cell composing 90-95 % of all bone cells [86, 88, 89], they are utilised in the maintenance of metabolism and nutrient exchange.

OSTEOCLASTS

These are bone reabsorption cells [87], they secrete enzymes and acids such as lysosome, hydrochloric acid and proteases [90], these dissolve the bone matrix and minerals, so it can be reabsorbed as part of normal development, osteoclasts also facilitate the regulation blood calcium levels [59].

1.2.6 BONE REMODELLING

Osteoclasts, osteoblasts and osteocytes all work together to create, remodel, and repair bone [86]. The first phase involves the osteoclasts who become active and digest old bone creating a large cavity [91], second phase involves reversal, when mononuclear cells appear on the bone surface [91], with the third phase being when osteoblasts deposit collagen matrix that is then mineralised [86]. It must be noted that in trabecular bone resorption takes place along the bone surface, whereas in the cortical bone, resorption tunnels through the bone itself [76].

The regulation of bone remodelling is both local and systemic, with the major systemic regulators being hormones such as glucocorticoids, thyroid hormones, growth hormones, sex hormones and parathyroid hormone (PTH) [91]. Other components such as growth factors, cytokines and certain membrane proteins such as receptor activator of NF-kappa B ligand (RANKL) are involved as well [91].

Due to the impact of these factors in bone remodelling and the strong association between cycles of absorption and formation, equilibrium must be sustained between osteoblast and osteoclast activity in order to maintain BMD levels.

1.3 RISK FACTORS THAT LOWER BMD

As stated in the previous section bone is in constant homeostasis equilibrium, during childhood and adolescence much more bone is formed than reabsorbed, so the skeleton grows in both density and size, as such this is a critical period for bone mass accumulation [62]. It must be noted that inability to establish an optimised BMD at the end of adolescence leaves the individual with much less

available in order to withstand the normal losses during later life [92]. Therefore, it is generally accepted that peak bone mass (PBM) is defined as the period at which BMD is stable and at its maximum [93]. PBM has been reported to be attained at any skeletal site in both sexes about the age of 35 years [94], with some reports stating the lumbar spine skeletal site takes the longest to reach, with PBM stability at ages 33 to 40 years in women, and 19 to 33 years in men [93]. After these years bone loss starts to gradually fall, with higher severity of loss seen in older patients [95]. A variety of genetic and environmental factors influence PBM and BMD. It has been suggested that genetic factors (gender and race) may account for between 50-90 % of PBM variance [96, 97], and environmental factors (exercise and diet) have been reported to account for around 25 % [98]. As previously stated, this loss of BMD can lead to higher fracture risk, with an estimated 10 % increase in BMD possibly reducing fracture risk by as much as 50 % [99]. The risk factors that influence BMD will now be discussed.

GENDER AND AGE

Before puberty, girls and boys acquire BMD at a comparable rate, after puberty; however, men tend to achieve greater BMD than women [98]. Gender also influences BMD due to age; women tend to experience minimal change in total BMD between age 30 and 40 years, with bone loss starting around age 40-44 [95]. This loss is exacerbated when patients transitioned from premenopausal to postmenopausal (around age 50-54 years) were the bone loss becomes particularly rapid [95]. This rate of decline is particularly seen in the total hip, with the decline accelerating again when the women are 70 years or older. In men bone loss gradually began around 25–39 years of age (measured at three skeletal sites). This rate of decline of BMD in the total hip was nearly constant among men 35 years and older, with this decline accelerating again among men older than 65 [95].

RACE

Ethnicity itself can affect BMD; African American females tend to achieve higher PBM than Caucasian females [98]. Reports have shown Black men had greater BMD than Hispanic or White men with femoral neck BMD being 13.3 % higher in Black men than in Hispanic and White men, respectively [100]. Other results

have shown a similar trend with United States (US) Caucasian men, being compared to Afro-Caribbean and African-American men, these results showed that Afro-Caribbean men had a higher BMD of between 8–20 %, and the African-American men had a 6–11 % increase in BMD (after age adjusted mean) compared to their US counterparts [101]. Furthermore, men of Asian origin had a BMD loss of 3-14 % when compared to US Caucasian men [101]. These differences in BMD are seen even during childhood and adolescence [98].

HORMONAL FACTORS

The hormone oestrogen has an effect on PBM. Girls going through puberty earlier had greater gains in bone mass especially during bouts of physical activity [102]. In addition, women, who had their first menstrual cycle at an early age and those who use oral oestrogen contraceptives, often have higher BMD (although this is influenced by the age of the woman) [98, 92]. Although it must be acknowledged that there are reports that show the short and long term impact on bone health remains unclear [103]. In contrast, young women who suffer from Amenorrhea (cessation of menstrual periods) because of extremely low body weight or excessive exercise, have been linked with a loss BMD [92], with research showing that it might not be recovered even after their periods return [98], resulting in a failure to attain PBM [92].

NUTRITIONAL IMPACT

There are two crucial nutrients in bone health; calcium and vitamin D (although there are others, of less importance). Calcium is critically important to diet and has been widely reported to increase BMD [104, 105]; it is also important in determining PBM [105, 106, 107, 108]. Therefore, calcium deficiencies in young people can account for a significant difference in PBM increasing the risk for hip fracture later in life [98]. The importance of calcium is such that it has been singled out as a major public health concern, with a national survey suggesting that the average calcium intake of individuals is far below the levels recommended for optimal bone health [92].

Vitamin D in contrast aids in the absorption and utilisation of calcium [92]. The main source of vitamin D is sunlight, by the conversion of precursors in the skin

to active vitamin D. It has been reported that there is a high prevalence of vitamin D insufficiency in nursing home residents, hospitalised patients, and adults with hip fractures [92]. Many factors can impede the creation of vitamin D by the skin, such as the location in which residents/patients reside [109].

PHYSICAL ACTIVITY

Physical activity is important for bone health throughout life. Young adults who exercise regularly generally achieve greater PBM than those who do not [98]. Physical activity helps to preserve and increase BMD and reduces the risk of falling [92], reducing the chances of fracture.

One study compared tennis players bone mineral content (BMC) with their dominant arm compared to their non-dominant, their results reported a BMD increase of 12-16 % due to exercise [110] (normal dominant to non-dominant arm comparisons range from 3-5 % BMC difference) [110]. All types of physical activity can contribute to bone health although the best activity is weight-bearing exercise [92]. This type of exercise forces you to work against gravity, such as hiking, jogging, climbing stairs, walking, dancing, and weight training [98].

Muir et al reported that even in the over 75 age group it was reported that an increase in exercise using simple, daily performed tasks can help prevent decrease BMD in post-menopausal women [111].

LIFESTYLE BEHAVIOURS

Lifestyle behaviours such as smoking have been reported to reduce BMD and increase fracture risk [92], with heavy cigarette smoking also showing a negative effect on the status of BMD [112]. This fact worsens the negative impact of smoking on PBM [98], with research supporting the argument that smoking may promote postmenopausal bone loss [113]. Women who smoke also have lower concentrations of oestrogen than women who do not smoke [114].

Another lifestyle factor affecting BMD is alcohol consumption. Research suggests that high consumption of alcohol has been linked to reduced BMD and increased fracture risk [115], with moderate consumption being associated with

increasing BMD [116, 117], although alcohol has been reported to inhibit bone remodelling, by possibly interfering with vitamin D, or by reducing bone formation and increasing calcium loss from the body [118].

Caffeine also influences BMD, with reports revealing a link between the intake of caffeine and lowering BMD [112], with excess caffeine consumption contributing to a decrease in BMD in both the femoral neck and lumbar spine in healthy white women aged 19-26 years [119]. Additionally, caffeine may interfere with the calcium absorption in the intestines ultimately encouraging BMD loss and leading to an increased fracture risk [120].

MEDICATIONS

Several prescription medications can also impact BMD through various mechanisms [92]. Anticonvulsants such as Phenytoin (Dilantin) and carbamazepine (Tegretol) have been associated with a reduction in BMD, possibly due to lowering vitamin D and interfering with intestinal absorption of calcium [121]. Additionally, high levels of glucocorticoid medications (both synthetic and natural) are associated with reduced activity of osteoblasts and increased activity of osteoclasts [121] leading to lower BMD.

Breast and prostate cancer drugs have also been associated with lowering BMD, with breast cancer drugs preventing oestrogen formation, lowering BMD and increasing fracture risk [121]. Whilst androgen deprivation therapy treatment for prostate cancer involves the removal of the male sex hormone, which has been linked to reducing BMD and increasing fracture risk [121].

Diuretics, such as furosemide (Lasix), which are commonly used to treat fluid retention in order to increase urination, which in turn promotes calcium excretion from the kidneys. As a result, they have been associated with reduced BMD at the hip. They have also been associated with an increased risk of hip fracture [121]. Heparin is a blood thinning treatment which is also connected with reducing BMD, when patients are on it for long-term use [121].

1.3.1 BONE DISEASES THAT AFFECT BMD

OSTEOARTHRITIS AND OSTEOPOROSIS

Two of the predominant and main pathological disorders that hugely affect BMD are osteoarthritis (OA) and OP; these conditions mainly affect the elderly population and are associated with high healthcare costs and morbidity [1].

Osteoporosis is a condition that decreases BMD and reduces the structural integrity of bone [2]. This results in them becoming fragile and increasing fracture risk. The most commonly affected sites are the wrist, hip, and vertebrae [3], with an estimated 8.9 million new osteoporotic fracture cases per year [3].

As well as OP, fractures can be caused by many different mechanisms such as: stressors, extreme loads, and sudden impacts [122]. The annual fracture incidence rate in England is 3.6 %, with a lifetime fracture prevalence exceeding 50 % for middle-aged men, and 40 % in women ≥75 years [122].

Osteoarthritis is a condition in which the joints of the body become damaged and painful, resulting in a reduction in mobility in the appendicular skeleton and spine [123]. It is the most common form of arthritis in the UK, with 8.7 million people having sought treatment for the condition, of which 33 % are aged ≥ 45 years; this percentage increases in the ≥75 years group to 49 % for women and 42 % for men respectively [123, 124]. Due to the destructive nature of OA on the joints and the resulting loss of mobility and function, surgery is a primary option and therefore OA accounts for between 80-90 % of all total knee replacement (TKR/arthroplasty) procedures [125, 126, 127, 128].

The relationship between OA and OP is complex and has been reported to be an inverse one [129], with OA being reported to increase BMD it might be assumed to increase fracture protection. With such a high percentage of cases of TKR due to OA it could be concluded that this protective effect would reduce fracture risk in TKR patients due to having higher BMD, but increased fracture rates have also been reported in OA.

RELATIONSHIP BETWEEN OA AND BMD

The relationship between OP and BMD is already firmly established within this paper (see section 1.1). Research on the relationship between OA, BMD, and the subsequent fracture risk has not been stated so far and has produced many controversial and conflicting results.

In 1972 Foss et al were the first to observe the correlation between OA and fracture risk, concluding that patients with OA had a greater BMD for their age and thus had fewer hip fractures [129]. This suggested the possibility of a protective effect of OA due to higher BMD, with several studies supporting this theory; Dequeker et al in 2003 reviewed the relationship between increased severity of OA resulting in higher BMD, discovering 36 previous studies across 16 countries (Europe, the US and Australia) covering a total of 37,774 subjects including 11,137 OA cases. Twenty eight of these studies showed an increase in BMD with the remainder eight studies showing there was no increase in BMD [130].

A study by Hart et al [131] of 95 women showed a higher hip and spine BMD versus controls (0.79 gm/cm^2 versus 0.76 gm/cm^2, or 3.9 %, and 1.01 gm/cm^2 versus 0.95 gm/cm^2, or 6.3 % for hip and spine respectively), this itself is supported by other research [132] that concluded that OA resulted in higher BMD in the hip and spine, than women without hip OA. This trend was also seen in elderly men, who showed higher BMD in both the lumbar spine and hip compared to age similar matched controls without OA [133]. This is further validated by research that shows an increase in BMD of the spine of patients with OA compared to controls [134, 135, 136].

There is research that states that although spine BMD might be high, hip BMD was not, as investigated by Lethbridge-Cejku et al [136] who recruited 402 men and 247 women with OA, reporting high levels of spine BMD but not hip BMD. This is supported by Arokoski et al [137] whose findings suggest that hip OA is not associated with an increase of BMD in the femoral neck or in the head of the femur. Although it must be stated that there is research to the contrary, a study by Varzi et al in 2015 states that OA lowers BMD compared to controls [138].

OA AND FRACTURE RISK

Due to the majority of research showing an increase in BMD in OA patients [129, 131, 132, 134, 135, 136] it is generally thought that this should have a protective effect on the bone and reduce fracture risk. This idea has been supported by several studies. Vestergaard et al [139] conducted a case controlled study using over 24,655 fractures matched for age and gender, with the main exposure being OA; their research showed that OA seemed to be associated with a decreased risk of fractures in multiple skeletal sites. This is agreed by Cummings et al [140] who examined 189 participants (65-79 years old) with self-reported OA; the subjects with OA had fewer reported hip fractures than randomly assigned controls (4 % compared to 13 %). Additionally, Cummings et al showed an inverse association between the number of joints reported to be affected by OA and the risk of hip fracture, with this protective effect being reported in both women and men [140].

In contrast a number of studies have argued against the protective nature of OA, reporting an increase in fracture risk despite subjects having increased BMD. One study reported a BMD increase of 5.3 % compared to controls but no reduction in fracture risk [141], this is further supported by the Rotterdam study [142] which utilised 2,773 subjects and concluded that patients with knee OA had an increased risk of both vertebral (2.0-fold) and non-vertebral (1.5-fold) fractures. Individuals with self-reported OA also had higher BMD but were not protected against non-vertebral osteoporotic fracture [143].

A study in 2014 [144] also demonstrated an increase in fracture rate amongst OA patients, in which 3864 subjects aged >45 years were analysed. Results revealed that fracture risk was significantly higher in women with OA than those without OA. A prospective randomised control trial conducted by Arden et al supports this argument where over 6,500 men and women ≥75 years were recruited over three years, concluding that patients with knee pain and knee OA had an increased risk of non-vertebral and hip fracture [145].

It must be acknowledged that a study by Arden et al, reported a lack of any relationship between OA and fracture risk despite increased BMD [146]. This is supported by additional research that used cohort studies and reported no

relationship between fracture risk and OA [140, 147]; contributing to the theory that OA does not have a protective effect on fracture risk.

Due to the contradiction and failure of the observed increase in BMD to translate into a protective effect and reduce fracture risk, several rationales were investigated. One explanation for increased fracture risk may be explained, in part, due to an increased fall tendency in patients with OA [146]. Studies by Vennu et al and Doré et al have shown that people with knee or hip OA have a greater number of falls and fracture risk compared to the general population [148, 149], even showing an increase in odds of falling correlated to the number of affected joints with OA [149]. This theory is shared by other research [150], with some stating this is due to OA causing worsened postural stability increasing their tendency to fall [143]. This is contradicted however by two cohort studies, [145, 146] that reported that increased risk of fracture was independent of the number of falls. Although this in itself may be explained due to the severity of the falls and not the number of falls [145]. However, this rationale may be difficult to justify as fall data are often incomplete [151].

Another rationale against the failed protective effective of high BMD from OA to translate into reduced fracture risk is demonstrated by Lee et al [152] whose cross-sectional study proposed that despite OA subjects having high systematic BMD, they were positively associated with vertebral fractures. Lee et al suggested that bone quality, and consequently bone strength, may be decreased at the systemic level in knee OA, resulting in a higher risk of fracture [152]. A similar idea is shared by Ding et al [153] whose research looked at OA in post mortem participants, using micro Computed Tomography (CT) scans of the microarchitecture of the proximal tibiae, this researched showed that medial OA trabecular bone was significantly denser, but had lower mechanical properties than normal bone. Ding et al suggested that bone remodelling in OA leads to deterioration in architecture; resulting in poor quality bone, so although BMD could be retained the bone quality was less, resulting in the possibility of greater fracture risk. This effect might be explained due to subjects with OA having a greater proportion of undermineralisation (immature matrix) in the bone [154]. This rationale is further supported by some research suggesting that bone trabecular microarchitecture was the key determinant of fractures in

addition to the BMD data [155].

Additional arguments [156] state that the BMD values themselves could be falsely elevated due to limitations in the DXA scans only measuring two-dimensions, and not accounting for bone depth. Moreover, Chaganti et al has demonstrated that osteophytes (these are more common in OA patients due to joint damage, so bone wears against bone creating bony spurs [157]) contribute between 16.6 % and 22 % of the lumbar spine BMD variation in DXA scans in women and men respectively [158], possibly leading to an overestimation of higher BMD without the increase in bone strength.

Due to the limitations and arguments put forward, other imaging techniques and methods have been investigated. Bousson et al created a tool called the trabecular bone score (TBS) [159], which is able to differentiate between two microarchitectures that exhibit, the same density [159]. This new method was investigated by Hopkins et al [23] who recruited 19 post-menopausal women pre and post TKR. The results exhibited that participants with TKR had higher mean lumbar BMD compared to controls but a lower TBS, suggesting that OA is potentially concealing poorer bone quality, even though it has a higher BMD. A further study by Hopkins et al investigated differences in bone quantity and quality assessed by spine BMD and TBS [160], these results demonstrated that the participants with TKR had higher BMD than the controls but poorer TBS scores [160].

TBS and BMD at the lumbar spine suggests that the generally higher BMD typically observed in OA patients may be disguising poor quality bone with less structural integrity [23], this is supported by the rationale and results of the previous studies mentioned [152, 153] and might be the main reason that OA with high BMD does not a have protective effect in reducing fracture risk.

OA PHENOTYPE INFLUENCE ON BMD

The majority of the research shows an increase in BMD in OA patients [129, 131, 132, 134, 135, 136] but it must be acknowledged that there are other factors in OA; the phenotypes within OA such as osteophytic (which is osteophyte predominant [133]), and atrophic (which is joint space narrowing

(JSN) predominant) both influence BMD. Chaganti et al study showed significant differences in the hip and lumbar spine of areal BMD (aBMD) measurements for the two radiographic hip OA (RHOA) phenotypes compared to the control group. The osteophytic RHOA group had a higher aBMD at all sites compared to the control group: +3.9 % at the total hip ($p = 0.002$); +8.5 % at the femoral neck ($p < 0.0001$); + 4.6 % at the trochanter site ($p = 0.002$); and +7.2 % at the lumbar spine ($p =0.0003$). In contrast, the atrophic phenotype was not significantly associated with any difference in aBMD compared to controls [133]. This is further supported by research that showed that obese patients have a more osteophyte dominant OA pattern compared to non-obese patients; 74.5 % compared to 34.8 % [161], this coupled with increasing obesity in the population and the association of obesity with the onset and progression of OA in the knee [162] resulting in more TKRs, might reflect the associated BMD change and OA diagnosis.

OA AND JOINT ALIGNMENT

Another factor that influences BMD in the hip and knee is the alignment and angulation of the joints, as OA deteriorates the joint spaces of the hips and knees these joints become more asymmetrical through changes in the load bearing mechanism, thus the knees become more varus (bow legged) or valgus (knock kneed). Czerwiński et al reported that 90 % of patients with knee OA have a varus deformity [163], this varus deformity causes weight to be distributed along the medial tibial aspect, with severe cases of OA (with a varus deformity) reporting a statistically higher BMD in the tibial medial region than the lateral region, the opposite is seen in those with a valgus deformity, reporting a higher BMD through the lateral tibial aspect [164] (and lower in the medial). This deviation in malalignment and increased BMD has been reported in other studies [163, 165], although correct realignment through surgery has been shown to improve BMD in these regions [166].

1.3.2 OTHER DISEASES AFFECTING BMD

DEPRESSION

Bone mineral density and bone quality are affected by many other factors, not only the influence of OA. Depression has been shown to alter behaviour and neuroendocrine systems, with participants with depression having lower BMD [167, 168]. Studies have reported that women with past or current depression have 6.5 % lower BMD than compared to controls at the spine, and 13.6 % lower at the femoral neck [168], with Vyas et al reporting that depression increases cortisol and inflammation leading to lower BMD [167].

OBESITY/DIABETES AND CHRONIC KIDNEY DISEASE

Obesity is associated with higher BMD [165] but has been reported to lead to a lower rate of bone formation [170], and has been linked to an increase in the risk of OA [37**,** 171]. Type two diabetes is also associated with higher BMD; whilst type one diabetes is associated with lower BMD, but both type one and type two have increased overall and hip fracture risk [172], with type one being greater than type two diabetes [86]. Research has shown that this might be due to changes in bone material properties rather than BMD, such as; bone strength, structure, and quality, encompassing the microstructural and tissue material properties [173]. This is further supported with research showing that type two diabetes patients have higher cortical porosity than normal controls [174]. Chronic kidney disease (CKD) has been reported to influence bone quality by altering bone turnover and mineralisation, resulting in micro damage and structural and material changes [175].

1.3.3 ANDERSON DEFECTS AND CLASSIFICATION

As stated there are many factors that affect BMD, the majority of the research stated affects BMD throughout the whole body, but as this study will review both systemic and local BMD loss it is important to understand BMD loss reported at the knee, especially due to the involvement of knee replacements, and more specifically total knee revisions. The reported BMD loss affects the implantation of the revision that the Anderson Orthopaedic Research Institute (AORI) have developed a classification system to describe the severity of the bone loss experienced by TKR/A patients prior to rTKR [176].

A defect is only classified under the AORI system when a TKR/A component has been removed. Each component (femoral or tibial) is assigned an individual defect classifications upon removal either type one, two, or three. Defects are classified from preoperative radiographs for anticipated bone deficiency and then the classification is either confirmed or changed intraoperatively [177]. The arguments for this apparent bone loss are multifactorial and caused by: polyethylene particle disease, stress shielding, wear-debris-induced osteolysis, implant loosening, and bone necrosis from infection. Bone loss can also be experienced during the removal of the prosthesis [178, 179].

TYPES OF DEFECT

Type one - Only minor bone defects and metaphyseal bone intact, stability of the component uncompromised [177, 180].

Type two - Metaphyseal bone damage and loss of cancellous bone that requires an area of cement fill, bone graft or metal augmentation is needed. Type two bone defects can occur singularly in a femoral condyle or tibial plateau, or in both condyles [177, 180].

Type three - Metaphyseal bone is deficient with bone loss that compromises a major portion of either condyle or plateau. These defects usually require a structural bone allograft or custom made implants [177, 180].

This AORI three part classification system is most frequently used [180]. It takes into consideration both the stability of the implants and the location of the defect. It also provides guidelines to managing treatment and enables preoperative planning on radiographs [177, 180].

Any associated BMD loss has real life implications in increasing fracture risk, thus any solutions of treatment or intervention that can lessen this loss of BMD must be considered.

1.4 TYPES OF BMD TREATMENT AND IMPLANTS

As stated there is a need to address the loss of BMD especially in TKR/A and rTKR patients, and this section will discuss the treatments, options and interventions available.

1.4.1 ANTIRESORPTIVE TREATMENTS

Agents categorised as antiresorptive are those that work to inhibit osteoclasts and bone absorption, these include bisphosphonates, estrogen, Selective Estrogen Receptor Modulators (SERM) (although estrogen is a weaker antiresorptive drug than bisphosphonates and might also affect bone formation [181]), cathepsin K inhibitors, and most recently anti-RANKL antibodies [181].

The most commonly used intervention to increase BMD or to reduce the loss of BMD are bisphosphonates (examples include Fosamax, Actonel, Boniva and calcitonin) these inhibit osteoclasts, slowing down the progression of BMD loss [59]. Hahn et al [36] investigated these, concluding that bisphosphate treatment just after TKR surgery prevented early BMD reduction in the hip, and would be beneficial in the prevention of later hip fracture. This is supported by research by Carulli et al [182], who proposed the use of bisphosphonate treatment in patients to not only prevent bone loss but increase implant survival. Other studies [183] reviewed the effectiveness of bisphosphonate use on post TKR fracture risk, recruiting patients who had received a TKR between 1986 and 2006 for knee OA. They concluded that bisphosphonate treatment after a TKR reduced the risk of fracture by 50-55 %. Additionally, a meta-analysis [184] in 2015 reviewed the long-term effects in using bisphosphonates, reporting a significant decrease in implant revision after TKA or total hip arthroplasty (THA). Although caution should be utilised when administering bisphosphonates for long term use, as research from 2017 has reported an increase in the size and number of microcracks, leading to higher fracture risk in those patients on long-term bisphosphate use [68]. Furthermore, there have been reports of long-term use leading to increased atypical femoral fractures [185].

HORMONE REPLACEMENT THERAPY

Some studies have looked at other possible antiresorptive treatments, such as hormone replacement therapy (HRT) which replaces oestrogen and

progesterone lost during and after menopause (example Prepro) to reduce BMD loss. This therapy influences osteoclast activity by reducing its impact in bone absorption [86]. Early and late postmenopausal women on HRT have shown an increase in BMD at all skeletal sites [186, 187], with some studies reporting a BMD increase of 5.3 % at the lumbar spine, and 7.6 % at the femoral neck compared to 0.2 % and 2.1 % in the control placebo group [188]. However, research by Legroux-Gerot et al reports no difference between groups [189], it must be stated that long term use of HRT has been strongly associated with breast cancer [190], and as such long term administration is no longer advisable [191]. Some research has investigated a similar therapy called Estrogen Replacement Therapy (ERT). This therapy replaces oestrogen lost during and after menopause (example Premarlin), ERT helps maintain and increase BMD, although it has also been associated with increasing the chances of stroke and blood clots [59]. Other possible antiresorptive treatments are SERM (examples include Raloxifene, Evista).These mimic the effects of estrogen [59] and have been reported to show an increase in BMD in the femoral neck by 2.1-2.4 % and in the spine by 2.6-2.7 % compared to placebo controls [192]. Unfortunately, there are side effects to SERM such as causing menopausal symptoms (breast pain, hot flushes) and resulting in an increase in thromboembolic events [193, 194].

Cathepskin K inhibitors (example odanacatib) are another antiresortive treatment option. These work by blocking a key osteoclast amino acid utilised in collagen degradation, reducing bone absorption [195], although this current treatment is unlicensed due to unresolved safety concerns [86]. As of 2016 the only candidate to continue in development was odanacatib [196], therefore a large multinational randomised, double-blind phase three clinical trial of odanacatib in postmenopausal women with osteoporosis was recently completed [196]. This study demonstrated clinically relevant reductions in fractures at multiple sites including the hip and spine, although odanacatib was found to be associated with an increased risk of cerebrovascular events [181] and ultimately withdrawn from the regulatory approval process.

Anti-RANKL is an antibody agent (example Denosumab) given via subcutaneous injection [197], this drug inhibits osteoclast activity and bone

resorption; unfortunately, it also inhibits bone formation [86, 198]. Additionally, there are potential side effects such as; osteonecrosis of the jaw, low calcium levels, and atypical fractures due to long term treatment [197].

1.4.2 ANABOLIC TREATMENTS

In contrast to the antiresorptive agents there are anabolic or pharmacologic agents. These promote osteoblast activity stimulating bone growth. This group is limited and made up of: parathyroid hormone (PTH), strontium ranelate, and anti-sclerostin antibodies.

Currently the only approved anabolic for systemic use is PTH [86].This treatment stimulates osteoblasts promoting increased BMD (example teraparatide [Forsteo]), although studies are limited [59]. PTH has been associated with side effects such as headaches, dizziness, joint pain, and depression [199].

Another anabolic treatment investigated was strontium ranelate (example Protelos) [62] this treatment is capable of encouraging osteoblast activity, and to a certain extend inhibit osteoclast activity [200]. This drug was withdrawn in 2017 [62] due to safety concerns [86], such as cardiovascular risks and an increased risk of death [201].

Additional anabolic research investigated sclerostin, which is a glycoprotein inhibitor of osteoblast cells [202]; as such anti-sclerostin antibodies (example blosozumab or romosozumab) reduce this inhibition of osteoblasts stimulating bone formation, but it also inhibiting bone resorption [86]. This type of treatment has shown an increase in BMD in the spine and hip [203], but is still undeveloped with a lack of published phase three clinical trial evidence [204] and thus efficacy and safety concerns have not been fully addressed yet [202].

1.4.3 SURGICAL OPTIONS

As the main body of this research will be investigating rTKR and given the current limited options in both bone anabolism treatments and antiresorptive therapies, coupled with an expanding elderly population that would likely benefit clinically from approaches to increase BMD, a clear need exists for additional

approaches that can reduce bone loss without inhibiting bone formation [181]. Therefore surgical implants addressing this problem are discussed in this section; these mainly come in the form of allografts and metal implants, and can be used in both tibial and femoral defects regardless of cementation, with the main design to reduce bone loss.

ALLOGRAFTS

Bone allografts are a biologic solution for the restoration of ‘bone stock’ in the knee almost to its original form [205]. Bone allografts have been used in rTKR; they can provide a stable and durable reconstruction of deficiencies [206]. The use of structural allografts is seen as a good option for younger patients [207] as it can restore bone stock for future revisions [207]. Unfortunately, this procedure is time consuming and technically challenging [208], and allografts are not always suitable for all defects in all patients, especially older patients, as well as the possible transmission of disease [209].

SLEEVES

Metaphyseal sleeves are normally made of titanium alloy with a porous surface that is sintered by titanium, with the porosity from 50 % to 80 %. Metaphyseal sleeves provide a stable scaffold for joint reconstruction [210, 211]. The metaphyseal sleeves come in variety of different shapes and are press fitted into bone allowing bony ingrowth. A paper by Watters et al reported excellent osseointegration and lasting fixation [212], showing ingrowth stability 3 month post-operation [213], with research by Agarwal et al reporting good osseointegration in 102 out of 104 knees at their final follow up scan [214]. Unfortunately, there appears a lack of data about metaphyseal sleeves in TKR/A affecting BMD; with the main priority being stabilisation and survivorship.

CONES

Cones are designed to act like a scaffold for osteoblast-mediated bone ingrowth, facilitating particulate graft incorporation as well as providing a porous surface with excellent properties to cement in the total knee revision implant in place [215]. These implants are primarily chosen due to being bioinert, able to support mechanical loads, and being highly porous, promoting osseointegration [216]. Furthermore, both metaphyseal sleeves and cones avoid issues of

disease transmission, graft resorption, and collapse associated with bone graft material [217]. A study by Lachiewicz et al reported that tantalum cone implants were fully integrated after two years [218], with other research reporting that all patients treated with a metaphyseal cone had radiographic evidence of osseointegration [219], with multiple studies demonstrating beneficial short term results [218, 219, 220, 221, 222, 223]. Furthermore, a paper by Harrison et al reported that cone implantation maintains tibial bone density [224]. Additionally, as well as the material tantalum, porous titanium cones have been investigated, this is due to porous titanium being considered the ideal graft material in orthopaedic surgery due to having similar structure and mechanical properties to normal trabecular bone [225]. This type of implant has been shown to increase BMD at particular regions by 8.1 % [226], with further research showing a similar favourable effect on BMD [227]. Although some research demonstrates that there is no significant difference in changes in BMD between the groups [228]. Titanium cone implants have also demonstrated better stability than their tantalum counterparts [229]. In addition to the cones some studies have investigated the effect of Hydroxyapatite bioceramic that resembles the mineral that constitutes human bones and teeth [76], coated onto the titanium implants to promote in-growth, this combination has demonstrated to increase shear strength [230], but has been reported to lead to decreased bone formation on porous coated titanium [231]. Further cone implantation research in rTKR produced a systematic review in 2014 [232] in which aseptic loosening rates of conal implantation against structural bone allografts were investigated. These results showed a significant decrease in loosening rates in the conal implantation group compared to allograft group, as well as substantially lower failure rates [232].

1.5 TYPES OF KNEE REPLACEMENT

In order to understand the application and implementation of cone implantation the knee replacement and revision procedure will now be discussed.

1.5.1 TOTAL KNEE REPLACEMENT

A TKR also called an arthroplasty (TKA) is a routine operation that replaces an arthritic, damaged diseased or worn knee with an artificial joint [233, 234]. The

procedure is carried out due to pain, reduction in mobility, and loss of function to the individual [233], with the typical patient age being 60 to 80 years old [234]. This option is normally only offered once other recommended treatments have been exhausted, such as physiotherapy and steroid injections [234].

During the operation the damaged cartilage is removed from the distal end of the femur, the femur is then resurfaced to fit a metal femoral component which is normally cemented to seal it into place [59]. The proximal end of the tibia is then operated on, with the damaged bone and cartilage excavated, the tibia is then resurfaced and fitted with a plastic and metal component, the metal component is fitted securely using bone cement to the tibial plateau whilst the plastic component made of polyethylene is placed on top of the tibial metal component (as shown in figure 1.6), this is in order to act as a buffer between the femoral and tibial components providing support to the knee joint [235]. In some cases, if the underside of the patella is also of poor quality then it might also be replaced with a plastic component [59, 235].

Figure 1.6. *Is an illustration of the structure of a knee once a TKR component has been implanted [236]*

During this type of surgery there are many potential complications including infection, increased risk of blood clots, stiffness and failure of the implant [59]. Although most studies demonstrate that between 85-90 % of TKR/A will last between 15 to 20 years [237], early failures may occur due to a variety of reasons. These include: infection, periprosthetic fracture, and loosening of the implant. When early failures occur, rTKR surgery is required [237].

1.5.2 TOTAL KNEE REVISION

As stated the need for rTKR has several causes, the most common reason for rTKR to be performed is due to loosening (25-40 %), infection (24-44 %), wear of the polyethylene component/osteolysis (9 %), failure of the implant (2.8-6 %), and periprosthetic fracture (2.8-4 %) [238, 239]. During surgery the most complex issue is when the old implant is removed resulting in a large cavity, this combined with patients having less bone to implant the new revision into, makes a secure and stable implant even more important in promoting bone ingrowth and osseointegration. Therefore, this cavity has to be either filled in or the new replacement secured elsewhere to ensure the rTKR is fixed for long term survival.

Various methods have been utilised to help achieve fixation and security within these cavities, including cemented or uncemented implants, using stems of differing lengths, and using additional methods to improve metaphyseal fixation (examples include: bone graft, augments, sleeves and cones).

Stems are intramedullary extensions of either the tibial or femoral implant in order to achieve distal fixation [240] and stabilise the joint, the length of the revision stem is determined by multiple factors with fully cemented and press fit stems being available [240], with both short and long stems having advantages and disadvantages.

Short metaphyseal stems suggested by Patel et al [240] are between 30-75 mm long, with the longer diaphyseal stems being greater than 75 mm in length, although it is suggested [240] that stem length is less important, and that the region the bone and stem achieve fixation is of the greater importance.

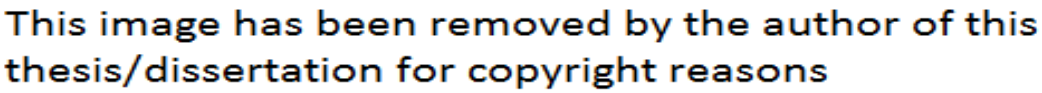


Figure 1.7. *Anteroposterior x-ray knee view of a rTKR patient with an implanted short (A [241]) and long (B [242]) stem. This visually shows the stem length differences.*

Both stem lengths (shown in figure 1.7) have positives and negatives. Short stems are generally cemented, have less end of stem pain, but tend to be more difficult to remove, which consequentially can lead to more bone loss [240]. Long stems are reported to be primarily uncemented in implantation and are easier to remove, although they are generally associated with an increase in end of stem pain, and a higher chance of periprosthetic fracture [240].

Research suggests an optimum stem length for greatest clinical outcome is missing [240] and as such an ideal stem length is one in which the greatest bone is maintained whilst allowing the greatest stabilisation [240]. Data have also shown that cemented short stems provide as much stability as long uncemented stems which might add to the confusion between the two lengths comparisons [243].

One method to address stabilisation as already stated in the introduction is conal implantation, with cones reported to have shown excellent stabilisation [229] as well as helping increase BMD [99, 100].

1.5.3 IMPLANTATION OF CONES

Cones both tibial and femoral, come in different variations of shapes and sizes which can be used for different defects as shown in figure 1.8 and 1.9.

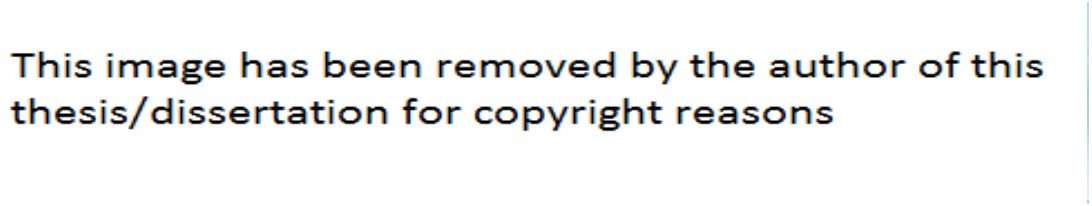


Figure 1.8. *This image shows three different variations of tibial cone implant shape, which can all be used in a rTKR. These are manufactured by Zimmer incorporated [244].*

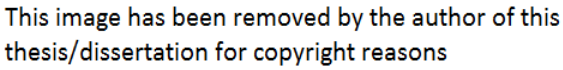


Figure 1.9. *This image shows three different types of femoral cone implants, which can be used in rTKR. These are manufactured by Zimmer incorporated [244].*

For the implantation of cones in both the tibial and femoral aspects certain protocols are followed, these ones stated below are from the Stryker TS triathlon cone implantation which will be utilised in this study.

TIBIAL PREPARATION

Tibial canal preparation involves creating a depth of a minimum of 175 mm to facilitate accurate cone reaming [245]. Cone reaming then takes place involving a tibial symmetric cone reamer producing a depth and diameter to match the tibial conal implant as shown in figure 1.10 below [245].

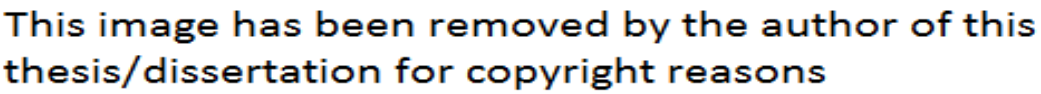


Figure 1.10. S*hows the letters and associated sizes (with optimum sizes highlighted in green [245]).It also shows the tibial symmetric cone reamer with the recorded diameter and how this correspondes to the cone size.*

The size of the cavity corresponds to the size of the conal implant, with size option of A-E spanning 21-25 mm in diameter.

Asymmetric cone preparation if needed depending on the type of tibial cone used can then be performed; this is similar to the tibial symmetric cone preparation but produces an offset cavity (see figure 1.11), which again should match the cone size already chosen [245].

Figure 1.11. S*hows different preparations for different cone shapes, for instance A [229] shows symmetric cone preparation [229], this is for a symmetrical cone B [229] is for an asymmetric cone hence the difference in shape and additional cavity, with image C showing the reamer position (shown in yellow) being placed offset needed to create the asymmetric cavity shown in B [245].*

The conal implant is then inserted into the cavity; cement may also be added [245].

FEMORAL PREPARATION

The femoral canal is prepared by creating a minimum depth of 175 mm [245] femoral sizing is then determined via a femoral sizing template (figure 1.12) or by measuring the previous implant. The femoral symmetrical cone reamer is then used (figure 1.13).

Figure 1.12. *A shows the femoral implantation sizes (optimum sizes highlighted in green [245]), with image B showing the femoral symmetrical cone reamer position (yellow) being placed into the femur in order to create the cavity [245].*

The femoral cone reamer is then placed either side of the cavity created by the femoral symmetrical cone reamer creating a void made up of three insertions, as shown in figure 1.13.

Figure 1.13. *Image A shows the femoral cone reamer (yellow) being placed to the left of the femoral symmetrical reamer [229]. Image B shows the three holes created in the femur [229], with the femoral cone reamer producing the holes either side of the central cavity, this is order so the femoral cone implant can be inserted.*

The femoral cone component is then inserted into the designed cavity. This is a simplified version of the surgical procedure in order to underlie the insertion technique of conal augmentations.

COMPLICATIONS

During rTKR there are similar complications as seen in TKR, although there are some additional issues as well, such as dislocation of the new implant, with this risk of dislocation being twice as high for rTKR than in TKR [246], there is also

an increase loss of bone tissue [246] and an increase in bone fractures during the operation; this is due to the forces of pressure used in order to remove the old components [246, 247].

1.6 IMAGING TECHNOLOGIES

Due to the associations between low BMD and fracture risk and its association in TKR/A an rTKRs, ways to image and report BMD will now be discussed in this section.

1.6.1 DUAL ENERGY X-RAY ABSORPTIOMETRY IMAGING

Dual energy x-ray absorptiometry (DXA) is the most commonly used imaging modality for OP diagnosis [248], it is utilised to assess BMD measurements and to calculate future fracture risk. It is simple, non-invasive, easy to set up, has short scan times [249] and it also uses low levels of radiation [249, 248] approximately one tenth a standard chest x-ray [250].

A DXA scanner works by utilising x-ray beams of two different energies (example 70 Kilovoltage peak (kVp) and 140 kVp [251]) resulting in two distinct peaks of x-ray radiation [248], these two different energies are attenuated differently based on the atomic number of the tissue being scanned. Low-energy photons are attenuated slightly more than high energy photons in soft tissues. The attenuation differential between the two photon energies is greater in bone because it contains calcium which has a high attenuation coefficient, whilst soft tissue contains hydrogen which has a low attenuation coefficient [252].

This difference in attenuation characteristics allows an estimate to be calculated for soft tissue absorption subtracted from that of the bone absorption [253]. This produces a 2 dimensional picture where the radiation energy per pixel has been detected and converted into an areal density measurement in g/cm. The number of pixels in the area is summed then the amount of bone in each pixel is calculated. This allows a bone density to be calculated for a specific bone [253].

Dual energy x-ray absorptiometry is used at several skeletal sites, with the primary scans being total body, hip, and lumbar spine, it can also be used in lateral vertebral assessment and in the peripheral regions such as the forearm, heel, hand or knee [251, 254, 255]. It must be noted these scans are primarily done in the posterioanterior (PA) projection, due to the fixed orientation of the DXA scanner, although a small amount of scanners such as the GE lunar Expert perform them in the anteroposterior (AP) projection [251]. As stated there are many different skeletal sites and positioning techniques and these must be kept consistent due to their impact on precision of the BMD readings.

T-SCORES AND Z-SCORES

Bone mineral density results are reported in g/cm^2 which is useful for intraoperator comparisons of the same position and patient across multiple periods of time. These BMD figures are also reported using T-scores and Z-scores. A T-score is related to how much a patient's BMD is higher or lower than the BMD of a healthy young adult of the same gender and race [254]. The World Health Organization (WHO) uses a classification system for patients score with the lowest T-score being used to determine its classification as follows:

- A T-score of -1.0 or above is normal bone density.
- A T-score between -1.0 and -2.5 means low BMD or osteopenia.
- A T-score of -2.5 or below is a diagnosis of osteoporosis.

The lower the T-score, the lower the BMD, additionally BMD results also include a Z-score that compares a patient's BMD to what is normal in someone of the age and body size. Most experts recommend using Z-scores rather than T-scores for children, teens, younger men and women under 50 years of age [256]. Although the national osteoporosis foundation does not recommend routine BMD testing in these age groups [256].

LIMITATIONS OF DXA

Dual energy x-ray absorptiometry scans have high precision [254], but there are several factors that should be considered when interpreting results from repeat scans.

Firstly, the variation in repeated scans of the same patient, these can cause measurement errors It is therefore advantageous to use the same DXA radiographer to do all repeat scanning, to avoid interoperator variables of different positioning techniques and training. Participants may also change their posture throughout the scanning period either due to degenerative disease or after the rTKR affecting their flexibility for the negative or for the positive. This is important in scans of the hip where a stated addition of 10° internal rotation over the standard position significantly changed hip BMD in 12 % of participants [257].

All DXA equipment is calibrated prior to scanning using a daily phantom, although precision errors within scans are still inherent as such any biological BMD changes seen between repeat scans could be due to positioning error. Interpretation of consecutive BMD tests depends on knowledge of the least significant change (LSC) this is the percentage that must be achieved in order to have 95 % confidence that the difference in BMD has actually occurred and beyond the range of error [258, 259]. In clinical terms, this percentage is reported as a LSC of 2.77 % assuming a precision error of 1 % [258]. Unfortunately, this precision error is calculated for standard DXA positioning; total body, lumbar spine, and bilateral hips, and not calculated for DXA knee scans.

Although it must be acknowledged that there have been multiple studies investigating the impact of knee positioning in DXA scanning [24, 178, 226, 255, 260, 261] and the associated precision errors inherent within those scans, these studies have investigated this positioning across multiple DXA machines including Norland, Lunar, and Hologic across a period of 1998 to 2016.

Soininvaara et al in 2000 [260] investigated precision error via repeat scanning a total of 45 knees (24 TKA operated knees and 21 non-operated knees), reporting a coefficient of variation (COV) precision score of 3.1 % in the femur and 2.9 % in the tibia of the TKA knees, and 3.2 % and 2.5 % in the non-operated knees. Jensen et al [178] also explored this, performing double scans of the proximal tibia in 11 participants (rTKR cone knees vs non cone knees) with a COV precision score of 3.6 % (cone knee) and 2.1 % (non-cone knee).

Trevisan et al [255] also investigated this and created a positioning protocol for DXA knee scans to improve precision and reduce errors (i.e. flexion of the lateral knee at 20 degrees, internal rotation of the PA knee at 15 degrees supported by the hip positioning device), in their study 10 TKA participants had repeated knee DXA scans reporting an overall precision score of 1.4 % on PA images and 2.5 % on lateral knee images. Petersen et al [24] also conducted a precision study on the proximal tibia, and distal tibia and fibula in TKA patients, reporting COV scores of 1.1 %, 0.9 %, and 1.1 % for the medial, lateral and distal ROI. Additionally, Winther et al [226] in 2016 investigated the precision of DXA TKA knee scans in utilising repeat scans on 10 patients of the proximal tibia reporting a COV of 2.3 %, 1.3 % and 1.8 % for three of the ROI. Therbo et al [261] investigated the precision in the distal femur in three different types of uncemented TKA; repeat scans of 28 participants resulted in DXA knee precision scores of 3.3 %, 3 % and 2.6 %.

Therbo et al [261] also investigated the influence of rotation on precision in the lateral knee DXA images. The distal femur was rotated in different positions and a DXA scan performed, reporting a COV precision of 0.5-0.6 % for 0 degrees rotation, 7.3-10.1 % for 20 degrees rotation, and 12.3-14.9 % for 40 degrees rotation.

All the studies reported low precision errors in both the PA and lateral knee DXA scans, therefore as there is a consensus of low precision errors, this study will be following the positioning protocol of Trevisan et al [255], therefore our study should produce similar precision errors as theirs. To test this a COV was calculated using a phantom knee (the knee from a the whole body phantom PBU-50 manufactured by Kyoto Kagaku corporation) following the positioning instructions of Trevisan et al [255], the phantom was placed in the PA position and a DXA scan performed, then the phantom was placed in the lateral position and another scan performed, this was repeated for 10 scans for the PA and nine for the lateral alternating between PA and lateral DXA scan positions between each scan, (one lateral image although scanned (resulting in 10 of each), was corrupted and therefore was excluded). The results reported a precision of 2.54 % for PA and 3.03 % for the lateral; the results are shown in table 1.1 below.

Table 1.1. *Showing the mean BMD score (g/cm^2), SD and COV for the PA and lateral phantom knee*

	PA	***Lateral***
Mean BMD g/cm^2	*0.632*	*0.706*
Standard Deviation	*0.016*	*0.021*
COV %	*2.541*	*3.032*

Unfortunately, positioning of the knee was difficult due to being a disembodied phantom knee, and although it was strapped it provided a lack of resistance to internal rotation and could not be held in place easily. The phantom was designed for x-ray imaging and not directly with DXA, thus the knee BMD was very low making any variation in BMD more prominent, increasing the COV precision error, also the classification of the edges of bone, soft tissue and artefact, was more problematic due to the variation in the phantom knee (as discussed in more detail in chapter 6). Figures 1.14 and 1.15 show the difference between the DXA scan of the phantom and a DXA scan of a "normal" knee, including different brightness setting to further show the variation.

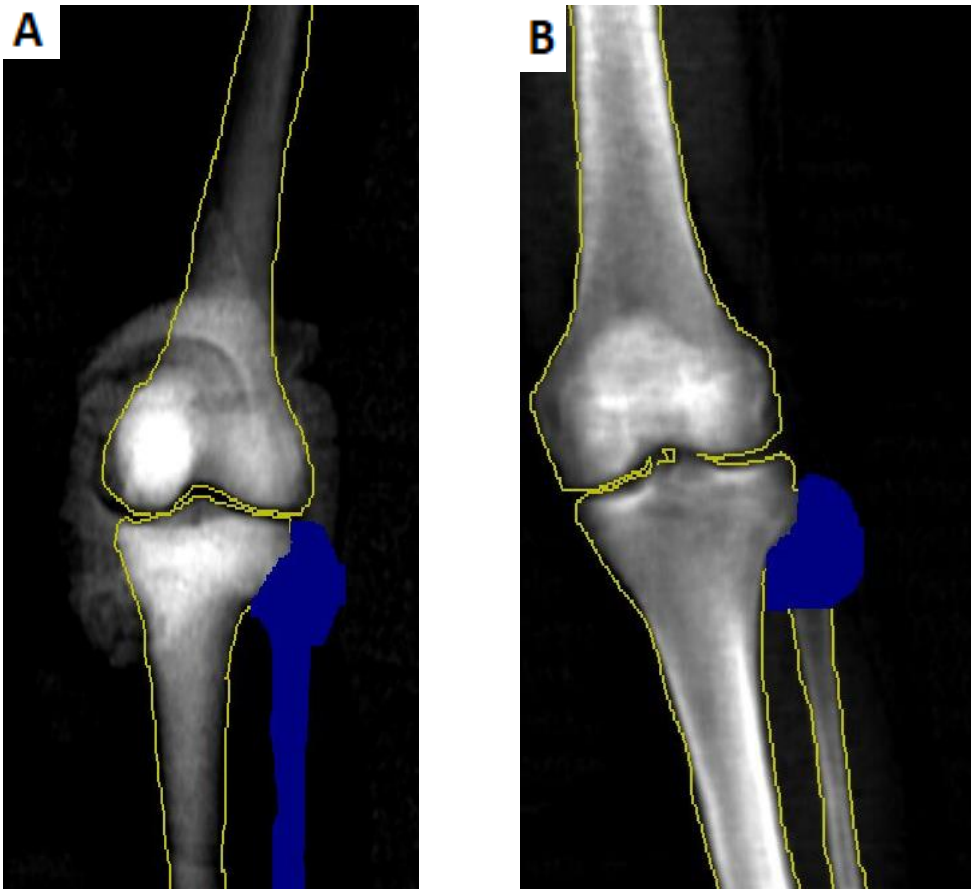


Figure 1.14. *A shows the DXA scan of the phantom knee on the thin setting. B is a DXA scan of a "normal" human knee (also done on a thin setting) (bone is defined as within the yellow border, blue is artefact which is defined as the fibula or fibula head, this excludes it from the data).*

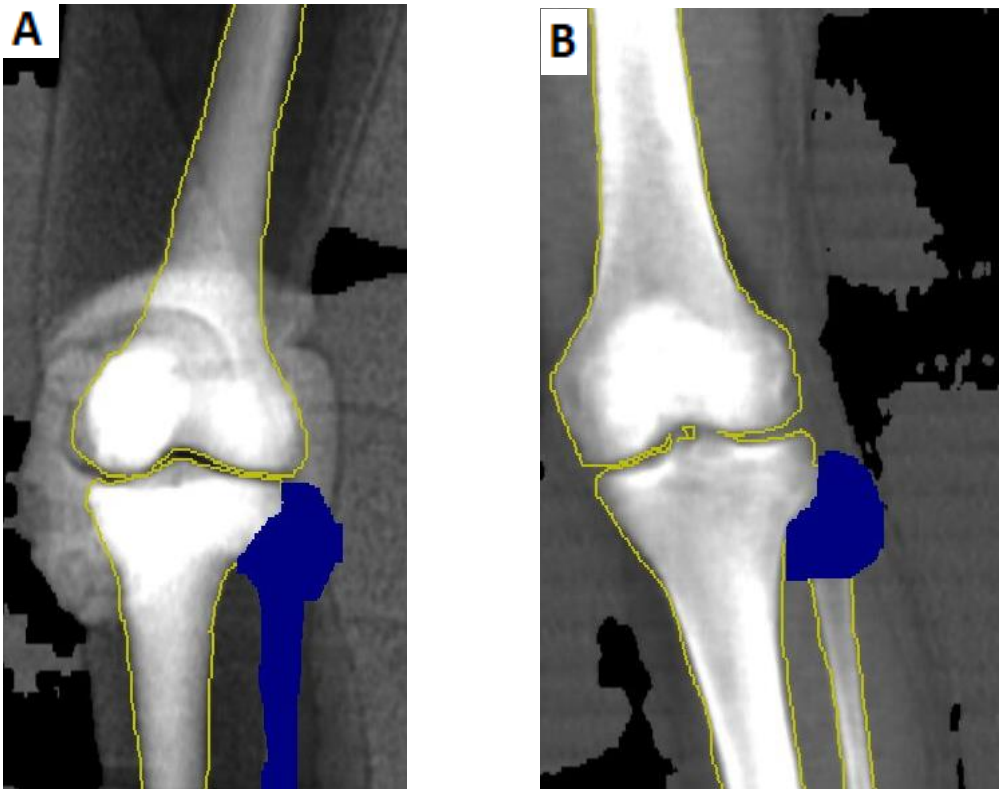


Figure 1.15. *Shows the same image as figure 1.14 but with brightness increased to show the difference in anatomy (bone is defined as within the yellow border, blue is artefact which is defined as the fibula, black is air, the grey around the knee is soft tissue or soft tissue substitute (rice bags))*

However, even with these reported issues the results are similar to those stated in the literature. Therefore, due to the drawbacks of the phantom study it was decided that the statistically significant changes required would be reported as the precision error provided by Trevisan et al's study multiplied by the LSC (i.e. greater than: PA 1.4 x 2.77 = 3.88 %, Lateral 2.5 x 2.77 = 6.93 %).

Additionally, DXA precision errors are affected by a higher body mass index (BMI), due to a decrease in signal to noise ratio in larger participants [262]. This signal may change over different time periods, especially if the patient increases or decreases in weight throughout the study, possibly changing the distribution of fat and soft tissue in the areas being scanned. It has been reported that patients of a higher BMI increase the precision errors in the DXA scans [263, 264], with the COV percentage in precision errors changing from 0.99 % in normal BMI (less than 25) individuals to 1.68 % in participants with a BMI over 30 for the lumbar spine, and 1.32 % for normal BMI (under 25) and 2.00 % for obese BMI (over 30) at the neck of femur. These type of precision errors must be acknowledged in the obese population as the LSC might be

higher that currently reported [189].

DXA also has other limitations it is highly influenced by bone size and does not distinguish between compact and spongy bone [265], therefore it cannot provide information on any treatments or medications that specifically target those particular bone types. Despite these limitations DXA is currently the gold standard for clinical diagnosis of OP and has many advantages in particular a consensus of BMD results by using the WHO T-score criteria, a proven ability to predict fracture risk, proven efficacy at targeting antifracture therapies, and the ability to monitor reactions to treatment interventions [254]. Furthermore, it is readily available and accessible for patients, has a low cost associated with it, has short scan times, high precision, and a low radiation dose [254].

1.6.2 X-RAY IMAGING

X-ray imaging has been used as a screening tool for BMD [266] and has also been used to investigate osseointegration of implants [267], additionally they are part of routine care on patients with rTKR and as such their use in implant analysis and rTKR care is relevant.

HOW AN X-RAY IMAGE IS PRODUCED

X-ray imaging creates a two dimensional radiograph of a three dimensional image, x-ray radiographs produce a higher more detailed image than DXA scans, resulting in a higher radiation dose to the patient. These radiographs are produced via x-ray photons that are emitted via a rotating anode, these photons have a certain amount of energy defined as kVp and the amount of photons produced defined via its milliamps per second (mAs), as these x-ray photons are emitted they interact with the patients' tissue [268] via two processes called Compton scatter and the photoelectric effect. During this phase the x-ray photons are attenuated based on the atomic number of the interacting tissue [268], similar to DXA, therefore x-ray photons moving through low attenuating soft tissue result in less interactions creating a greyer image, with air in the lungs being one of the most radiolucent (almost black) on the radiograph, likewise as the x-ray photons pass through a denser material such as bone the attenuation is higher resulting in more scattered photons, meaning fewer reach the cassette producing a more white region on the radiograph.

LIMITATIONS OF X-RAY

Similar to DXA patient positioning repeatability and interoperator variability increases errors in the images produced. Although there are limitations in the x-ray imaging, its ability to give high detail should allow a pixel density difference to be measured across multiple serial images, as well as the ability to distinguish the possible reduction in radiolucent lines between the conal implant and the surrounding bone, presenting evidence of bone in-growth around the implant. Furthermore, the issue of possible errors in repeatability will be addressed via the use of quality assurance (QA) systems and calibrated machines, also an item of known density (an aluminium step wedge) will be placed within every image in order to address and standardise the density being measured. This has been shown to produce accurate bone density measurements even in the advent of post processing changes [269].

1.6.3 COMPUTED TOMOGRAPHY IMAGING

Computed Tomography (CT) is used in BMD measurements via Quantitative CT (QCT) in which measurements of the spine can be taken [254] as well the axial skeleton [270], it has also been used to help in with preoperative rTKR planning in determining dimensions of a defect and whether it is contained or not [207]. Furthermore, micro-CT has also been utilised to look at bone ingrowth in porous implants [271, 272, 273, 274] with some directly testing bone ingrowth in TKR in CT images [275].

HOW A CT IMAGE IS PRODUCED

Computed Tomography scanner uses an x-ray source that rotates around the patient instead of stationary tube, like in x-ray and DXA. During a CT scan, the patient lies either supine or prone on the bed, this bed then slowly moves through the gantry while the x-ray tube rotates around the patient, producing narrow beams of x-rays through the body. These x-rays attenuate in the same way as x-ray imaging with the x-ray photons finally hitting a special digital detector located directly opposite the x-ray source [276]. One full tube rotation produces one slice, with the thickness of these slices predetermined via the scanning setup, but usually between 1-10 mm [276], the bed then moves forward and the scan repeats creating another slice, these slices are then stacked on top of each other to create an entire 3D image [276].

As CT scanning produces a 3D image it provides volumetric data [248] instead of 2D data; as such CT has a higher resolution of both x-ray and DXA and therefore has the highest radiation dose of the three imaging methods stated, although this increased dose allows the visualisation of more subtle bone structural and mechanical qualities [96].

LIMITATIONS OF CT

Unfortunately, as stated with the x-ray and DXA data, the conal implants and other parts of the rTKR will create artefact on the image which is a larger issue on CT imaging due to increased dose leading to more attenuation, additionally being a volumetric image the streak artefact will be more prominent. Furthermore, the assessment of the actual region between the metal implant and bone tissue is less straightforward due to metal-induced artefacts such as beam hardening and scattering, as these effect the voxels closest to the implant surface [277]. As such Dual Energy CT (DECT) imaging will be utilised, as this type of scan can suppress beam hardening, scatter, and in some cases metal artefacts [278]. Furthermore, the conal implants being studied are composed of titanium so the degradation should be less pronounced especially compared to stainless steel implants [279]. Moreover, titanium has also been reported to minimise streak artefact [280].

Additional actions to reduce errors in imaging will also be taken into account; this includes the standardised calibration of the machinery every day via a QA phantom. The biggest limitation in this imaging method utilised is the high radiation dose, although this is offset by the prospect of visualising in-growth behaviour of the conal implant, and the creation of higher resolution 3D volumetric images.

1.7 AIMS OF THESIS

In summary this thesis will develop and test different modality options. This will be done in order to assess what effect a newly implanted metaphyseal tritanium cone has on local and systemic BMD changes in rTKR patients. With these recommendations made prior to a full trial.

As per the protocol thirty-four total knee revision patients were to receive conal implants, 17 with long stems and 17 with short stems, additionally 17 participants were to be used as controls and would not receive the conal implants. Furthermore, these 17 were to be allotted a stem length decided at the discretion of the attending orthopaedic surgeon. Those implanted with the cones would be compared to the non-cone group, with the primary question being: How do conal implants impact BMD changes both locally and systemically and when does this change happen. This aim is addressed in the forthcoming chapters below;

Chapter 2. Presents a systematic review investigating the link between r/TKR/A and BMD at the knee, hip, spine, and total body, assessed via DXA scans. This was addressed to provide systematic evidence to establish any known association between BMD changes and r/TKR/A directly via DXA imaging. It also provided information on region placement analysis.

Chapter 3. Details the development phase, this involved testing the conal implants after insertion into a bovine model substitute, and situated in a calcium phosphate bath solution, and then imaged via DXA, x-ray, and CT. This was addressed to review possible protocol issues and problems within imaging and analysis of the BMD, and allowed the development of the any modifications to the imaging to be implemented prior to starting the feasibility study.

Chapter 4. Analyses a new piece of 3D modelling SHAPER Glago software was tested on TKR, rTKR, and control participants. Utilising DXA hip images at different post-surgery visit intervals. This included the separation of cortical and trabecular bone results in different sub regions of the hip. Participants' data were then compared to their: baseline pre-op figures, contralateral hip, and between the three groups. This software was tested in parallel with the main study starting and provided an alternative method to DXA, x-ray and CT imaging and analysis.

Chapter 5. Reported the participant numbers and attrition of the main study, and the subsequent BMD results from the DXA scans for the total body, lumbar spine, and bilateral hips, including cone and the non-cone group data. These

were recorded at pre-op, and six weeks, three months, six months and 12 months post-op. The data was compared between groups, visits and between ipsilateral and contralateral hips.

Chapter 6. Reported the BMD knee results from main study for DXA, for both the cone and non-cone control groups. This included sub regions selected within the PA and lateral knee, as well as the different visits (pre-op, six weeks, three months, six months and 12 months post-op). The data were compared between groups and visits.

Chapter 7. Reported the long leg x-ray imaging investigating pixel density differences, and hip and knee alignment angulation at six and 12 month visits.

Chapter 8. Reported the CT imaging method, the analysis and recommendations.

Chapter 9. Reported the questionnaire data including Lower Extremity Functionality Score (LEFS), Quality of Life (EQ-5D-3L), Oxford Knee Score (OKS) and Hospital Anxiety Depression Scale (HADS) compared between visits and between the cone and non-cone groups. These were recorded at pre-op, six weeks, three months, six months and 12 months.

Chapter 10. Summary, conclusion, further work/recommendations for full trial.

These methods will be discussed in more detail in later chapters but should provide adequate data in answering the aim of this study regarding the feasibility and effect a newly implanted metaphyseal tritanium cone has on BMD changes in rTKR.

CHAPTER 2 A SYSTEMATIC REVIEW TO ASSESS THE IMPACT TOTAL KNEE REPLACEMENT/ARTHROPLASTY/REVISION HAS ON BONE MINERAL DENSITY

2.1 INTRODUCTION

The impact of low bone mineral density (BMD) increasing fracture risk is well established and several studies have shown this link- Legrand et al [6] investigated BMD and vertebral fractures in 200 men, reporting a relationship between fracture numbers and femoral neck BMD, vertebral BMD, and age; concluding that low trochanteric BMD and age were the best predictors for vertebral fracture. Additionally, Marshall et al [7] conducted a meta-analysis on 229 studies evaluating BMD and fracture risk in women and concluded that low BMD can identify people who are at increased fracture risk.

This link is further supported by a study by De Laet et al involving 5814 men and women [8], concluding similar results, stating that hip fracture risk was determined by age and BMD. Cummings et al [9] developed this idea further, stating that low hip BMD was a stronger predictor of fracture than BMD at other sites. Furthermore, they also reported that loss of BMD in the proximal femur was a major risk factor for hip fracture in the aged population [10].

A study by Melton et al [11] concurred with the research of Cummings et al and Legrande et al in demonstrating that the more the BMD decreased the greater the risk of a femoral neck and inter-trochanteric fracture; concluding that hip fractures were uncommon in women with a femoral bone density above or equal to 1.0 g/cm^2, and as BMD declined fracture frequency increased, this is due to a proportional correlation between the breaking strength and the square of the bone density.

The association between low BMD with increased fracture risk is strongly supported by the evidence base. In patients undergoing total knee replacement/arthroplasty (TKR/A) or total knee revisions (rTKR) they themselves can experience reduced BMD (as shown in section 1.1.2). This is primarily due to the associated periods of inactivity and reduced weight bearing

experienced post-surgery resulting in disuse osteopenia [23]. Furthermore, low BMD contributes to periprosthetic fracture risk [281]. Periprosthetic fractures post TKR/A occurs in 0.3-2.5% [42, 282] of patients, although in rTKR it has been reported as high as 38% [283]. These fractures can lead to increased hospital readmissions, functional decline, and higher mortality rates [281, 284, 285]. Currently no systematic review has been conducted to establish a consensus on when and where the greatest BMD changes occur post-surgery. Therefore, this systematic review was created and registered with PROSPERO under code CRD42017072714.

2.1.1 AIM

The aim of this systematic review was to investigate BMD changes locally and systemically in patients undergoing TKR, rTKR or TKA, and determine both the regions most affected and the time period. This aim was broken down into separate specific review questions.

2.2 REVIEW QUESTIONS

2.2.1 PRIMARY QUESTION

What is the effect of total knee replacement (TKR), total knee arthroplasty (TKA) or total knee revision (rTKR) on bone mineral density (BMD) at the hip, knee, spine, or total body?

2.2.2 SECONDARY QUESTION

- Which anatomical sites (hip, knee, spine) experience the greatest changes (between time periods) in BMD or in bone mineral content (BMC)?
- What is the post-operative timeframe for changes in BMD/BMC and what is the period of greatest difference?

2.3 SEARCHES

Pre-specified search terms and keywords were searched, as stated below:

“bone mineral*” AND “total knee*”

“BMD” AND “total knee*”
“bone mineral*” AND “TKR”
“BMD” AND “TKR”
“bone mineral*” AND “TKA”
“BMD” AND “TKA”
“bone mineral*” AND “rTKR”
“BMD” AND “rTKR”
“BMC” AND “total knee*”
“BMC” AND “TKA”
“BMC” AND “rTKR''
“BMC” AND “TKR”

This search strategy was combined when searching MEDLINE (Ovid) (including the EMBASE database and nine others) (see appendix 1), including the term:

bone mineral* OR BMD OR BMC AND Total knee* OR TKR OR rTKR OR TKA

All searches were recorded in a search log (See results table 2.2), alongside the database name, date, and the number of results retrieved. The reference list of any eligible backward citation chasing, were also retained if relevant to the topic of review.

2.4 TYPES OF STUDY INCLUDED

All papers meeting eligibility criteria were included. Predominantly this was cohort studies, as randomised control trials were unlikely in this type of research. Opinion pieces, ideas, case studies of single patients, and editorials were excluded. Additionally, only papers in English were retained. (see table 2.1 for Patient Intervention Comparison Outcome (PICO) criteria).

2.5 CONDITION/DOMAIN BEING STUDIED

BMD/BMC difference at the hip, spine, knee, or whole body measured via DXA scans following TKR, rTKR or TKA.

2.6 PARTICIPANTS/POPULATION

Included participants: human studies only, all participants were adults (over 18 years) having a TKR, rTKR or TKA and undergoing a DXA scan to determine BMD/BMC. DXA is the ‘gold standard’ for bone density imaging, furthermore, given its extremely low dose and ease of scanning, makes it the most viable and robust imaging option (the scans are short, and can be done in addition to a routine DXA scans). Excluded participants included: Children (under 18 years);- participants who had any other type of operation or joint replacement for example a total hip replacement (THR);- Participants with a BMD or BMC which was measured via another method other than DXA were also excluded.

2.7 INTERVENTION/EXPOSURE

TKR, TKA, and rTKR

2.8 COMPARATOR/CONTROL

Either baseline measurement via DXA scans of BMD/BMC, contralateral leg to that operated on, or matched control groups.

2.9 OUTCOME

2.9.1 PRIMARY OUTCOME

Studies were included if they reported BMD/BMC at the hip, spine, knee or total body using DXA assessment at baseline and at any of the following time points: six weeks post operation, and at three, six, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post operation, at the hip, spine, knee or total body. Change in BMD between baseline and these designated time points and anatomical locations will be the primary outcome.

2.9.2 SECONDARY OUTCOME

BMD/BMC changes between set time periods compared to matched controls or contralateral leg measurements, at baseline, and then six weeks post operation,

three, six, 12, 18, 24, 30, 36, 42, 48, 54 and 60 months post operation, at the hip, spine, knee or total body.

Which anatomical site has the highest gain/loss in BMD/BMC compared to the other anatomical sites (e.g. spine, hip, knee) within the same time period.

What time period results in the highest BMD difference compared to the baseline at the knee, spine, hip and total body.

Table 2.1. *Paper inclusion and exclusion criteria*

	Inclusion criteria	**Exclusion criteria**
Population	Human participants adults over 18 having either a TKR, TKA or rTKR and a DXA scan	THR or other type of replacement, children, animals
Intervention	TKR, TKA, or rTKR	THR or other replacement
Comparator	Matched control group, BMD baseline or contralateral leg to surgery	
Outcome	Bone mineral density/BMD at the hip, knee, spine or whole body recorded via DXA	Other type of measurement of BMD other than DXA
Study Design	RCTs, Systematic reviews, meta-analysis, observational studies	Opinions, ideas, Editorials, individual case studies
Date	Not set	
Language	English only	

2.10 DATA SELECTION – EXTRACTION AND CODING

Identified studies utilising the search terms stated were imported to EndNote (version 19.2.0.13018), and de-duplicated. Studies identified by the initial searches were reviewed by two researchers for title and abstract screening against the PICO criteria. Studies which passed this stage were retrieved in full for full text screening. All studies were then again screened against the PICO

criteria to determine inclusion. Any disagreements between screeners were resolved by third party acting as arbitrator.

The number of studies identified, screened, excluded and included was recorded and reported using the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) flow diagram (results figure 2.1).

Data extraction of the final included studies was conducted by the researcher through a standardised data extraction form (appendix 2) based on: study first author, title, year of publication, study design, study setting and country, sample demographics and recruitment method, specific intervention, comparator, BMD/BMC scores and calculated differences (including when (e.g. six months post-surgery) and anatomically where (e.g. spinal BMD).

2.11 RISK OF BIAS (QUALITY) ASSESSMENT

Risk of bias/quality was assessed by the researcher using the Newcastle-Ottawa Scale (NOS) (appendix 3). Furthermore, quality appraisal was not used to exclude studies, but was utilised to assess weight quality and any possible bias within the studies.

2.12 STRATEGY FOR DATA SYNTHESIS

A narrative synthesis was utilised to describe the features of the reviewed studies. If there were enough studies of similar design a meta-analysis would have been performed by producing pooled estimate of effect and a forest plot of the difference in BMD at set intervals via DXA scans. A meta-analysis was not appropriate, so the results were described narratively.

2.13 RESULTS AND ANALYSIS

Table 2.2 below shows the search log results of the searches performed based on the key terms already stated.

Table 2.2 *Systematic reivew search log*

Database	Date	Hits
PubMed	20th September 2017	705
MEDLINE(Ovid) (10 resources selected including EMBASE)	20th September 2017	911
Scopus	20th September 2017	438
Web of Science	20th September 2017	374
Grey Literature (conference abstracts and unpublished works) including the database:		
OpenGrey	20th September 2017	3
Total		2,431

Of the 2,431 papers 1,474 were duplicates, after these were removed 957 papers remained, (including a duplicate which was a PhD thesis), this was removed as a full paper based on the thesis work was recovered as part of the search), all papers were reviewed and either excluded or retained, with only 33 in disagreement, resulting in an agreement of 96.55 % between the two researchers. These 33 papers were adjudicated on by a third party and resulted in 57 retained papers and 900 rejected based on title and abstract alone.

These 57 papers were then reviewed for full text eligibility. Of the 57; four were excluded for being in a foreign language (the original abstract was in English, but the full article was not), 13 papers had incomplete BMD data, e.g. only having pre-op scans with no follow up or not reporting the BMD at all, in one case it only stated if patients were reported as osteoporotic or osteopenic. A further 6 papers did not use DXA but another type of scan, three papers were under the term other (e.g. not a knee replacement, reviewed precision measurements in BMD not BMD itself). Finally, four papers added no new data to the review. Data from the abstract paper of one of the included papers Christ et al 2001 [286] was excluded due to reporting the same participants, analysis and results as Hagena et al 2001 [287] (they were also authors on each other's papers and share a near identical title). Wang et al 2003 [288] had both an abstract and full article included with the same data on it, therefore the abstract was excluded, and the full paper included. Of the other two papers; one paper

Lin et al 2012 [289] was a meta-analysis on joint replacement and bisphosphonates this contained 14 papers; 12 were regarding THR and two were TKA, these two were already included as part of the original search, thus this paper was not part of the results or analysis. Furthermore, Bhandari et al 2005 [290] was also excluded from the analysis as it is a systematic review on bisphosphonate use, reporting on six papers involving joint arthroplasty and BMD, of these six, five involved THR and the sixth involved a TKR, although this paper had already been discovered during the original search. A PRISMA diagram of the screening and vetting is shown in figure 2.1.

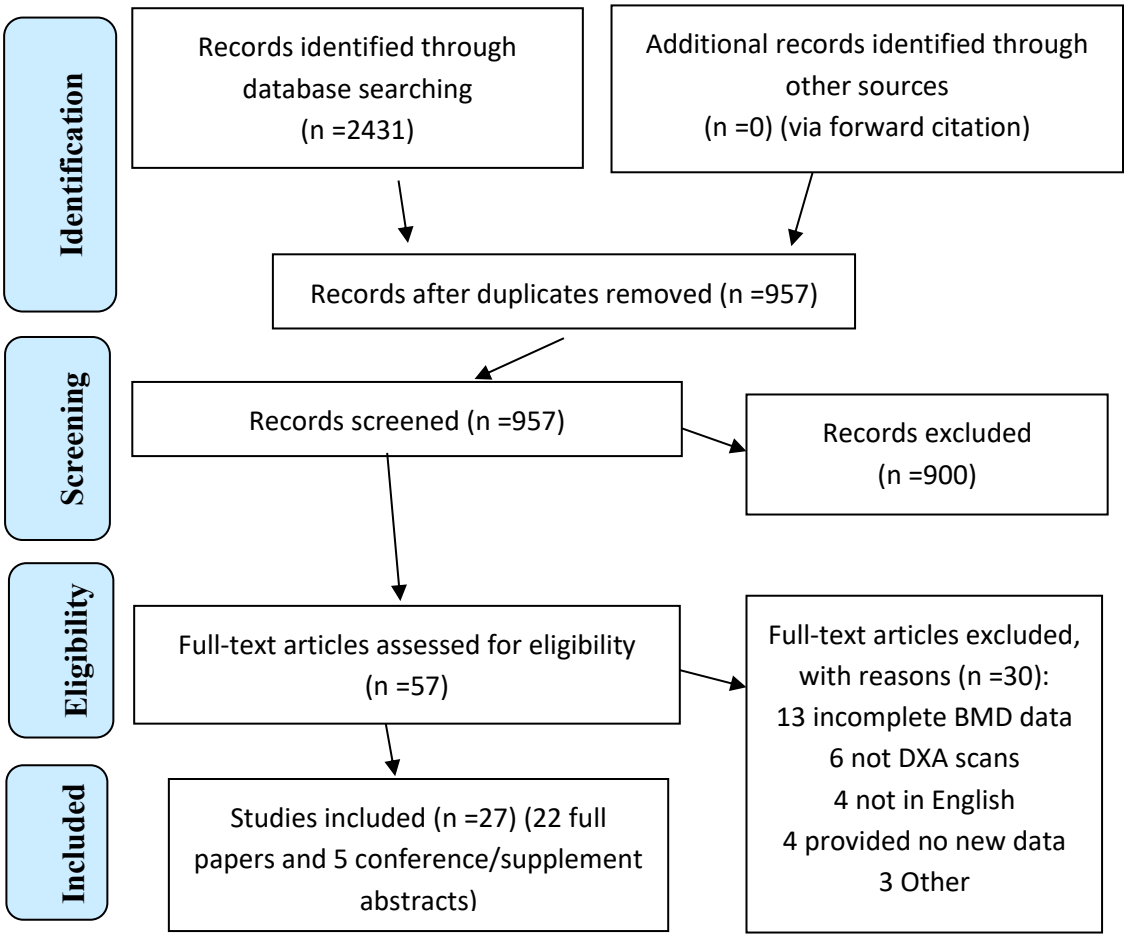


Figure 2.1. *PRISMA flow diagram reporting the inclusion/exclusion of studies prior to and after screening.*

Five of the 27 papers only included the abstract as these were conference presentations so were included as supplements in journals and contained no fully published articles. These were not excluded as “abstract only” was not part of the exclusion criteria.

The results from the 27 papers were highly heterogeneous, with different types of joint implant (e.g. cones, coated implants, fixed bearing, high press stems etc…) also these were under different types of replacement or revision. Furthermore, regional analysis varied between studies reviewing different aspects of the bone or area. Therefore, a meta-analysis was not appropriate, so results were described narratively and through a collection of modified forest plots.

Only four papers reported BMD changes at the lumbar spine or hip, none reported the total body. The majority of papers investigated the BMD changes around the knee, therefore changes in the knee will be the primary focus (although this chapter will also discuss the results of the lumbar spine and hips), whilst still addressing the primary and secondary questions of the impact of TKR, rTKR and TKA on BMD changes, and when and where those changes are greatest.

To further understand changes at the knee, the regions of interest (ROI) selected within each paper was investigated, these ROI were overlaid on a knee image in order to create a heat map of all ROI across all papers as shown in figure 2.2, the ROI in turquoise were only investigated by one paper (e.g. the patella) with the red areas showing 15 papers investigating that ROI (e.g. under the tibial component). It must be noted some ROI data were not clearly stated within the papers (e.g. ROI results were 0.834 g/cm^2) or are ambiguous to their placement (e.g. just stating femur), as per some abstract or conference data. Therefore, these three have not been included in the heat map data due to being undefined. It must also be noted that ROI stating the same area might be of a different size as shown in figure 2.3 with the larger ROI having a higher chance of overlap.

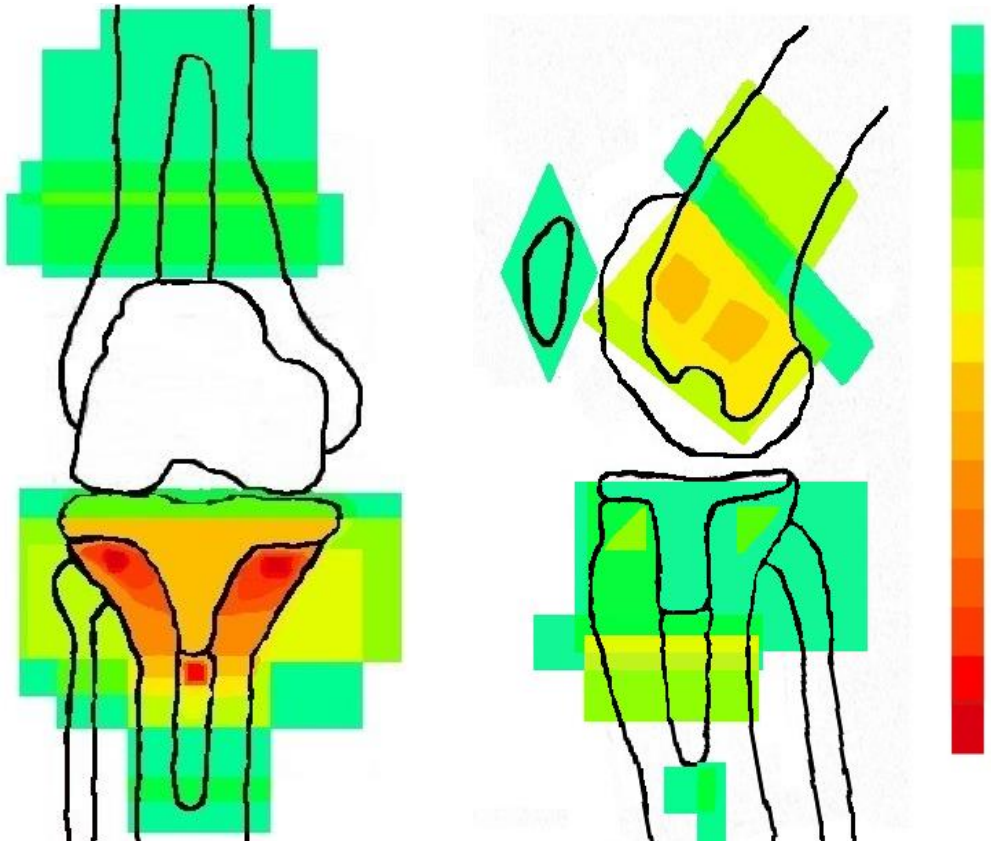


Figure 2.2. *Heat diagram showing ROI overlap, turquoise = low overlap, orange= middle overlap, red = high overlap*

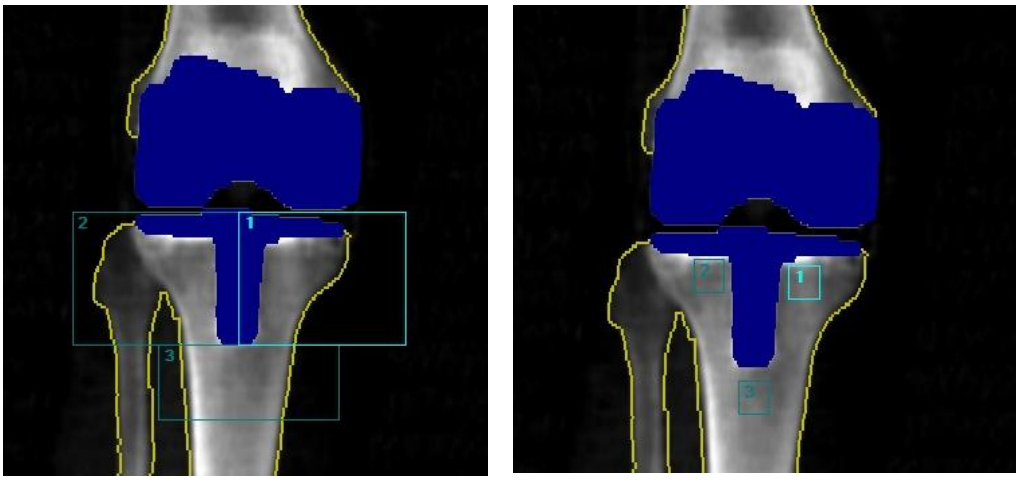


Figure 2.3. *Example of ROI selected within different papers, both papers are selecting the same regions: ROI 1 medial, ROI 2 lateral, ROI 3 under the implant*

Due to this ROI heat map data (figure 2.2) showing the intensity of investigation, the knee was divided into the two main bones (femur and tibia), and into specified regions as determined by the paper. For AP/PA tibia, three regions were chosen; lateral tibia, medial tibia, and under the implant, total was also included. For PA/AP femur only above the implant and total was included; this was due to very few data investigating the AP/PA femur during TKR/rTKR or

TKA, with not one paper researching the femoral condyles (as shown on the heat map). For the lateral tibia, the regions were anterior tibia, posterior tibia, under implant and total. The lateral femur was divided into anterior of the distal femur, middle of distal femur, posterior of the distal femur, above the implant and total. All regions were categorised via either as stated within the paper (e.g. the lateral tibial condyle BMD was 0.875 g/cm^2) or inferred from an image of the ROI selected within the paper. These ROI comparisons will answer the primary and secondary questions, especially regarding the anatomical site that is affected most by a TKR, rTKR or TKA.

All the studies gathered reported a comparison to baseline data, due to this and a lack of contralateral data, and matched participants not undergoing a TKR. The data was only analysed and presented via comparisons to the baseline.

Data from the papers were recorded in two ways; a reported score (normally a percentage difference) as determined by the author via their own calculation, or a relative score this was determined by myself and involved calculating the BMD difference as a percentage in which the new figure (e.g. a six month scan result) for a given ROI was subtracted from the baseline result (for the same ROI) and then divided by the baseline score and that answer multiplied by 100 to give a relative percentage change. Confidence intervals (CI) were also included in all results when reported, furthermore, if the paper reported the standard error (SE) or standard deviation (SD) then were possible a CI was calculated using confidence interval equals sample mean plus/minus 1.96 (95% CI) multiplied by SD/square root of the sample size. If only the SE was known, then the SE would be multiplied by the square root of the sample size (in order to get the SD). These figures were included in the results as well as a Cohen's D effect calculation.

Additionally, five of the 27 papers were investigating bisphosphonates were included in the study, although it must be stated that only their control participant data were included in this analysis, due to the impact of bisphosphonates increasing BMD (the results between the controls and the bisphosphonate groups are shown in appendix 4). It was also decided that a minimum of three papers would be needed for each time period per ROI, as it

was deemed there would not be enough data due to the variations in ROI size and implant design. The number of papers for each time period is shown in table 2.3.

Table 2.3. *Number of papers for each time period*

	Weeks	Months									
	6	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
AP/PA femur	0	2	5	5	0	2	0	1	0	0	0	0
Lateral femur	0	5	5	7	0	6	0	0	0	2	0	1
AP/PA tibia	0	6	9	13	1	12	0	1	0	2	0	2
Lateral tibia	0	3	4	5	0	5	0	0	0	2	0	0

The data for the modified forest plots are of the three, six, 12, and 24 month data for both the lateral and AP/PA tibia and femoral ROI data.

2.13.1 BASELINE COMPARED TO THREE MONTHS

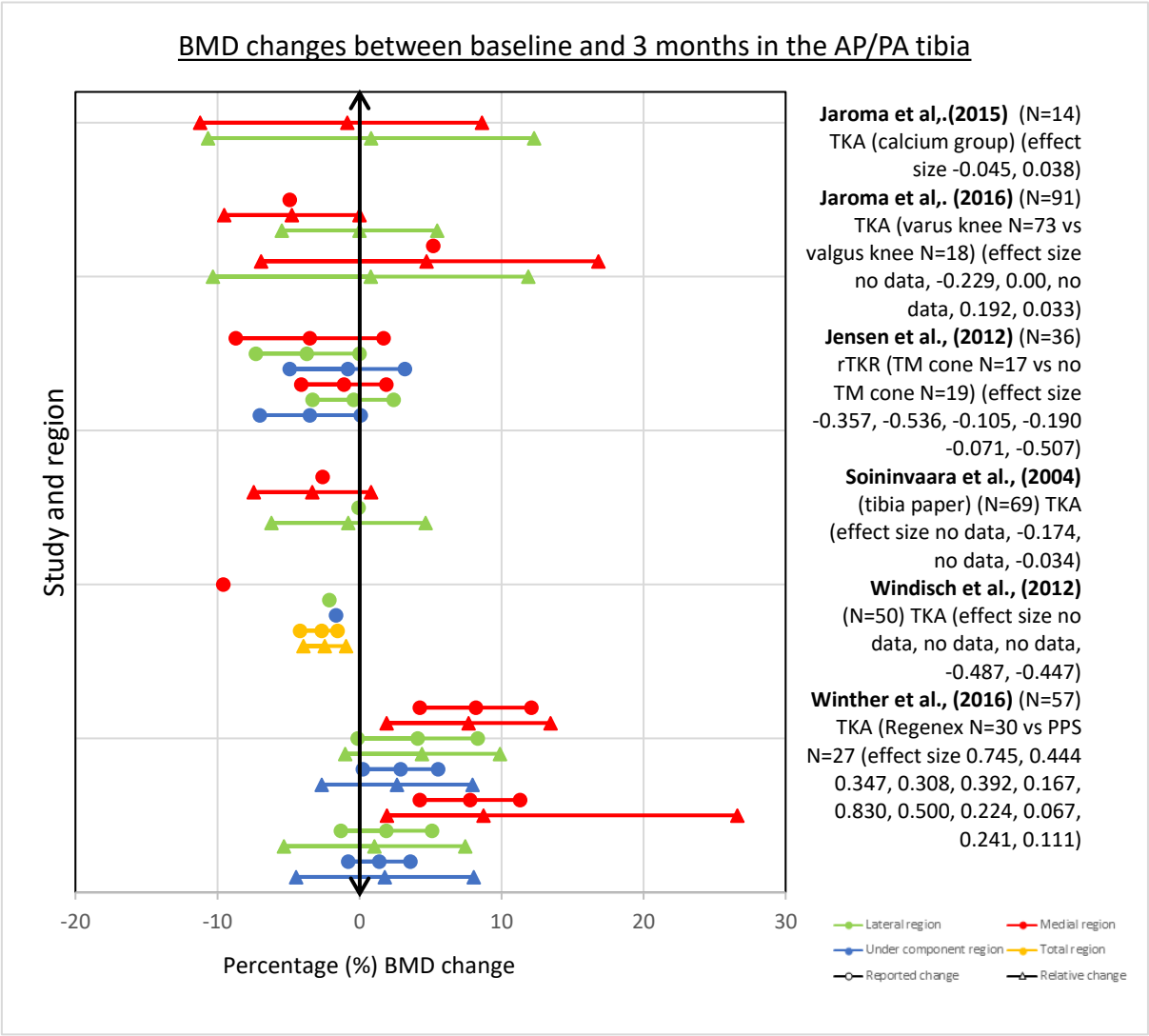


Figure 2.4. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 3 months in the AP/PA tibia*

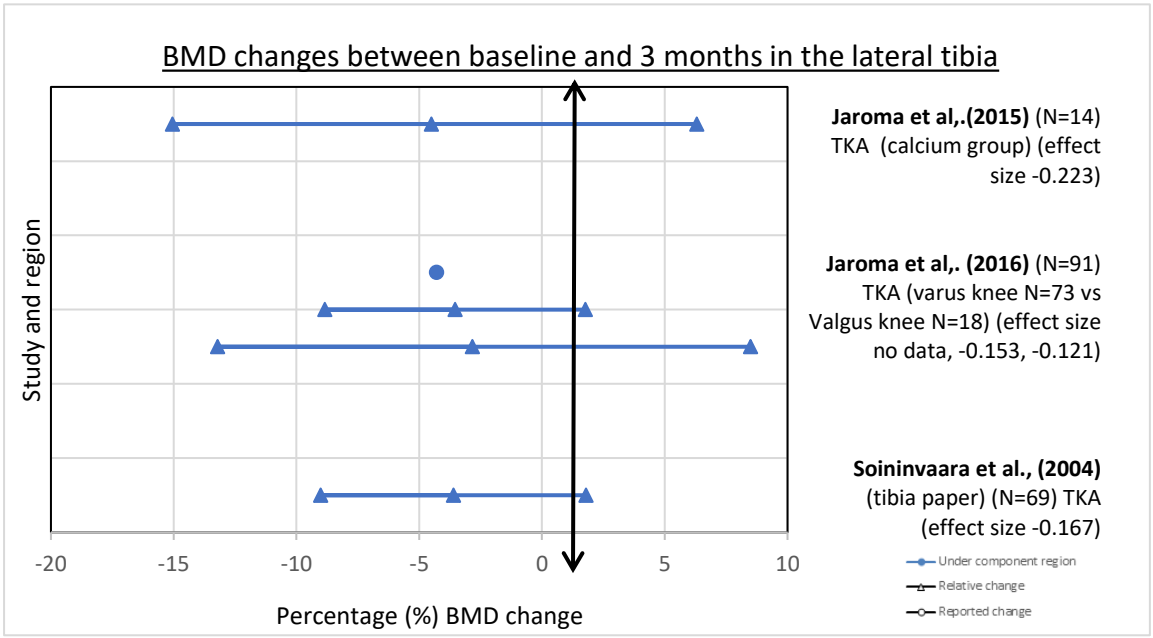


Figure 2.5. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 3 months in the lateral tibia*

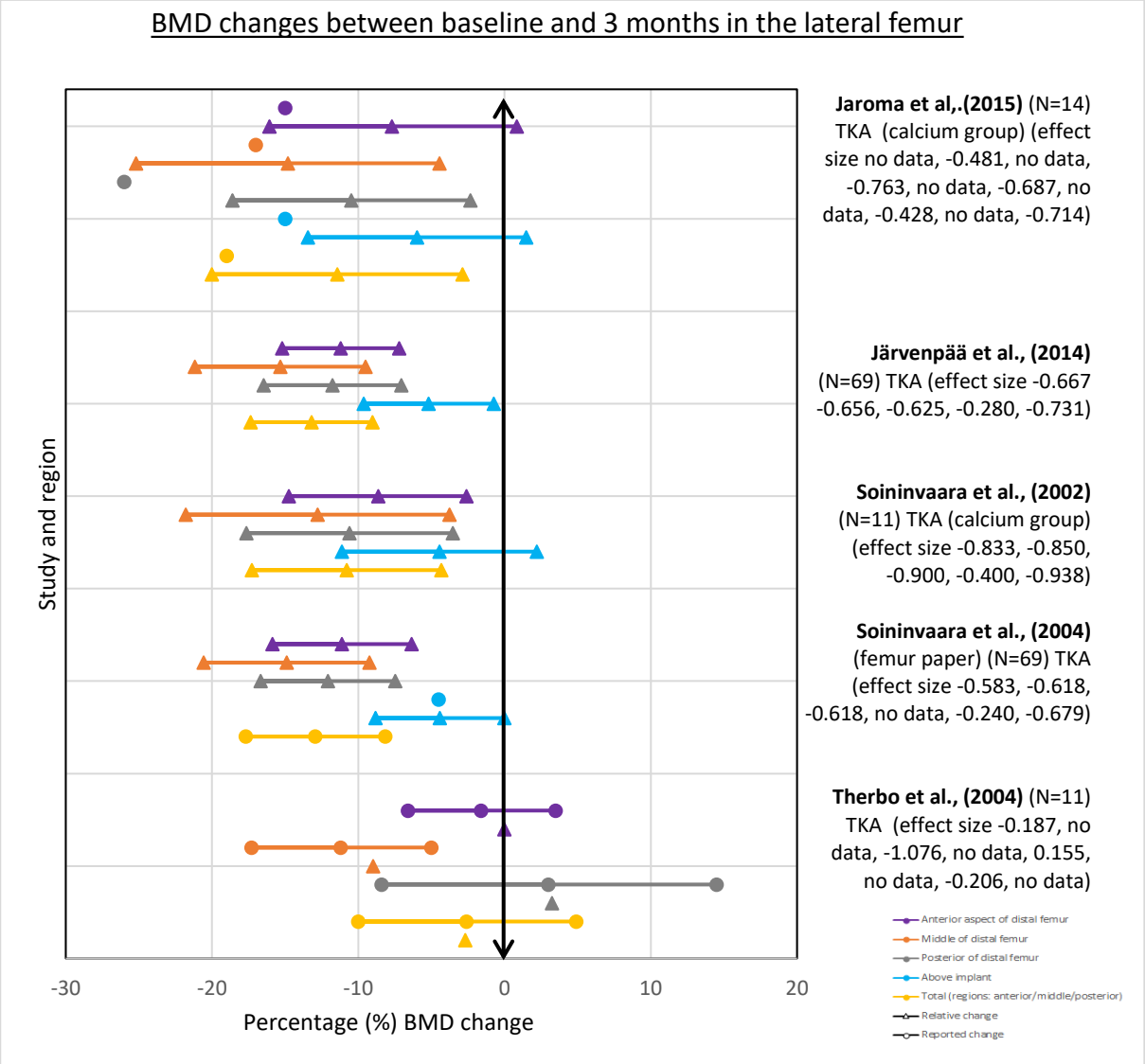


Figure 2.6. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 3 months in the lateral femur*

The greatest reported loss in AP/PA tibia (figure 2.4) is Windisch et al 2012 [291] with a reported loss of -9.59 % in the tibial medial region, although no CI are stated for the individual ROI, the total of all the regions are reported as -2.66 % (CI -1.55 to -4.17), and the relative change was calculated as -2.44 % (CI -0.93 to -3.95). It must be acknowledged that Winther et al 2016 [226] actually showed an increase in BMD with the highest reported being 8.2 % (CI 4.26 to 12.1), a relative percentage change of 7.69 % (CI 1.92 to 13.46). Figure 19 shows 35 data points, of which 19 are negative and 16 positive; although 12 of the 16 positive results are from one paper (Winther et al 2016 [226]).

The lateral tibia (figure 2.5) only investigated under the tibial component, all of these five data points (three papers) show a BMD loss, with the highest calculated relative average of -4.5 % (CI -15.05 to 6.31) (Jaroma et al 2015

[292]) and reported average loss of -4.3 % (no CI) (Jaroma et al 2016 [29]). For the entire tibial data (lateral and AP/PA) eight of the nine papers show some form of average loss.

The lateral femur three month data (figure 2.6) show a loss of BMD in a high majority of data points including the CI, the highest loss reported is in the Jaroma et al 2015 [301] paper reporting a loss of -26 %, this was calculated as a relative loss of -10.47 % (CI -18.6 to -2.33), this was at the posterior aspect of the femur. The highest relative loss was -15.33 % (CI -21.17 to -9.49) with the next highest relative change being -14.81 % (CI -25.19 to -4.44) these two figures are from different papers (Järvenpää et al 2014 [19] and Jaroma et al 2015 [292]) but are both refer to losses in the middle of the distal femur. In total there are 34 data points, 31 show an average BMD loss, two show a positive (and one is reported as 0 (no change)).

2.13.2 BASELINE COMPARED TO SIX MONTHS

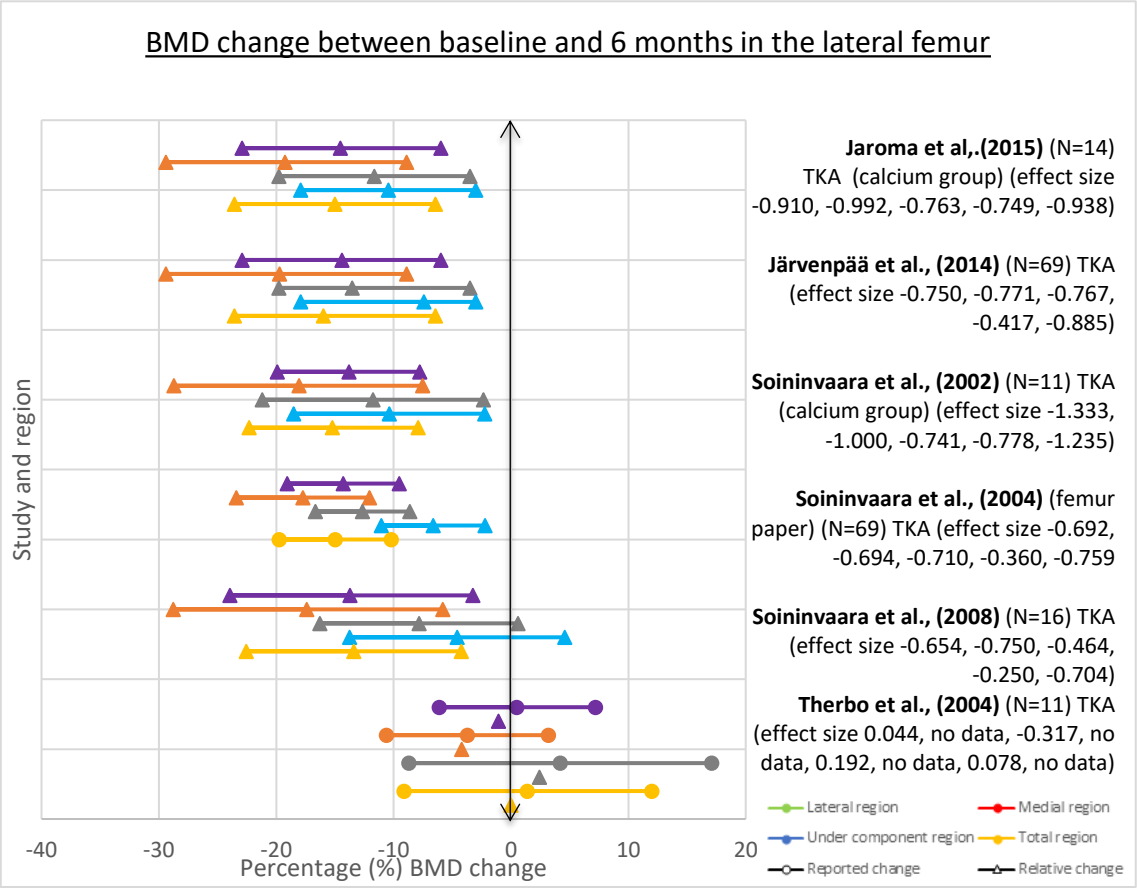


Figure 2.7. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 6 months in the lateral femur*

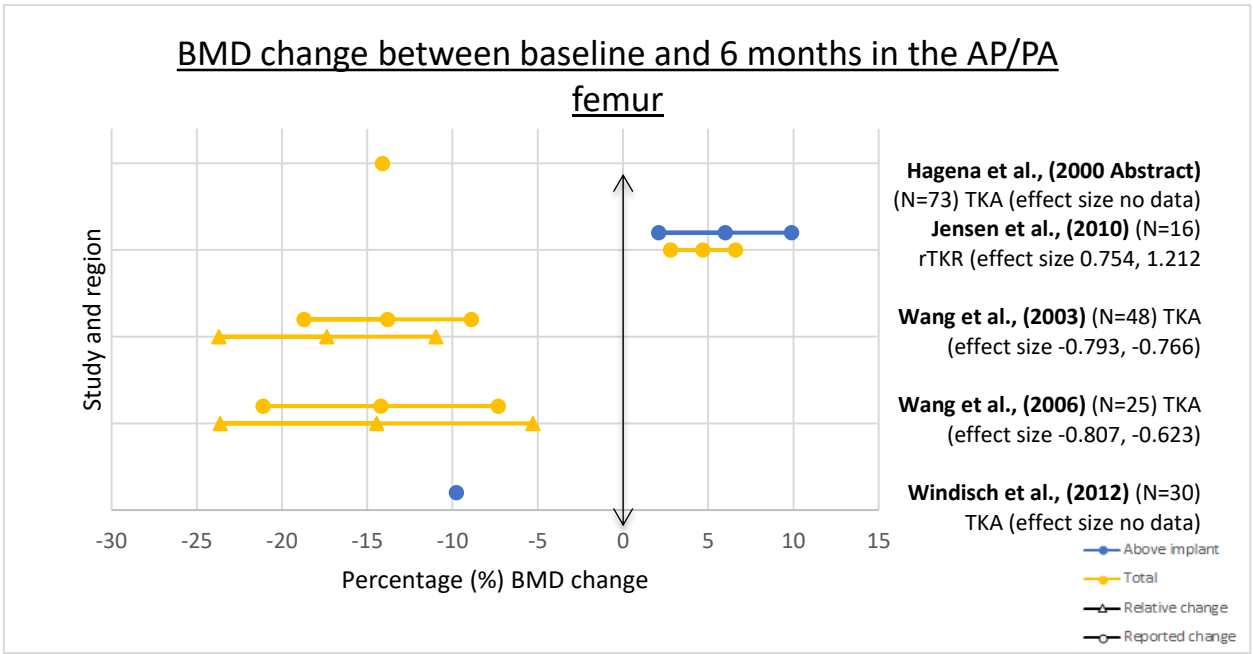


Figure 2.8. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 6 months in the AP/PA femur*

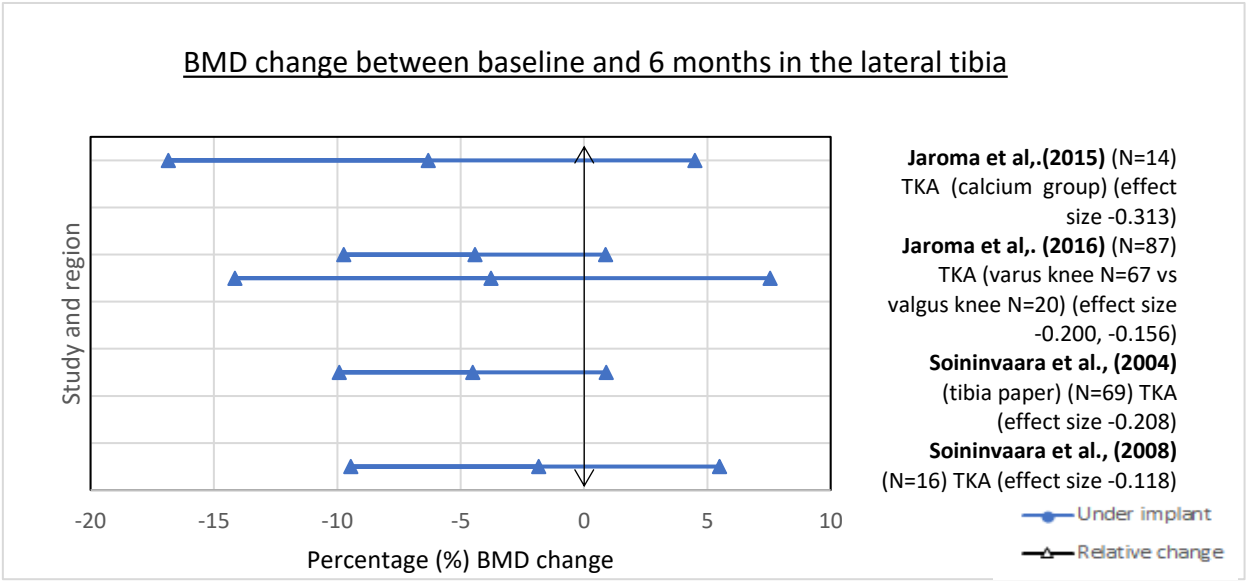


Figure 2.9. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 6 months in the lateral tibia*

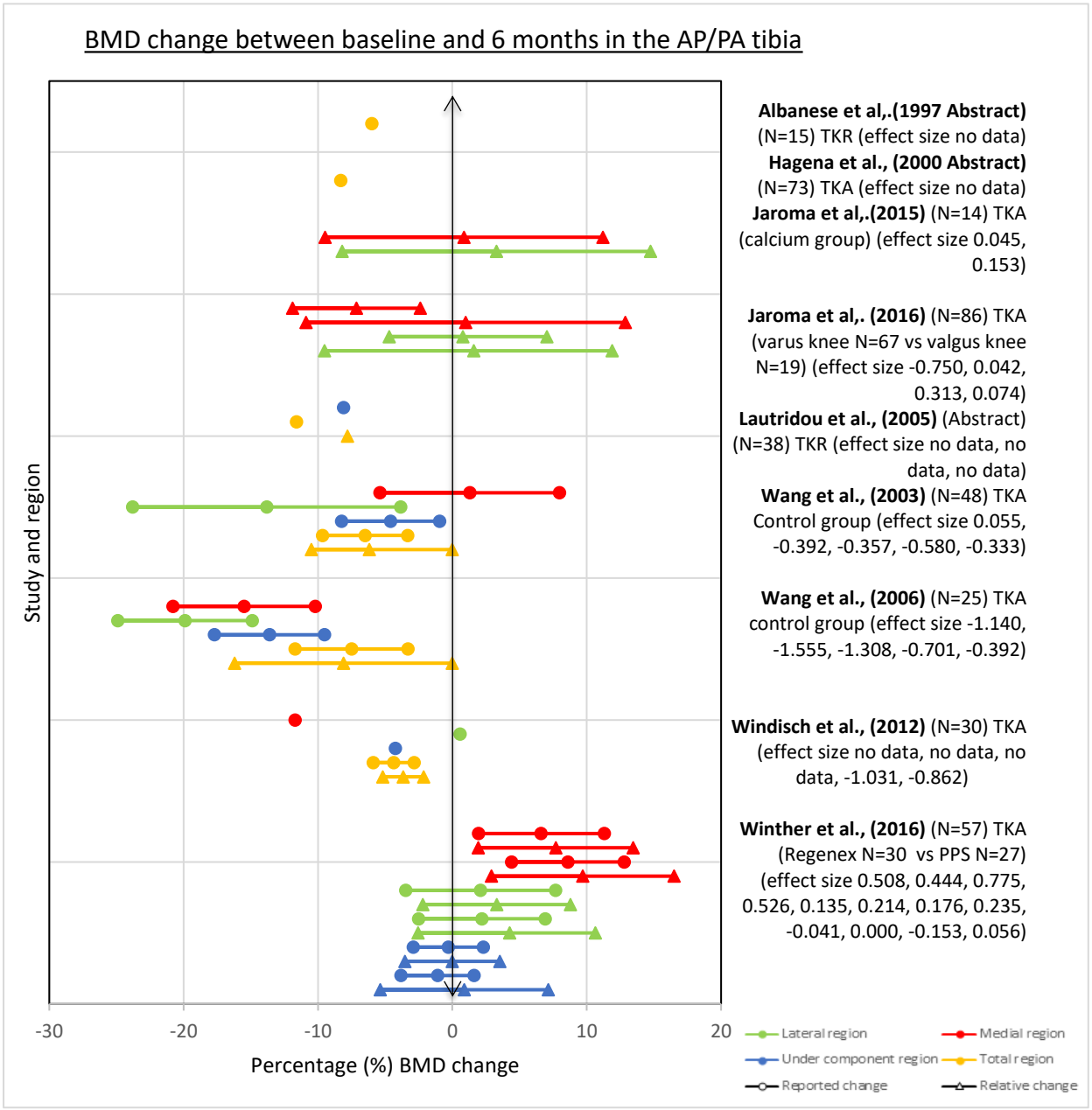


Figure 2.10. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 6 months in the AP/PA tibia*

At six months the lateral femur (figure 2.7) shows only four of the 33 data points reporting an increase, with 28 stating a loss of BMD (one with no change), 23 of these data points have CI that do not overlap the 0 line, showing a loss of BMD of statistical significance. The highest loss is in the middle of the distal femur with a relative loss of -19.71 % (CI -29.41 to -8.89). Furthermore, all of the papers show the greatest loss in the middle distal femur reported as: relative loss -19.26 % (CI -29.41 to -8.89), -17.39 % (CI -28.77 to -5.8), -17.73 % (CI -23.4 to -12.06), -18.05 % (CI -28.72 to -7.52), reported -3.7 % (CI 3.2 to -10.6), relative change -4.19 % (no CI).

The AP/PA femur (figure 2.8) mainly reported the total of the regions with six of the eight data points showing a loss of BMD. With the greatest relative loss of -14.45 % (CI -23.63 to -5.27) this was reported as -14.20 % (CI -21.1 to -7.3).

The lateral tibia (figure 2.9) only reviewed the area under the implant with all five data point averages showing a BMD loss, with greatest loss reported as -6.31 % (CI -16.85 to 4.5). The AP/PA tibia (figure 2.10) shows 38 data points with 22 showing a BMD loss, with the highest reported loss was -19.9 % (CI -24.9 to -14.9) with this loss reported at the lateral aspect of the tibia. Furthermore, Winther et al [226] had a BMD increase of relative change of 9.71 % (CI 2.91 to 16.5) this was reported at the medial aspect region. It must be noted the six papers reporting totals all show an average loss including the reported differences of -7.5 % (CI -11.7 to -3.31), -6.5 % (CI -9.67 to -3.33), -6 % (no CI), -8.3 % (no CI), -11.6 % (no CI) and -4.37 % (CI -5.89 to -2.85).

2.13.3 BASELINE COMPARED TO 12 MONTHS

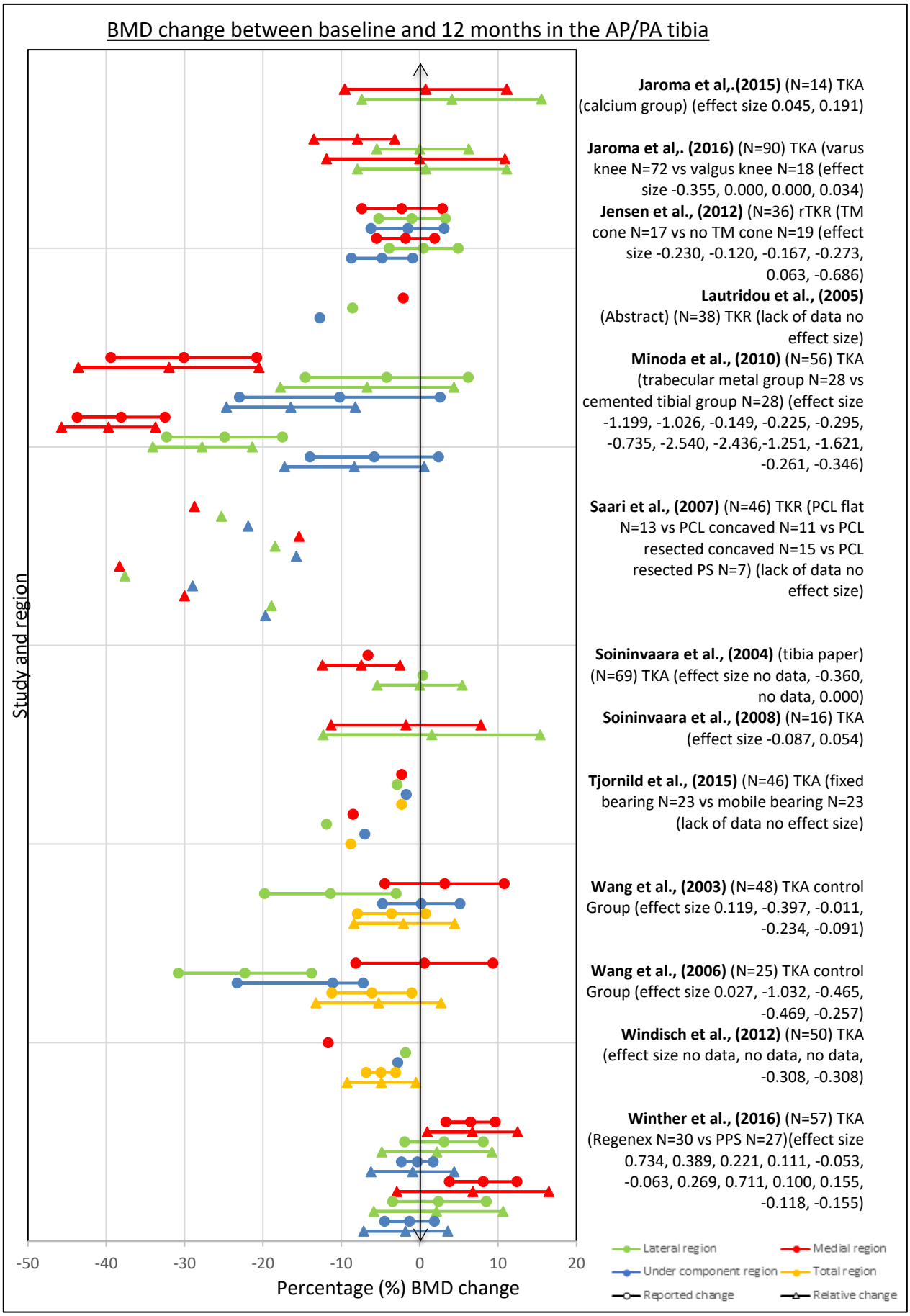


Figure 2.11. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 12 months in the AP/PA tibia*

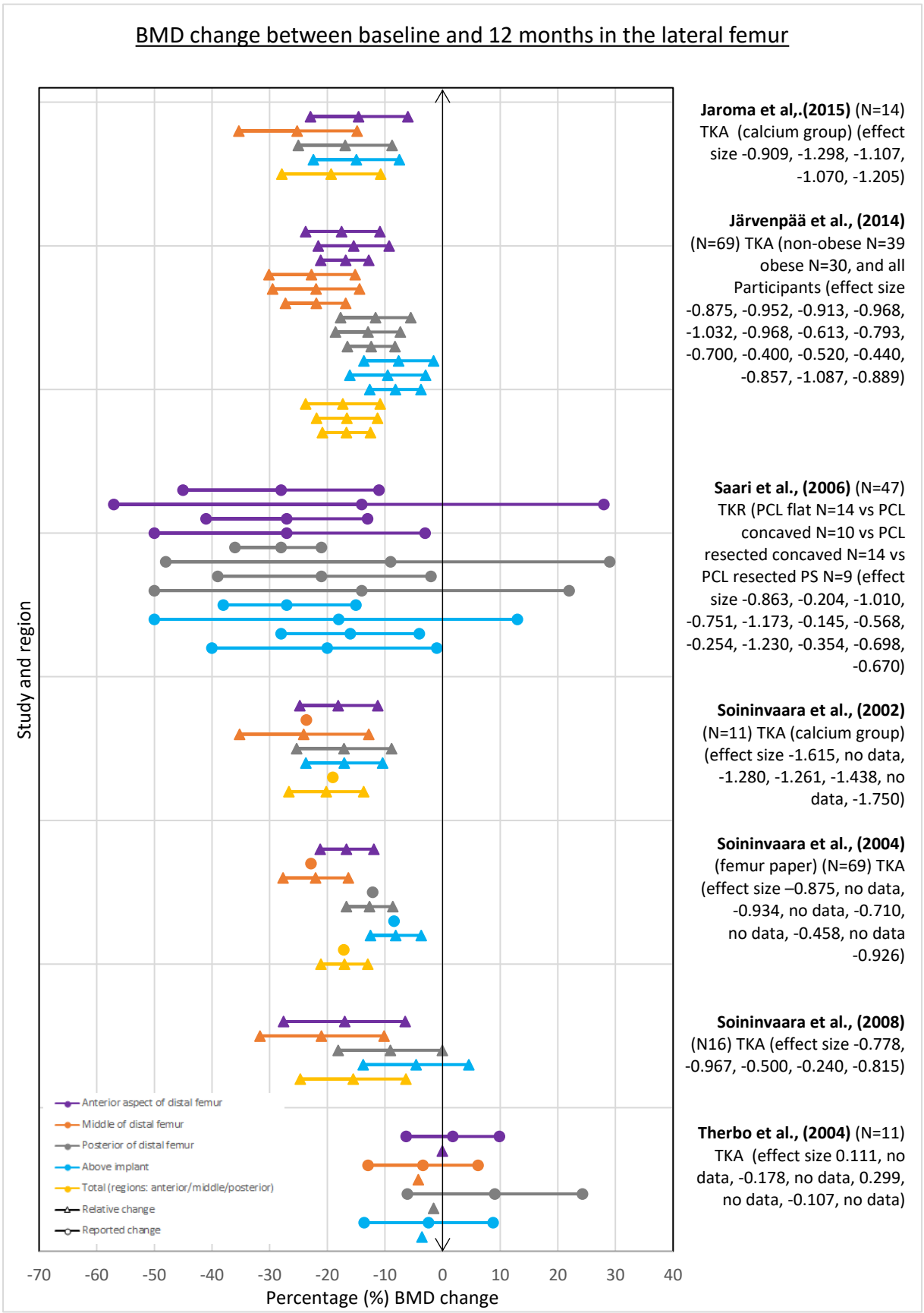


Figure 2.12. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 12 months in the lateral femur*

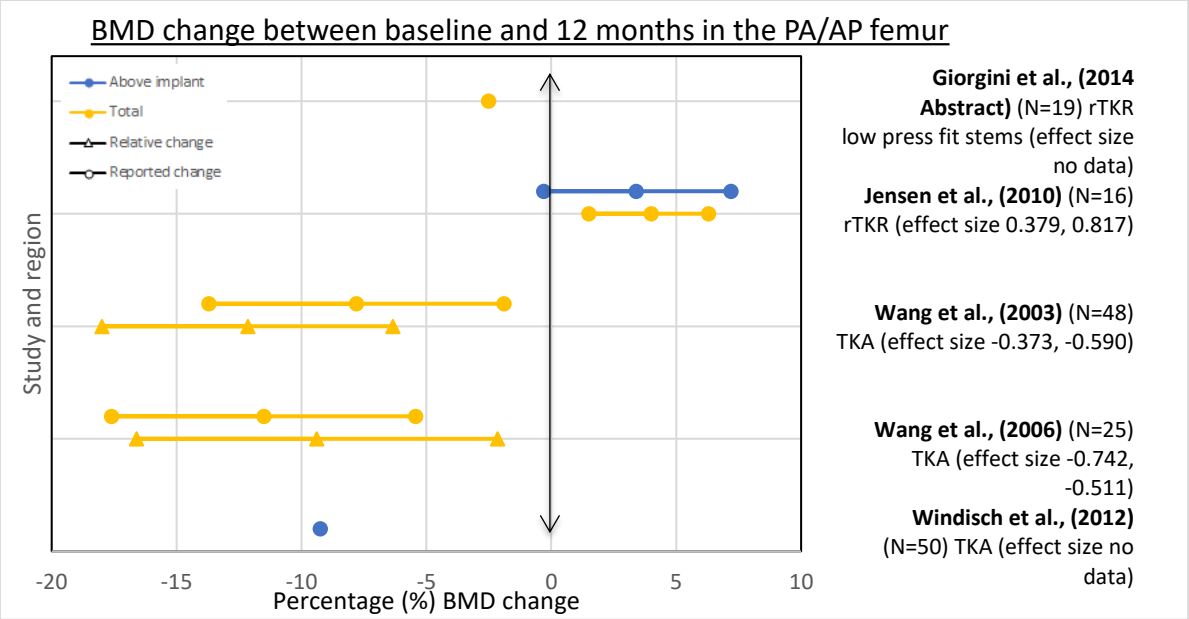


Figure 2.13. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 12 months in the AP/PA femur*

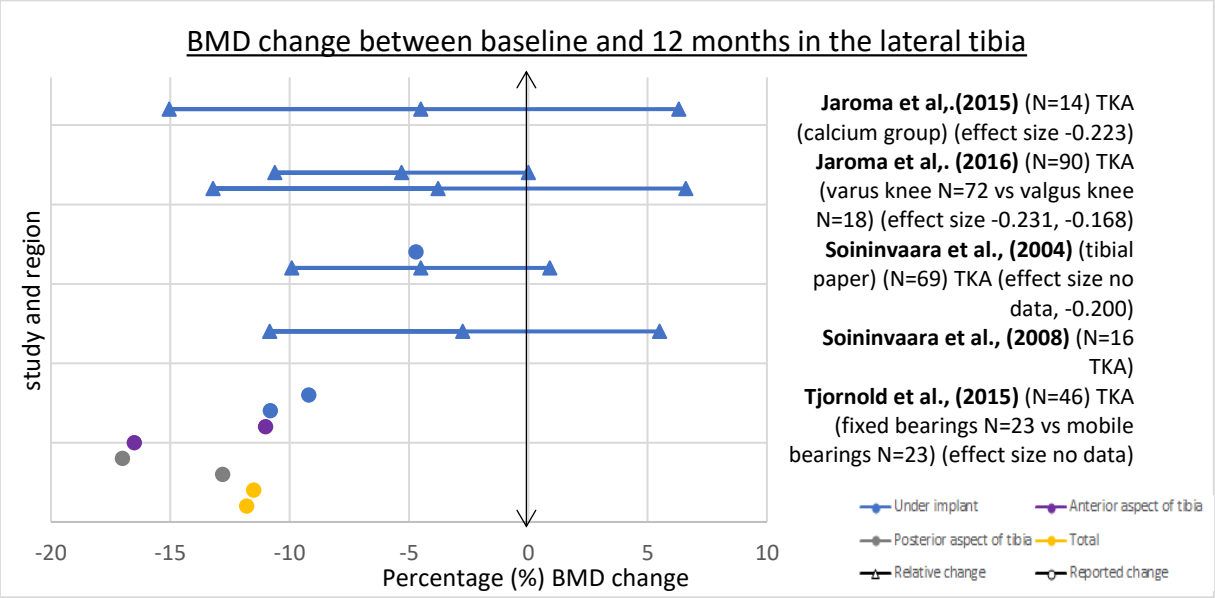


Figure 2.14. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 12 months in the lateral tibia*

At 12 months the AP/PA tibia (figure 2.11) has 83 data points, of which 63 report a BMD loss (three are 0 change, and 17 show a positive increase; nearly half of these increases are from the Winther et al 2016 paper [226]). The highest loss is reported as -38.10 % (CI -32.5 to -43.7) and a calculated relative change of -39.71 % (CI -33.7 to -45.72) this is in the medial aspect of the tibia. Furthermore, the majority of the papers show a decrease in the BMD at the medial aspect, although Winther et al 2016 [226] shows an increase in BMD

(reported as 8.1 % (CI 3.8 to 12.4), which was also calculated as a relative change of 6.73 % (CI 0.96 to 12.5).

In the lateral tibia (figure 2.14) all 14 data points show a BMD loss, with the highest loss is reported as -17 % (no CI) at the posterior aspect of the tibia, closely followed by the anterior aspect reporting a BMD loss of -16.5 % (no CI).

The 12 months lateral femur (figure 2.12) data show 58 out of 61 data points as a BMD loss (one data point reporting no change, and two showing an increase), the BMD greatest loss is in Saari et al 2006 [293] with a reported loss of -28 % (CI -45 to -11). The greatest loss for each paper is the middle of the distal femur (with the exception of Saari et al 2006 [293] although the middle aspect region is not reported), with a relative change of -25.19 % (CI -35.33 to -14.81), -21.01 % (CI -31.67 to -10.14), -22 %, -21.99 % (CI -27.66 to -16.31), -23.6 %, -24.06 % (CI -35.19 to –12.78), -3.4 % (CI -12.9 to 6.2) -4.19 %, -22.73 % (CI -30.08 to -15.15), -21.92 % (CI -29.45 to -14.38), -21.9 % (CI -27.23 to -16.79).

With the AP/PA femur (figure 2.13) six of the eight data points show a BMD loss, the total regions show the greatest loss in the reported data, with the highest loss reported as -11.5 % (CI -17.6 to -5.42), a relative change of -9.38 % (CI -16.6 to -2.15).

2.13.4 BASELINE COMPARED TO 24 MONTHS

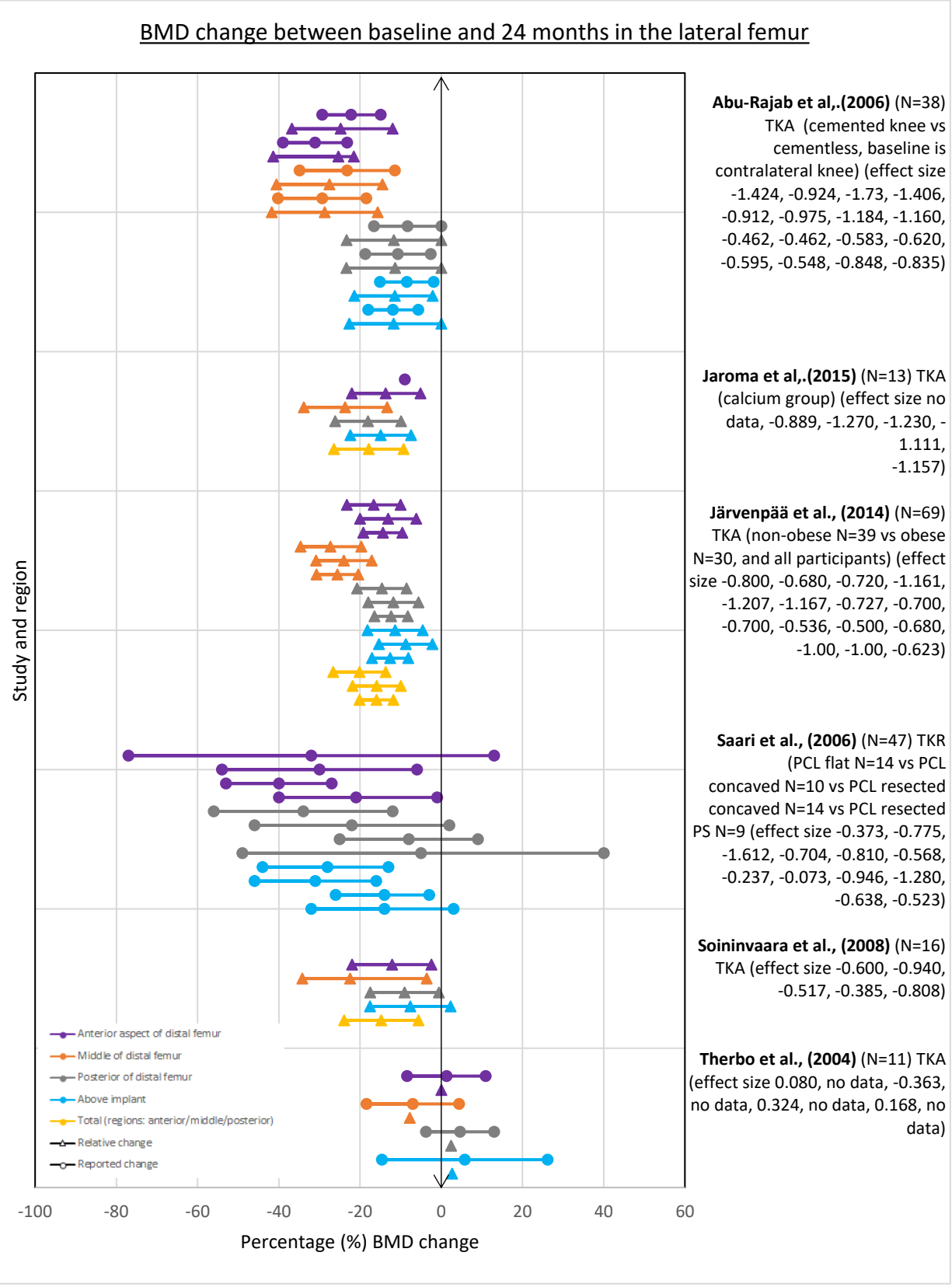


Figure 2.15. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 24 months in the lateral femur*

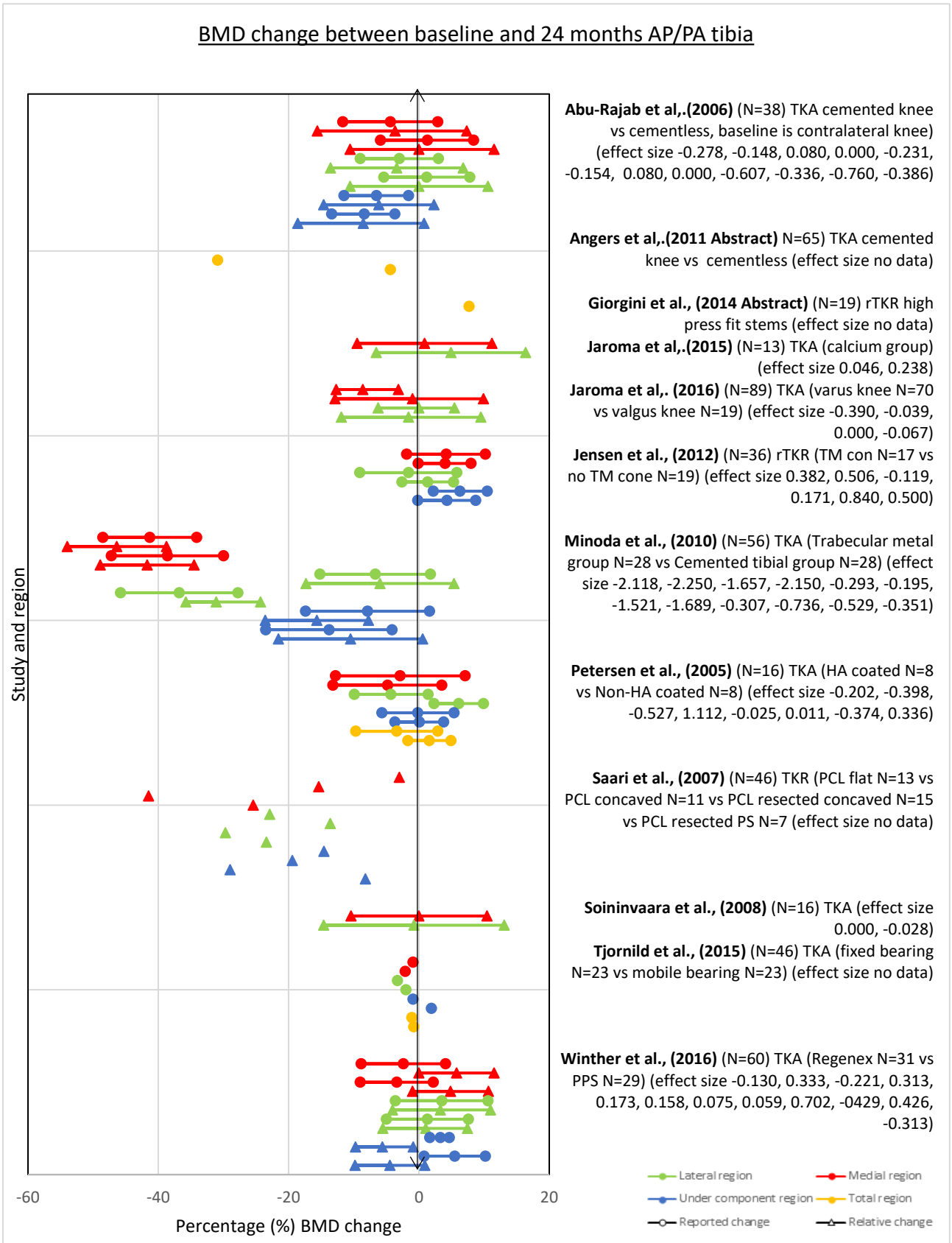


Figure 2.16. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 24 months in the AP/PA tibia*

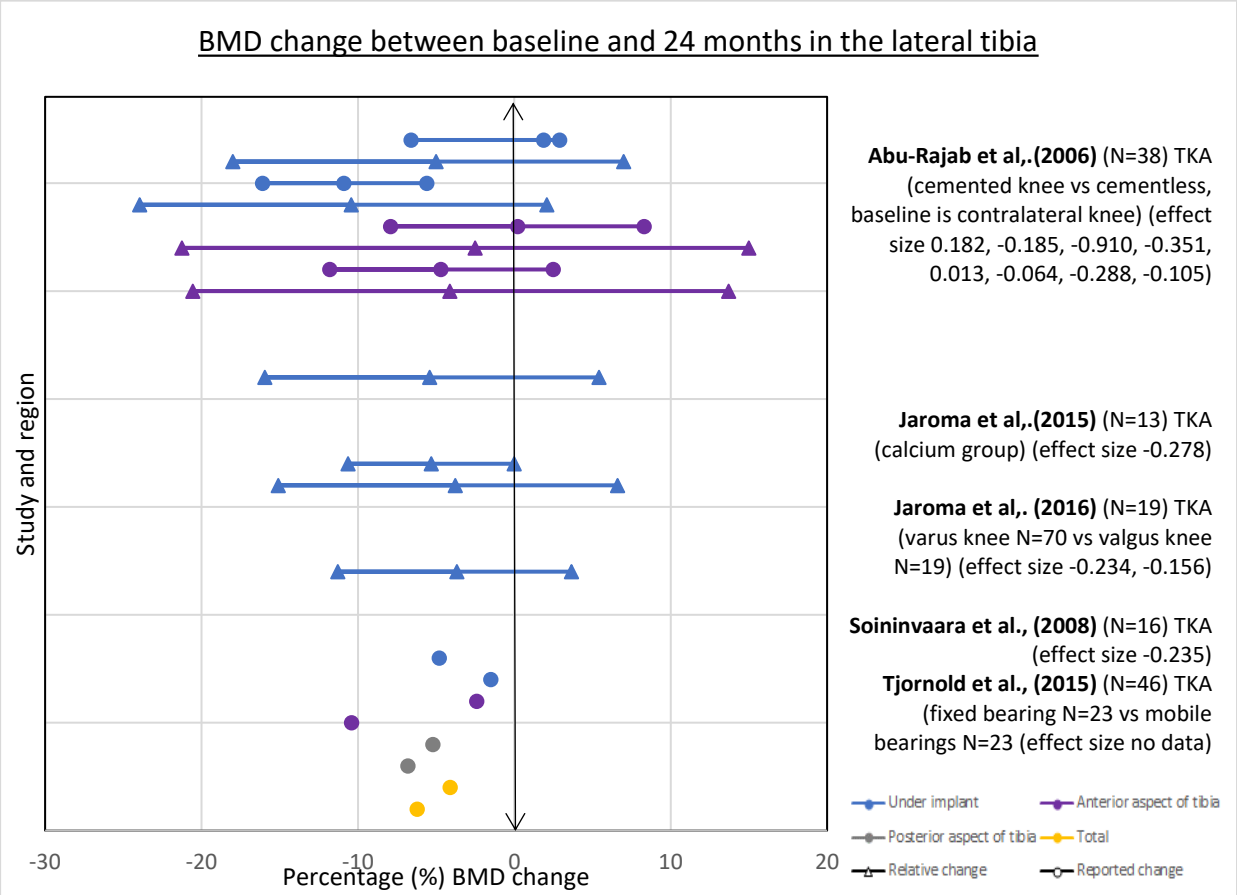


Figure 2.17. *Forest plot showing the average BMD difference +/-95 % CI (were reported/calculated) between baseline and 24 months in the lateral tibia*

At 24 months the lateral femur (figure 2.15) shows a similar pattern as the previous months with 58 of 64 data points showing a BMD loss (five positive and one 0 change), with the greatest loss reported of -40 % (CI -53 to -27) at the anterior aspect, but the majority of the research papers showing a loss of BMD in the middle region of the distal femur when compared to the other regions (four of the six papers have their highest loss reported as the middle of distal femur).

At 24 months the PA/AP tibia (figure 2.16), the reported greatest loss is in the Minoda et al 2010 [294] paper of -46.37 % (CI -53.98 to -38.76). Of the 81 data points, several papers (22 data points) showed an average increase in BMD since the baseline. With 54 data points showing a decrease, and 5 data points showing 0 change.

The lateral tibia (figure 2.17) shows 19 of the 20 data points as a loss of BMD with the higher loss on the anterior aspect, with a reported loss of -10.9 % (-5.6 to -16.1).

2.13.5 HIP, TOTAL BODY, AND LUMBAR SPINE

As stated many of the papers do not report the lumbar spine or bilateral hips, and not a single paper reported the total body data. Most papers mainly concentrated on the changes in and around the knee**.** Furthermore, some papers did include data about the hips and lumbar spine although these have had to be excluded as they have only reported T-scores and not the BMD or a percentage change (Abu-Rajab et al 2006 [395], Windisch et al 2012 [291]), or have only reported pre-op BMD, without follow up data (Minoda et al 2010 [294]) so have been excluded from the analysis.

Of the 27 papers only four have reported changes in BMD in either the lumbar spine or bilateral hips. These four are shown below in tables 2.4 and 2.5.

Table 2.4. *Papers which investigated hip BMD, m = months, wks = weeks*

Study name	**Homolateral hip in BMD (g/cm^2)**				**Contralateral hip in BMD (g/cm^2)**			
Lautridou C, et al (2005) (reported as femoral neck) (N=38)	**Baseline** 0.768			**60 m** 0.750				
Soininvaara TA, et al (2004), (hip paper) (N=67)	**Pre op** 0.99			**12 m** 0.977	**Pre op** 1.022			**12 m** 1.009
Hopkins SJ, et al (2016) (N=19)	**Baseline** 0.981	**6 wks** 0.969	**6 m** 0.965	**12 m** 0.966	**Baseline** 0.994	**6 wks** 0.992	**6 m** 0.995	**12 m** 0.993

Table 2.5. *Papers which investigated lumbar spine BMD*

Study name	**Lumbar spine BMD (g/cm^2)**			
Minoda Y, et al (2010) (N=56)	**2 weeks pre op**			**24 months**
Trabecular metal group (N=28)	0.937+/-0.199			0.881+/-0.113
Cemented tibial group (N=28)	0.874+/-0.120			0.946+/-0.210
Hopkins SJ, et al (2016) (N=19)	**Baseline** 1.21	**6 months** 1.197	**12 months** 1.199	

All 12 month scans show a BMD loss when compared to baseline, both for the hip and lumbar spine, yet at 24 months there is report of an increase in the lumbar spine cemented group (Minoda et al 2010 [294]).

2.14 QUALITY OF STUDIES

The quality of the studies was determined using the NOS, this was divided into three sections (selection, comparability, and outcome):

Selection

- Representative of the exposed cohort a) The participants/patients are a true representative of the average TKR/TKA/rTKR in the community b) Somewhat representative of the average TKR/TKA/rTKR in the community c) A selected group of users d) No description of the derivation of the cohort.
- Selection of non-exposed cohort a) Are they drawn from the same community as the exposed cohort b) Drawn from a difference source c) No description of the derivation of the non-exposed cohort
- Ascertainment of exposure a) Secure record (e.g. surgical records) b) Structured interview c) Written self-report d) No description
- Demonstration that outcome of interest was not present at start of study a) Yes b) No

Comparability

- Comparability of cohorts on the basis of the design or analysis a) Study controls for (select most important factor) (e.g. age, BMI, gender etc.) b) Study controls for any additional factor (these criteria could be modified to indicate specific control for a second important factor).

Outcome

- Assessment of outcome a) Independent or blind assessment (e.g. by reference to secure records such as x-rays or medical record b) Record linkage (identified through ICD codes on database records) c) Self-reported d) No description.

- Was follow-up long enough for outcome to occur a) Yes (three month minimum) b) No
- Adequacy of follow-up of cohorts a) Complete follow-up - all subjects accounted for b) subjects lost to follow-up unlikely to introduce bias - small numbers lost >20 % follow-up, or description provided of those lost) c) Follow up rate <20% and no description of those lost d) No statement

The majority of the 27 papers all have very high quality (see table 2.6), this is mainly due to the criteria such as: all using DXA scans (reducing bias/interpretation), recording baseline measurements, recording data at appropriate time intervals, patients used as their own controls compared to their previous scans (or contralateral knee), thus variation and bias during comparison was reduced. The main reductions in quality were either the undefined loss of participants, in some cases this was not disclosed (especially in abstracts), the other issue was mainly the selection and recruitment criteria, and it being unclear if/how the group was recruited, and if the sample was representative.

Table 2.6 *Quality check for all 27 papers*

Study	Selection (max 4 stars)	Comparability (max 2 stars)	Outcome (max 3 stars)	Total (max 9 stars)
Abu-Rajab RB, et al 2006 [295]	****	**	***	*********
Albanese C, et al 1997 [296]	***	**	**	*******
Angers M, et al 2011 [297]	***	**	**	*******
Giorgini, M, et al 2014 [298]	**	*	**	*****
Hagena FW, et al 2001 [287]	**	-	**	****
Hopkins S, et al 2016 [23]	****	**	***	*********
Jaroma A, et al 2015 [292]	****	*	***	********
Jaroma, A, et al 2016 [29]	****	*	***	********
Järvenpää J, et al 2014 [19]	****	*	***	********
Jensen CL, et al 2010 [179]	****	*	**	*******
Jensen CL, et al 2012 [178]	****	**	***	*********
Lautridou C, et al 2005 [299]	****	*	**	*******
Minoda Y, et al 2010 [294]	***	**	***	********
Petersen MM, et al 2005 [37]	****	*	***	********
Saari T, et al 2006 [293]	***	**	***	********
Saari T, et al 2007 [300]	***	**	***	********
Soininvaara TA, et al 2002 [301]	****	**	***	*********
Soininvaara TA, et al 2004 (hip paper) [26]	****	*	**	*******
Soininvaara TA, et al 2004 (tibia paper) [17]	****	*	***	********
Soininvaara TA, et al 2004 (femur paper) [302]	****	*	***	********
Soininvaara TA, et al 2008 [303]	****	*	**	*******
Therbo M, et al 2004 [304]	****	**	***	*********
Tjornild M, et al 2015 [305]	****	**	***	*********
Wang CJ, et al 2003 [288]	****	**	***	*********
Wang CJ, et al 2006 [306]	****	**	***	*********
Windisch C, et al 2012 [291]	****	*	**	*******
Winther N, et al 2016 [226]	****	**	***	*********

2.15 DISCUSSION

To answer the questions set out, and to review the impact of TKR, rTKR and TKA on BMD we must first review the BMD changes throughout the time period.

As reported in the literature in chapter one, one of the most important time periods is 5-12 weeks [17-19] due to the significant BMD decrease, with most research reporting data at three months and patients not fully ambulatory post-operation. At three months the majority of papers show a loss of BMD within most ROI. Within the tibia the medial region seems the most affected reporting the highest BMD loss of -9.59 % (no CI) (although Winther et al 2016 [226] reports an increase in BMD in this region). For the femur this loss is more severe than the tibia, a loss of -26 % (no CI) was reported at the posterior aspect of the distal femur. Furthermore, the distal middle ROI within the femur shows a consistent loss across all papers (the highest relative loss in all papers, and the highest reported loss in four out of five of the papers). Looking at the data points; 54.29 % of them in the PA/AP tibia show BMD loss, with the lateral femur reporting 91.18% of the data points as a BMD loss.

At six months this overall loss increases, although some regions in the tibia show an increase, the reported totals of all the ROI show a decrease (with six papers reporting as such). The highest reported AP/PA tibia loss was -19.9 % (CI -24.9 to -14.9) reported at the lateral aspect of the tibia. This overall loss increase is seen in the data points as well, with 57.89 % of the data points now showing a loss.

This BMD loss is more prominent in the lateral femur, were 23 of the 33 data points that have CI do not overlap the 0 line, showing a loss of BMD of statistical significance with all reporting large effect sizes. The highest relative loss is in the middle of the distal femur with a result of -19.71 % (CI -29.41 to -8.89). Furthermore, all of the papers in the lateral femur each show the greatest loss in the middle distal femur. The PA/AP femur adds to the overall reported loss showing a similar result of -14.45 % (CI -23.63 to -5.27). Interestingly although the BMD loss is greater in percentage across most points, only 84.85 % of data points show a loss in the lateral femur (compared to 91.18 % at 3 months).

At 12 months the AP/PA tibia loss seems to increase, with the tibial medial aspect reporting large losses with the highest reported as -38.10 % (CI -32.5 to -43.7). This is reflected in the data points as 75.90 % (63 of 83) of the data

points show a BMD loss, this is also supported by the lateral femur data points reporting 95.08 % (58 of 61) of data reported as a BMD loss. The highest reported loss in the lateral femur was reported by Saari et al 2007 [300] with a reported loss of -28 % (CI -45 to -11) in the anterior region. The greatest relative loss was for the middle of the distal femur (it must be noted that Saari et al 2007 [300] did not investigate the middle aspect region) with a relative change of -25.19 % (CI -35.33 to -14.81). The greatest regional loss in every single lateral femur paper at 12 months was in the middle femoral region (but only if the paper investigated this region).

At 24 months the PA/AP tibia data points reporting a BMD loss drops to 66.67 % (54 out of 81), this change is reflected in the lateral femur as well, although not as dramatically reporting a bone loss of 90.63 % (58 out of 64) and in the lateral tibia from 100% loss (14 out of 14) to 95% loss 19 out of 20). The greatest loss reported in the femur was at the anterior aspect reported as -40 % (CI -53 to -27), although the majority of the research papers reporting a BMD loss report it at the middle region of the distal femur, when compared to the other regions (four of the six papers have their highest loss reported as the middle of the distal femur). The AP/PA tibia (figure 28), reported the greatest loss of -46.37 % (CI -53.98 to -38.76) (Minoda et al 2010 paper) [294], although several papers report an average increase.

To answer the primary question regarding the effect of TKR, rTKR or TKA on BMD over a period of time, the research would suggest that at three months post-op there is BMD loss, this is reflected in the reported highest loss of -4.5 % (CI -15.05 to 6.31) on the lateral tibial image, and the -9.59 % in the AP/PA image on the medial side, with the femoral aspect more affected by this implantation. At six month this loss seems to have increased with the lateral femur suffering greater losses especially in the middle of the distal femur. At 12 months this seems to reach its height in terms of BMD regions suffering loss, with high amounts of data points showing BMD loss in both the tibia (75.90 % of PA/AP data points, and 100% lateral tibia points), and the femur (95.08 % of the lateral, 75 % for the AP/PA). At 24 months there seems more of a turnaround, 22 data points show a positive increase (27.16 % of data points, increasing to

33.33 % if you include the results that are now the same as baseline i.e. 0 % change) in BMD at 24 months.

The secondary question regarding period of greatest difference is unclear, although it is this author's opinion that 12 months shows the greatest difference in both terms of being compared to six months and compared to 24 months. The data points show the highest average loss of BMD across the tibia and femur compared to all time periods, and an increase in BMD loss compared to 6 months, although this might be due to there being more data points at 12 months (compared to six or three months), so this change in loss might be due to more data availability rather than an actual change, especially as 12 months also has the highest amount of papers (13).

The difference between 24 months and 12 months is easier to argue and shows a similar comparison; 24 months has 12 papers, 81 data points for the AP/PA tibia, 20 data points for the lateral tibia and 64 data points for the lateral femur, and 12 months has 13 papers, 83, 14 and 61 data points respectively. The difference seems to be that 24 months is moving towards a more positive BMD (33.33 % in the PA/AP tibia, 5 % lateral tibia, lateral femur 9.38 %, compared to 24.10 %, 0 % and 4.92 %). This is backed up by the data from the Soininvaara et al papers (2002 [301] and 2008 [303]) which both show the highest BMD loss (in the lateral femur) at 12 months, furthermore Jaroma et al 2015 [292], Järvenpää, et al 2014 [19], and Soininvaara et al 2008 [303] which reported a BMD increase in the total regional data of the lateral femur for between 12 months and 24 months (an increase reported of +1.43 %, +0.7 % and +0.7 % respectively), although this was still a loss compared to the baseline, but it does show a change towards regaining BMD. Although, it must be acknowledged the other two papers (Therbo et al 2004 [304] and Saari et al 2006 [293]) that investigated the lateral femur between 12 months and 24 months showed both losses and increases in BMD at 24 months depending on the region and implant investigated, unfortunately no total region was reported in either of these two papers. In the lateral tibia when comparing 12 months to 24 months Soininvaara et al 2008 [303] showed a loss under the implant (-0.92 %), with Jaroma et al 2015 [292] also showing a similar loss under the implant (-0.91 %), but Jaroma et al 2016 [29] reported no change (0.00 %) in either the valgus or

varus group. Furthermore, Tjornild et al 2015 [305] actually showed an increase at 24 months compared to 12 months in all regions; anterior, posterior, under the implant, and the total region, across both testing groups (mobile bearing vs fixed bearings) with a difference of; +8.6 %, +6.1 % (anterior), +8.8 %, +6.0 % (posterior), +4.4 %, +9.3 % (under) and +7.4 %, +5.6 % (total), it must be noted all regions still reported a BMD loss when compared to the baseline, but the difference between 12 months and 24 months was an increase.

In the AP/PA tibia comparison between 12 and 24 months this increase in BMD is supported by several papers such as: Jaroma et al 2015 [292] (+0.86 %), Jensen et al 2012 [178] (+5.8 %, +6.5 %, +9.1 %, +7.8 %), Saari et al 2007 [300] (+13.75 %, +7.92 %, +11.47 %, +4.55 %, +7.3 +4.86 %), Tjornild et al 2015 [305] (+8.9 %, +9.9 %, +6.4 %, +8.0 %) all showing increases in BMD when compared to 12 months. Although certain papers still report a loss; Winther et al 2016 [226] reported a BMD difference as high as -11.5 % in the medial aspect, but also reports changes such as +6.8 % under the implant, or +1.1 % in the lateral aspect. Furthermore, Minoda et al 2010 [294] reports a continued loss compared to 12 months with changes of -11.2 %, -11.9 % and -8.0 %.

This change in BMD difference increasing at 24 months when compared to 12 months might be due to the plateau effect, in which due to movement, load bearing and additional adaptions and stressors the BMD is starting to return to the baseline figure, this theory is supported in the literature. It must also be noted that bone loss continues naturally at approximately 1.4 % [307] loss per year (depending on age and gender), thus the difference between 12 months and 24 months is probably far greater than reported and this natural decline might explain some results between the 12 and 24 month BMD (examples such as the lateral tibial data of Soininvaara et al 2008 [303] and Jaroma et al 2015 [292] both reporting losses under 1 %).

These data would suggest that 12 months is the most useful time period in assessing BMD loss, due to the increases reported at 24 months. This would mean that at 12 months patients have their lowest BMD making it their most vulnerable time period, increasing their chance of fracture should they fall.

Although it must be noted that a meta-analysis has not been performed due to high heterogeneity within the studies, and these variations could be the reason behind some of the results, therefore it is difficult to conclude with confidence that this is the case.

Furthermore, when reviewing the four papers investigating the lumbar spine and hip, all figures reported at 12 months show a BMD loss when compared to baseline both for the hip and lumbar spine, yet at 24 months there is reported increase in the lumbar spine cemented group. Although these data are extremely limited and there is a lack of overlap within the time periods the result would agree with the theory of BMD plateau effect at 24 months.

Although, it must be acknowledged that at 24 months Minoda et al 2010 [294] was still reporting increasing BMD losses (when comparing 24 months to 12 months), including reporting the highest loss reported by any paper. This division between the slight increases and increasing losses might be a reason for contradictions in the literature about the plateau effect of two years**.** Furthermore, it must be understood that the differences between this one paper and the other 11 (in the AP/PA tibia) might be due to the type of implant or participants used.

In reference to the additional secondary question regarding which anatomical area is affected by the most change, there is one region that throughout different papers shows a consistent change. This is reported throughout as the middle of the distal femur (on the femoral lateral image), as this is shown strongly across all time periods, were in nearly every report the greatest loss is in this region.

Although the greatest loss from any individual paper is that of 24 months in PA/AP tibia, reported by Minoda et al 2010 [294] reporting a loss of -46.37 % (CI -53.98 to -38.76) on the medial aspect. This is not considered consistent enough, furthermore Winther et al 2016 [226] has shown in that same area (medial tibial aspect) an increase in BMD throughout starting from three months, even though both papers had a high-quality score (eight and nine respectively), the score is inconsistent with the other results but may well be

due to the implant type being investigated (i.e. the Regenex and PPS inserts). Therefore, the middle of the distal femur is the most anatomically affected area. This ROI information is useful as it could be useful clinically in helping to develop TKR implants that specifically target this area, or due to its consistent loss across multiple papers over multiple types of implant, this ROI could be used clinically to investigate BMD changes between various participants implant and interventions, with all studies reporting the same standardised ROI. So as previously stated no meta-analysis was performed, so it is unclear how accurate or confident we can be with these results.

2.16 LIMITATIONS

As stated several papers were excluded due to incomplete data, and some forest plot graphs were not created for the time periods due to lacking data as shown in table 2.3 (two papers or fewer per area were excluded). As reported one of the most consistent losses within the papers was on the lateral femur in the distal middle region, unfortunately no study reviewed the impact of TKR, rTKR or TKA on the femoral condyles on the PA/AP images, therefore the exact region is only defined by the lateral image so there is a limit in defining that anatomical region.

It must be noted that the 27 papers showed good generalisability as they covered seven different countries such as Denmark, Japan and England. Unfortunately, the sample groups for all studies were small, with an average of 41 participants a range of 11-86.

Other limitations within the studies were the inaccuracies of the region selection, with variation due to lack of consensus in ROI selection, as shown in figure 2.3.

Although it must be acknowledged that these regions were grouped together depending on stated region (or via visual confirmation), this inconsistency might still impact the results. Moreover, the possibility that incorrect positioning, especially medially and laterally might impact the precision errors of the study (although it must be noted several studies investigated their positioning precision). Furthermore, as stated some regions were not included (Jensen et al

2012 [178]) within the analysis due to being regions around the stem as well as the primary implant, the stem ROI could not be compared to the other papers due to lack of regional data (no other papers reported these ROI), so were excluded.

Data set comparisons were also limited in this study due to heterogeneity because of different types of implant, which might explain some of the extreme BMD figures in both the positive and negative BMD differences.

Further limitations are due to the calculations used, in some studies it is only reported as a percentage difference, without any definition of the calculation. As for the relative calculations the author performed, these are consistent for comparisons between studies but neglect natural BMD changes such as the reported loss of approximately 1.4 % [307] of BMD per year. This would impact the possible plateau effect**.** Additionally, the reported figures might take this difference into account and might represent a more accurate figure, although different DXA systems might use different algorithms to reach such calculations and conclusions.

Finally, papers lacking SD, SE or CI (or were CI could not be calculated) influenced results and conclusion especially given the low number of participants, and those with reported CI tended to have a wide range, influencing their statistical significance.

2.17 CONCLUSION

Based on this systematic review and the literature available, the primary and secondary questions have not been fully answered. Although the data does suggest the ROI of the lateral image of the middle of the distal femur is the most consistent in its loss across multiple papers. The data discussed also supports the possible idea of a two-year plateau effect, with losses shown throughout but appear greatest at 12 months with BMD increasing at around 24 months. The limitations regarding the sample size and lack of data especially for the total body, lumbar spine, and bilateral hips means these specific questions remain unanswered and further study including scans of the lumbar spine and bilateral

hips are needed. Furthermore, the BMD loss seen throughout post-surgery adds to the supporting idea of using either pharmaceuticals such as bisphosphonates (which as shown in appendix 4 show an increase in BMD), or the utilisation of next generation implant designs to helpfully reduce the impact of TKR, rTKR, and TKA has on BMD. It must be noted that due to the variations and limitations and heterogenicity of the studies stated, a meta-analysis was not performed, this impacts the importance of the data presented and the confidence associated with it, for both the primary and secondary questions, therefore the results should be treated with caution.

2.18 FUTURE WORK

This systematic review data provide DXA/BMD knee regional information and appointment intervals which can form part of any recommendations for future full trials.

CHAPTER 3: DEVELOPMENT PHASE – INVESTIGATING THE METHODS AND ANALYSIS OF THE DATA IN A BOVINE MODEL IN PREPARATION FOR THE FEASIBILITY RANDOMISED CONTROL TRIAL

3.1 INTRODUCTION

This chapter will help develop, confirm or modify the procedures, methods and analysis required prior to the main feasibility randomised control trial. In order to achieve this a femoral and tibial Stryker cone (the same ones which will be used in the main study) were acquired and investigated for BMD changes through integration of calcium phosphate in a bovine femur and tibia model. Discussed within this will be the selection and justification of the apparatus employed, the different imaging modalities applied (DXA, x-ray and CT), and any modifications needed to the methods or analysis utilising these approaches. The results of the pixel density and BMD differences across multiple exposures at different time periods within this bovine model will be tested on using the same proposed analysis as the main study.

3.1.1 AIM

The aim of this study was to highlight osteointegration of the cones and investigate BMD analysis, whilst determining if the three imaging methodologies proposed (DXA, x-ray and CT) were feasible in how this osteointegration could be analysed, including any modifications required.

3.2 METHODOLOGY

This study utilised two Stryker Triathlon TS cone implants (size C); consisting of a femoral cone (figure 3.1) and a tibial cone (figure 3.2). The femoral cone measured 2.3 cm medially to laterally (ML) at the top, 5.5 cm ML at the base aspect, 4.3 cm caudally to cranially (CC), with a maximum anterior to posterior (AP) or depth measurement of 3.6 cm. The tibial cone implant was 3 cm CC, 2.3 cm ML at the base, and 5.2 cm ML at the top, with a maximum AP or depth of 3.6 cm.

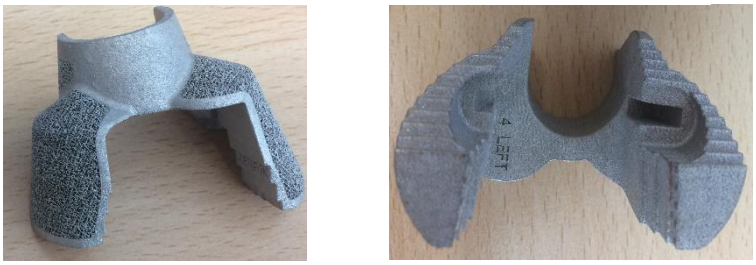


Figure 3.1. *Photographs of the femoral cone*

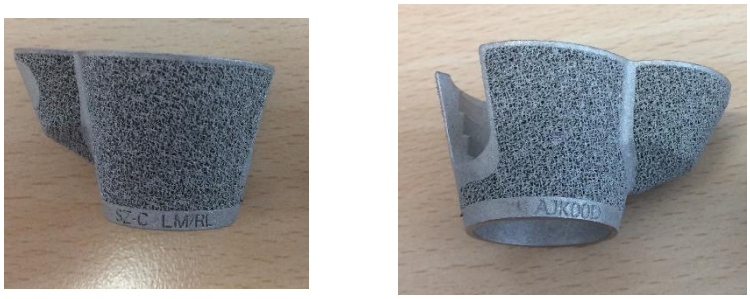


Figure 3.2. *Photographs of the tibial cone*

The cones had been 3D printed into predetermined shapes specifically designed to press fit into AORI grade two defects, they were created via a highly porous metal alloy called tritanium which was derived from pure titanium powder [308]. Titanium was used due to being bioinert [309, 310], and has a proven history having been employed across orthopaedic and dentistry fields from metaphyseal sleeves [311] to dental implants [312]. Furthermore, titanium components have been reported to increase BMD in or around the implant [313]**,** this effect of titanium is then coupled with the cones trabecular bone porous design pattern, promoting bone adhesion and osseointegration [312]. Research has shown that the relationship between titanium and osseointegration is based on composition and surface roughness, allowing bone anchoring and biomechanical stability [310, 312], allowing a stronger bone response [314].

It must be noted that current research into cone implants tend to utilise tantalum instead of titanium, showing similar results to the titanium implants [315], although research from June 2017 which utilised the same titanium metaphyseal Stryker cones used in this study, reported results showing that the stability of the titanium cones was equal to, or superior to that of tantalum cones [229].

Prior to any imaging, the cones where first placed into a plastic box (Lock and Lock 3.9 litre), this type of container was preferential for three specific reasons:

1. It was water tight
2. It was constructed from plastic
3. Its dimensions; measured 23.2 cm (L) by 16.2 cm (H) by 16.5 cm (W)

The container being water tight was essential due to the cones being submerged in water; which was used as a viable substitute for human muscle tissue, due to having similar attenuating and absorbing properties: water reports an atomic number of 7.42, a density of 1.0 g/cm^3, and an electron density of 3.34 x10^{23} per gram [316]. Muscle reports similar figures of 7.42, 1.0g/cm^3, and 3.36 x10^{23} per gram [316]. Because of these values coupled with waters low cost and almost universal availability it is regarded as an acceptable substance for this BMD study, in addition it has been utilised in numerous papers and research, were water baths have been employed as tissue equivalent materials [317, 318, 319, 320]. Furthermore the container being water tight was significant for both transport and movement, especially during CT scanning where the bed conveys through the scanner.

The container being constructed of plastic (also known as Lucite or Perspex) was relevant due to having a similar atomic number, density, and electron density to water [316], so is deemed as an acceptable tissue equivalent substitute for density measurements.

Thirdly the dimensions of the container had to be comparable to a human knee, prior to TKR the average human knee circumference (as defined at the position of the mid-patellar around the knee, whilst in the supine position) is 43.7 cm (+/- 4.2 cm) [321], and after one month post-operative is 45.3 cm (+/- 4.4 cm), and after two months is 43.1 cm (+/- 4 cm) [321], the upper limit figure of 49.7 cm was utilised in order to represents the highest possible knee circumference. Due to the human knee not being spherical, the ratio of width to depth was calculated in order to purchase a plastic container that closely represented the knee dimensions, thus a ratio against the circumference from the available research data were calculated.

For this calculation the human knee was divided into the two main bones: the femur, and the tibia (with the fibula and patella not being included in the cone implantation testing). Based on information from two studies the average femoral ML distance was between 6.78 cm (+/-0.40 cm) [322] and 8.12 cm (+/- 0.62 cm) [323] (depending on sex and ethnicity). The femoral AP distance was calculated as between 6.15 cm (+/- 0.49 cm) [322] and 7.03cm (+/- 0.47 cm) [322]**.** The tibial ML measurements were between 6.96cm (+/- 0.43 cm) [322] and 7.98 cm (+/-0.58 cm) [322] and the tibial AP distance calculated to be 4.60cm (+/- 0.40 cm) [322] to 5.39 cm (+/-0.61 cm) [322].

The ratio was then calculated from the upper and lower limits of each bone giving a range and variability in the measurements and ratios; as such:

1. Highest Femur ML 8.74 cm AP 7.5 cm = ratio of 1:1.165
2. Lowest Femur ML 6.38 cm AP 5.64 cm = ratio of 1:1.131
3. Highest Tibia ML 8.56 cm AP 6.0 cm = ratio of 1:1.427
4. Lowest Tibia ML 6.53 cm AP 4.2 cm = ratio of 1:1.555

Each ratio results in the upper measurement of both the femur and tibia for the AP and ML figures, thus representing the highest amount of tissue equivalent mass to be penetrated making the test more representative. By utilising the circumference of 49.7 cm the external width and depth measurements were calculated within 0.05 cm:

1. Highest Femur Ratio 1.165 = 13.37 cm (ML) by 11.48 cm (AP) = 49.71 cm
2. Lowest Femur Ratio 1.131 = 13.20 cm (ML) by 11.67 cm (AP) = 49.74 cm
3. Highest Tibia Ratio 1.427 = 14.61 cm (ML) by 10.24 cm (AP) = 49.70 cm
4. Lowest Tibia Ratio 1.555 = 15.13 cm (ML) by 9.73 cm (AP) = 49.72 cm

The largest AP result (11.67 cm) and the largest ML result (15.13 cm result in the maximum figures for depth (AP) and width (ML), meaning these are the minimum figures for the plastic container. The length of the plastic container was computed using an additional test utilising a whole body phantom (PBU-

50), this involved collimating to the phantoms knee (in the supine position) using the standard protocol for an AP knee radiograph: a height of 100 cm, centering point of 2.5 cm below the apex of the patella [324], and collimating to include all the required knee anatomy. This collimation (13.9 cm by 20.8 cm) was recorded and imaged (figure 3.3), the figure 20.8 cm was then used for the Perpex container minimum length, as such this knee positional set up and collimation setting was used for all subsequent x-ray projection imaging within this study.

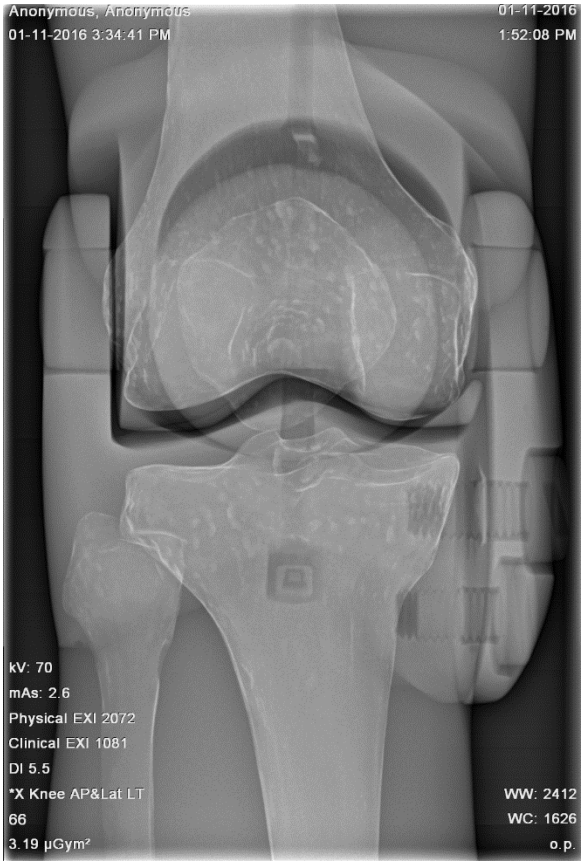


Figure 3.3. *X-ray of whole body phantom (PBU-50) to determine knee length and collimation requirements*

A plastic container with similar dimensions of 11.67 cm by 15.13 cm by 20.8 cm was sought, and it was decided that the depth (AP) of the container was the least important issue due to that being controlled by the water level, the length as well, as long as it was over 21 cm did not impact the imaging as dramatically due to collimation restrictions, the most important issue was the width (ML) of at least 15.13 cm being required. A water tight plastic container was found and ultimately purchased which had a width (ML) of 16.2 cm, a length of 23.4 cm, and a maximum height (depth/AP) of 16.5 cm.

Due to the dimensions now available, and other studies research reviewing knee imaging [325, 326], it was concluded to scan the cone implants at a submerged depth of 15 cm. The cones were then imaged through the three different modalities: DXA, CT and X-ray.

3.3 IMAGING THE CONES

The cones were positioned in the centre of the plastic container and orientated in a similar manner as if they were in vivo, they were then separated from each other by a 1 cm gap to simulate the joint space, tap water was then poured into the plastic container up to the 15 cm depth line, with conal orientation checked prior to any imaging. All three types of imaging were photographed prior to starting any scans and were used as positional reference; additionally any previous scan results were also used as positional aids in making sure consistency on positioning was seen throughout all imaging modalities.

3.3.1 DXA IMAGING

Dual energy X-ray absorptiometry imaging was conducted on a GE lunar prodigy (Bedford, MA) utilising enCore GE Healthcare software (version 14.10.22), which was calibrated prior to each session with a quality assurance (QA) block phantom, and once a week with a spine phantom.

The cones were imaged three times per setting to investigate variation:

1) AP spine, thin mode, collimation was set at 20.2 cm by 19.8 cm, exposure factors were 76 Kv 0.75 ma, time: 56 seconds, dose 9.0 uGy
2) AP spine, standard mode, collimation was set at 20.2 cm by 19.8 cm, exposure factors were 76 Kv, 3 ma, time: 56 seconds, dose 37.0 uGy
3) AP spine, thick mode, collimation was set at 20.2 cm by 19.8 cm, exposure factors were 76 Kv, 3 ma, time: 1 minute 59 seconds, dose 83.0 uGy

These setting had been predetermined and used in previous and current DXA knee studies, and as such were not changed. With the thin setting being used for most DXA knee scans [179, 228], this is due to a lack of a knee DXA setting

on DXA machines, with the “spine” on thin setting giving the most optimum image for dose (the thin setting relates to the obesity of the patient which is important in spine imaging (a thick setting for an obese patient, a standard for standard, and thin for a thin patient), with knees an obese patient is still scanned on a thin setting as the knee thickness does not vary enough to exceed the thin range). Although a wide range of setting was investigated in this section due to this setup involving the highest possible knee thickness features. This was also why rice bags were not used in these scans due to the large amount of water placed within the plastic container which is providing the same soft tissue substitute as the rice bags do.

Positioning was kept constant throughout, with the DXA positioning laser line through the inferior aspect of the plastic box intersecting at the midsagittal plane, and through the cones.

3.3.2 CT IMAGING

Computed Tomography imaging was conducted on a Siemens somatom definition edge scanner, used clinically at the RD&E hospital and was calibrated everyday using a standard QA phantom (Siemens Healthcare, Germany).

The dual energy CT settings used in the scan were: extremity feet first, supine, 80 kVp and 47 mAs and 140 kVp 15 mAs, 1 mm slices, field of view (FOV) of 134 mm. Due to a positional issue of the plastic container originally being outside the FOV, and thus the centering laser, the plastic container was elevated by 7.6 cm (via a glove box), this was deemed acceptable as the glove box was outside the FOV and would not affect the image, the laser line was then placed through the central axis of both cones. This positional setup was repeated for all CT imaging.

3.3.3 X-RAY PROJECTION IMAGING

X-ray imaging was conducted on a Siemens multi fusion XPB2-100.620.04.03.02 (Siemens Healthcare, Germany) which was calibrated weekly for dose, and yearly as part of maintenance. The positioning and imaging of the cones was done in the same manner as the positioning already stated regarding the AP phantom knee, with the modification to the central beam so

that the centre point was the axis between the two cones. Five scans were produced at the kVp and mAs of 60 and 2.5, 60 and 8, 70 and 2.8, 70 and 5, and 81 and 3.2 respectively. These were chosen in order to create a range of the most common exposures in x-ray imaging [327, 328].

3.4 CONE IMPLANTATION INTO A BOVINE SUBSTITUTE

In addition to the cones being imaged on their own (submerged in water), they were also inserted into a bovine tibia and femur in order to investigate the development and confirmation needed to establish conal bonding and in-growth within a substitute model and solution.

Ovine (sheep) bones were originally considered as the best possible representation available for a human knee, as research has already demonstrated their use in investigating osseointegration in porous coated implant knee arthroplasty's [329], in-growth assessment in implants [330] and in other orthopaedic research [331]. They have also been utilised in representing the human knee in many other studies such as osteoporosis [332], cruciate ligament reconstruction [333], OA [334], bone repair [335] and tibial osteotomy [336]. There are many reasons for their use, with two of the strongest arguments being the femoral cortical index being nearly the same as a humans; 0.33 (+/- 0.08) compared to sheep 0.32 (+/- 0.04) [323], and their intercondylar ratio of the femur and the tibial aspect appearing almost identical [323].

Unfortunately, the tibial ML width measurement of a human was recorded as 7.64 cm (+/- 0.54 cm) compared to a sheep's tibial ML width of 5.17 cm (+/- 0.20 cm) these data were based on 24 measurements of skeletally mature merino sheep, and 24 alcohol fixated human cadaver knees [323]. Furthermore the femoral ML width measurement of a human was recorded at 8.12 cm (+/- 0.62 cm) compared to the sheep femoral ML width of 4.72 cm (+/- 0.18 cm) [323].

This size disparity meant the ovine bones would only be viable for scaled down prosthetic replacements; this issue was also evident in similar animals such as goats, pigs, and rabbits [337]. Therefore larger animals were investigated with a

bovine model the forerunner; having themselves been used in diverse knee studies from: cruciate ligament investigations, tibial osteotomy, mechanisms of cartilage repair, osteoarthritis, drug treatments and current reconstructive surgery [338, 339, 340, 341, 342, 343]. Furthermore, bovine bones had several advantages over other possible candidates due to being easily accessible, technically feasible, affordable, and with transferable results due to bovine structure.

Two bovine knees (approximately two years old) were collected by a third party from the Ashburton Abattoir (after being hung up for 48 hours first), these were then stored in the University of Exeter's physics department at the Streatham campus in a refrigerator for 24 hours, and transferred to another freezer for the rest of the study, a photo of the bovine knees is shown in figure 3.4.

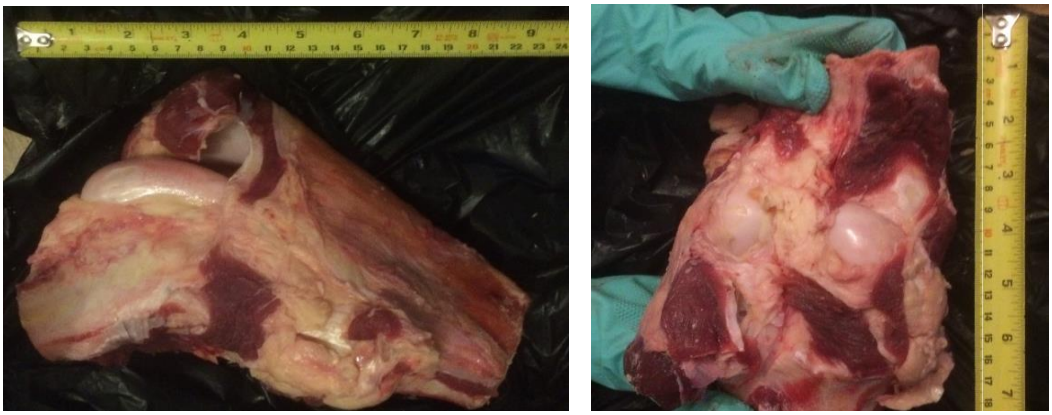


Figure 3.4. *Photographs of the left bovine femur, tibia and patella, showing the amount of tendons, ligaments and muscles still on the bone that needed to be removed prior to insertion/ scanning. Measuring tape used to show size.*

The muscles, tendon, ligaments and superfluous bones (patella and fibula) were removed via a hacksaw, with both the femoral and tibial bones reduced in length to fit the plastic box whilst maintaining the knee proportions reported.

Finer cuts using a scalpel were utilised In order to remove excess flesh and to cut through the tougher ligamentous structures. The bones were then exposed to the water maceration technique [344], in which the bones were placed into a plastic box containing nine litres of warm tap water and four table spoons of biological washing powder, thoroughly stirred twice daily (a ratio of one gallon to two tablespoons [344])**,** this process was repeated for six weeks with the water and powder being replaced weekly, this maceration procedure was

implemented in order to denature the proteins in the tissue, and weaken and remove loose ligaments and any remaining tendons.

Due to time restraints imposed by scanning arrangements, and the slowness of the maceration process the bones were not fully defleshed at the end of the six weeks, although some of the tissue remained on the bones these were mainly the ligaments at root insertion points and some muscle attachments, several additional attempts were made to remove the excess tissue but were unsuccessful.

In order to create the cavities for the cone implantation, the instructions from the Stryker triathlon revision knee system were followed [245]. Although unfortunately due to time constraints, cost, and the availability of the correct tools (reamers), the method had to be modified, therefore a Bosch SDS-plus drill was utilised in conjunction with several drill attachments, and a Soriace titanium coated step drill bit (10-45 mm). This was employed to match the maximum cavity size required for each cone, with the tibial cone being reported as the widest at 40 mm in diameter.

The excavations of the drilling applied an ever increasing bit size until the Soriace step drill bit was administered creating a cavity approximately the width and depth of the implants as shown in figure 3.5.

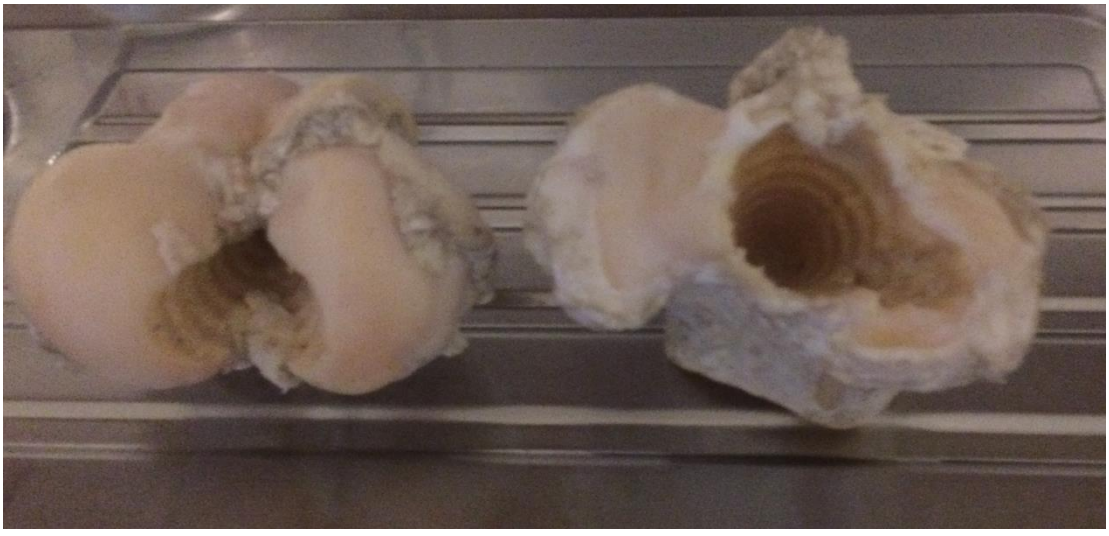


Figure 3.5. *Photographs of the bovine tibia (right) and femur (left) with the cavities for the implants to be inserted created.*

These bovine bones were then orientated in their in vivo position as shown in figure 3.6.

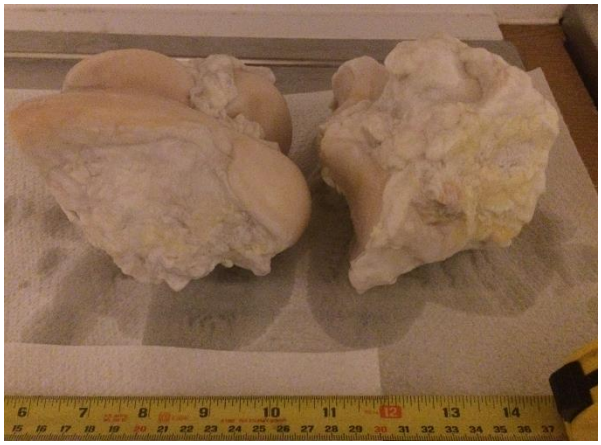


Figure 3.6. *Photographs of the bovine tibia (right) and femur (left) placed in their in vivo position, which will be their orientation for all positioning images.*

The bovine bones, prior to cone implantation were then submerged in 15 cm of water in the pre-specified plastic box, and x-rayed (figure 3.7) and DXA (figure 3.8) imaged following the positional set up mentioned previously (section 3.3.1, 3.3.3).

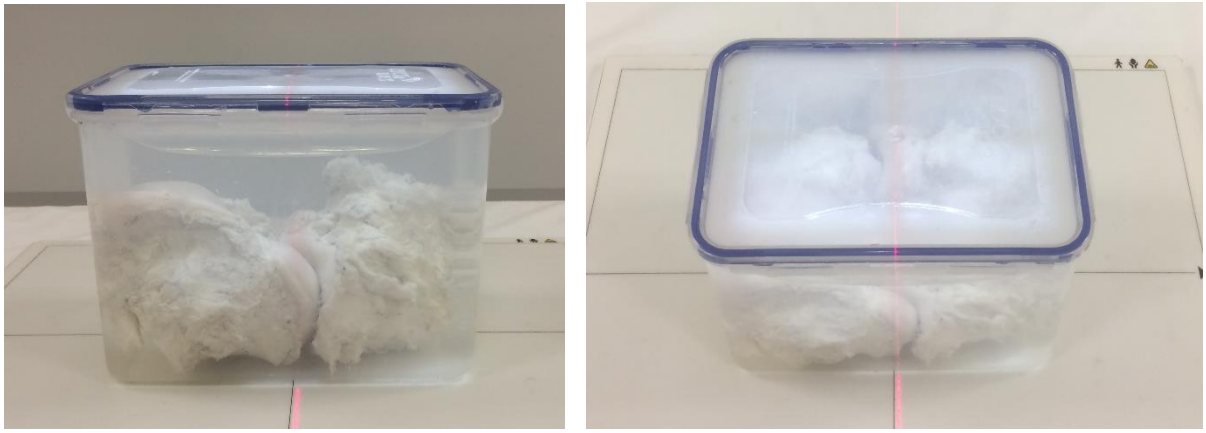


Figure 3.7. *Photographs of the bovine bones positional x-ray setup on an imaging plate (laser in red). Left shows the lateral image of the bones, and right shows the AP image.*

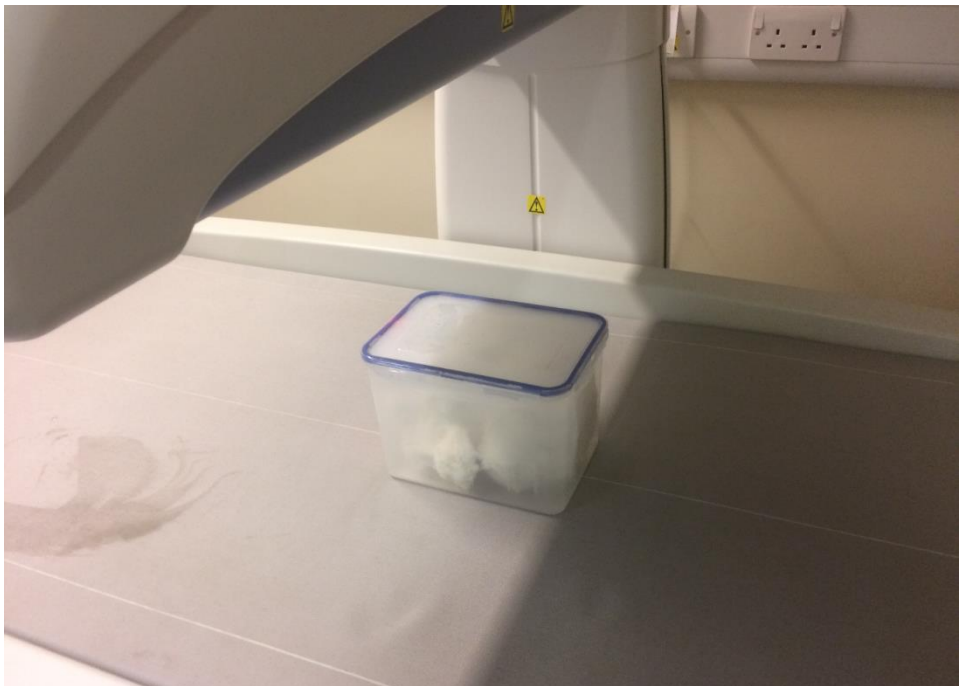


Figure 3.8. *Photograph of the DXA scanner bed and positional setup used in DXA scanning the bovine bones. The starting position is shown via the red targeting laser is on the left of the plastic box (it scans left to right in this setup).*

The cones were then implanted into the bovine bones and another set of images taken via x-ray and DXA, again using the same positional set up and settings as mentioned. These first conal images created a baseline score both in DXA and x-ray which would then be utilised as a comparator to future imaging post solution immersion.

3.5 SELECTION, IMMERSION AND DIFFUSION

In order to investigate the tritanium cones ability to osseointegrate it was decided to submerge the bovine bones with the implanted cones in a substitute solution.

A simple substitute solution to encourage bone integration was researched. Unfortunately most of these substitute solutions were complex solutions mimicking entire tissue responses and required advanced chemical controls which could not be established with limited time and resources. An aqueous solution combining calcium carbonate and water was considered, but upon reviewing the research it became apparent that calcium carbonate was not utilised as much as calcium phosphate (CaP) also called hydroxyapatite. CaP

makes up 70% of human bone [345] and has similar bioactive and osteoconductive properties [346], it also improves osseointegration [347].

Calcium phosphate has been utilised as a bone substitute [348] with the first CaP bone graft substitutes launched over 40 years ago [345]. Since then CaP has been utilised in orthopaedic surgeries [349], and used in coating medical devices [350], such as porous metal implants [351], femoral stems [352] and dental implants [353].

A study by Tas et al [354] investigated calcium phosphate bonding at room temperature on a titanium alloy using a concentration of 10 times the amount of calcium and phosphate ions in human plasma, with them investigating bonding over a two to six hour period. Although no additional buffering solutions were used a surface treatment and reagents were applied to raise the pH level [354]. Due to scarce means, agents and treatments were not available, due to this limitation pH was not controlled or recorded during the session. For this study, the main aim was to investigate osteointegration into the cones and how this osteointegration might be visualised on the image and change over time, with this imaging setup and analysis feeding into the main study.

The reported literature of bonding after two to six hours, implies that an even longer time period might yield a greater result. Therefore, two hundred and forty calcium hydroxyapatite capsules (NOW – sports bone and health) were purchased, each capsule contained 250 mg of calcium (25 % the recommended daily dose for an adult) and 100 mg phosphorus (10 % the daily recommended dose for an adult). It was decided to start with a small concentration over a five-day period, and then increase it later on. Twenty-five capsules (6250 mg of calcium and 2500 mg of phosphorus) (6.25 times the recommended dose for calcium and 2.5 times for phosphorus) were opened and emptied into nine litres of water and were stirred to diffuse in the aqueous solution over a five-day period prior to imaging, after imaging this process was repeated until the fourth and final scan, were a total of 139 capsules placed into nine litres of water (34,750 mg calcium and 13,900 mg phosphorous equating to 34.75 times the recommended dose for calcium and 13.9 times for phosphorus). This was in

order to create an exaggerate saturation point to determine osteointegration areas more visually within the imaging modalities utilised.

For each solution soaking session, the bovine bones where then placed in a non-vivo orientation into the calcium phosphate solution in order to maximise diffusion through the bones and cones themselves. In order to maintain this diffusion throughout the day a waterproof fan (MasterPal Telego cooling fan - waterproof with 10,000 rotations per minute) was situated into the water and placed at an angle to maximise diffusion towards the bovine bones, (shown in figures 3.9 and 3.10). Additionally, the solution was also stirred twice daily to help diffusion, and the temperature recorded Due to a lack of time and resources, a large limitation was that a true reflection of internal temperature in vivo could not be maintained or replicated, although the temperature was recorded, and varied between 21 and 23 degrees Celsius throughout the study (which is considered as room temperature [355]).

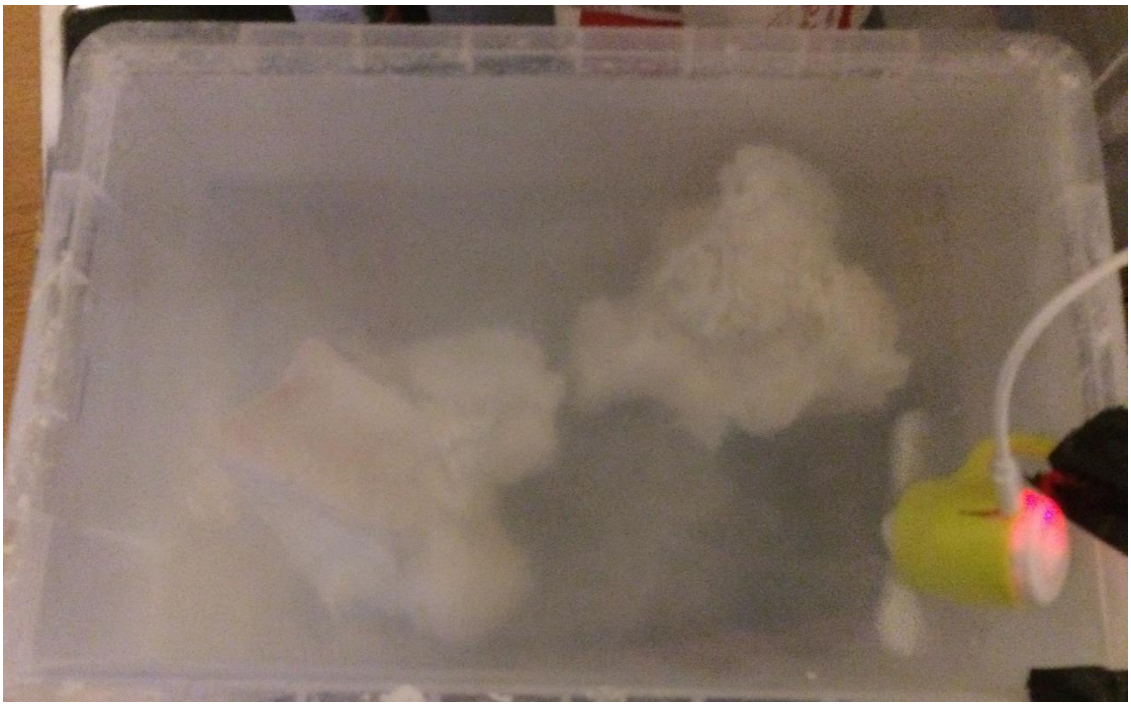


Figure 3.9. *Photograph (from the top) of the positional setup of the waterproof fan in order to diffuse the calcium phosphate solution*

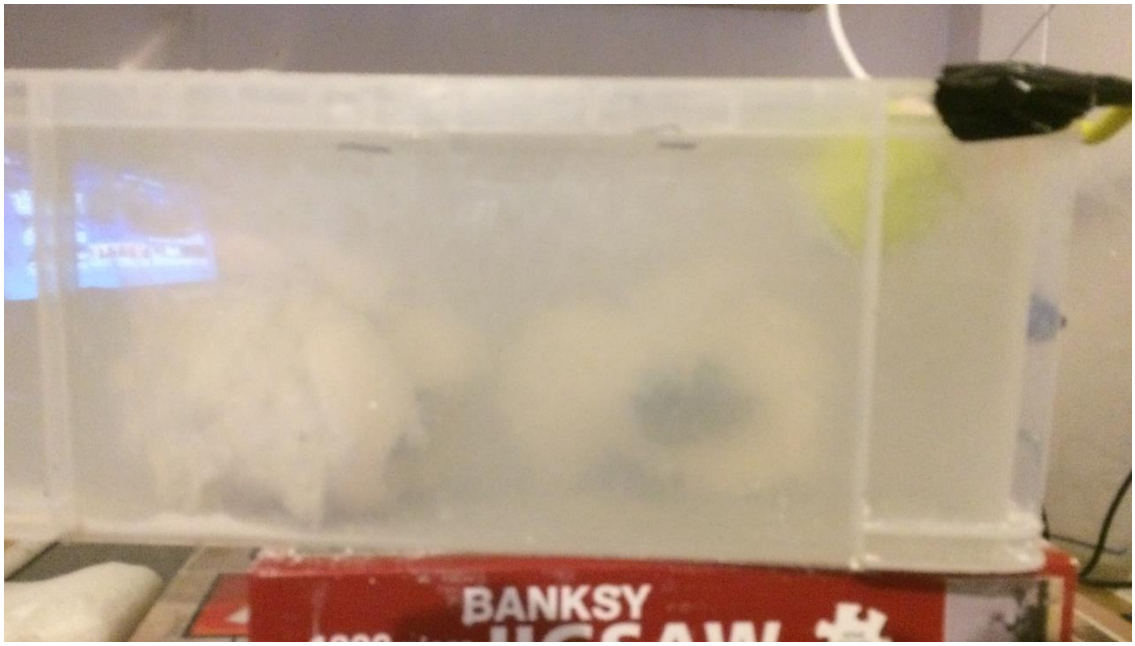


Figure 3.10. *Photograph (from the side) of the positional setup of the waterproof fan in order to diffuse the calcium phosphate solution*

Although the fan was tested in the solution prior to beginning the experiment, after 11 hours the fan began to only work intermittently, this fan was then cleaned and dried, but failed completely after approximately 14 hours. An exact replacement was purchased as well as an additional two different types (a sourcing map 80 x 80 x 25 mm DC Brushless Cooling Blower Fan USB Charger 5V 0.4A and an ARCTIC Breeze Mobile - 92 mm USB Fan), these were all placed in the same position as shown above. These also failed after 10-15 hours, as these had worked competently in the beginning the most likely cause was the bonding of the calcium phosphate resulting in intermitted rotation and eventual failure. Due to the diffusion issue an aquatic environment specialist was contacted regarding the use of a fan or pump that was robust enough but would not filter out the calcium phosphate. It was recommended to use the Eheim compact 300 pump (pumps through 300 litres per hour) which was utilised replacing the fan in the same position for the rest of the study period, without any future incident.

The bovine bones were left in the calcium phosphate solution for five consecutive days, after which they were removed from the solution, rinsed, and placed into the plastic box; tap water was then decanted into the box up to the 15 cm depth mark. This was then x-rayed and DXA imaged in the positional process already stated. Upon completion the bones were then returned to the

larger plastic box (in the position shown in figures 3.6 and 3.7) and refilled with nine litres of fresh tap water and another 25 capsules (6250 mg of calcium and 2500 mg of phosphorus), these bones were then left in calcium phosphate solution for another five days, and the same preparation and imaging was repeated. This entire method was repeated three times, creating post calcium one, post calcium two and post calcium three, upon the fourth time, the set up was repeated but rather than 25 capsules, a total of 139 capsules were placed into nine litres of tap water (34,750 mg calcium and 13,900 mg phosphorous) this was in the hope to create a saturation point (post calcium four), this fourth and final scan followed the same preparation and positional set up as the previous ones and only varied in the solution concentration as stated.

After the baseline and post calcium one were imaged it was concluded there was a drawback to this method in providing adequate data for the analysis section of the x-ray imaging. Therefore it was decided to include a metal marker in order to have a known size comparator regardless of magnification impact, and to have a consistent measure of known density. This meant it could be used as a calibration device to allow standardisation to the pixel density score, instead of using the water density as a comparator which was the current situation.

This marker was measured using a Mitutoyo absolute digimatic calliper (code no 500-191U model no CD-6”CP serial number 007750); recording the marker at 16.14 mm ML, and 25.64 mm superior to inferiorly (see figures 3.11 and 3.12).

Figure 3.11. *Photograph of calliper measuring the mediolateral dimensions of the marker*

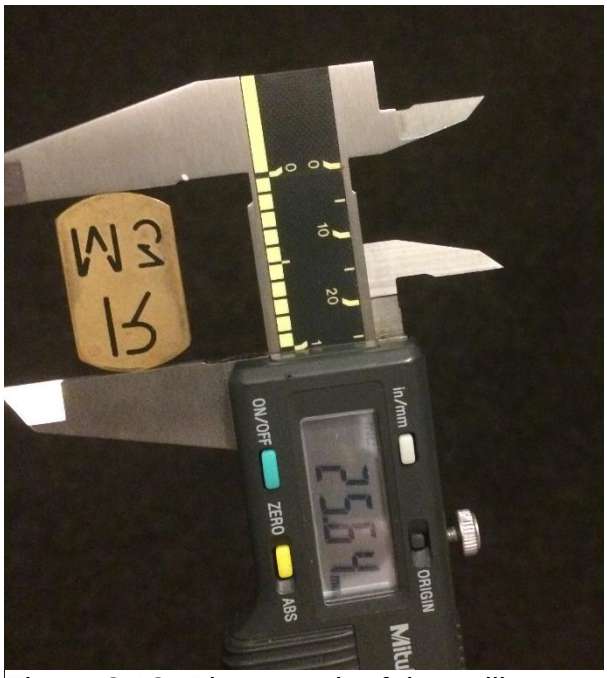


Figure 3.12. *Photograph of the calliper measuring the inferior and superior dimensions of the marker*

This marker was placed into the plastic box 4.6 cm inferior to the central line and 5.6 cm away from the central line and adhered in place; additionally its position was outlined in permanent marker. Post calcium one was then reimaged with the marker in place and used in all subsequent imaging.

3.6 IMAGES PRODUCED

3.6.1 CONES DXA AND X-RAY IMAGES

As stated the cones were placed in 15 cm of water and were imaged via DXA (figure 3.13), on the AP spine setting; thin mode

Figure 3.13. *DXA scan of just the cones submerged in water (thin setting)*

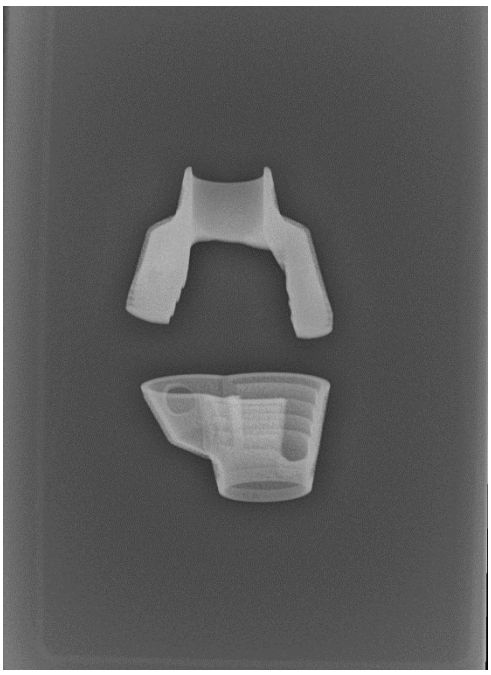


Figure 3.14. *X-ray scan of just the cones submerged in water 81kv and 3.2 mAs*

They were also imaged through x-ray, as shown in the example in figure 3.14.

3.6.2 CONE CT IMAGES

Using the CT positional setup described previously (section 3.3.2) it produced a three dimensional image of the cones submerged in 15 cm of water. Unfortunately these tritanium implants caused a minor starburst streaking artefact on the image as shown in figures 3.15 and 3.16, although the dual energy set up of the CT scanner suppressed this issue it could not be fully removed.

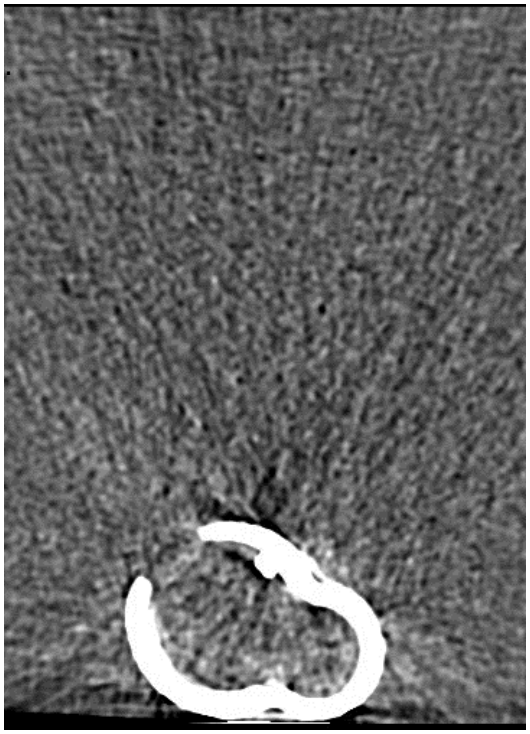


Figure 3.15. *CT scan showing the anterior portion of the tibial cone, this image shows streaking artefact*

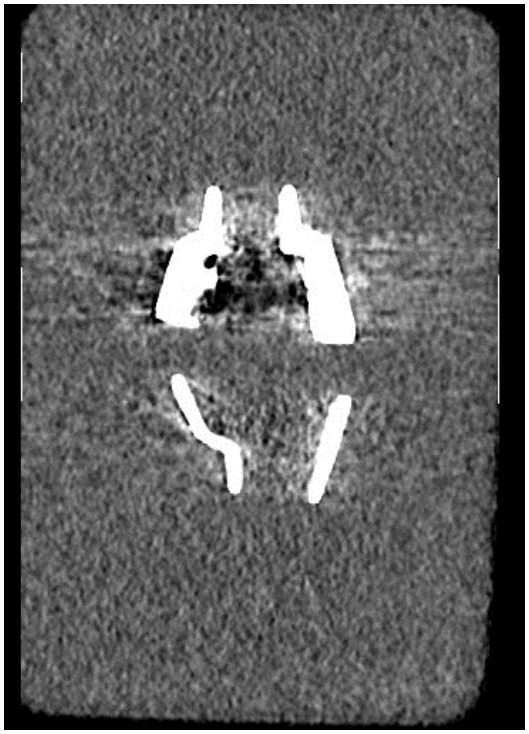


Figure 3.16. *CT scan showing the lateral view of both cones, this image shows streaking artefact*

Regrettably due to artefact on the image from the tritanium conal implants, it was decided to now only CT the implants after the final full saturation of post calcium four, as this would allow the maximum deposition of the calcium phosphate into the implanted cones to occur increasing, the chances of visual change. Furthermore, with the surrounding bovine bone and concentration of calcium phosphate this might subdue, or at least supress the artefact affect, compared against the current cones in water.

3.6.3 COW BONE DXA AND X-RAY IMAGES

The cow bones (bovine femur and tibia) were DXA scanned (figure 3.17) prior to conal implantation across the three DXA scan modes (thin, standard and thick) all utilising the same positional setup as stated. Furthermore, the bovine bones were imaged via x-ray (figure 3.18) again using the positional setup stated.

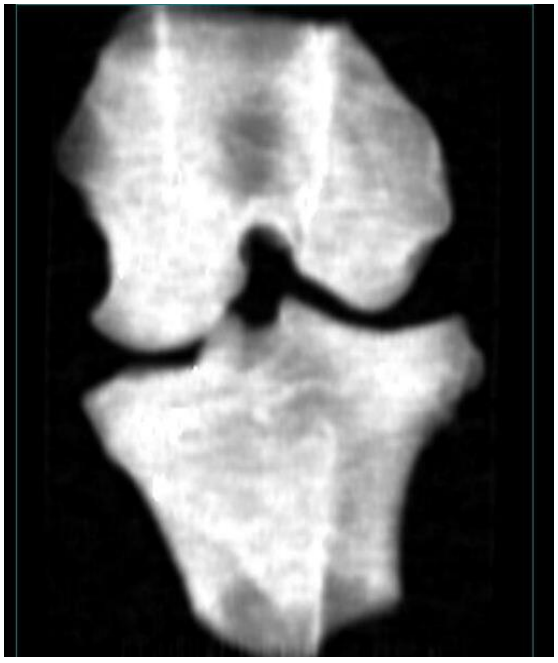


Figure 3.17. *DXA scan (thin mode) of cow bones in 15 cm of water in plastic container*

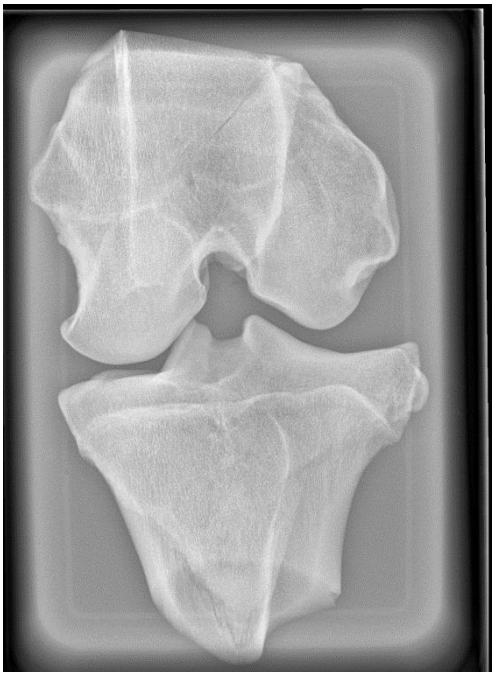


Figure 3.18. *X-ray (81kv 3.2 mAs) of cow bones in 15 cm of water in plastic container*

3.6.4 CONES AND BONES DXA IMAGES

After conal implantation the cow bones were DXA scanned across the three settings as shown in figures 3.19-3.21.

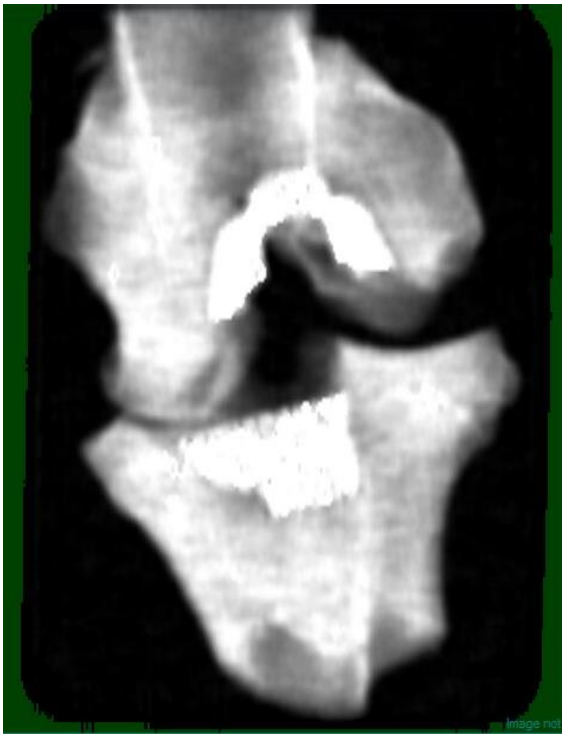


Figure 3.19. *DXA scan (thin setting), of cones and bones in 15 cm water*

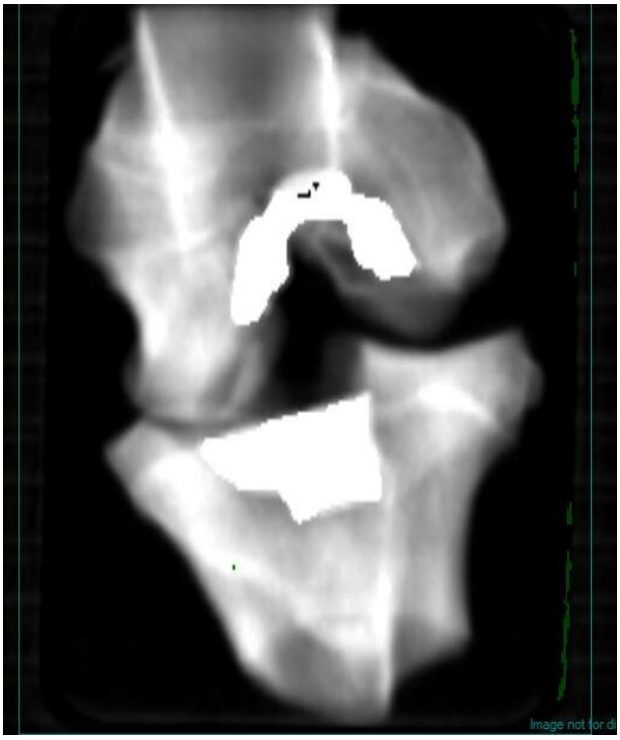


Figure 3.20. *DXA scan (standard setting), of cones and bones in 15 cm water*

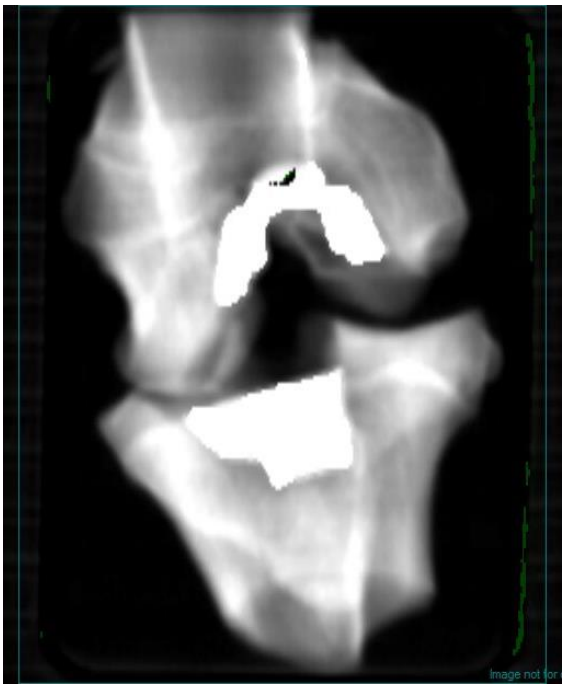


Figure 3.21 *DXA scan (thick setting), of cones and bones in 15 cm water*

3.6.5 CONES AND BONES X-RAY IMAGES

Furthermore, the bone implanted with the cones were x-rayed an example of these are shown in figure 3.22-3.24 (with different exposure settings).

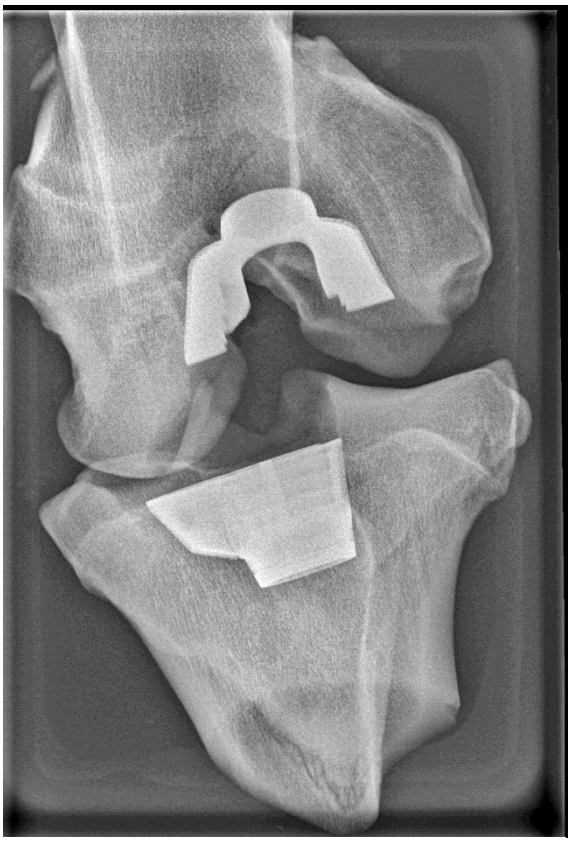


Figure 3.22. *Baseline x-ray done at 60 kv 8 mAs*

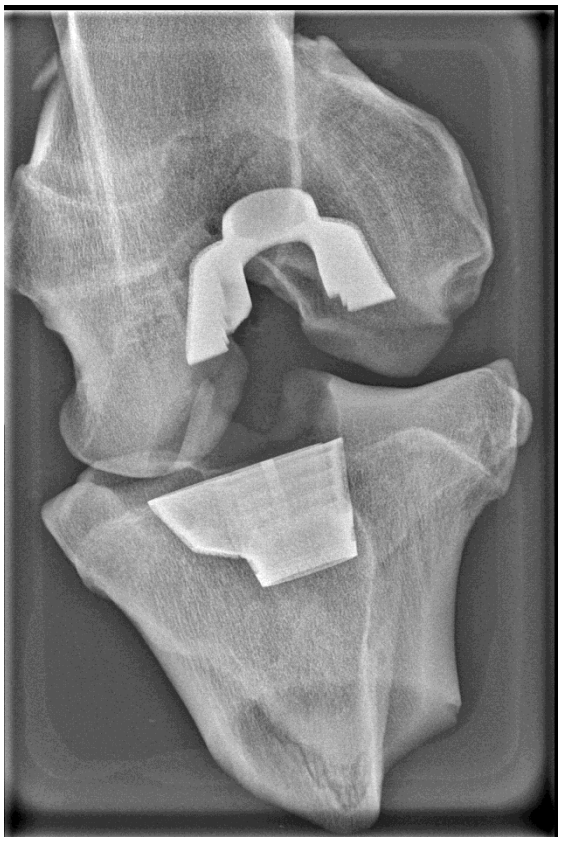


Figure 3.23. *Baseline x-ray done at 70 kv 5 mAs*

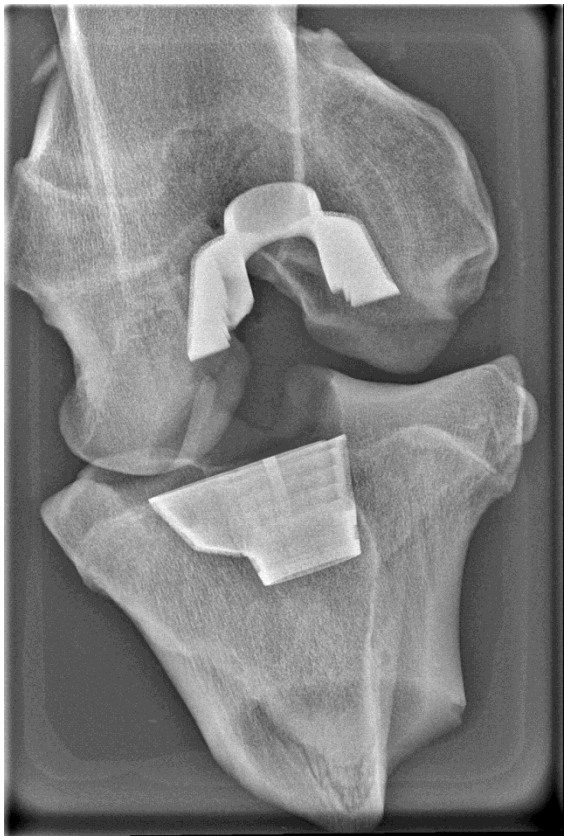


Figure 3.24. *Baseline x-ray done at 81 kv 3.2 mAs*

Additionally an example of the DXA and x-ray images that were taken after the inclusion of the marker are shown in figures 3.25 and 3.26.

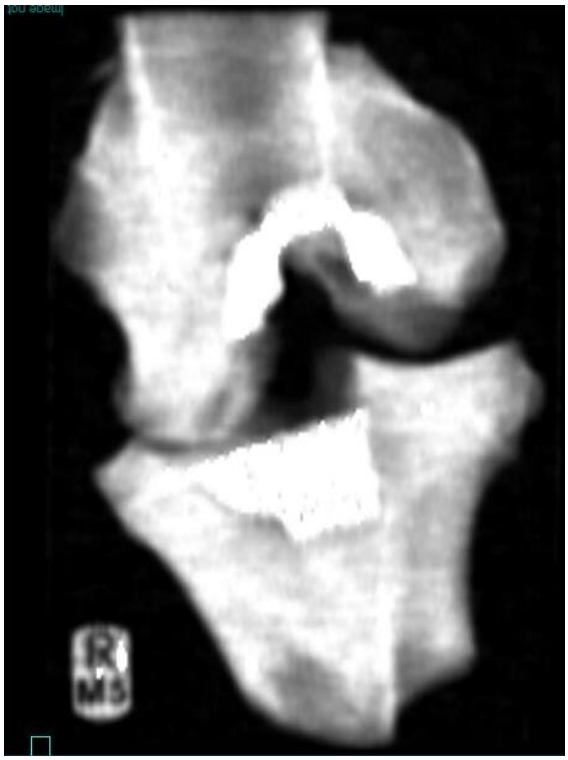


Figure 3.25. *Post calcium 1 with marker DXA scan on thin setting*

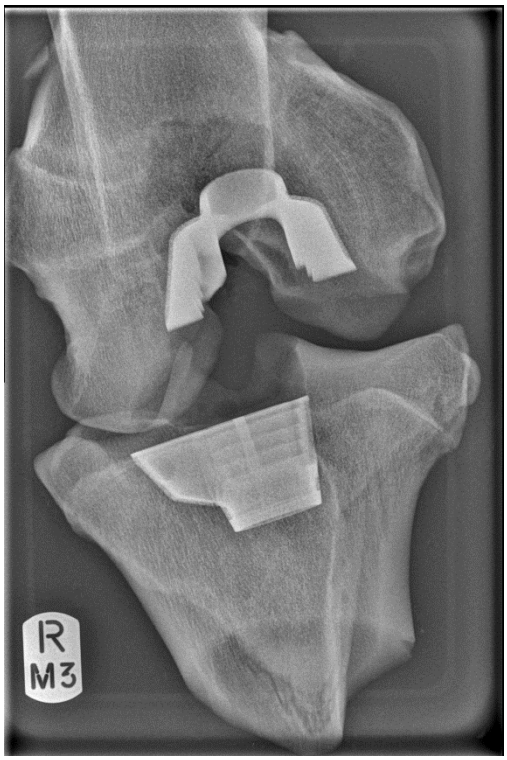


Figure 3.26. *Post calcium 1 with marker x-ray on 81 kv 3.2 mAs*

3.6.6 CONES AND BONES CT IMAGES

Computed tomography images were also produced after the final fourth saturation as shown in figure 3.27.

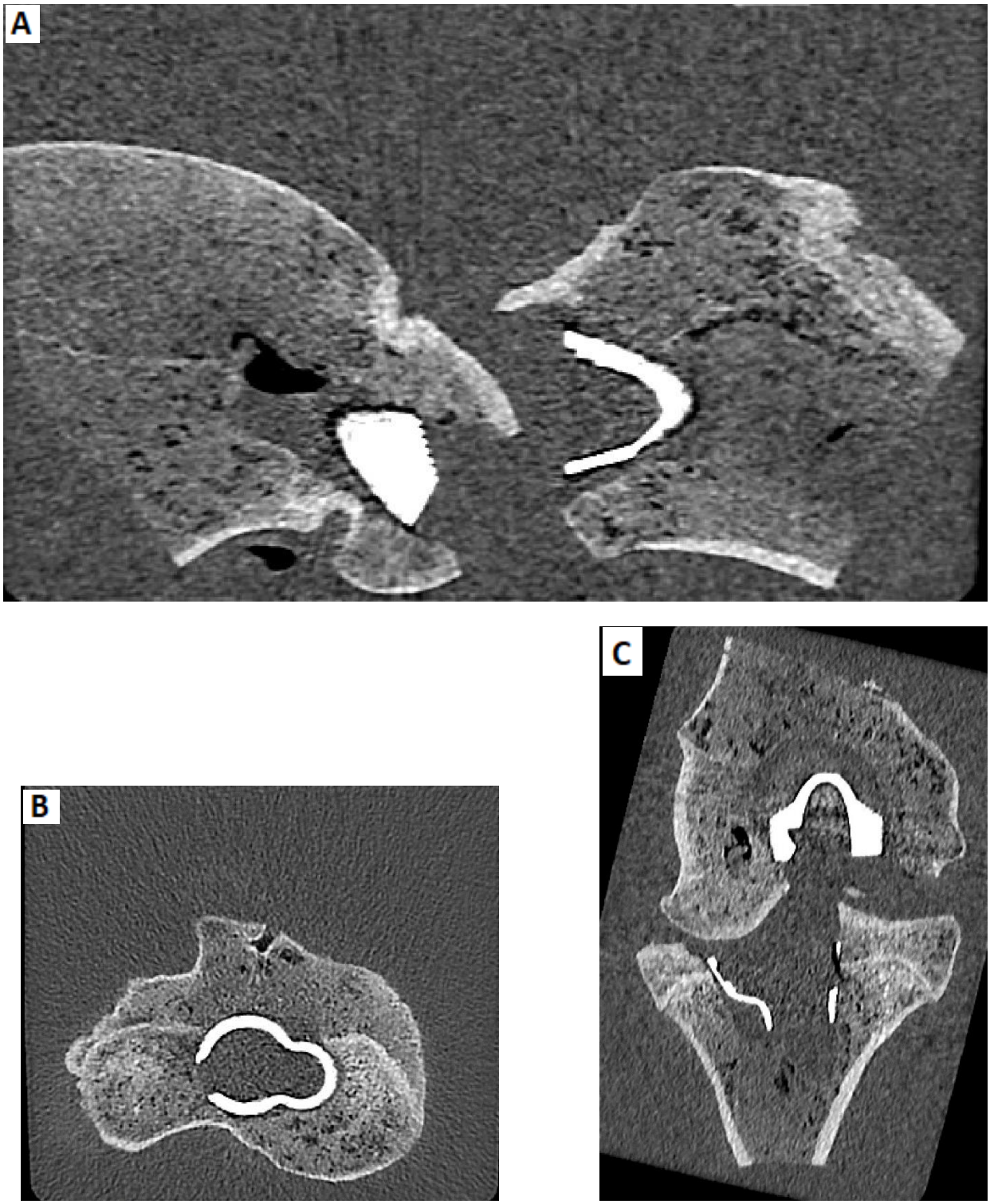


Figure 3.27. *CT images produced of post calcium 4, A shows a sagittal plane through th bovine model, B shows a transverse slice of the tibial cone in the bovine model, C shows a coronal slice through the cones and bones*

3.7 ANALYSIS

3.7.1 ANALYSIS OF X-RAYS AND INTRAOPERATOR DATA

Prior to any density analysis of the x-ray images, radiographs in their DICOM format were all rotated left 90 degree and their canvas size normalised to 1052 by 1552 pixels (the range for all images was 1012 to 1052 pixels by 1536 to 1552). The window level (WL) and window width (WW) was then standardised across all images and across all doses, this was standardised as WL 1800 and WW 2100, then all images were converted to eight bit from 16 bit and saved as TIFF images in order to allow standardisation and comparison across all images.

The mean pixel density of water was originally utilised as the standardised measure as the comparator of known density in which future images would be compared, as this was standardised to depth (15 cm) and was repeatable. After the baseline images were taken it was decided to supersede this by introducing the metallic marker which had a known and consistent density, as this would be a more dependable measure, as such all subsequent images were taken with the marker included within the image. It was decided to normalise all the images to the marker pixel density average, therefore marker reading were taken across all images and averaged, and a normalised coefficient applied to each image. Unfortunately this meant that the baseline image already taken could not be included in the calculation due to being utilised with the water density measure, therefore additional images were taken without the marker in order to quantify and compare the pixel density to that of water in the same area and allow a comparator to the baseline, albeit it a less comparable one.

This resulted in 28 images being analysed (via using ImageJ), 16 of these were made up of four post calcium time intervals (first, second, third, fourth (full saturation)) with a marker across four different exposure factors (60 kVp 8 mAs, 70 kVp 2.8 mAs, 70kVp 5 mAs, 81 kVp 3.2 mAs), and 12 images (the baseline, the first post calcium and the full saturation or fourth post calcium) across the same four exposure factors. It must be noted that although a 60 kVp 2.5 mAs dose was imaged and recorded, the images were rejected from the analysis as the imaging resulted in a stretched canvas prior to any normalisation resulting in

the majority of the images being unable to be compared, this stretching is evidenced in figure 3.28.

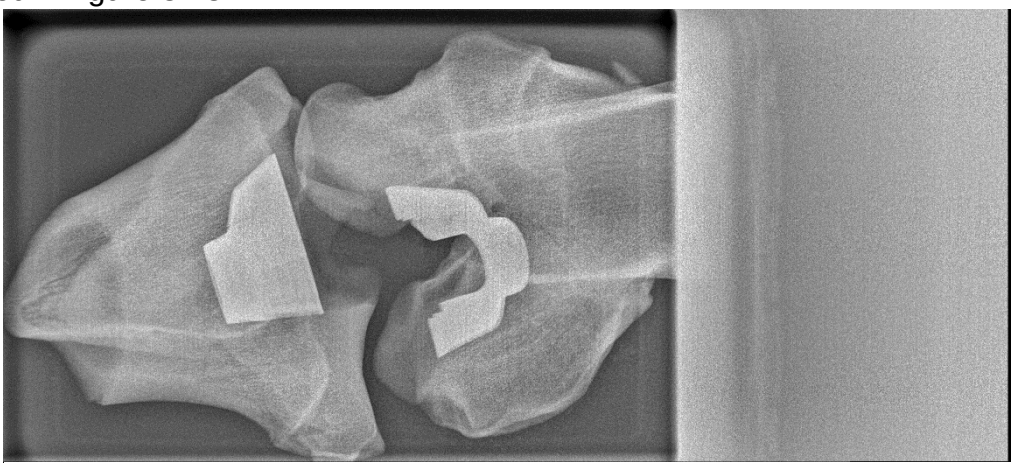


Figure 3.28. *X-ray of baseline image of cow cones on exposure setting 60 kVp 2.5 mAs, showing stretched canvas issue*

The x-ray images themselves were then divided into regions in order to calculate pixel density differences within parts of the cones themselves. These regions were based on similar region analysis used in DXA research [178, 305]. The regions selected are shown in figure 3.29.

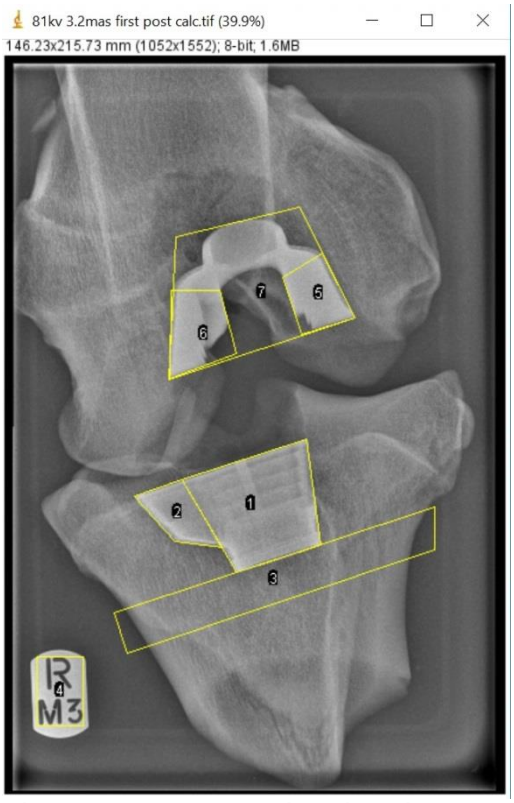


Figure 3,29. X*-ray showing the regions used in the analysis*

Each region was numbered one to seven and measured via their pixel density mean; this was then recorded in an Excel spreadsheet. Multiple regions were sampled in order to create a fair reflection on the pixel density changes, but additionally to provide information where these possible changes might occur within the porous cones. Additionally, these images were converted via a look up table (LUT) to show express the pixel density visually.

These regions were created and saved in a ROI manager, (within imageJ) and were loaded onto each image and adjusted, this adjustment was due to the research mimicking repeated knee x-rays thus there

was no perfect alignment between imaging weeks, as such, the regions were adjustable as long as they contoured to the conal implants and were positioned correctly over the marker. An example of the regions not lining up is shown in figure 3.30.

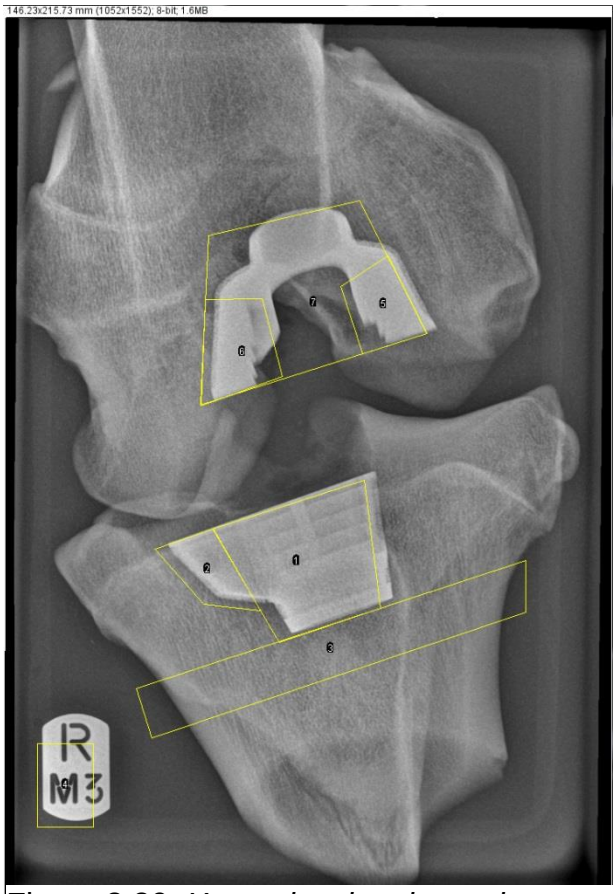


Figure 3.30. *X-ray showing the regions prior to adjustment*

Due to possibility of bias within the region adjustment placement it was decided to conduct an intraoperator variability study of the region placement within the x-ray images. Due to imaging across exposures not being affected by the positional adjustment these were not included in the intraoperator study i.e. the positional set up was not modified or touched between exposures only between post calcium weeks, and thus to include them would lower the variability and provide misleading information.

Therefore the exposure setting of 70 kVp 5 mAs was chosen, as this was close to the average of the analysed exposures. Five images were chosen: baseline, first post calcium (marker), second post calcium (marker), third post calcium (marker) and fourth post calcium/full saturation (marker). The first post calcium (no marker) and fourth post calcium (no maker) were not included due to similarly having been minimally moved (i.e. the marker was removed and reimaged without moving the bones). The standardised regions were loaded from the ROI manager from the second post calcium file (as they were during the original analysis) and modified to fit each image. Furthermore in order to reduce bias the second post calcium image was done last out of the five, in order that enough adjustments had been made throughout the first four that it

itself would need to be adjusted and would not reflect the original regions. Besides that there was no order to the region analysis, each image was loaded, the regions placed on top and adjusted measurements taken and the process repeated until all five images had been analysed, these measurements were then placed in an Excel spreadsheet and recorded under their date, on average 8.2 days (range six – 12 days) would pass until the analysis was repeated, this time period separation was in order reduce learning or remembering bias.

3.7.2 ANALYSIS OF THE DXA IMAGES

In order to analyse the DXA images first the classification of the anatomy within the image had to be corrected, thus manual classification of the bones, tissues and artefacts had to be annotated via post processing as shown below in figure 3.31, hence it was decided to only analyse the thin setting knee scans, this was due to the thin setting being used on human DXA knee scans and would provide the most representative of the BMD changes in the knee.

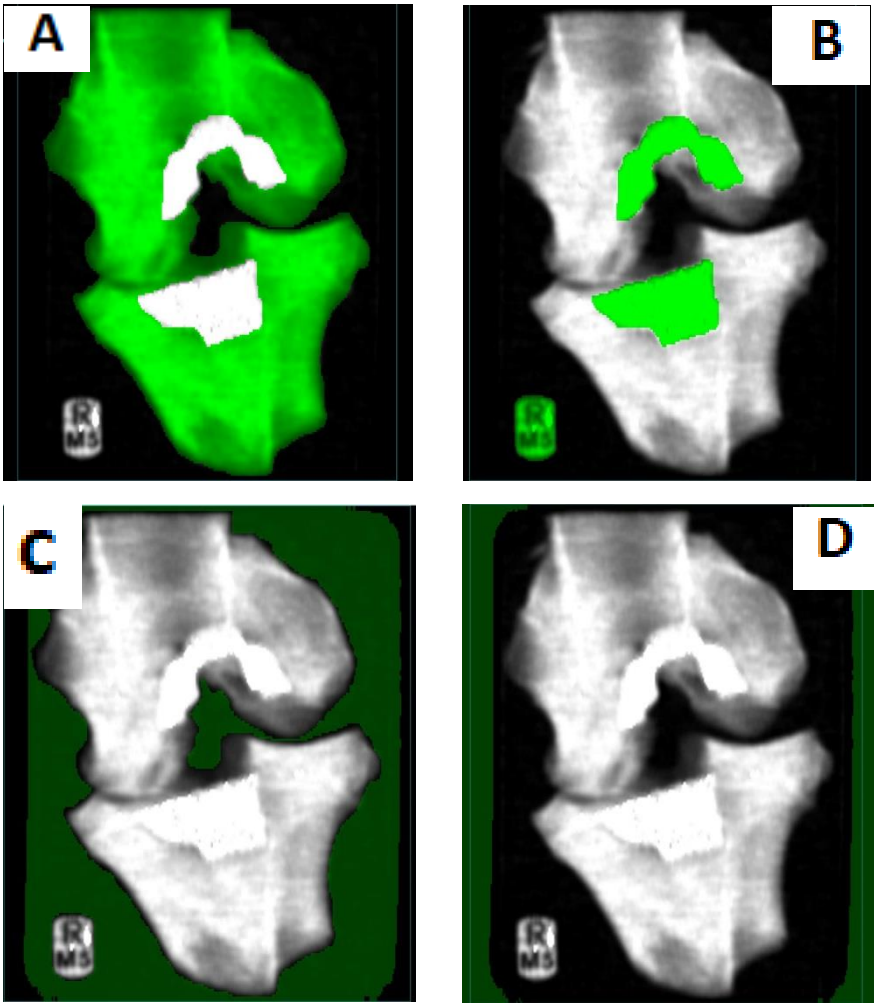
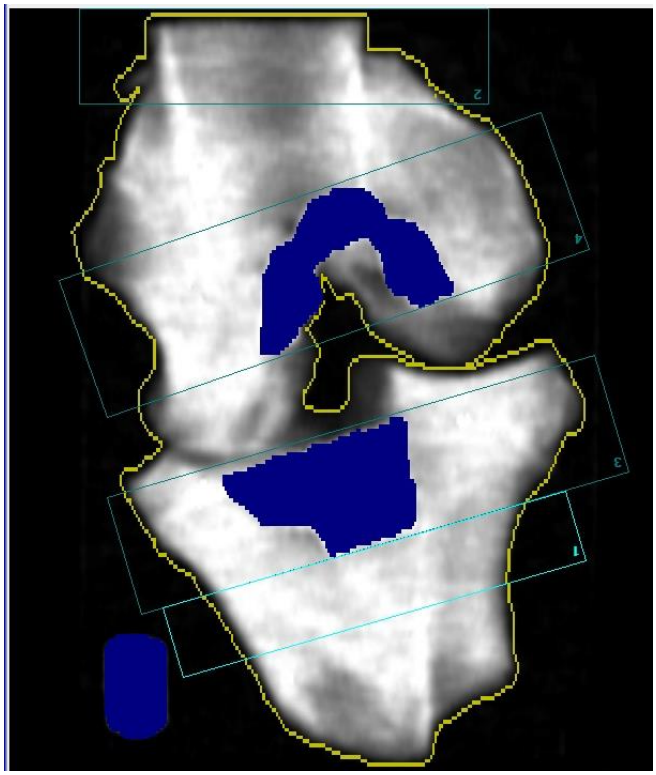


Figure 3.31. *DXA image showing the selected classifications highlighted in green; A shows bone, B shows artefact, C tissue, D air*

Four regions were chosen within the DXA image to be analysed as shown in figure 3.32 in order to calculate BMD differences across the different post calcium weeks.



In total seven images were analysed for their BMD across the DXA images; post calcium one, post calcium two, post calcium three and post calcium four (full saturation) all with their marker, and baseline, post calcium one and post calcium four without a marker.

Figure 3.32. *DXA regions selected and analysed*

3.7.3 ANALYSIS OF CT IMAGES

Due to the limitations stated in the CT imaging it was decided to only analyse the CT images visually, as although the CT images provide positional data in the form of transverse sectional data and in-growth data they do not contain comparison data. Additionally the results will support or argue possible positional density difference data revealed via the x-ray or DXA images, and thus might help finer pinpoint the difference in positional. As such LUT were applied to the image (via ImageJ) in order to show any density difference in and around the implant in colour.

3.8 RESULTS

3.8.1 X-RAY RESULTS

Tables 3.1 to 3.4 show the pixel density results (post coefficient marker normalisation) for all four post calcium scores for each region across the different exposures (region four is the marker and therefore has not been included), Due to only small value differences figures 3.33-3.36 show data only comparing the pixel density differences and not the total pixel score, thus have been expressed as each regions final digit plus three significant figures, e.g. 175.032 is now 5.032, 179.354 is 9.354 and 180.063 would be 10.063.

Table 3.1. *Pixel density difference of 60 kv 8 mAs for each region across four post calcium visits*

Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
Post calcium 1	177.710	186.415	134.039	179.354	162.147	145.002
Post calcium 2	174.790	184.911	130.419	175.032	160.530	140.677
Post calcium 3	176.367	185.978	132.911	176.930	163.608	145.072
Post calcium 4 (full sat)	179.210	187.538	135.616	180.063	166.991	148.837
Difference between 1 and 4	1.500	1.123	1.577	0.709	4.844	3.836

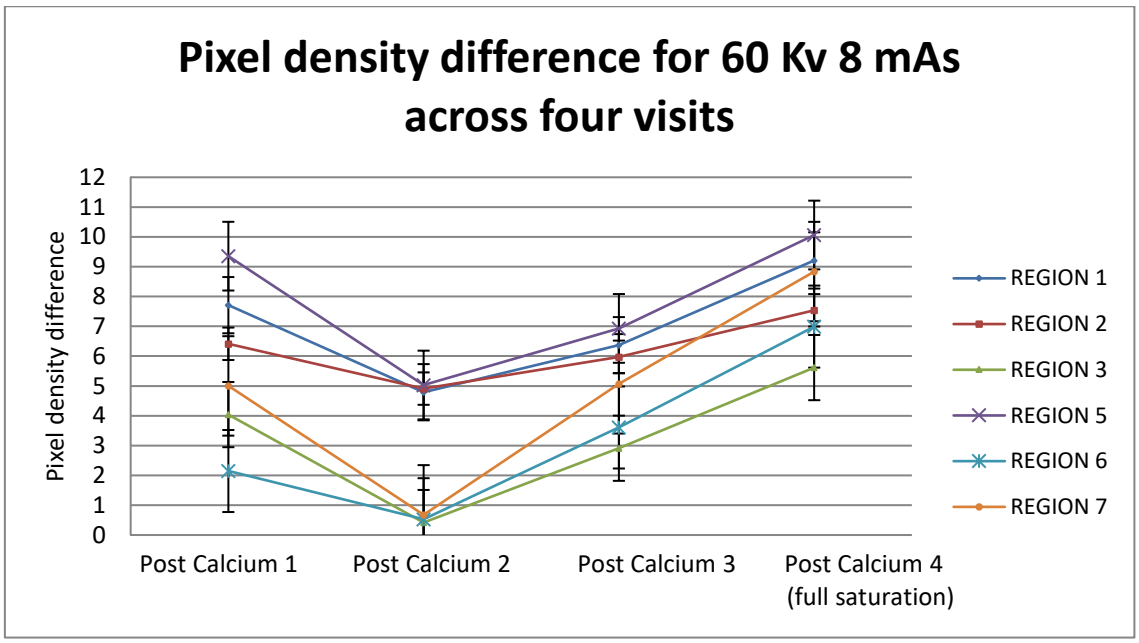


Figure 3.33. *Pixel density differences for 60 kv 8 mAs across four visits and seven regions, errors bars are standard error*

Table 3.2. *Pixel density difference of 70 kv 2.8 mAs for each region across four post calcium visits*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
Post calcium 1	169.658	176.123	135.300	175.970	162.369	145.896
Post calcium 2	168.036	175.473	132.559	170.969	160.964	142.602
Post calcium 3	169.170	176.605	134.306	174.815	162.670	146.283
Post calcium 4 (full sat)	172.073	180.955	128.270	177.232	163.707	144.508
Difference between 1 and 4	2.415	4.832	-7.030	1.262	1.338	-1.388

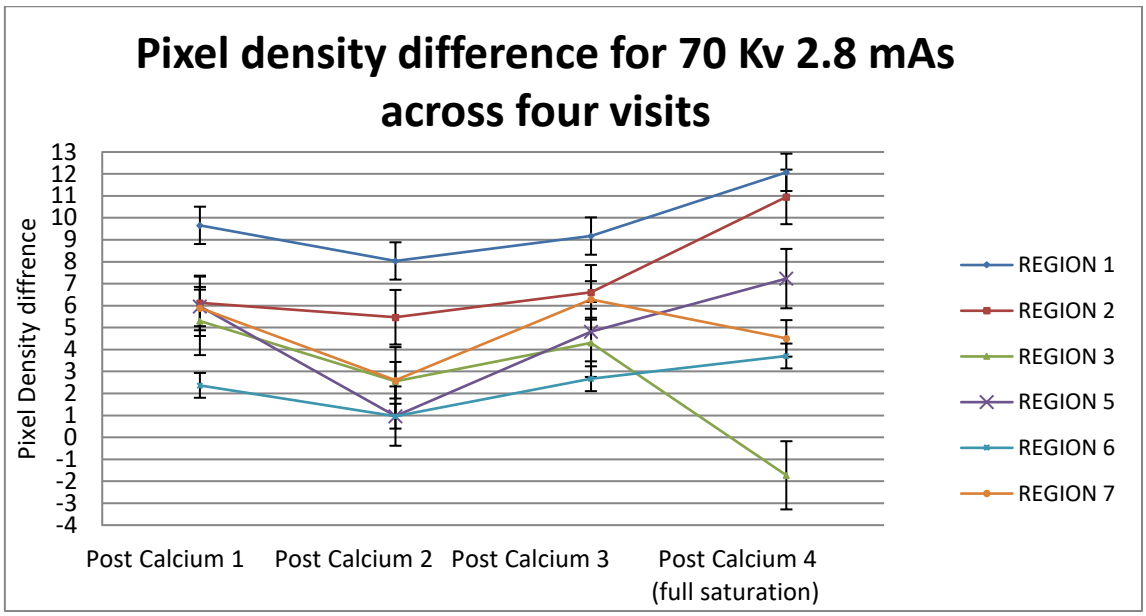


Figure 3.34. *Pixel density differences for 70 kv 2.8 mAs across four visits and multiple regions, errors bars are standard error*

Table 3.3. *Pixel density difference of 70 kv 5 mAs for each region across four post calcium visits*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
Post calcium 1	169.278	177.224	127.806	177.033	160.905	141.035
Post calcium 2	167.225	176.365	124.901	170.967	159.236	137.281
Post calcium 3	168.685	177.796	126.951	175.804	161.386	141.701
Post calcium 4 (full sat)	171.455	179.849	129.610	176.376	163.601	145.104
Difference between 1 and 4	2.177	2.626	1.804	-0.658	2.696	4.069

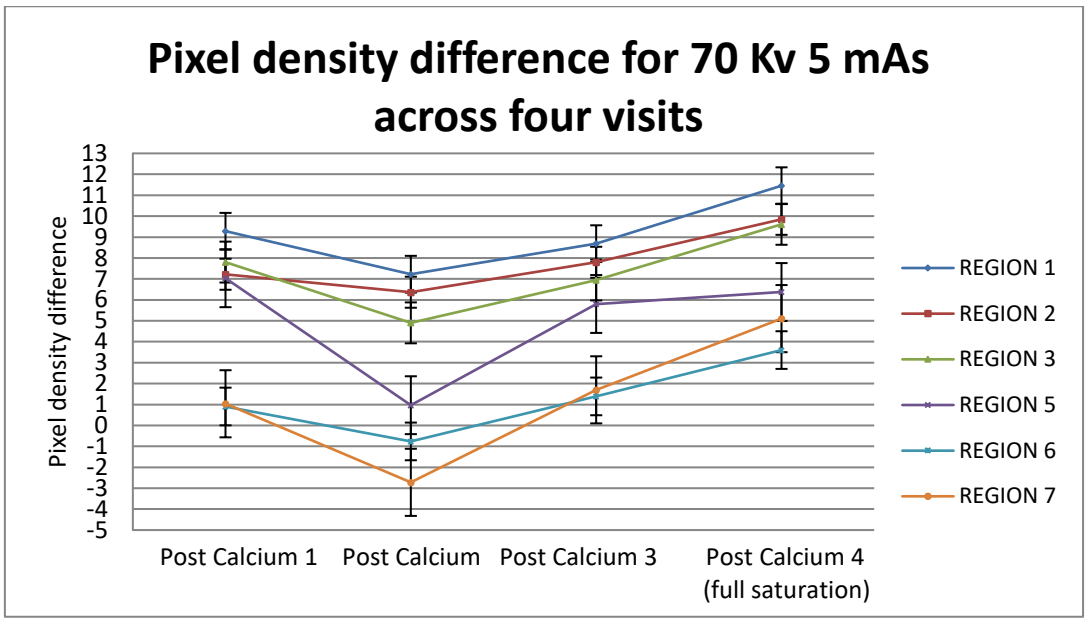


Figure 3.35. *Pixel density differences for 70 kv 5 mAs across four visits and multiple regions, errors bars are standard error*

Table 3.4. *Pixel density difference of 81 kv3.2 mAs for each region across four post calcium visits*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
Post calcium 1	164.540	171.387	129.046	175.705	161.315	142.709
Post calcium 2	161.981	170.295	125.867	173.048	161.610	138.944
Post calcium 3	163.795	172.035	127.699	175.687	162.948	143.465
Post calcium 4 (full sat)	166.358	173.728	130.638	175.865	164.310	146.620
Difference between 1 and 4	1.818	2.341	1.593	0.160	2.995	3.912

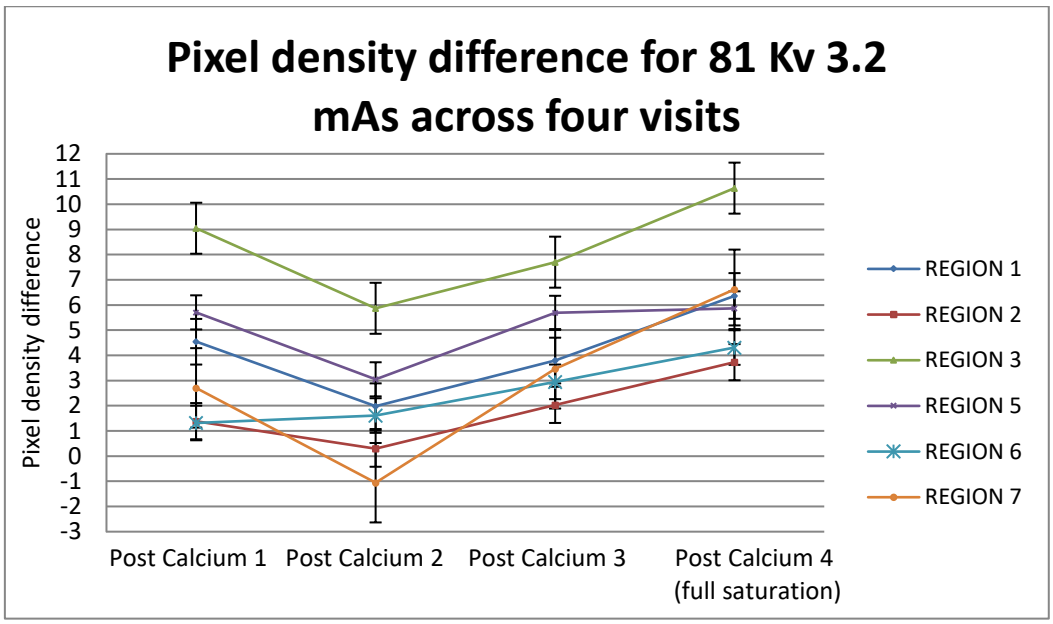


Figure 3.36. *Pixel density differences for 60 kv 8 mAs across four visits and multiple regions, errors bars are standard error*

Across all four exposures 21 out of 24 results show an increase in pixel density between post calcium one and full saturation, with the largest increase 4.832 seen in region two of 70 kVp 2.8 mAs, incidentally the largest negative difference is also seen in 70 kVp 2.8 mAs with a pixel density average loss of 7.030 seen in region three. The trends across exposures shows a similar pattern of low pixel density in post calcium two (compared to post calcium one) which gradually increases in post calcium three and exceeding post calcium one at the point of imaging post calcium four.

Additionally, data were analysed by using the water density average for coefficient normalisation across the three time periods which were scanned without a marker (baseline, post calcium one and full saturation), as shown in tables 3.5 to 3.8 which again covers all the exposure settings used.

Table 3.5. *Pixel density difference of 60 kv 8 mAs for each region across three post calcium visits normalised to the coefficient of water*

60 kv 8 mAs						
Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
Baseline	351.668	367.753	273.569	347.394	328.217	293.236
Post calcium 1	464.011	501.504	338.111	449.738	430.347	370.966
Post calcium 4 (full sat)	401.668	423.519	307.159	402.662	373.389	335.246
Difference between baseline and 4	50.000	55.766	33.589	55.268	45.172	42.010

Table 3.6. *Pixel density difference of 70 kv 2.8 mAs for each region across three post calcium visits normalised to the coefficient of water*

70 kv 2.8 mAs						
Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
Baseline	327.274	342.677	254.152	335.277	313.662	277.494
Post calcium 1	334.164	355.220	259.002	335.618	323.517	283.539
Post calcium 4 (full sat)	385.353	406.637	289.952	398.576	369.520	325.824
Difference between baseline and 4	58.079	63.960	35.800	63.299	55.858	48.331

Table 3.7. *Pixel density difference of 70 kv 5 mAs for each region across three post calcium visits normalised to the coefficient of water*

70 kv 5 mAs						
Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
Baseline	315.607	329.949	247.951	323.504	303.460	269.859
Post calcium 1	321.138	340.524	251.677	321.318	311.546	274.749
Post calcium 4 (full sat)	365.197	384.879	278.014	376.793	351.115	310.562
Difference between baseline and 4	49.590	54.930	30.063	53.290	47.656	40.703

Table 3.8. *Pixel density difference of 81 kv 3.2 mAs for each region across three post calcium visits normalised to the coefficient of water*

81 kv 3.2 mAs						
Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
Baseline	277.173	288.713	225.252	291.120	275.556	245.566
Post calcium 1	279.475	293.890	225.464	288.099	278.875	247.462
Post calcium 4 (full sat)	309.314	324.075	244.368	327.830	307.305	273.689
Difference between baseline and 4	32.142	35.362	19.116	36.710	31.750	28.123

These tables show a similar trend to the marker data albeit with a much larger density difference average increase between the baseline and full saturation, with the highest average pixel difference being 63.960 in region two on image 70 kVp and 2.8 mAs which is shown in the marker data analysis, although there is no negative pixel data, the lowest pixel average density increase is 19.116 as seen in region three (again this trend is seen in the marker data) albeit in image 81 kVp 3.2 mAs. The data also show an increase in average pixel density between the baseline and post calcium one.

The main two results of the data are to demonstrate the increase of pixel density for the full saturation compared to the baseline or post calcium one, as well as mathematically through calculation of average pixel density difference it is also shown visually (figures 3.37 and 3.38), which shows where the density changes (via an applied LUT representation). With figure 3.38 showing full saturation (with marker) compared to figure 3.34 showing post calcium one (with marker). It must be stated these figures are pre normalisation to the marker so are an exaggeration of the difference but highlight where the differences are recorded.

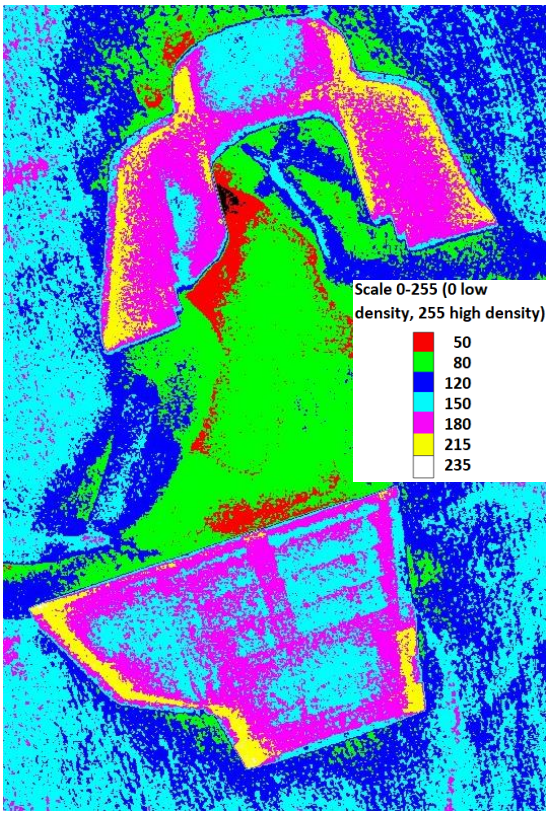


Figure 3.37. *X-ray post calcium 1 after a LUT has been applied, low pixel density is in red and high pixel density is in yellow.*

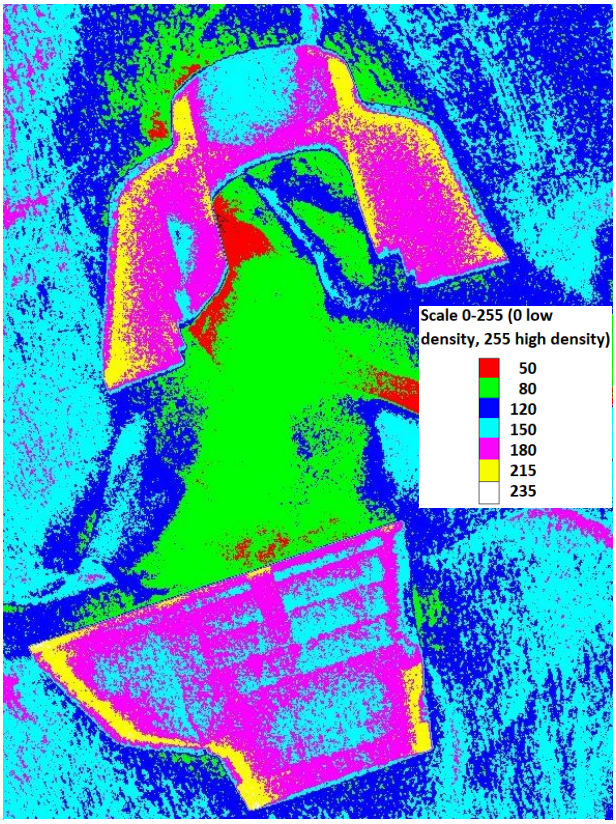


Figure 3.38. *Shows an X-ray image of the cones at full saturation after a LUT has been applied, low pixel density is in red and high pixel density is in yellow.*

This representation was repeated with the baseline and full saturation images that did not contain the marker; these are shown in figures 3.39 and 3.40 and are pre normalisation to water.

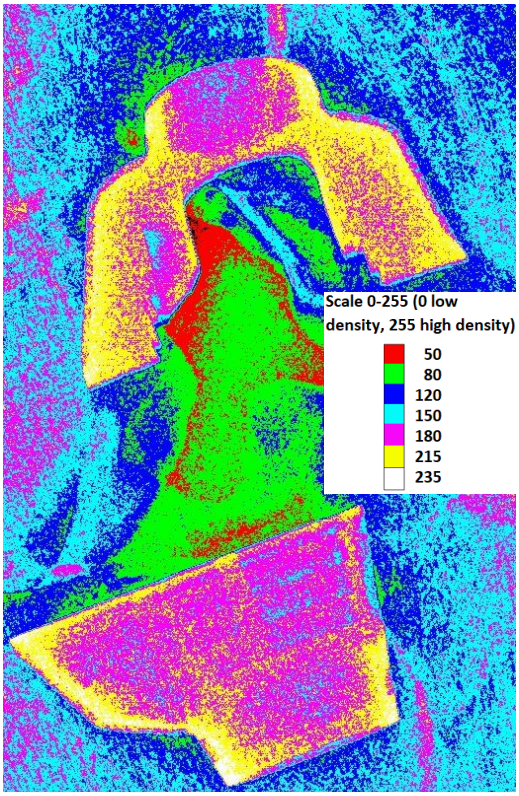


Figure 3.39. *X-ray baseline after a LUT has been applied, low pixel density is in red, and high pixel density is in yellow.*

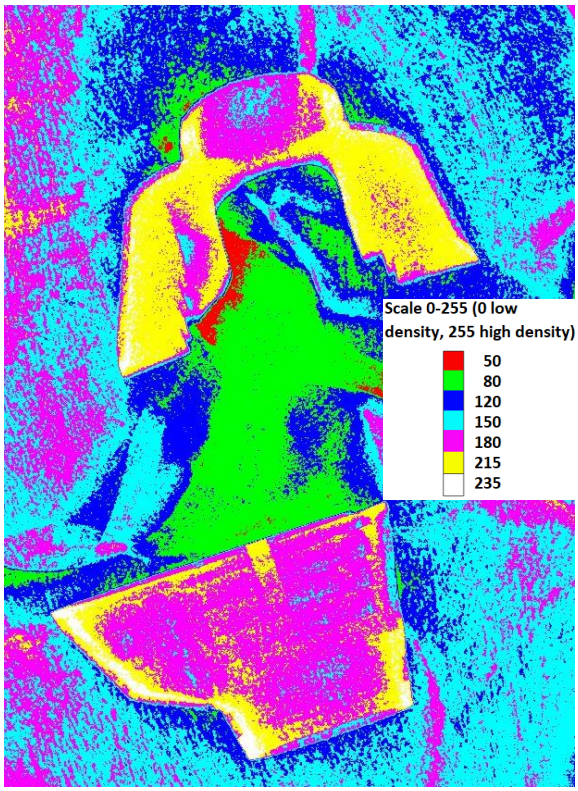


Figure 3.40. *X-ray full saturation after a LUT has been applied, low pixel density is in red, and high pixel density is in yellow.*

These four figures 3.37-3.40 are shown for illustrative purposes only, in order to indicate where average pixel density difference of deposited calcium phosphate has most likely occurred, but again these images have been produced prior to any pre normalisation so are a hyperbolic reflection of the true result.

3.8.2 INTRAOPERATOR RESULTS

Following the analysis discussed in section 3.7.1 five tables were produced covering the baseline (table 3.9), post calcium one (table 3.10), post calcium two (table 3.11), post calcium three (table 3.12), and post calcium four (full saturation) (table 3.13), calculating the COV. It must be stated that region four is not included as this was the marker region and to include the data from this region would reduce the variation and create an erroneous result.

Table 3.9. *Average pixel density for baseline for each region for 70 kVp and 5 mAs across 10 repeats, this includes variation within each region and total variation.*

Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
FIRST (7/7/17)	181.170	189.403	142.333	185.703	174.197	154.909
SECOND (19/7/17)	181.135	189.311	142.551	185.365	174.668	155.097
THIRD (31/7/17)	181.293	188.534	142.694	186.086	175.695	154.968
FOURTH (7/08/17)	181.233	188.951	142.456	186.086	176.234	155.492
FIFTH (14/08/17)	181.052	188.820	142.598	186.565	175.694	155.191
SIXTH (21/08/17)	181.088	189.235	142.806	186.269	174.776	154.756
SEVENTH (29/8/17)	181.134	189.164	142.685	186.750	176.444	155.526
EIGHTH (04/09/17)	181.290	189.105	142.649	185.858	176.330	155.192
NINTH (11/09/17)	181.287	188.899	142.582	185.858	175.890	155.314
TENTH (19/09/17)	180.982	188.883	142.929	185.276	175.890	154.885
Variation	0.01173	0.068758	0.028432	0.224603	0.593994	0.067252
COV %	0.237302					

Table 3.10. *Average pixel density for post calcium 1 for each region for 70 kVp and 5 mAs across 10 repeats, this includes variation within each region and total variation.*

Time period	**Region 1**	**Region 2**	**Region 3**	**Region 5**	**Region 6**	**Region 7**
FIRST (7/7/17)	155.780	163.092	117.615	162.917	148.075	129.789
SECOND (19/7/17)	155.219	163.513	117.435	162.258	148.011	129.781
THIRD (31/7/17)	155.446	163.361	117.544	162.042	149.420	130.099
FOURTH (7/08/17)	155.914	163.861	117.824	161.302	148.423	129.665
FIFTH (14/08/17)	155.533	164.336	117.833	161.832	148.170	129.862
SIXTH (21/08/17)	155.722	163.681	117.548	161.736	146.424	129.369
SEVENTH (29/8/17)	155.670	163.344	117.548	162.042	147.432	129.832
EIGHTH (04/09/17)	155.746	163.385	117.783	161.736	148.316	129.696
NINTH (11/09/17)	155.697	163.204	117.574	162.042	149.420	130.036
TENTH (19/09/17)	155.677	164.066	117.700	162.222	149.047	129.621
Variation	0.038275	0.158044	0.0187	0.179465	0.833242	0.043449
COV %	0.314931					

Table 3.11. *Average pixel density for post calcium 2 for each region for 70 kVp and 5 mAs across 10 repeats, this includes variation within each region and total variation.*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
FIRST (7/7/17)	152.746	161.095	114.087	156.164	145.449	125.395
SECOND (19/7/17)	152.637	161.183	114.006	158.501	146.995	125.683
THIRD (31/7/17)	152.745	161.512	114.001	157.551	146.239	125.421
FOURTH (7/08/17)	152.319	160.983	114.102	157.245	146.644	125.693
FIFTH (14/08/17)	152.469	161.229	114.260	158.278	146.746	125.290
SIXTH (21/08/17)	152.548	161.469	113.986	158.278	146.125	124.916
SEVENTH (29/8/17)	152.562	161.618	114.050	158.077	146.614	125.591
EIGHTH (04/09/17)	152.741	161.608	114.012	157.551	147.416	124.833
NINTH (11/09/17)	152.597	161.539	114.260	158.814	146.614	125.361
TENTH (19/09/17)	152.187	161.881	113.988	157.791	145.607	125.654
Variation	0.03492	0.07785	0.011072	0.57285	0.363529	0.092679
COV %	0.306647					

Table 3.12. *Average pixel density for post calcium 3 for each region for 70 kVp and 5 mAs across 10 repeats, this includes variation within each region and total variation.*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
FIRST (7/7/17)	157.602	166.114	118.610	164.253	150.783	132.391
SECOND (19/7/17)	157.296	165.660	118.754	162.996	151.593	132.491
THIRD (31/7/17)	157.663	166.070	118.626	164.056	150.124	132.777
FOURTH (7/08/17)	157.781	166.350	118.648	163.684	150.553	132.745
FIFTH (14/08/17)	157.546	166.876	118.589	163.750	151.688	132.728
SIXTH (21/08/17)	157.639	165.942	118.686	162.079	151.101	132.127
SEVENTH (29/8/17)	157.444	165.930	118.581	163.750	151.490	132.490
EIGHTH (04/09/17)	157.545	165.813	118.727	163.560	151.423	132.352
NINTH (11/09/17)	157.226	166.070	118.656	164.056	151.871	132.493
TENTH (19/09/17)	157.518	165.767	118.790	164.253	150.926	132.546
Variation	0.028088	0.121194	0.005061	0.44239	0.310194	0.040226
COV %	0.267983					

Table 3.13. *Average pixel density for post calcium 4 (full saturation) for each region for 70 kVp and 5 mAs across 10 repeats, this includes variation within each region and total variation.*

Time period	Region 1	Region 2	Region 3	Region 5	Region 6	Region 7
FIRST (7/7/17)	160.805	168.678	121.559	165.420	153.439	136.091
SECOND (19/7/17)	160.925	168.505	121.379	166.975	153.497	136.536
THIRD (31/7/17)	160.705	168.323	121.256	167.282	153.086	136.282
FOURTH (7/08/17)	160.760	168.602	121.244	166.272	153.497	136.288
FIFTH (14/08/17)	160.787	168.133	121.265	166.975	153.279	136.131
SIXTH (21/08/17)	160.776	168.320	121.265	166.920	153.350	136.380
SEVENTH (29/8/17)	160.658	168.011	121.244	166.272	153.497	135.891
EIGHTH (04/09/17)	160.733	168.391	121.275	167.282	155.417	136.118
NINTH (11/09/17)	160.753	167.644	121.409	166.690	154.558	136.482
TENTH (19/09/17)	160.776	166.980	121.388	167.380	154.539	136.577
Variation	0.004899	0.263312	0.010685	0.369163	0.569148	0.048894
COV %	0.303848					

Across all five images the coefficient of variation was reported as 0.237 %, 0.315 %, 0.307 %, 0.268 % 0.304 % (to three significant figures), all showing a similar result. Additionally the highest variation within the individual regions was seen in region six with a reported variation of 0.833, with the lowest reported seen in region one recording 0.005. The average for each region (across all five images) shows the highest variation is seen in region six an average of 0.534, closely followed by region five with an average of 0.358, with the lowest score reported in region three of 0.015, and region one with an average of 0.024.

3.8.3 DXA RESULTS

Table 3.14 and figure 3.41 show BMD across the four regions measured using g/cm^2 compared between the intervals of post calcium one, post calcium two, post calcium three and full saturation

Table 3.14. *BMD result (g/cm^2) between four selected regions across four visits*

	Region (g/cm^2)			
Time period	**1**	**2**	**3**	**4**
Post calcium 1	2.939	1.894	2.879	2.517
Post calcium 2	2.984	1.952	2.866	2.553
Post calcium 3	2.960	1.915	2.959	2.543
Post calcium 4 (full sat)	2.964	1.953	2.851	2.464
Difference between 1 and 4	0.025	0.059	-0.028	-0.053

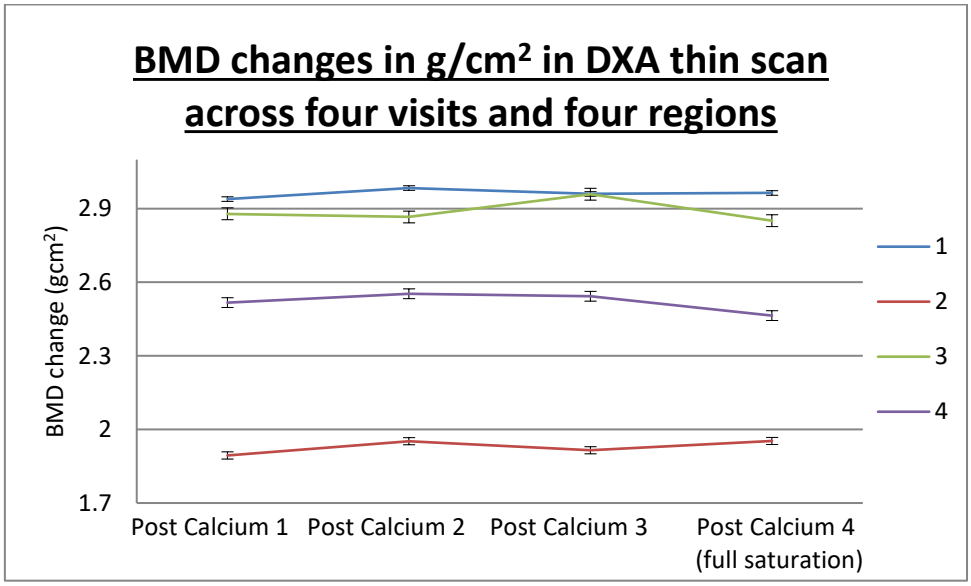


Figure 3.41. *DXA BMD results across four visits, error bars are COV*

DXA results show minimal difference between figures, although there is a loss of BMD in regions three and four which is where the cones are situated. Although it must be noted the cones themselves are not included in the calculation as they are excluded due to being artefacts in the DXA image. Both region one and region two show a very slight increase in BMD across the visits.

Table 3.15 and figure 3.42 show the BMD differences across three visits; baseline, post calcium one, and post calcium four without the marker.

Table 3.15. *BMD difference (g/cm²) between four selected regions across three visits*

	Region (g/cm²)			
Time period	**1**	**2**	**3**	**4**
Baseline	2.950	2.136	2.952	2.620
Post calcium 1	2.913	1.832	3.089	2.500
Post calcium 4 (full sat)	2.913	1.933	2.838	2.546
Difference between 1 and 4	-0.037	-0.203	-0.114	-0.074

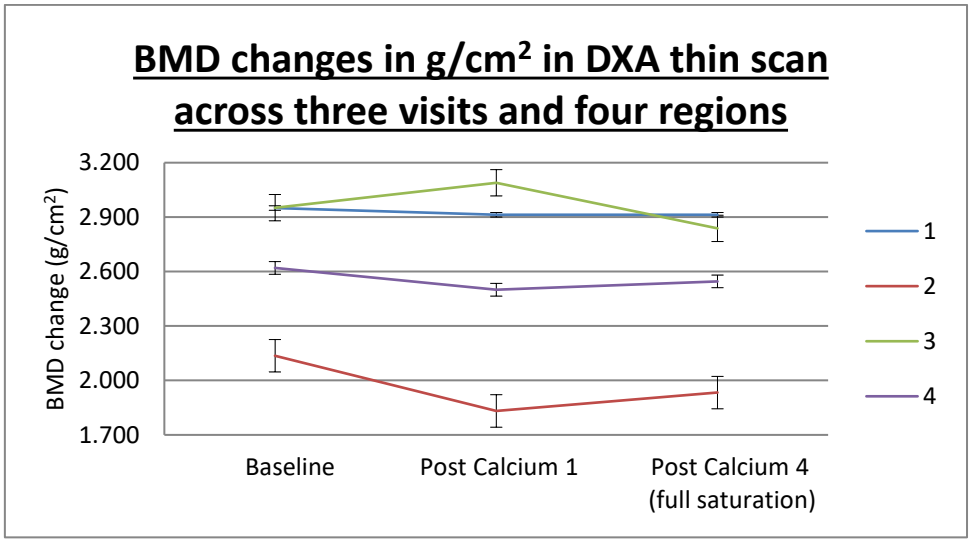


Figure 3.42. *DXA BMD results across three visits and four regions, error bars are COV*

Table 3.15 and figure 3.42 show a BMD loss between the baseline and the full saturation across all four regions.

3.8.4 CT RESULTS

Figure 3.43 shows a LUT applied to an axial slice of a CT eight bit image (via imageJ), in order to visualise possible ingrowth. Unfortunately, the white and yellow pixels which would represent high pixel density and in-growth around the conal implants, are minimal, and as such might be obscured by artefact caused by the implant instead of calcium phosphate deposits, as discussed in 3.6.2 and show in figures 3.15 and 3.16.

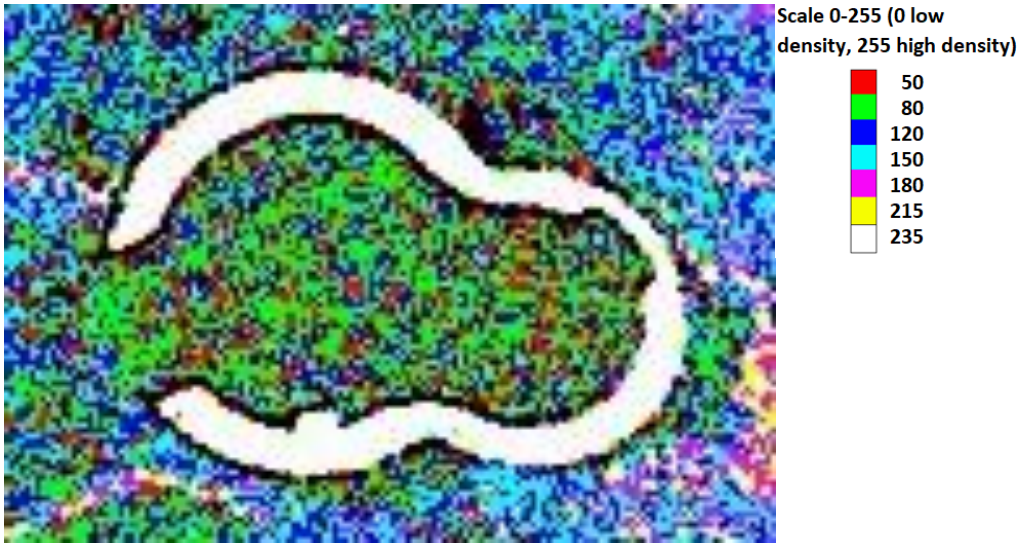


Figure 3.43. *Shows a CT image of the tibial cone in the axial plane, with the application of a LUT via ImageJ having been applied to in order to determine the possibility of in-growth. Red shows low density, and white shows high density.*

3.9 DISCUSSION

3.9.1 X-RAY IMAGES

The x-ray images show an increase of average pixel density between post calcium one and full saturation across 21 of the 24 images, and in all of the no marker images when comparing baseline to full saturation, with the largest increase seen in region two across both sets of data. Incidentally, the largest negative difference is an average pixel density loss of 7.030 and is seen in region three which does not cover the cones but is actually the area under the tibial cone. This negative result might be due to deterioration of the tissue and bone itself, this is further supported by region seven which also encompasses some of the surrounding tissue and also shows a negative result (-1.388) in the same exposure factor, even though region seven includes region five and six (both regions of the femoral cone and showing positive results +1.262 and +1.338). Although it must be noted both regions four and seven show positive results for the other exposures. The overall average pixel density increase across multiple regions when comparing post calcium one and full saturation might be due to the calcium phosphate depositing itself within the conal pores, whilst the negative result might be due to deterioration of the surrounding structures.

3.9.2 INTRAOPERATOR

The intraoperator variability results show a small deviation of the figures across all repeats (0.237-0.315 %) and address the issues of error margins and bias within the region selection and division**.** If this largest percentage 0.315 is applied to the results of the x-ray images only one result is affected (region 5 81 kVp 3.2 mAs), furthermore one x-ray result has a recorded loss of -0.658 between post calcium one and full saturation which is also in region five and this loss might be explained due to high average variation within region five (0.358). Furthermore, region six produces some of the largest average pixel density differences and this again might be explained by the average variation reported (0.534), with region six having the largest variation out of all the regions.

The intraoperator figures were only produced reviewing one set of exposures (70 kVp 5 mAs), although as the other exposures were done at the same time and thus the cones and bones in the plastic box was not moved neither was the x-ray tube or digital detector, the results should be generalisable to the other exposures used in the same post calcium visit.

3.9.3 DXA IMAGES

Dual energy X-ray absorptiometry results show a small amount of change of BMD density across all regions, with six out of eight of the results (either post calcium one compared to full saturation, or baseline compared to full saturation) showing a loss of BMD. This loss of BMD may well be due to the deterioration of tissue and bone which would correspond to the results mentioned in the x-ray imaging as a possible reason for the pixel density differences. It must also be noted that the DXA images do not include the information of the bone integration within the cones (as these are classed as artefacts). Incidentally there might be region selection or artefact inclusion bias within the study; with this artefact inclusion bias possibly being the reason two of the results are very slightly positive (0.025, 0.059).

3.9.4 CT IMAGES

The CT images show the possibility of in-growth, although it must be noted this could easily be artefact from the imaging system, and therefore cannot be concluded on, although if it is in-growth it shows a similar slight pixel density

change around the implants which would coincide with the pixel density differences reported in the x-ray imaging.

3.10 LIMITATIONS

The results themselves lack generalisabilty to any real world reported changes, this is due to several issues including temperature, saturation, and osteointegration. As this study was conducted in a non-biologically active ex vivo bovine stifle, this means the main premise of osteointegration involving osteoblast activity, bone remodelling and mechanical loading; resulting in bonding between the implant and the bone as a living tissue could not occur due to the limitations of the study. Resulting in only the deposited changes being registered, this is coupled with the research being done at room temperature (21-23 ^{o}C) with some reports stating that hydroxyapatite bonding to tritanium is problematic at room temperature [356], which would further exacerbate the integration issue. The saturation of calcium phosphate may have also been too low at the beginning, and only the full saturation produced a large enough positive effect (comparing post calcium three to full saturation). This solution also lacked the biochemistry present, or a representative pH level in tissue and bone matrix present to promote and compliment bone integration, which again may have impacted the result.

Additionally, the one odd result was that of a loss of pixel density during the post calcium two visit across multiple regions (see tables 3.1-3.4 and figures 3.33 to 3.36), this loss of density may have been due to the fault of the fans losing diffusion reducing deposition time and bonding, which was then rectified by the pump prior to the third post calcium visit. This loss of deposition may well have also been exacerbated by heavy vibrational transportation. For example if during the diffusion five day session 10 pieces of CaP were deposited on to the conal implants, then during transport (which was a train journey of 60-80 minutes and additional walking of 30-40 minutes) eight pieces became dislodged or unintegrated, the scan will still produce a positive difference of two, if the deposition is insufficient during the five day diffusion session then the build-up might only be six, but with the same loss of eight during transport resulting in negative of two.

Furthermore, the depositing of calcium phosphate might have been affected by the cavities that were originally created during the implantation phase. The press fit design nature of cones, and how they bond via close proximity to the bone could have been comprised due to the modified implantation technique utilised, due to the limitations already mentioned regarding lacking correct surgical tools. This idiosyncratic preparation may have influenced the implants ability to bond to the bone due to a gap being present between the cavity and the cone.

Allowances must also be made for the use of cow bones over human bones which are not a fair reflection on human integration and density. Furthermore, the removal of the patella and the fibula made the results less generalisable and applicable reducing surfaces for the CaP to adhere to.

The limitations stated although important address more about the bovine model than the development of the imaging methods and analysis. Limitations such as not having a standardised marker from the beginning (to allow calibration and standardisation across the pixel densities for x-ray imaging), and being aware of possible limitations with the CT imaging artefacts can feed into the main study.

3.11 CONCLUSION

The cone results are very limited but do show promise, with 21 out of 24 results showing an increase in average pixel density in multiple regions (when comparing first post calcium to full saturation). The loss in BMD across multiple visits and regions as reported by the DXA results is in contradiction to the x-ray analysis, although both investigated differing regions of interest (ROI) and the inert non vivo system makes a standardised conclusion problematic, thus It must be acknowledged that there are many variables and limitations which need to be addressed before a true significant conclusion can be reached, as such caution should be taken with these results until they can be verified in a more robust in vivo clinical trial.

Due to these factors and limitations stated the results cannot be generalised or provide representations of true osteintegration or BMD change, that being said,

the imaging methods presented here, and the ability to investigate, record and track those changes are feasible as methods for investigating BMD change and osteointegration.

3.12 FUTURE WORK

Bringing these procedures and methods into the main feasibility study, there were several learned lessons that were brought forward. For example, in addition to DXA PA images, lateral DXA images were also to be produced, in order to investigate BMD changes in both planes. This addressed some of the issues of BMD ROI changes caused due to superimposition of bone.

Moreover, for the feasibility study a metal of known density was included (an aluminium step wedge) so standardisation was available for all images from the start. Incidentally due to not being able to control the saturation of calcium and other chemicals clinically within our participants, medical history was recorded for any medications, calcium or multi vitamins the participants were prescribed, addressing the issue of differences between the two groups (if any) of certain drugs had on BMD/osteointegration [310].

CHAPTER 4 AN ANALYSIS USING 3D SHAPER MODELLING SOFTWARE ANALYSIS OF THE HIP – A COMPARISON BETWEEN DIFFERENT BASELINE AND FURTHER VISITS, AND BETWEEN IPSILATERAL AND CONTRALATERAL HIPS IN RTKR, TKR, AND CONTROL PARTICIPANTS

4.1 INTRODUCTION

From the systematic review, it has been shown that there are limited data regarding ipsilateral and contralateral hip BMD reported via Dual-energy X-ray absorptiometry (DXA) scans in the pre- and early post- surgery periods for total knee replacements (TKR). Furthermore, there are no reported DXA data available regarding BMD changes at the hip post total knee revision (rTKR).

4.1.1 AIM

In addition to the methods and analysis stated in the previous chapter which will be utilised in the full trial. I also investigated an alternative method, with the aim of this chapter to investigate 3D-SHAPER modelling software in determining bone quality in hip DXA images. This chapter will therefore provide an additional method for analysing bone quality, and will provide a set of descriptive data for the various populations to help provide sample data for future comparisons.

The impact of bone changes in the bilateral hips will be investigated across three groups; rTKR, TKR, and a control group (whom have not had any previous joint replacements), applying 3D-SHAPER software to analyse DXA scans. This software enables measurements of:

- **Cortical surface BMD (cortical sBMD**) in mg/cm^2; calculated as the multiplication of the cortical thickness (in cm) by the cortical volumetric density (in mg/cm^3). Cortical sBMD is associated with the strength of the cortex, the higher the cortical thickness and/or the cortical volumetric density, the higher the cortical sBMD [357].

- **Trabecular volumetric BMD (trabecular vBMD)** in mg/cm^3, measures the mean density in the trabecular compartment. Trabecular vBMD is associated with the strength of trabecular bone [357].

- **Integral volumetric BMD (integral vBMD)** in mg/cm^3, measures the mean density in the integral (union of the cortical and trabecular) compartment. Integral vBMD is associated with the global strength of the proximal femur. All measurements are calculated in the total femur ROI [357].

- **Cross sectional moment of inertia (CSMI)** in cm^4 describes geometric structure and density in the femoral neck and is a measure of the index of structural rigidity around the axis of the neck [358, 359]. It is calculated via the Hip structural analysis (HSA) definition of the sum of pixel mass at each point and multiplied by the square of its distance from the centre of mass [360].

- **Cross sectional area (CSA)** – reported in cm^2 measures the minimum of the CSMI section within the femoral neck. An index of axial compression strength [358].

Figure 4.1. *Diagram illustrating geometric location of CSMI and CSA in the hip [361]*

Both the CSMI and CSA (figure 4.1) impact the femoral strength index score and subsequent fracture risk [358]. Calculated via the HSA definition in which the area of each pixel is weighted by the amount of bone in the pixel [362].

Bone mineral density and the characteristics and architecture of bone have already been discussed in Chapter 1 section 1.2.2. Further to this, there is a direct link between the influences of both cortical and trabecular bone and hip strength; cortical bone supports the flexibility of the hip in the distal regions of the femoral neck, with trabecular bone supporting the proximal loads the hip has to undergo [363]. Both of these bone types combine in a complex relationship to provide hip strength through support, flexibility, and enable weight bearing.

The ability to separate cortical from trabecular bone might allow greater understanding of bone loss increasing fracture risk. This is due to BMD predominantly accounting for only 60% of variation in bone fragility [364], and with DXA scans being unable to differentiate differences in BMD composition and structural design [365], other options must be investigated. Furthermore, the importance in defining exact areas of weaknesses or bone loss is important, especially with the advent of atypical femoral fractures, and the issue that BMD measurements only calculate an average of mineral content over a given area and thus exclude structural detail [359]. In contrast, cross-sectional geometric measurements of CSMI and CSA can provide detailed data about mechanical properties, based on the distribution of the bone [359].

4.1.2 PREVIOUS RESEARCH

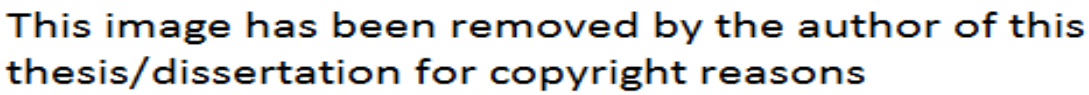
The 3-D Shaper modelling software was developed in 2011 and tested against a collection of Quantitative Computed Tomography (QCT) images. This involved a reconstruction experiment, where a model was constructed from a database of QCT scans of 85 subjects. The accuracy was evaluated by comparing the reconstructions with 30 DXA images with same subject QCT scans [366]. This model has since been evaluated further using a database of 157 study subjects, by comparing 3D-DXA analysis (using DXA scanners from three manufacturers) with measurements performed by QCT [367]. Since 2017 there have been published papers using the 3D-SHAPER software, for example: “Structural Parameters of the Proximal Femur by 3-Dimensional Dual-Energy X-ray Absorptiometry Software: Comparison With Quantitative Computed Tomography [368]”. The software has also been involved in investigating osteoporosis drug treatments on cortical and trabecular bone

impact [369]. In patients with Down syndrome [370], investigating cortical and trabecular bone changes in professional dancers [371], and analysing the evolution of cortical and trabecular bone compartments in the proximal femur after spinal cord injury by 3D-DXA [372]. These research papers are all very specific and limited, and none have covered either TKR or revisions, so unfortunately there is a lack of comparison data for this study.

4.2 THE 3D MODELLING SOFTWARE

Three-Dimensional Shaper is processing software (version v2.7.3) developed by Galgo Medical SL which incorporates model based algorithms via statistical shape and density modelling of 3D patient specific mapping onto DXA hip scans [373, 374]. This software utilises mathematical modelling across the femoral surface [374, 375], and has been evaluated for accuracy and validity using comparisons with quantitative computed tomography (QCT) imaging (an imaging modality which has been shown to be equal to DXA [376]) as shown in table 4.1 [375]. The software has been tested clinically via other fields, including treatment monitoring, fracture discrimination, and secondary osteoporosis [357, 377, 378, 379].

Table 4.1. *Shows the 3D-SHAPER software compared to QCT*



The 3D-SHAPER software was created from a population database of QCT images, overlaid onto the DXA scans of the patients [357], resulting in patient specific shape and density 3D models, with cortical and trabecular bone segmentation [374].

The software reports the BMD, but can also calculate both cortical and trabecular BMD from standard DXA hip images, with the addition of generating

a report and a 3D visual model, as well as providing percentage change for tracking changes throughout subsequent participant visits. Furthermore, the software is compatible with a multitude of different DXA scanners [357]. As stated the software calculates three main outcomes of the hip DXA scans; the cortical sBMD, the trabecular vBMD and the integral vBMD, as well as reporting the CSMI and CSA.

4.3 METHOD

The testing involved recruiting participants from three groups:

rTKR group – This group was from the main feasibility study undergoing a rTKR and cone implantation. At the point of utilising the software 27 participants had undergone pre-op scans. The group included both male and female (seven female, 20 male, mean age 71.6 (SD 7.403), mean weight 89.78 kg (SD 17.141), mean height 171.36 cm (SD 9.490)) resulting in a mean body mass index (BMI) of 30.57 (see table 4.2), 12 of these were due their revision on their left side, and 15 on their right. Data were recorded at pre-op (N=27), six week post rTKR (17 completed), three months post rTKR (17 completed), six months post rTKR (14 completed), 12 months post rTKR (seven completed). As part of the analysis there was no separation between the participants receiving a cone and those without, as all participants underwent a rTKR.

TKR group – This group was from an existing study (Hopkins et al [23]) and the data had already been collected, so only required software input and analysis. The participants were scanned following the same protocol and on the same make and model of DXA scanner as the rTKR and control groups. The group started with 23 postmenopausal women (mean age 65.3, (SD 6.708), mean weight 89.74 kg (SD 18.177), mean height 161.33 cm (SD 5.859)) resulting in a mean BMI of 34.48 (see table 4.2), with seven participants having their left side replaced, and 16 having their right. Data were recorded at pre-op (N=23), six week post TKR (15 completed), six months post TKR (17 completed), 12 months post TKR (15 completed).

Controls – This group was from the Hopkins et al study [23]. This group started with 45 postmenopausal women (mean age 64.4, (SD 7.828), mean weight 68.12 kg (SD 9.991), mean height 163.56 cm (SD 5.926)) resulting in a BMI of 25.46 (see table 4.2), with the left hip being compared to right, as neither side had a TKR. Data were recorded at their 1st visit (mimicking the pre-op in the other groups) (N=45), six months (43 completed), and 12 months (36 completed).

All participants had to pass exclusion criteria prior to their inclusion in the study, the exclusion criteria for the rTKR study (which is discussed in chapter five). For the disuse osteopenia study this excluded: participants who had used Corticosteroids >2.5 mg for more than three months within last five years, participants who had suffered a lower limb fracture or TKR post age 21 years, immobilisation of a lower limb for greater than four weeks within last 10 years or in the postmenopausal period, and participants who were unable to give consent.

After initial recruitment and data collection the only excluded participants across all three groups were those who had been placed on bisphosphonates during the study, and those who had had a previous total hip replacement (THR) on either side. This was due to impact of bisphosphonates increasing BMD, and due to the DXA scanner and computer software unable to read THR scans, and thus those participants would lack a contralateral hip for comparison, analysis, and interpretation.

388 files from the disuse osteopenia study (controls and TKR) and 164 rTKR files were loaded into Galgo software. After importation the hip scans had a mask applied over the DXA image and registered via the 3D-SHAPER software's own acquisition tool, after this was applied an analysis result and 3D model of the hip, as well as a DXA style report was produced (including calculated figures for the aforementioned categories) as shown in figure 4.2.

Figure 4.2. *Galgo 3D-SHAPER software creating a 3D heat map model via the analysis of the hip data*

4.4 ANALYSIS OF IMAGES

After all the files were analysed the data were exported to a Microsoft Excel spreadsheet and separated based on group, side (replacement or revision side), and time period (pre-op, six weeks, three months, six months, and 12 months).

Data were analysed via comparison to the pre-op/first appointment baseline result, these data provided changes between visits compared to a known baseline measurement. Therefore, for each visit the participants were only compared to the group mean baseline i.e. at 12 months for the rTKR group only had seven participants completed this visit, thus this mean figure was compared to the baseline mean score of only those seven.

This analysis involved each appointment date being compared to the first appointment e.g. the rTKR six week appointment on the ipsilateral side was compared to the pre-op scan on that same side, this was repeated for the three month, six month, and 12 month appointments for both the ipsilateral and contralateral hips with standard deviation (SD), standard error (SE), paired

samples t-test, percentage change (calculated as new BMD figure minus baseline figure divided by baseline figure multiplied by 100), and 95 % Confidence intervals (CI) calculated. This method was repeated across all three groups with each being compared to their pre-op/first appointment DXA scan.

Further analysis was performed with a comparison between ipsilateral and contralateral hips for reporting differences between the two sides. First the pre-op data for the rTKR group was analysed; the data were compared between the ipsilateral (the hip side the revision was located) and contralateral (the opposite side) hips for the pre-op time period, with the ipsilateral mean minus the contralateral mean calculated. The difference between the means were calculated across all rTKR participants as well as the SD, SE, a paired samples t-test was also performed. The difference between the means was also calculated as a percentage difference between the two sides and a 95 % CI e.g. an ipsilateral mean of 170 and a contralateral mean of 175 would result in a percentage difference of -2.86 %. This process was repeated for the TKR, and the control group (instead of pre-op this was referred to as first appointment). This analysis was again repeated for the six week, three month, six month, and 12 month appointments, with the ipsilateral hip compared directly to the contralateral hip.

4.5 3D-SHAPER RESULTS

4.5.1 BASELINE FIGURES

Table 4.2. *Shows the baseline characteristics of each of the three groups*

	Participant numbers (N)	Mean Age (years)	Mean height (cm)	Mean weight (kg)	Mean BMI
Controls	45	64.4 (+/-7.83)	163.56 (+/-7.83)	68.12 (+/-9.99)	25.46
rTKR	27	71.6 (+/-7.40)	171.36 (+/-9.49)	89.78 (+/-17.14)	30.57
TKR	23	65.3 (+/-6.70)	161.33 (+/-5.86)	89.74 (+/-18.18)	34.48

Table 4.3. *Shows the mean BMD baseline/pre-op scores of each of the three groups for each hip, including SD and SE prior to any comparisons*

RTKR GROUP

3D-SHAPER Measurements	IPSILATERAL	SD	SE	CONTRALATERAL	SD	SE
Cortical sBMD (mg/cm^2)	170.996	26.951	5.187	176.175	24.173	4.652
Trabecular vBMD (mg/cm^3)	168.482	49.015	9.433	175.602	49.894	9.602
Integral vBMD (mg/cm^3)	316.949	58.600	11.278	326.937	57.744	11.113
Neck CSA (cm^2)	1.194	0.263	0.051	1.246	0.256	0.049
Neck CSMI (cm^4)	1.975	0.713	0.137	2.070	0.705	0.136
InterTroch CSA (cm^2)	2.078	0.648	0.125	2.158	0.589	0.113
InterTroch CSMI (cm^4)	9.377	4.275	0.823	9.543	3.791	0.729

CONTROL GROUP

3D-SHAPER Measurements	IPSILATERAL	SD	SE	CONTRALATERAL	SD	SE
Cortical sBMD (mg/cm^2)	163.858	24.832	3.702	163.748	25.631	3.821
Trabecular vBMD (mg/cm^3)	164.511	42.384	6.318	164.739	44.100	6.574
Integral vBMD (mg/cm^3)	322.585	58.292	8.690	321.208	58.570	8.731
Neck CSA (cm^2)	1.032	0.200	0.030	1.031	0.181	0.027
Neck CSMI (cm^4)	1.386	0.354	0.053	1.371	0.301	0.045
InterTroch CSA (cm^2)	1.703	0.382	0.057	1.706	0.394	0.059
InterTroch CSMI (cm^4)	5.853	1.594	0.238	5.930	1.616	0.241

TKR GROUP

3D-SHAPER Measurements	IPSILATERAL	SD	SE	CONTRALATERAL	SD	SE
Cortical sBMD (mg/cm^2)	167.055	20.143	4.200	170.213	24.189	5.044
Trabecular vBMD (mg/cm^3)	172.895	39.761	8.291	173.880	43.604	9.092
Integral vBMD (mg/cm^3)	331.391	47.481	9.900	334.314	55.373	11.546
Neck CSA (cm^2)	1.077	0.206	0.043	1.052	0.219	0.046
Neck CSMI (cm^4)	1.375	0.364	0.076	1.354	0.347	0.072
InterTroch CSA (cm^2)	1.715	0.359	0.075	1.751	0.407	0.085
InterTroch CSMI (cm^4)	5.764	1.473	0.307	6.024	1.623	0.338

4.5.2 CORTICAL sBMD BONE RESULTS

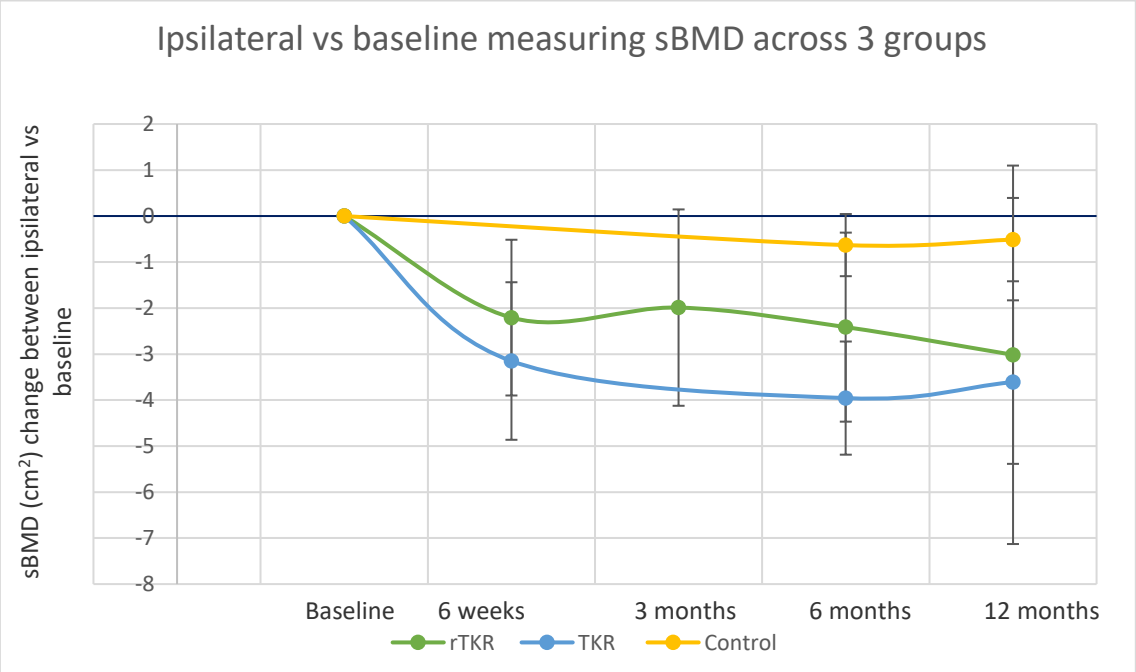


Figure 4.3. *Shows the changes in cortical sBMD in the ipsilateral hip across the three groups (error bars are SE) over 12 months*

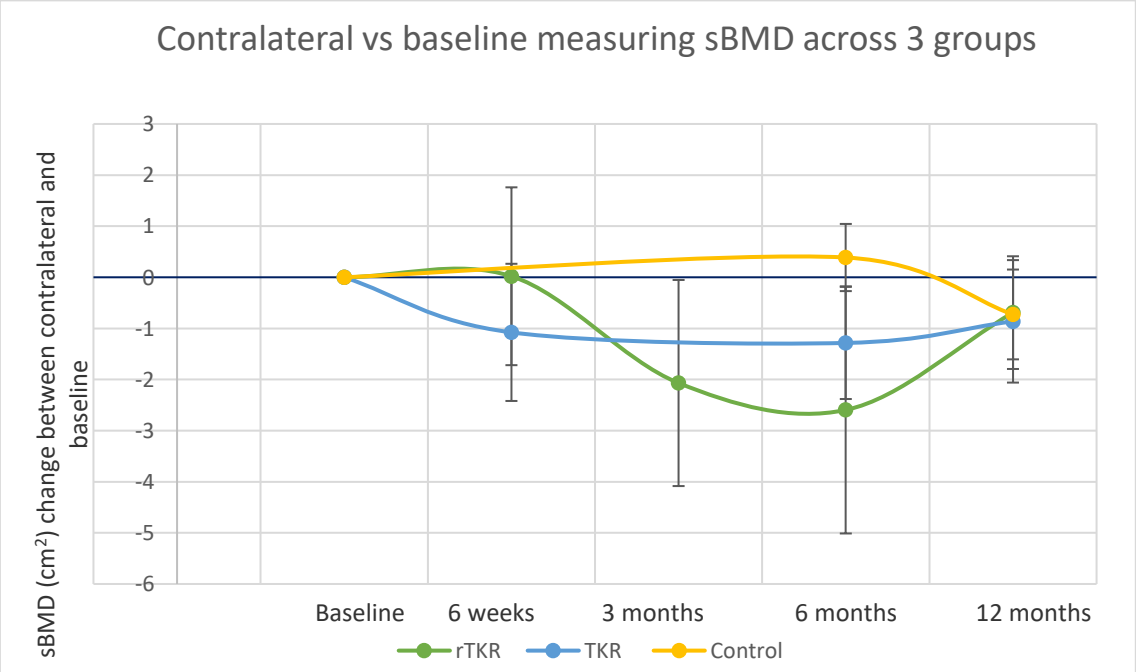


Figure 4.4. *Shows the changes in cortical sBMD in the contralateral hip across the three groups (error bars are SE) over 12 months*

Table 4.4. *Shows the data compared to baseline for the cortical sBMD, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

6 WEEK (RTKR N=17, TKR N= 15)							
	Change between means	SD	SE	T-Critical (P-value)	% Change	95 % CI	
rTKR (mg/cm²)	-2.208	6.979	1.693	1.304 (0.21)	-1.249	-10.525	8.026
TKR (mg/cm²)	-3.151	6.632	1.712	1.840 (0.09)	-1.911	-8.435	4.612
Control (mg/cm²)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm²)	0.020	7.172	1.739	-0.012 (0.99)	0.011	-7.826	7.848
TKR Contralateral (mg/cm²)	-1.077	5.196	1.342	0.803 (0.44)	-0.645	-7.230	5.940
Control Contralateral (mg/cm²)	-	-	-	-	-	-	-
3 MONTH (RTKR N=17)							
	Change between means	SD	SE	T-Critical (P-value)	% Change	95 % CI	
rTKR (mg/cm²)	-1.990	8.800	2.134	0.932 (0.36)	-1.126	-9.901	7.649
TKR (mg/cm²)	-	-	-	-	-	-	-
Control (mg/cm²)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm²)	-2.068	8.311	2.016	1.026 (0.32)	-1.144	-9.334	7.046
TKR Contralateral (mg/cm²)	-	-	-	-	-	-	-
Control Contralateral (mg/cm²)	-	-	-	-	-	-	-
6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)							
	Change between means	SD	SE	T-Critical (P-value)	% Change	95 % CI	
rTKR (mg/cm²)	-2.415	7.688	2.055	1.175 (0.26)	-1.429	-11.037	8.179
TKR (mg/cm²)	-3.957	5.071	1.230	3.217 **(0.01)**	-2.360	-8.625	3.904
Control (mg/cm²)	-0.632	4.430	0.676	0.936 (0.35)	-0.386	-4.913	4.141
rTKR Contralateral (mg/cm²)	-2.595	9.044	2.417	1.074 (0.30)	-1.491	-10.024	7.043
TKR Contralateral (mg/cm²)	-1.284	4.524	1.097	1.170 (0.26)	-0.753	-7.804	6.299
Control Contralateral (mg/cm²)	0.387	4.308	0.657	-0.589 (0.56)	0.236	-4.410	4.882
12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)							
	Change between means	SD	SE	T-Critical (P-value)	% Change	95 % CI	
rTKR (mg/cm²)	-3.016	10.882	4.113	0.733 (0.49)	-1.735	-11.767	8.298
TKR (mg/cm²)	-3.609	6.884	1.777	2.031 (0.06)	-2.139	-8.919	4.640
Control (mg/cm²)	-0.512	5.433	0.906	0.566 (0.58)	-0.307	-5.029	4.415
rTKR Contralateral (mg/cm²)	-0.691	2.700	1.102	0.627 (0.55)	-0.391	-8.833	8.051
TKR Contralateral (mg/cm²)	-0.862	4.639	1.198	0.719 (0.48)	-0.502	-8.725	7.721
Control Contralateral (mg/cm²)	-0.727	5.270	0.878	0.827 (0.41)	-0.434	-4.944	4.075

Figure 4.3, 4.4 and table 4.4 show the cortical sBMD data compared to baseline (pre-op/first appointment from table 4.2) for both the contralateral and ipsilateral hip. The control group as expected shows a low range of changes (-0.386 %, 0.236 %, -0.307 %, -0.434 %). The rTKR ipsilateral has a six week change of -

1.249 %, at six months this loss reaches -1.429 % and -1.735 at 12 months. The rTKR contralateral side has a six week change of 0.011 % but this decreases at three months (-1.144 %) at six months this loss has increased to -1.491 %, at 12 months this loss has been reduced to -0.391 %. The TKR shows a statistical significant and steady loss throughout the visits on the ipsilateral side, at six months there is a reported loss of -2.360 % (p-value 0.01), at 12 months this loss is reported as -2.139 % (p-value 0.06). The TKR contralateral side shows a decline at six weeks, six months, and at 12 months. All three groups show a similar change at 12 months on the contralateral side when compared to baseline figures.

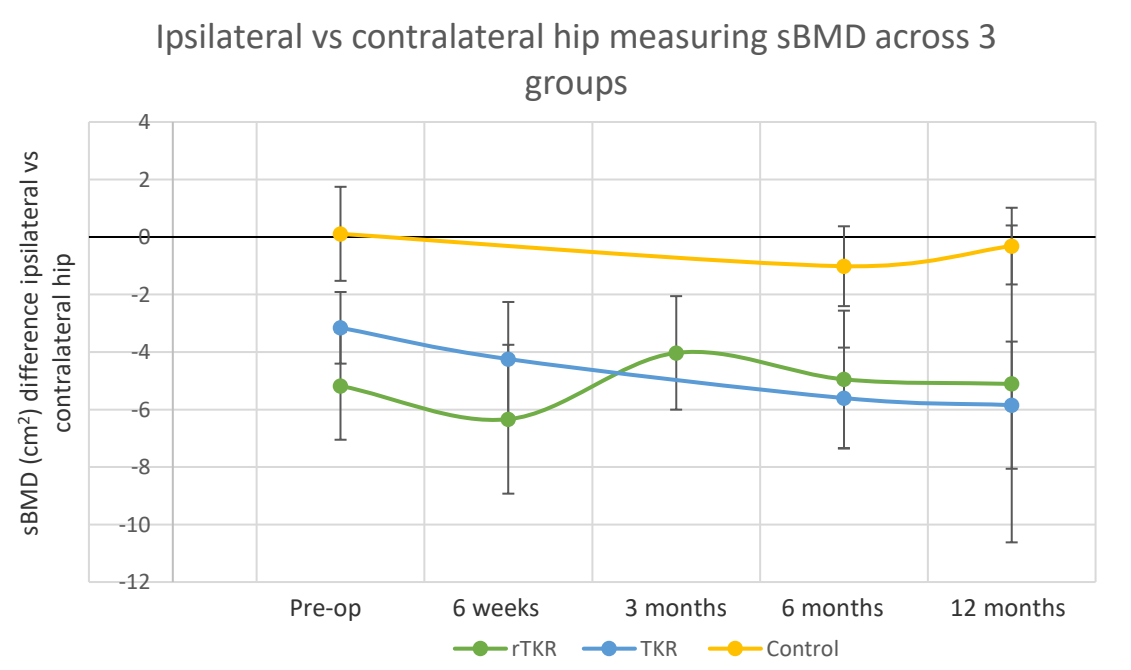


Figure 4.5. *Shows the difference in cortical sBMD between the ipsilateral vs contralateral hip for each of the three groups (error bars are SE) over 12 months*

Table 4.5. *Shows the difference in cortical sBMD between ipsilateral and contralateral data, including percentage difference, CI (95 %), t-test, and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	PRE-OP (RTKR N=27, TKR N=23, CONTROL N=45)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm²)	-5.179	9.725	1.871	2.767 **(0.01)**	-2.940	-8.729	2.850
TKR (mg/cm²)	-3.158	8.679	1.245	1.745 (0.09)	-1.855	-6.691	2.980
Control (mg/cm²)	0.110	8.354	1.635	-0.088 (0.93)	0.067	-4.367	4.501
	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm²)	-6.337	10.673	2.589	2.448 **(0.03)**	-3.504	-12.568	5.559
TKR (mg/cm²)	-4.245	7.689	1.985	2.139 **(0.05)**	-2.558	-9.039	3.923
Control (mg/cm²)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm²)	-4.031	8.138	1.974	2.042 (0.06)	-2.255	-10.929	6.420
TKR (mg/cm²)	-	-	-	-	-	-	-
Control (mg/cm²)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm²)	-4.951	8.938	2.389	2.072 (0.06)	-2.887	-12.353	6.579
TKR (mg/cm²)	-5.602	7.240	1.756	3.190 **(0.00)**	-3.309	-9.513	2.895
Control (mg/cm²)	-1.016	9.102	1.388	0.732 (0.47)	-0.619	-5.135	3.898
	12 MONTH RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm²)	-5.109	13.499	5.511	0.927 (0.39)	-2.903	-12.816	7.010
TKR (mg/cm²)	-5.849	8.565	2.212	2.645 **(0.02)**	-3.421	-10.112	3.269
Control (mg/cm²)	-0.317	8.003	1.334	0.237 (0.81)	-0.190	-4.918	4.538

Figure 4.5 and table 4.5 show the cortical sBMD bone across the three groups with the ipsilateral compared to the contralateral. In the control group there is a lack of difference or fluctuation a pre-op/first appointment 0.067 % difference and a reported difference of -0.190 % at 12 months. In the TKR group it was reported as a difference in the ipsilateral of -1.855 % pre-op, and in the rTKR side it was reported as a difference of -2.940 % (p-value 0.01). This trend continues in the rTKR group with a reported difference at six weeks of -3.504 % (p-value 0.03) (-2.558 % (p-value 0.05) in the TKR group), this difference continues in the six and 12 month TKR data (-3.309 % (p-value 0.00) and -3.421 % (p-value 0.02) respectively), this is similar in the rTKR group (-2.887 %

and -2.903 % for six and 12 months.

4.5.3 TRABECULAR vBMD BONE RESULTS

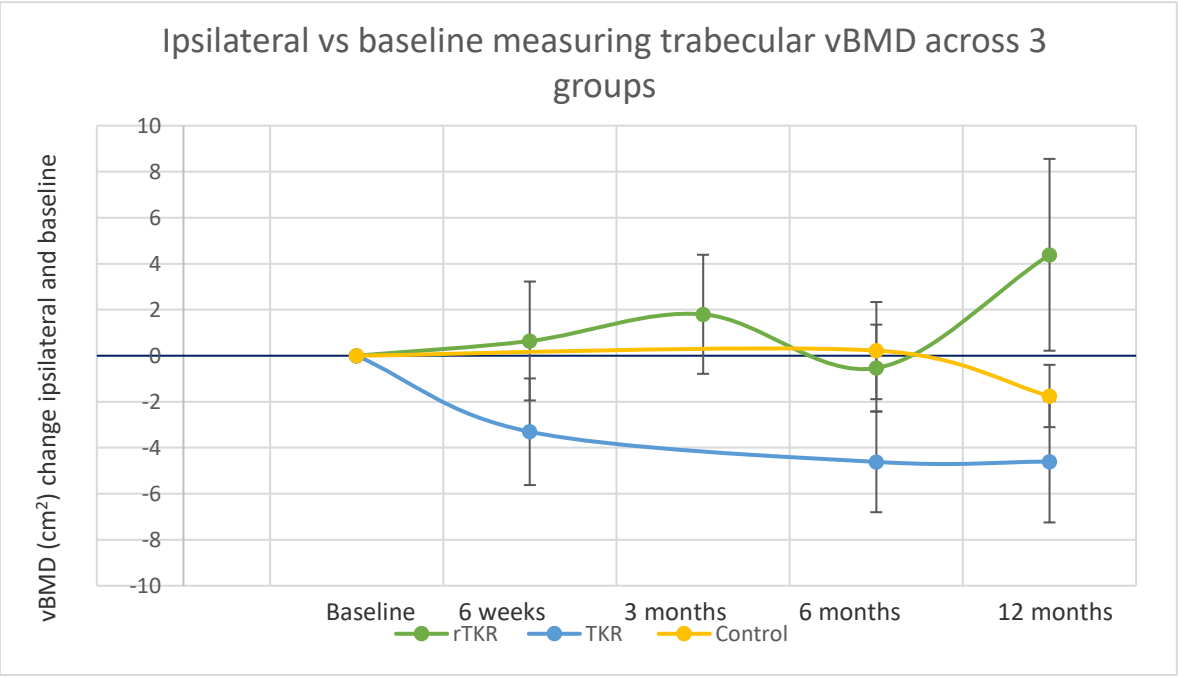


Figure 4.6. *Shows the trabecular vBMD changes in the ipsilateral hip across the three groups (error bars are SE) over 12 months*

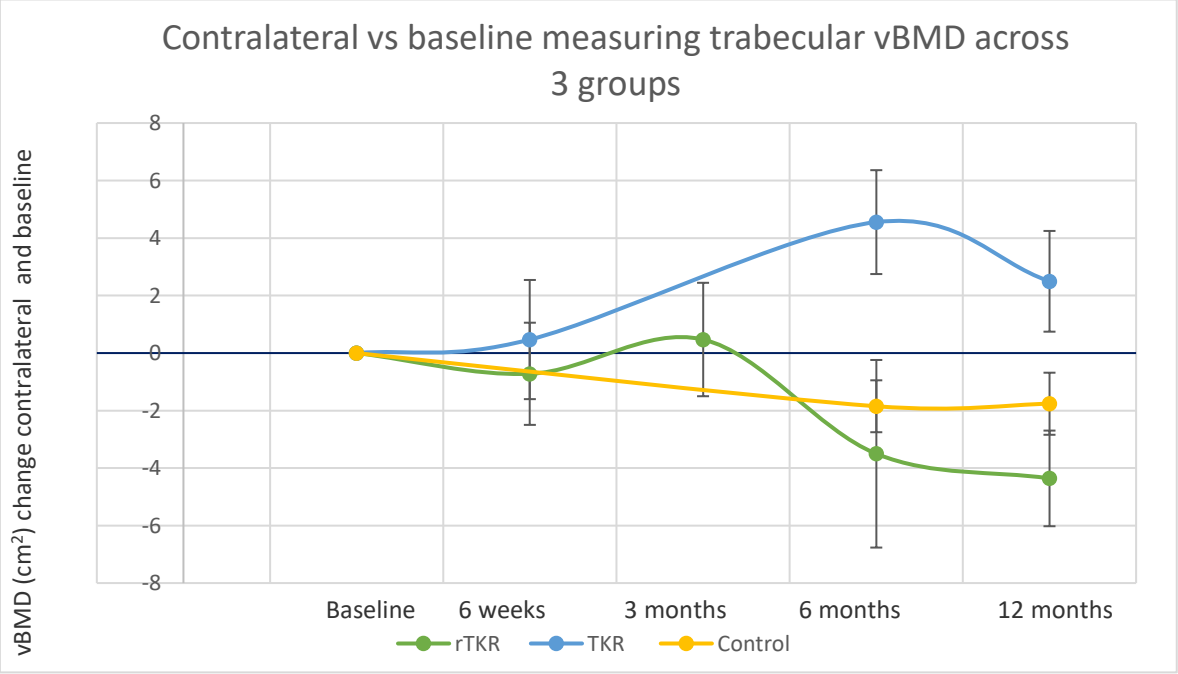


Figure 4.7. *Shows the trabecular vBMD changes in the contralateral hip across the three groups (error bars are SE) over 12 months*

Table 4.6. *Shows the data compared to baseline for the trabecular vBMD, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	0.640	10.656	2.584	-0.248 (0.81)	0.365	-14.542	15.273
TKR (mg/cm³)	-3.305	8.977	2.318	1.426 (0.18)	-1.968	-11.943	8.007
Control (mg/cm³)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm³)	-0.721	7.325	1.777	0.406 (0.69)	-0.398	-15.513	14.717
TKR Contralateral (mg/cm³)	0.470	8.025	2.072	-0.227 (0.82)	0.274	-10.257	10.805
Control Contralateral (mg/cm³)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	1.800	10.671	2.588	-0.696 (0.50)	1.028	-14.093	16.149
TKR (mg/cm³)	-	-	-	-	-	-	-
Control (mg/cm³)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm³)	0.471	8.131	1.972	-0.239 (0.81)	0.260	-13.992	14.512
TKR Contralateral (mg/cm³)	-	-	-	-	-	-	-
Control Contralateral (mg/cm³)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-0.535	7.055	1.885	0.284 (0.78)	-0.331	-17.851	17.190
TKR (mg/cm³)	-4.617	9.016	2.187	2.111 **(0.05)**	-2.640	-12.322	7.043
Control (mg/cm³)	0.223	13.846	2.112	-0.106 (0.91)	0.136	-7.666	7.937
rTKR Contralateral (mg/cm³)	-3.502	12.206	3.262	1.074 (0.30)	-2.095	-18.981	14.791
TKR Contralateral (mg/cm³)	4.554	7.448	1.806	-2.521 **(0.02)**	2.575	-8.606	13.757
Control Contralateral (mg/cm³)	-1.850	5.922	0.903	2.049 **(0.05)**	-1.124	-9.079	6.831
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	4.387	11.032	4.170	-1.052 (0.33)	2.477	-13.740	18.695
TKR (mg/cm³)	-4.605	10.240	2.644	1.742 (0.10)	-2.579	-13.403	8.245
Control (mg/cm³)	-1.750	8.126	1.354	1.292 (0.20)	-1.029	-8.748	6.690
rTKR Contralateral (mg/cm³)	-4.359	4.074	1.663	2.621 **(0.04)**	-2.347	-19.249	14.555
TKR Contralateral (mg/cm³)	2.496	6.784	1.752	-1.425 (0.18)	1.394	-10.716	13.504
Control Contralateral (mg/cm³)	-1.762	6.477	1.080	1.632 (0.11)	-1.032	-8.418	6.353

In figure 4.6, 4.7 and table 4.6 the trabecular vBMD data was compared to the baseline of ipsilateral and contralateral hips (table 4.3). One of the largest increases is reported in the rTKR ipsilateral group at 12 months; with an increase of 2.477 %, although prior to this there was a loss reported at six months (-0.331 %) but an increase at six weeks (0.365 %) and three months

(1.028 %). The contralateral side of rTKR follows a similar trend with a loss at six weeks and a small increase at three months, although at six and 12 months both report large losses (-2.095 % and -2.347 % (p-value 0.04)) in contradiction with the rTKR ipsilateral increase at 12 months. The TKR ipsilateral shows a similar trend to the rTKR contralateral side with large losses at six months (-2.640 % p-value 0.05) and at 12 months (-2.579 %), as oppose to increases in the contralateral TKR side reported as 2.575 % (p-value 0.02) and 1.394 % at both the six and 12 month visits respectively. The control group reported six month differences of -1.124 % (contralateral) and 0.136 % (ipsilateral) although these figures are of nearly equal difference at 12 months, reported as -1.032 % and -1.029 %.

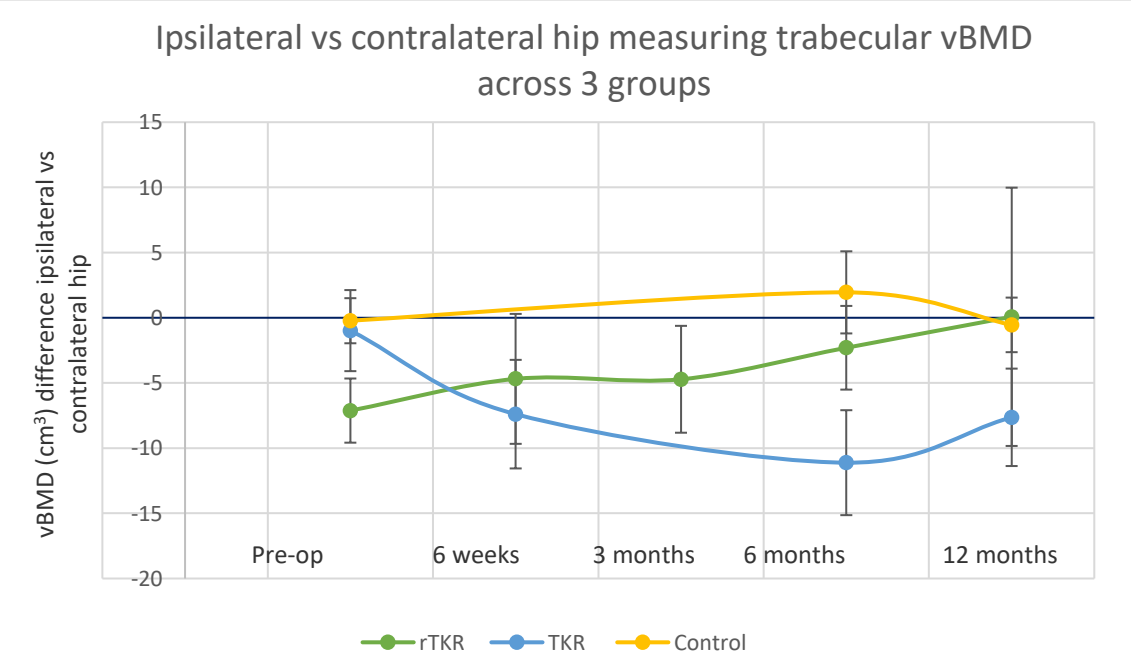


Figure 4.8. *Shows the trabecular vBMD difference between ipsilateral and contralateral hip for each of the three groups (error bars are SE) over 12 months*

Table 4.7. *Shows the difference in trabecular vBMD between ipsilateral and contralateral data, including percentage difference, CI (95 %), t-test, and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	PRE-OP (RTKR N=27, TKR N=23, CONTROL N=45)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-7.120	12.782	2.460	2.894 **(0.01)**	-4.055	-14.590	6.481
TKR (mg/cm³)	-0.985	14.907	3.108	0.317 (0.75)	-0.567	-9.883	8.750
Control (mg/cm³)	-0.228	11.596	1.729	0.132 (0.90)	-0.138	-7.665	7.389
	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-4.687	20.546	4.983	0.941 (0.36)	-2.597	-17.065	11.871
TKR (mg/cm³)	-7.394	16.126	4.164	1.776 (0.10)	-4.299	-14.037	5.439
Control (mg/cm³)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-4.719	16.900	4.099	1.151 (0.27)	-2.598	-17.176	11.981
TKR (mg/cm³)	-	-	-	-	-	-	-
Control (mg/cm³)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-2.302	12.008	3.209	0.717 (0.49)	-1.406	-18.737	15.925
TKR (mg/cm³)	-11.115	16.592	4.024	2.762 **(0.01)**	-6.127	-15.463	3.208
Control (mg/cm³)	1.948	20.653	3.149	-0.618 (0.54)	1.197	-6.688	9.081
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	0.074	24.264	9.906	-0.007 (0.99)	0.041	-15.791	15.872
TKR (mg/cm³)	-7.636	14.471	3.736	2.044 (0.06)	-4.206	-14.849	6.4371
Control (mg/cm³)	-0.547	12.557	2.093	0.261 (0.80)	-0.324	-8.0977	7.4503

Figure 4.8 and table 4.7 show the differences in trabecular vBMD with ipsilateral compared to contralateral hips. The control group maintains a difference for all visits (-0.138 %, 1.197 %, -0.324 %), all within the SE of a recorded zero difference for trabecular vBMD. For the other two group at pre-op the data states: -4.055 % difference for the rTKR group and -0.567 % for the TKR group. The rTKR ipsilateral group shows a reported mean difference of -4.055 % (p-value 0.01) pre-op, -2.597 % at six weeks, -2.598 % at three months, -1.406 % at six months, and a difference of 0.041 % at 12 months. For the TKR group the difference is reported as -4.299 % (p-value 0.10) at three months and then -6.127 % at six months (p-value 0.01), at 12 months this difference is reported

as -4.206 % (p-value 0.06).

4.5.4 INTEGRAL vBMD RESULTS

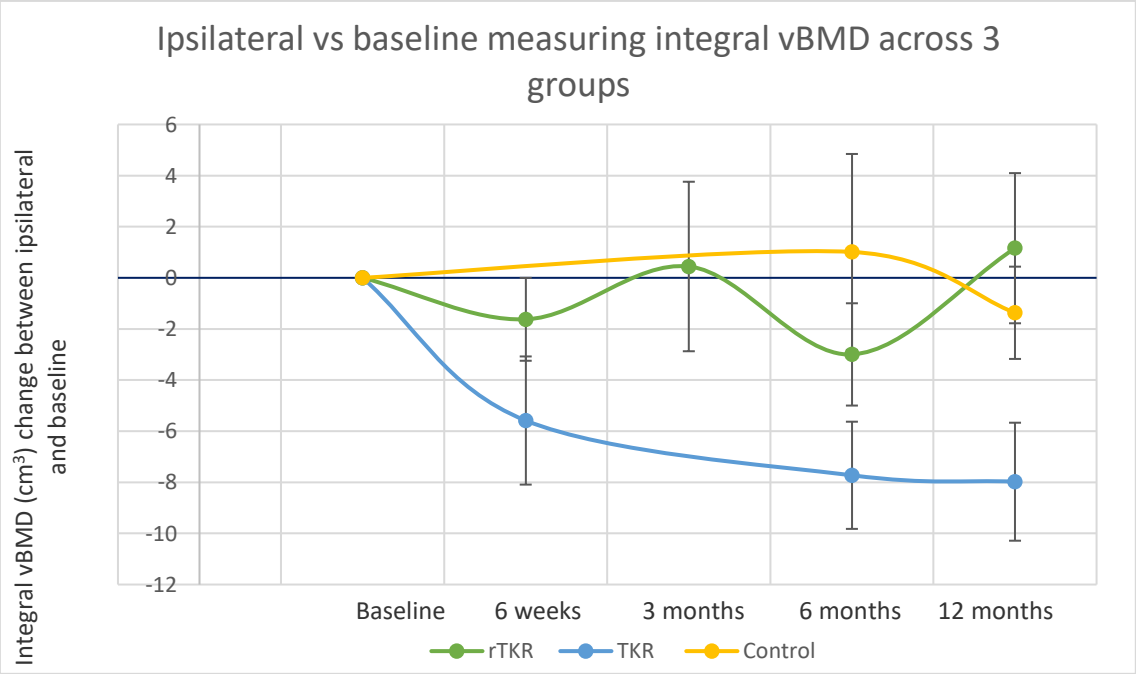


Figure 4.9. *Shows the integral vBMD changes in ipsilateral hip across the three groups (error bars are SE) over 12 months*

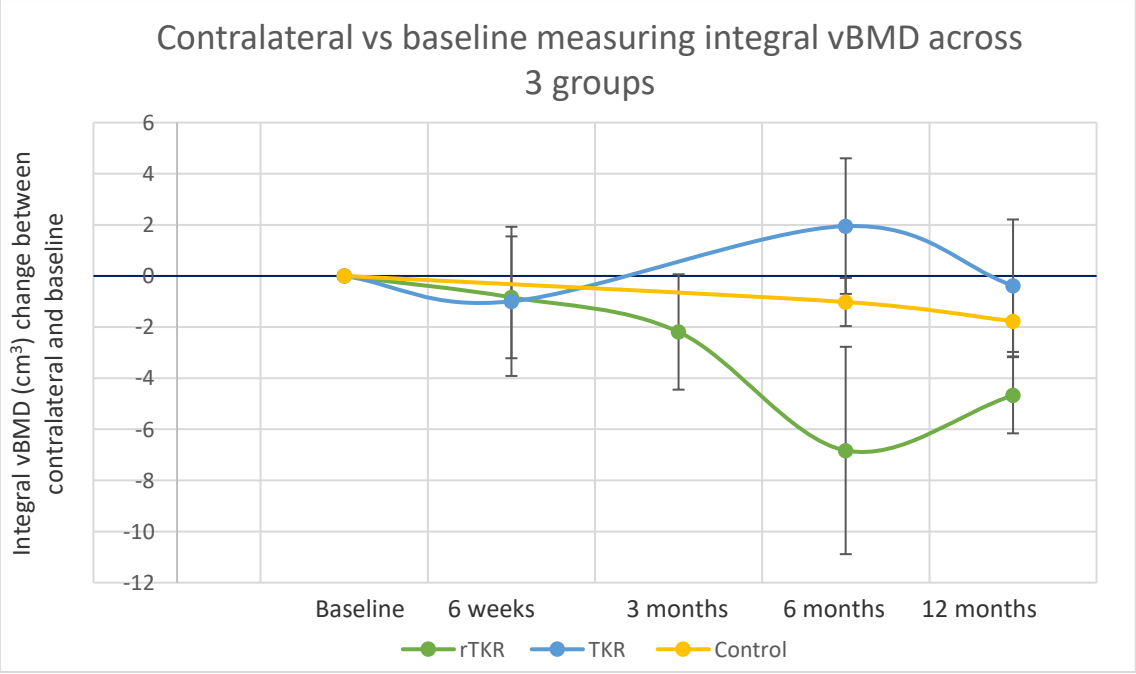


Figure 4.10. *Shows the integral vBMD changes in the contralateral hip across the three groups (error bars are SE) over 12 months*

Table 4.8. *Shows the data compared to baseline for the integral vBMD, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-1.624	6.686	1.622	1.001 (0.33)	-0.500	-10.322	9.323
TKR (mg/cm³)	-5.583	9.709	2.507	2.227 **(0.04)**	-1.706	-8.251	4.840
Control (mg/cm³)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm³)	-0.836	9.827	2.383	0.351 (0.73)	-0.250	-9.564	9.063
TKR Contralateral (mg/cm³)	-0.994	11.299	2.918	0.341 (0.74)	-0.301	-7.108	6.507
Control Contralateral (mg/cm³)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	0.443	13.671	3.316	-0.134 (0.90)	0.136	-9.338	9.611
TKR (mg/cm³)	-	-	-	-	-	-	-
Control (mg/cm³)	-	-	-	-	-	-	-
rTKR Contralateral (mg/cm³)	-2.192	9.302	2.256	0.972 (0.35)	-0.656	-9.992	8.680
TKR Contralateral (mg/cm³)	-	-	-	-	-	-	-
Control Contralateral (mg/cm³)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-2.997	7.486	2.001	1.498 (0.16)	-0.965	-11.750	9.820
TKR (mg/cm³)	-7.726	8.644	2.097	3.685 **(0.00)**	-2.300	-8.733	4.132
Control (mg/cm³)	1.012	25.135	3.833	-0.264 (0.79)	0.314	-5.189	5.816
rTKR Contralateral (mg/cm³)	-6.829	15.177	4.056	1.684 (0.12)	-2.135	-12.916	8.647
TKR Contralateral (mg/cm³)	1.951	10.941	2.653	-0.735 (0.47)	0.575	-7.339	8.488
Control Contralateral (mg/cm³)	-1.020	6.171	0.941	1.084 (0.28)	-0.317	-5.734	5.099
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	1.159	7.771	2.937	-0.394 (0.71)	0.358	-10.641	11.357
TKR (mg/cm³)	-7.977	8.940	2.308	3.456 **(0.00)**	-2.344	-9.556	4.867
Control (mg/cm³)	-1.368	10.830	1.805	0.758 (0.45)	-0.416	-5.888	5.056
rTKR Contralateral (mg/cm³)	-4.669	3.650	1.490	3.133 **(0.02)**	-1.393	-11.939	9.153
TKR Contralateral (mg/cm³)	-0.382	10.038	2.592	0.147 (0.88)	-0.111	-8.780	8.558
Control Contralateral (mg/cm³)	-1.773	8.243	1.374	1.290 (0.20)	-0.539	-5.763	4.685

Figure 4.9, 4.10 and table 4.8 show integral vBMD compared to the baseline visit for the ipsilateral and contralateral hips. TKR ipsilateral at six weeks report a loss, this loss steadily continues at six and 12 months, accumulating in the highest loss reported across all group (-2.344 % p-value 0.00). The contralateral TKR hip shows a small loss at six weeks (-0.301 %) first, with an increase then

reported at six months (0.575 %) and a minimal loss again at 12 months (-0.111 %). The control group is around the zero figure including SE with the 12 month data reporting both the ipsilateral and contralateral hips having a loss of -0.416 % and -0.539 % respectively. The rTKR ipsilateral side shows both non-statistically significant increases and decreases throughout the visits with it reaching a reported 0.358 % at 12 months. The contralateral rTKR shows a loss across all four visits, with the largest loss reported at 6 months as -2.135 % (p-value 0.10).

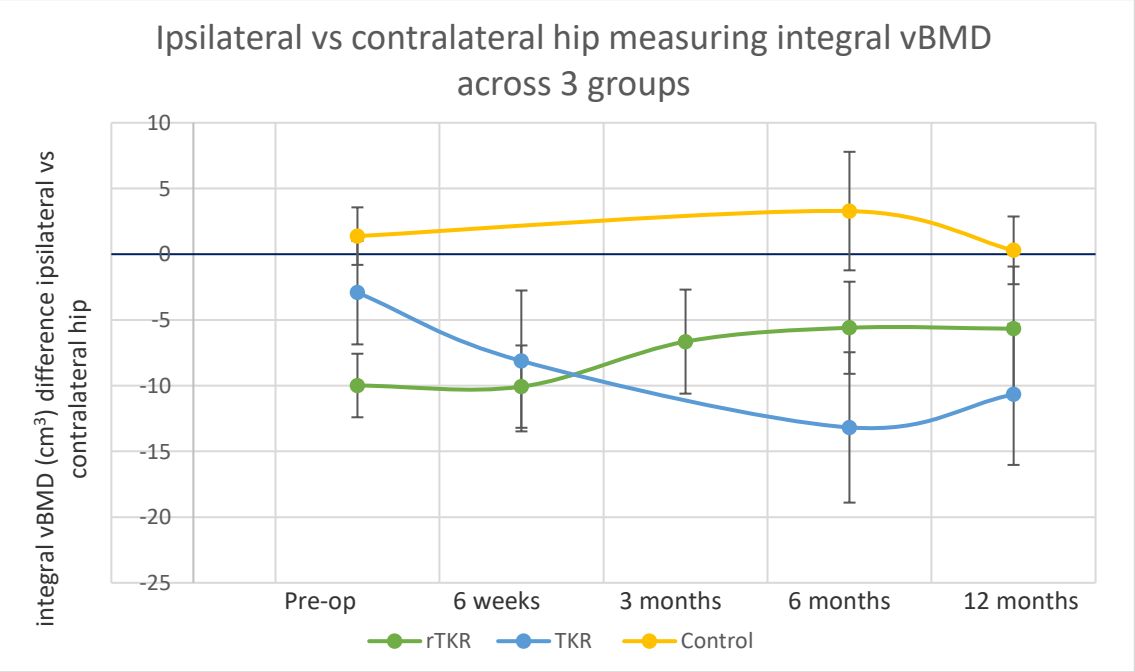


Figure 4.11. *Shows integral vBMD difference between ipsilateral vs contralateral hip for each of the three groups (error bars are SE) over 12 months*

Table 4.9. *Shows the difference in integral vBMD between ipsilateral and contralateral data, including percentage difference, CI (95 %), t-test, and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	PRE-OP (RTKR N=27, TKR N=23, CONTROL N=45)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-9.988	12.559	2.417	4.132 **(0.00)**	-3.055	-9.815	3.705
TKR (mg/cm³)	-2.923	18.887	3.938	0.742 (0.47)	-0.874	-6.677	4.929
Control (mg/cm³)	1.377	14.676	2.188	-0.629 (0.53)	0.429	-4.864	5.721
	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-10.073	12.917	3.133	3.215 **(0.01)**	-3.022	-12.595	6.552
TKR (mg/cm³)	-8.120	20.756	5.359	1.515 (0.15)	-2.461	-8.956	4.034
Control (mg/cm³)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-6.650	16.314	3.957	1.681 (0.11)	-2.003	-11.275	7.269
TKR (mg/cm³)	-	-	-	-	-	-	-
Control (mg/cm³)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-5.597	13.111	3.504	1.597 (0.13)	-1.788	-12.483	8.908
TKR (mg/cm³)	-13.178	23.582	5.720	2.304 **(0.03)**	-3.861	-10.191	2.469
Control (mg/cm³)	3.280	29.565	4.509	-0.728 (0.47)	1.024	-4.518	6.566
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
rTKR (mg/cm³)	-5.670	11.586	4.730	1.199 (0.28)	-1.716	-12.487	9.056
TKR (mg/cm³)	-10.667	20.776	5.364	1.988 (0.07)	-3.110	-10.265	4.0451
Control (mg/cm³)	0.294	15.455	2.576	-0.114 (0.91)	0.090	-5.4101	5.5898

Figure 4.11 and table 4.9 show Integral vBMD results of ipsilateral compared to contralateral hips. At pre-op rTKR reported difference of -3.055 % (p-value 0.00) after pre-op the integral vBMD difference is–3.022 % (p-value 0.01) at six weeks, -2.003 % (p-value 0.11) at three months, -1.788 % at six months and -1.716 % at 12 months. The TKR group had a reported difference of -2.461 % (p-value 0.15) at six weeks, -3.861 % (p-value 0.03) at six months and then -3.110 % (p-value 0.07) at 12 months. The control data are still all within the overlap of 0 via the SE for all appointment dates, with the highest difference reported at six months of 1.024 %.

4.5.5 CSMI RESULTS

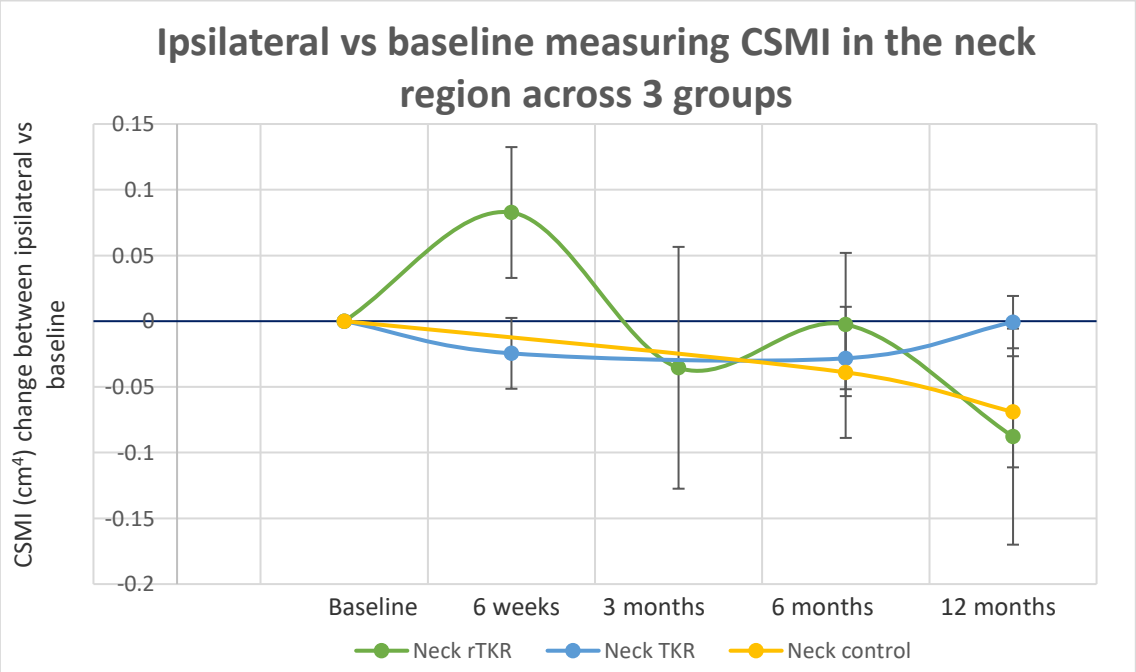


Figure 4.12. *Shows CSMI changes in the ipsilateral neck region across the three groups (error bars are SE) over 12 months*

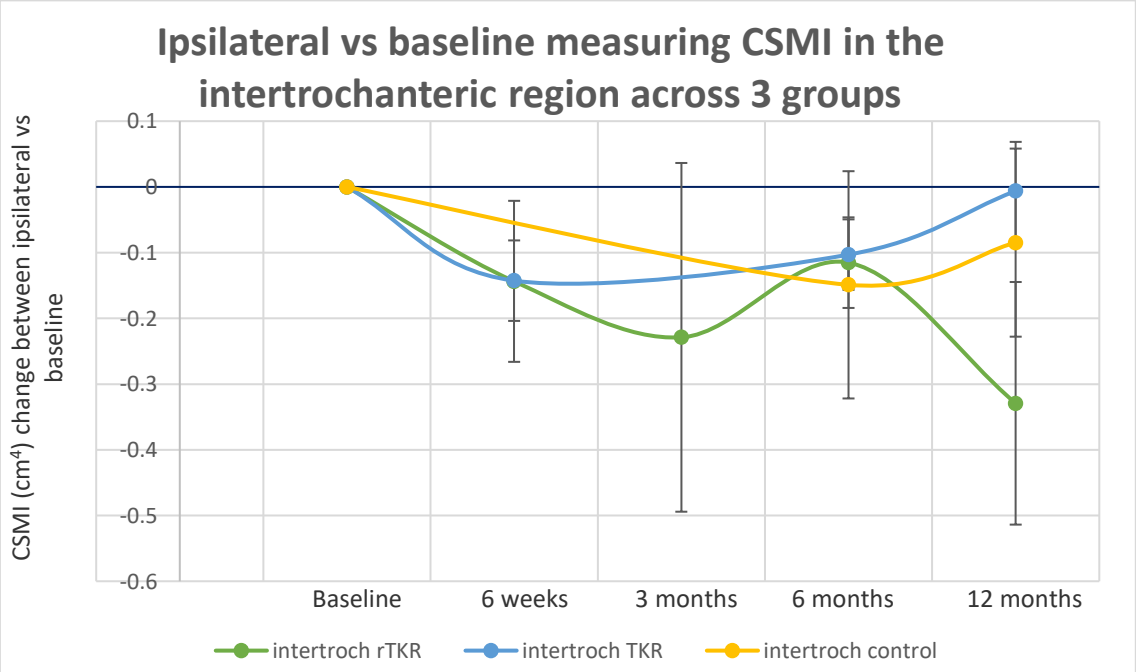


Figure 4.13. *Shows CSMI changes in the ipsilateral hip in the intertrochanteric region across the three groups (error bars are SE) over 12 months*

Table 4.10. *Shows the data compared to baseline for the CSMI, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	0.083	0.205	0.050	-1.661 (0.12)	3.905	-16.472	24.283
neck TKR (cm^4)	-0.024	0.104	0.027	0.908 (0.38)	-1.858	-15.813	12.097
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	-0.144	0.505	0.123	1.173 (0.26)	-1.388	-20.996	18.220
intertroch TKR (cm^4)	-0.143	0.237	0.061	2.330 **(0.04)**	-2.597	-17.637	12.444
intertroch control (cm^4)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.035	0.379	0.092	0.385 (0.71)	-1.674	-22.336	18.988
neck TKR (cm^4)	-	-	-	-	-	-	-
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	-0.229	1.094	0.265	0.863 (0.40)	-2.211	-23.652	19.229
intertroch TKR (cm^4)	-	-	-	-	-	-	-
intertroch control (cm^4)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.003	0.204	0.054	0.046 (0.96)	-0.128	-24.122	23.866
neck TKR (cm^4)	-0.028	0.097	0.024	1.200 (0.25)	-2.179	-13.392	9.033
neck control (cm^4)	-0.039	0.327	0.050	0.781 (0.44)	-2.815	-10.703	5.073
intertroch rTKR (cm^4)	-0.115	0.258	0.069	1.672 (0.12)	-1.238	-26.769	24.293
intertroch TKR (cm^4)	-0.103	0.221	0.054	1.921 (0.07)	-1.882	-13.485	9.721
intertroch control (cm^4)	-0.149	1.134	0.173	0.862 (0.39)	-2.542	-10.991	5.907
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.088	0.217	0.082	1.069 (0.33)	-4.325	-18.091	9.442
neck TKR (cm^4)	-0.001	0.077	0.020	0.035 (0.97)	-0.053	-11.878	11.772
neck control (cm^4)	-0.069	0.254	0.042	1.630 (0.11)	-4.734	-11.694	2.226
intertroch rTKR (cm^4)	-0.329	0.488	0.185	1.784 (0.12)	-3.226	-21.382	14.931
intertroch TKR (cm^4)	-0.006	0.289	0.075	0.083 (0.94)	-0.113	-12.987	12.762
intertroch control (cm^4)	-0.085	0.858	0.143	0.593 (0.56)	-1.377	-9.198	6.444

Figures 4.12, 4.13 and table 4.10 show the CSMI ipsilateral hip compared to the baseline, the greatest loss reported in the rTKR group is reported in the neck region, reported as -4.325 % at 12 months. The highest positive figure across all groups was reported in the rTKR in the neck at six weeks reported as 3.905 % (p-value 0.12). The control data cross the SE for the 0 value in three of the four data reported, although this is small (-0.069 cm^4), there is a reported loss of

-4.734 % (p-value 0.11) in the femoral neck at 12 months which is the highest change in the neck reported. At 12 months the TKR intertrochanteric group show a positive gain as the rTKR intertrochanteric group shows a large decline.

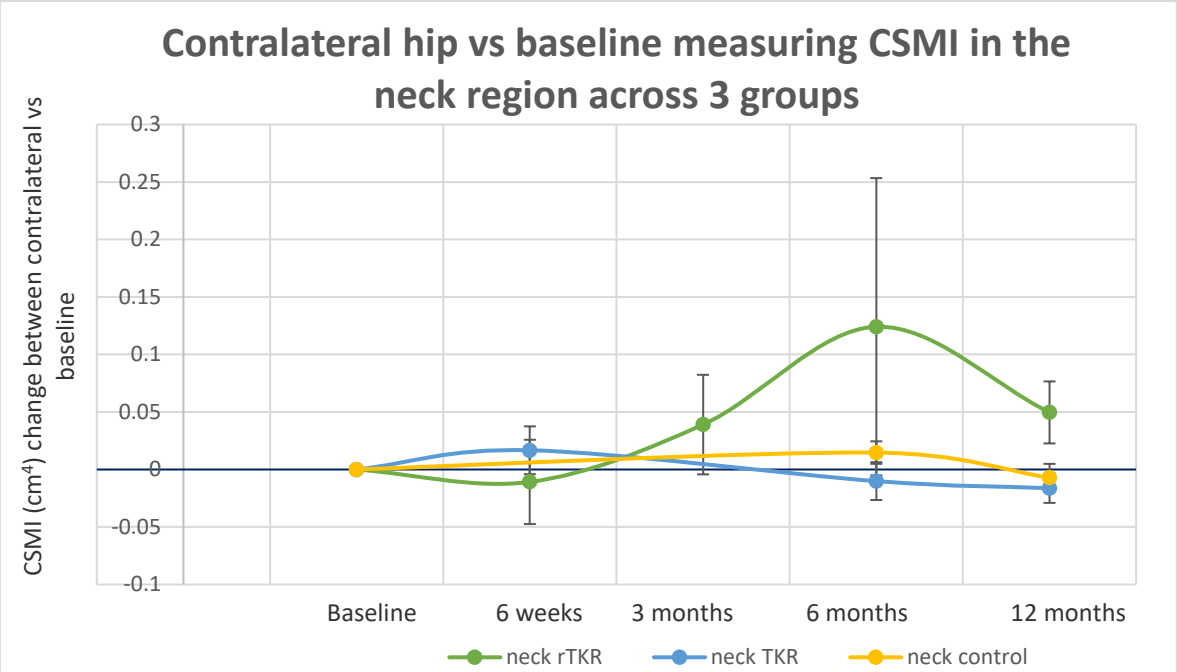


Figure 4.14. *Shows CSMI changes in the contralateral neck region across the three groups (error bars are SE) over 12 months*

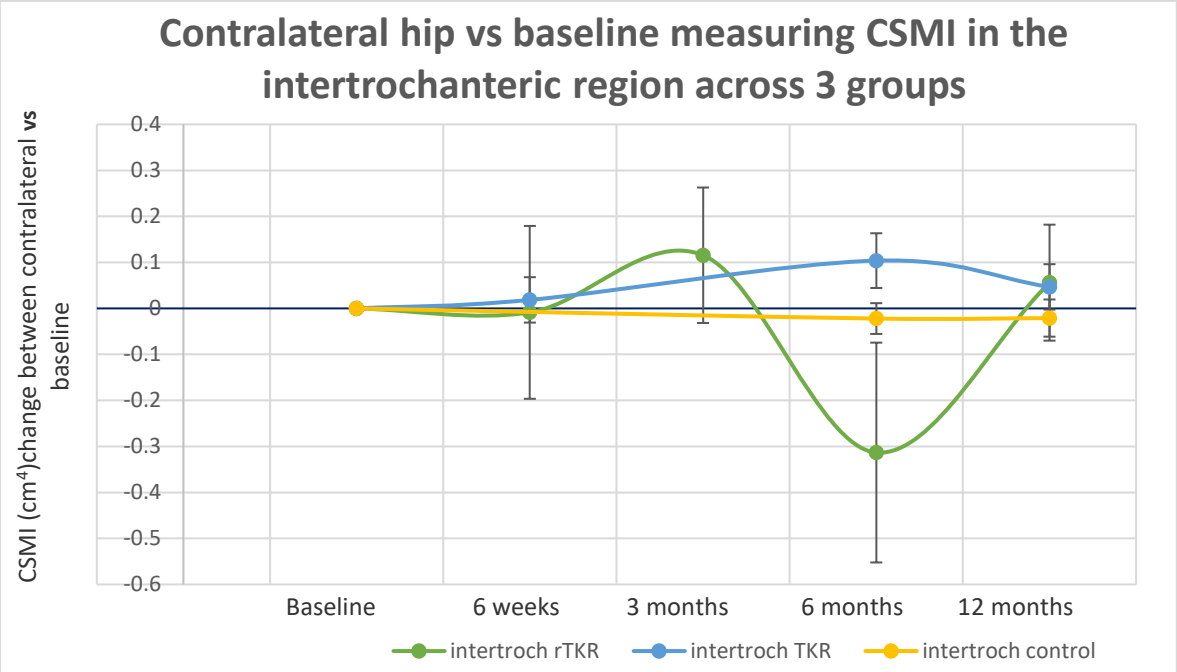


Figure 4.15. *Shows CSMI changes in the contralateral hip in the intertrochanteric region across the three groups (error bars are SE) over 12 months*

Table 4.11. *Shows the data compared to baseline for the CSMI, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

6 WEEK (RTKR N=17, TKR N=15)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.011	0.151	0.037	0.294 (0.77)	-0.488	-17.862	16.886
neck TKR (cm^4)	0.017	0.080	0.021	-0.805 (0.43)	1.288	-12.886	15.462
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	-0.009	0.775	0.188	0.046 (0.96)	-0.085	-17.227	17.056
intertroch TKR (cm^4)	0.019	0.191	0.049	-0.375 (0.71)	0.322	-13.999	14.642
intertroch control (cm^4)	-	-	-	-	-	-	-
3 MONTH (RTKR N=17)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	0.039	0.178	0.043	-0.903 (0.38)	1.770	-15.453	18.992
neck TKR (cm^4)	-	-	-	-	-	-	-
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	0.116	0.607	0.147	-0.785 (0.44)	1.144	-16.933	19.222
intertroch TKR (cm^4)	-	-	-	-	-	-	-
intertroch control (cm^4)	-	-	-	-	-	-	-
6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	0.124	0.483	0.129	-0.961 (0.35)	6.007	-18.416	30.430
neck TKR (cm^4)	-0.010	0.068	0.016	0.614 (0.55)	-0.780	-10.013	8.453
neck control (cm^4)	0.015	0.064	0.010	-1.506 (0.14)	1.076	-5.897	8.048
intertroch rTKR (cm^4)	-0.313	0.894	0.239	1.312 (0.21)	-3.423	-27.345	20.498
intertroch TKR (cm^4)	0.104	0.245	0.059	-1.745 (0.10)	1.783	-10.289	13.855
intertroch control (cm^4)	-0.022	0.220	0.033	0.659 (0.51)	-0.372	-8.530	7.786
12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	0.050	0.066	0.027	-1.840 (0.12)	2.403	-8.886	13.692
neck TKR (cm^4)	-0.016	0.049	0.013	1.277 (0.22)	-1.257	-12.053	9.539
neck control (cm^4)	-0.007	0.072	0.012	0.591 (0.56)	-0.501	-7.669	6.668
intertroch rTKR (cm^4)	0.056	0.309	0.126	-0.444 (0.67)	0.567	-12.960	14.094
intertroch TKR (cm^4)	0.047	0.191	0.049	-0.948 (0.36)	0.805	-12.058	13.667
intertroch control (cm^4)	-0.021	0.242	0.040	0.520 (0.61)	-0.339	-8.516	7.837

Figure 4.14, 4.15 and table 4.11 shows the CSMI contralateral hip in every group compared to the baseline. The majority of the results show a positive increase compared to the baseline hip score. The highest being a change of 6.007 % (p-value 0.35) in the neck region at six months in the rTKR group, which is also the time period and group in which the greatest loss is reported; reported as -3.423 % (p-value 0.21) in the intertrochanteric region, although this

loss is regained at 12 months with an increase to 0.567 %. The control group shows no statistically difference across all visits and regions.

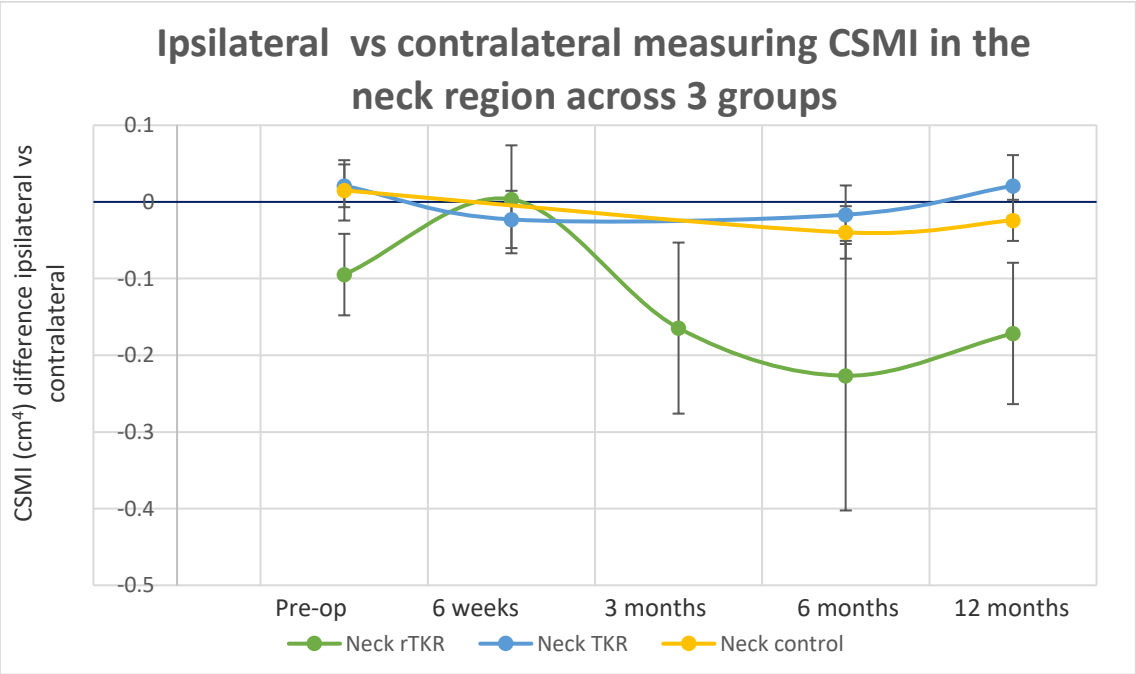


Figure 4.16. *Shows the CSMI differences between ipsilateral and contralateral hips in the neck region across the three groups (error bars are SE) over 12 months*

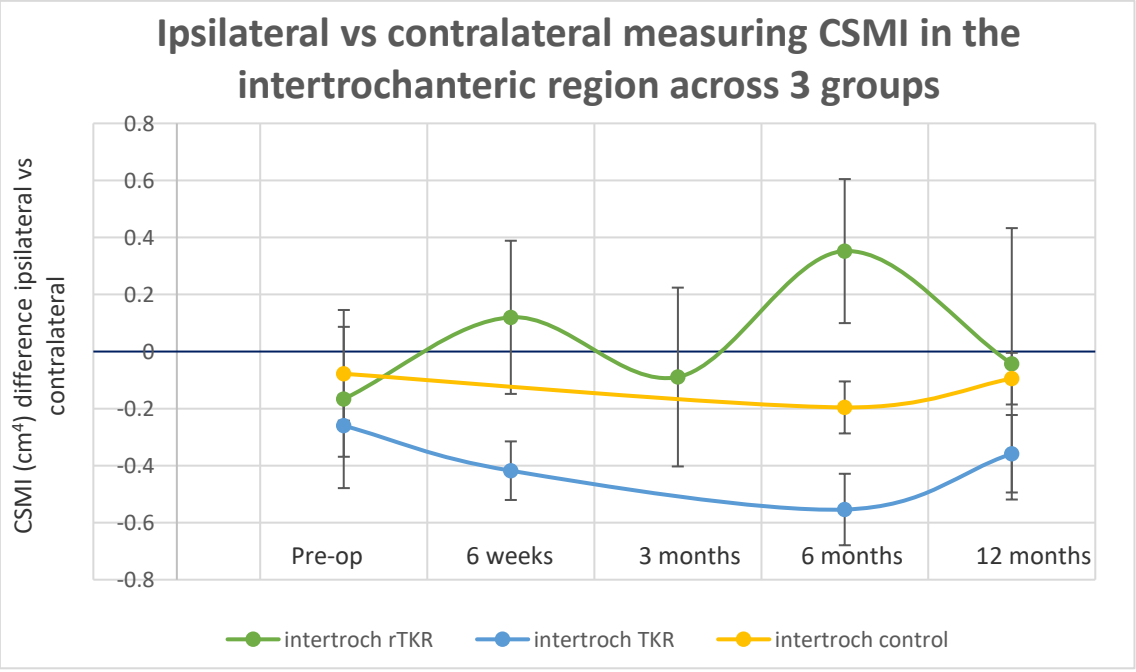


Figure 4.17. *Shows the CSMI differences between ipsilateral and contralateral hips in the intertrochanteric region across the three groups (error bars are SE) over 12 months*

Table 4.12. *Shows the difference in CSMI between ipsilateral and contralateral data, including percentage difference, CI (95 %), t-test, and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	PRE-OP (RTKR N=27, TKR N=23, CONTROL N=45)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.095	0.276	0.053	1.783 (0.09)	-4.579	-17.574	8.417
neck TKR (cm^4)	0.021	0.134	0.028	-0.753 (0.46)	1.552	-9.452	12.556
neck control (cm^4)	0.015	0.264	0.039	-0.383 (0.70)	1.100	-6.412	7.512
intertroch rTKR (cm^4)	-0.167	1.623	0.31	0.533 (0.60)	-1.745	-18.616	15.125
intertroch TKR (cm^4)	-0.260	0.521	0.11	2.393 **(0.03)**	-4.319	-14.316	5.669
intertroch control (cm^4)	-0.078	1.103	0.16	0.474 (0.64)	-1.314	-10.942	8.314
	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	0.003	0.29	0.070	-0.048 (0.96)	0.155	-19.487	19.797
neck TKR (cm^4)	-0.023	0.145	0.037	0.612 (0.55)	-1.738	-15.709	12.234
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	0.120	1.107	0.269	-0.447 (0.66)	1.189	-18.932	21.310
intertroch TKR (cm^4)	-0.418	0.398	0.103	4.068 **(0.00)**	-7.242	-21.565	7.082
intertroch control (cm^4)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.165	0.460	0.112	1.475 (0.16)	-7.326	-26.800	12.148
neck TKR (cm^4)	-	-	-	-	-	-	-
neck control (cm^4)	-	-	-	-	-	-	-
intertroch rTKR (cm^4)	-0.089	1.293	0.313	0.285 (0.78)	-0.876	-22.609	20.858
intertroch TKR (cm^4)	-	-	-	-	-	-	-
intertroch control (cm^4)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.227	0.658	0.176	1.289 (0.22)	-10.343	-31.883	11.197
neck TKR (cm^4)	-0.017	0.157	0.038	0.437 (0.67)	-1.300	-12.613	10.014
neck control (cm^4)	-0.040	0.224	0.034	1.162 (0.25)	-2.874	-10.757	5.009
intertroch rTKR (cm^4)	0.352	0.945	0.253	-1.395 (0.19)	3.984	-22.897	30.865
intertroch TKR (cm^4)	-0.554	0.516	0.125	4.422 **(0.00)**	-9.348	-20.068	1.372
intertroch control (cm^4)	-0.196	0.598	0.091	2.149 **(0.04)**	-3.317	-11.699	5.065
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^4)	-0.172	0.226	0.092	1.861 (0.11)	-8.113	-21.334	5.109
neck TKR (cm^4)	0.021	0.155	0.040	-0.526 (0.61)	1.647	-10.379	13.673
neck control (cm^4)	-0.024	0.161	0.027	0.897 (0.38)	-1.704	-8.885	5.478
intertroch rTKR (cm^4)	-0.043	1.166	0.476	0.090 (0.93)	-0.434	-19.114	18.246
intertroch TKR (cm^4)	-0.358	0.526	0.136	2.639 **(0.02)**	-6.116	-18.217	5.984
intertroch control (cm^4)	-0.095	0.544	0.091	1.049 (0.30)	-1.541	-9.350	6.267

The data in figures 4.16, 4.17 and table 4.12. The control group show the least amount of difference between the ipsilateral and contralateral, although a figure at six months reports a difference of -2.874 % (p-value 0.25) in the femoral neck and -3.317 (p-value 0.04) in the intertrochanteric region, both of these are at six months. Interestingly at six months we also see some of the biggest differences of CSMI; reported as -10.343 % (p-value 0.22) (neck) and 3.984 % (p-value 0.19) (intertrochanteric) in the rTKR group, and -9.348 % (p-value 0.00) (intertrochanteric) in the TKR group.

4.5.6 CSA RESULTS

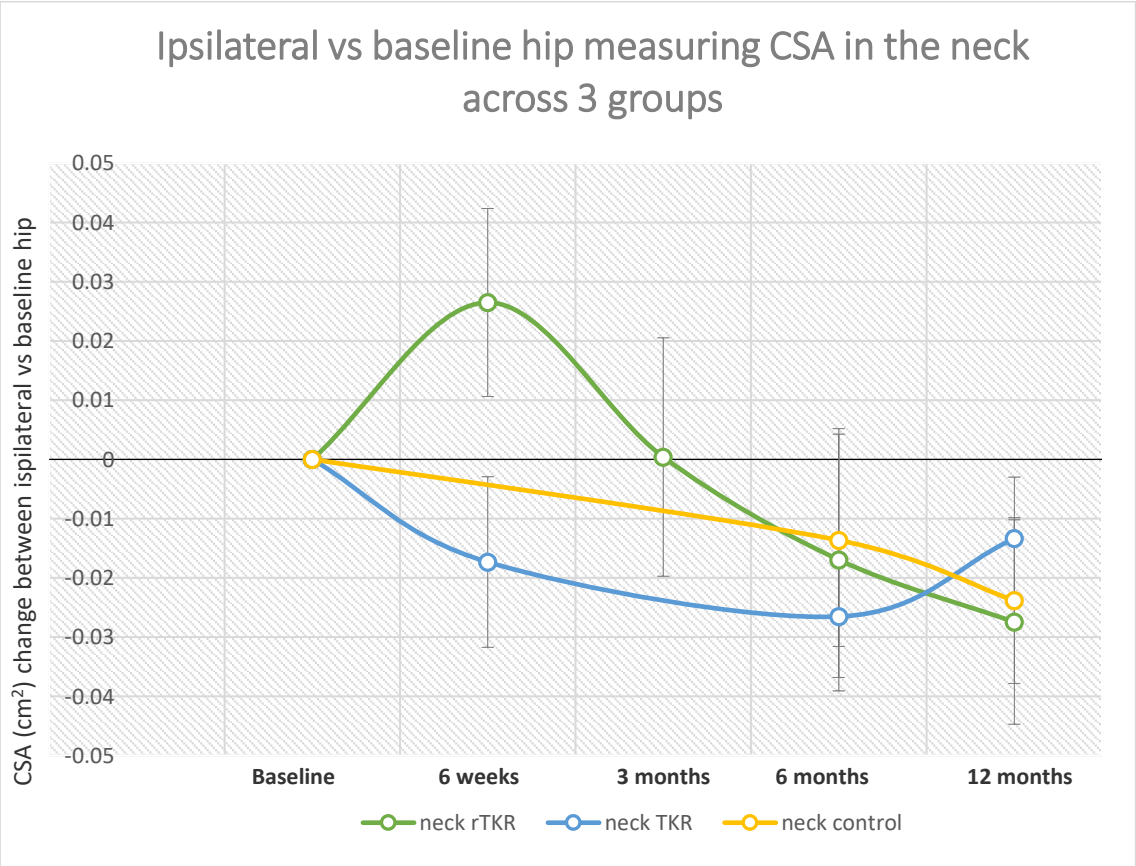


Figure 4.18. *Shows CSA changes in the ipsilateral neck region across the three groups (error bars are SE) across 12 months*

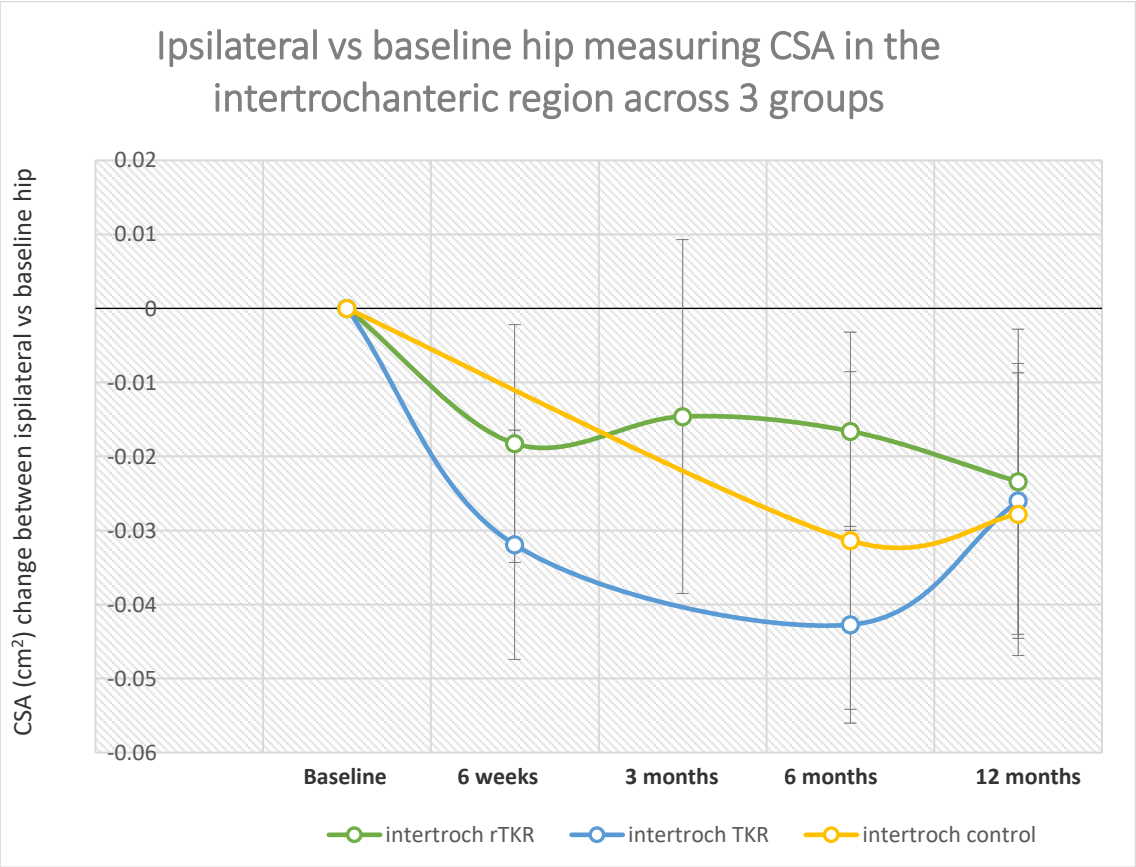


Figure 4.19. *Shows CSA changes in the ipsilateral intertrochanteric region in all three groups (error bars are SE) across 12 months*

Table 4.13. *Shows the data compared to baseline for the CSA, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	0.026	0.065	0.016	-1.668 (0.11)	2.132	-11.609	15.873
neck TKR (cm^2)	-0.017	0.056	0.014	1.204 (0.25)	-1.649	-11.383	8.084
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.018	0.066	0.016	1.137 (0.27)	-0.815	-16.077	14.446
intertroch TKR (cm^2)	-0.032	0.060	0.015	2.060 (0.06)	-1.922	-13.197	9.353
intertroch control (cm^2)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	0.000	0.083	0.020	0.020 (0.98)	0.032	-13.813	13.877
neck TKR (cm^2)	-	-	-	-	-	-	-
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.015	0.099	0.024	0.611 (0.55)	-0.652	-16.895	15.590
intertroch TKR (cm^2)	-	-	-	-	-	-	-
intertroch control (cm^2)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.017	0.083	0.022	0.766 (0.46)	-1.446	-16.799	13.907
neck TKR (cm^2)	-0.027	0.042	0.010	2.583 **(0.02)**	-2.510	-10.381	5.361
neck control (cm^2)	-0.014	0.118	0.018	0.761 (0.45)	-1.325	-7.401	4.752
intertroch rTKR (cm^2)	-0.017	0.050	0.013	1.238 (0.24)	-0.810	-19.298	17.678
intertroch TKR (cm^2)	-0.043	0.055	0.013	3.218 **(0.01)**	-2.528	-12.003	6.946
intertroch control (cm^2)	-0.031	0.150	0.023	1.375 (0.18)	-1.838	-8.852	5.177
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.027	0.046	0.017	1.593 (0.16)	-2.260	-14.678	10.158
neck TKR (cm^2)	-0.013	0.040	0.010	1.286 (0.22)	-1.254	-10.136	7.627
neck control (cm^2)	-0.024	0.084	0.014	1.705 (0.10)	-2.229	-7.946	3.489
intertroch rTKR (cm^2)	-0.023	0.055	0.021	1.136 (0.30)	-1.045	-16.096	14.006
intertroch TKR (cm^2)	-0.026	0.072	0.019	1.400 (0.83)	-1.520	-12.066	9.026
intertroch control (cm^2)	-0.028	0.115	0.019	1.456 (0.15)	-1.560	-8.122	5.003

Figure 4.18, 4.19 and table 4.13 show the CSA change in the ipsilateral hip compared to baseline across all three groups. The largest increase was seen in the six week data of the rTKR in the femoral neck an increase of 2.132 % (p-value 0.11) at three months there is a beginning of a decline; reported as 0.032 %, at six months this loss is -1.446 % with the greatest loss reported at -2.260 % (p-value 0.16) at the 12 month visit. In the rTKR group the intertrochanteric

region shows a similar but smaller decline; three months reported as -0.652 %, six months -0.810 % and 12 months -1.045 %. The TKR group reports its greatest loss at six months reported as -2.510 % (p-value 0.02) (neck) and -2.528 % (p-value 0.01) (intertrochanteric), at 12 months there is a recovery but still a loss (-1.254 % neck, and -1.520 % intertrochanteric). Again, the highest loss in the control group are reported as -1.325 % (neck) and -1.838 % (intertrochanteric) at six months, and -2.229 % (p-value 0.10) (neck) and -1.560 % (intertrochanteric).

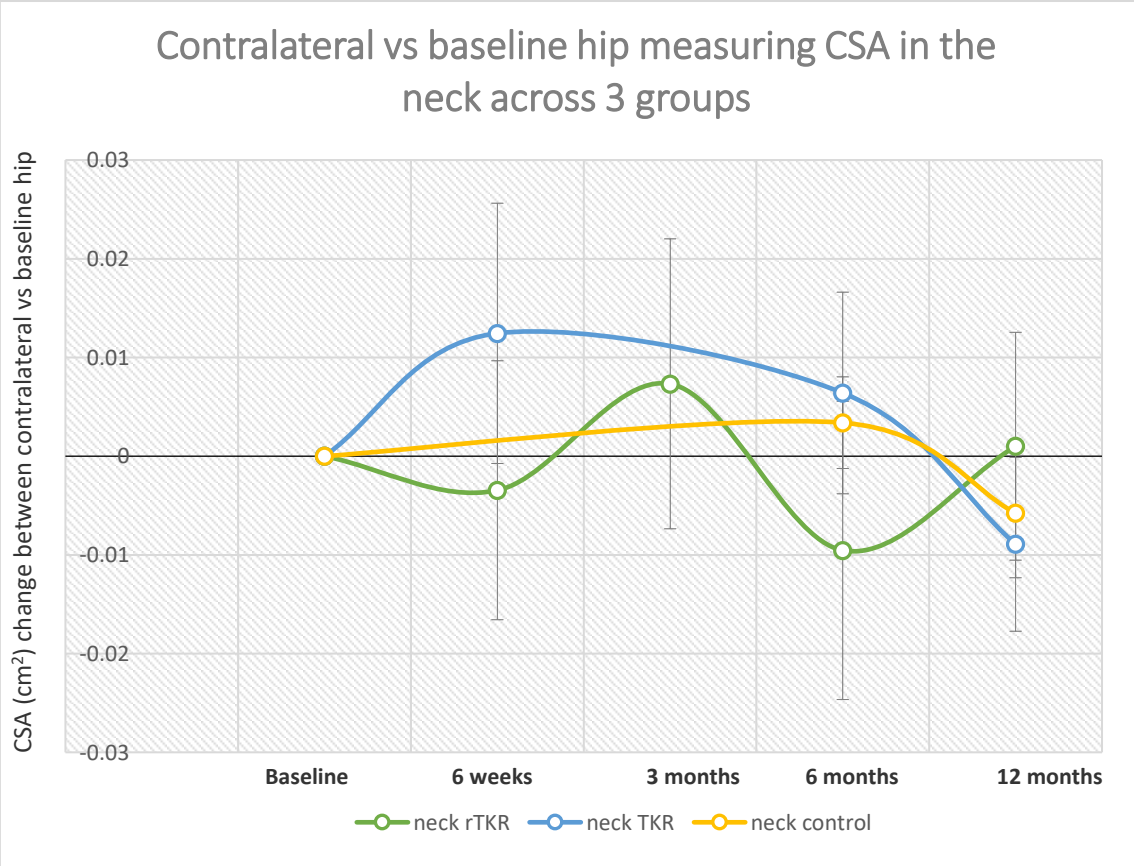


Figure 4.20. *Shows CSA changes in the contralateral neck region across the three groups (error bars are SE) over 12 months*

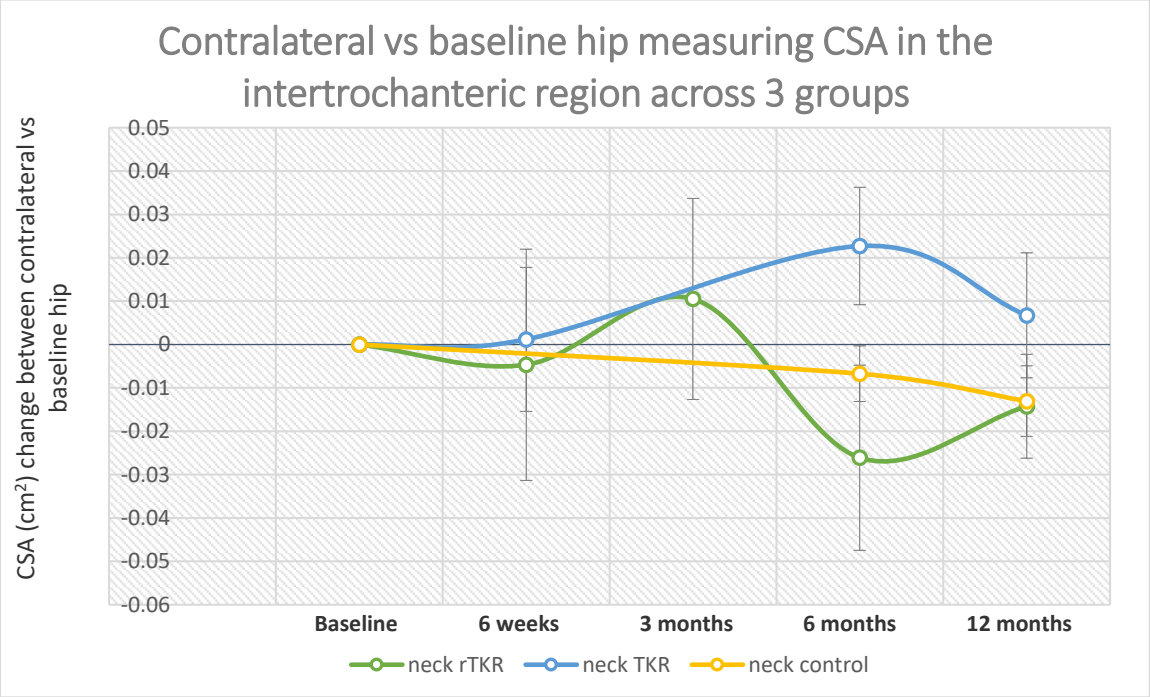


Figure 4.21. *Shows CSA changes in the contralateral intertrochanteric region across the three groups (error bars are SE) over 12 months*

Table 4.14. *Shows the data compared to baseline for the CSA, including percentage change, CI (95 %), and the t-test and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

	6 WEEK (RTKR N=17, TKR N=15)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.003	0.054	0.013	0.263 (0.80)	-0.266	-12.268	11.736
neck TKR (cm^2)	0.012	0.051	0.013	-0.944 (0.36)	1.204	-9.057	11.465
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.005	0.110	0.027	0.175 (0.86)	-0.205	-14.228	13.818
intertroch TKR (cm^2)	0.001	0.064	0.017	-0.072 (0.94)	0.070	-10.928	11.067
intertroch control (cm^2)	-	-	-	-	-	-	-
	3 MONTH (RTKR N=17)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	0.007	0.061	0.015	-0.499 (0.62)	0.565	-10.994	12.124
neck TKR (cm^2)	-	-	-	-	-	-	-
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.009	0.775	0.188	-0.454 (0.66)	0.463	-14.019	14.945
intertroch TKR (cm^2)	-	-	-	-	-	-	-
intertroch control (cm^2)	-	-	-	-	-	-	-
	6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.010	0.057	0.015	0.632 (0.54)	-0.777	-13.767	12.212
neck TKR (cm^2)	0.006	0.042	0.010	-0.627 (0.54)	0.616	-7.396	8.628
neck control (cm^2)	0.003	0.030	0.005	-0.731 (0.47)	0.330	-4.871	5.530
intertroch rTKR (cm^2)	-0.026	0.080	0.021	1.222 (0.24)	-1.248	-17.992	15.496
intertroch TKR (cm^2)	0.023	0.056	0.014	-1.676 (0.11)	1.306	-8.878	11.490
intertroch control (cm^2)	-0.007	0.042	0.006	1.052 (0.30)	-0.395	-7.197	6.408
	12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)						
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	0.001	0.028	0.012	-0.088 (0.93)	0.080	-10.150	10.309
neck TKR (cm^2)	-0.009	0.034	0.009	1.013 (0.33)	-0.848	-9.773	8.076
neck control (cm^2)	-0.006	0.039	0.007	0.882 (0.38)	-0.543	-5.628	4.541
intertroch rTKR (cm^2)	-0.014	0.029	0.012	1.189 (0.28)	-0.629	-14.344	13.086
intertroch TKR (cm^2)	0.007	0.056	0.014	-0.466 (0.65)	0.383	-10.780	11.546
intertroch control (cm^2)	-0.013	0.049	0.008	1.606 (0.12)	-0.733	-7.097	5.632

Figure 4.20, 4.21 and table 4.14 show the CSA change in the contralateral hip compared to the baseline measurement for each group. The greatest loss is reported by rTKR group in the intertrochanteric region of -1.248 % at six months, with the greatest reported as 1.306 % in the intertrochanteric region of the TKR group. At 12 months across all groups (in both the neck and intertrochanteric region) the percentage change is minimal reported as 0.080 %,

-0.848 %, -0.543 %, -0.629 %, 0.383 %, and -0.733 %.

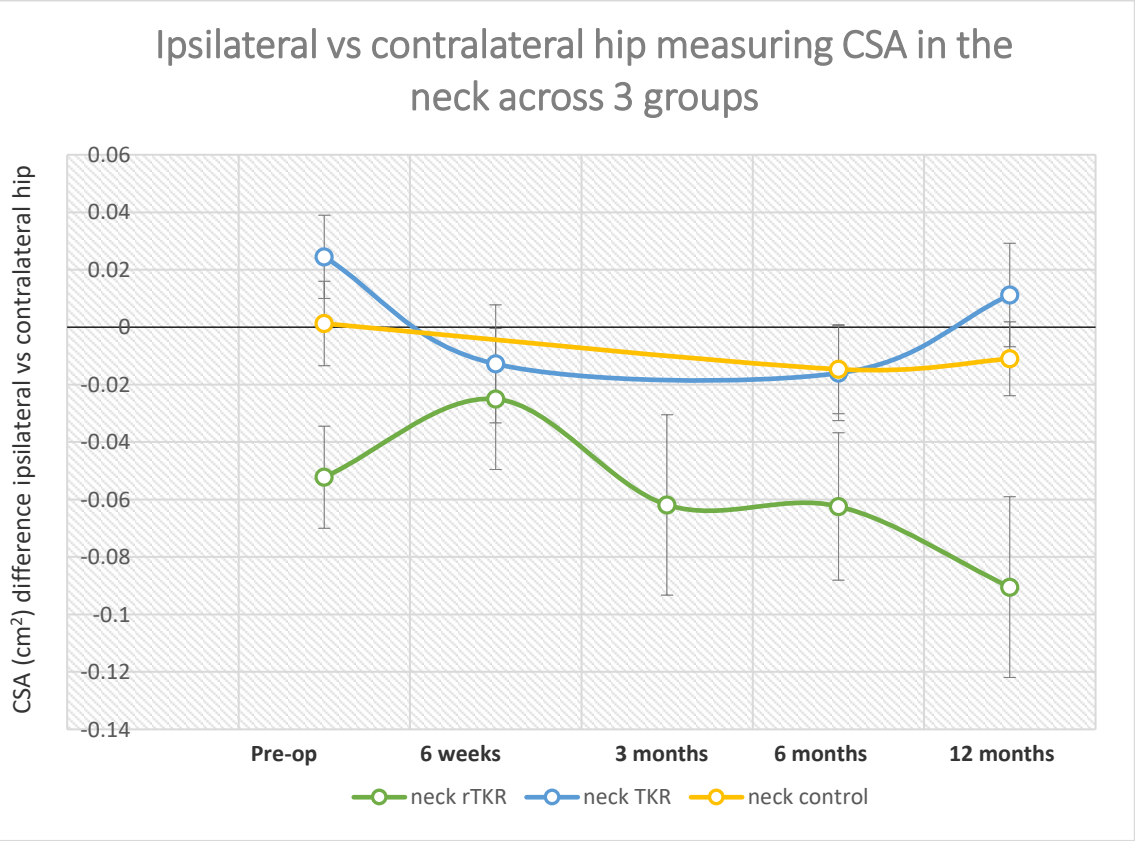


Figure 4.22. *Shows CSA differences between ipsilateral and contralateral in the neck region for each of the three groups (error bars are SE) over 12 months*

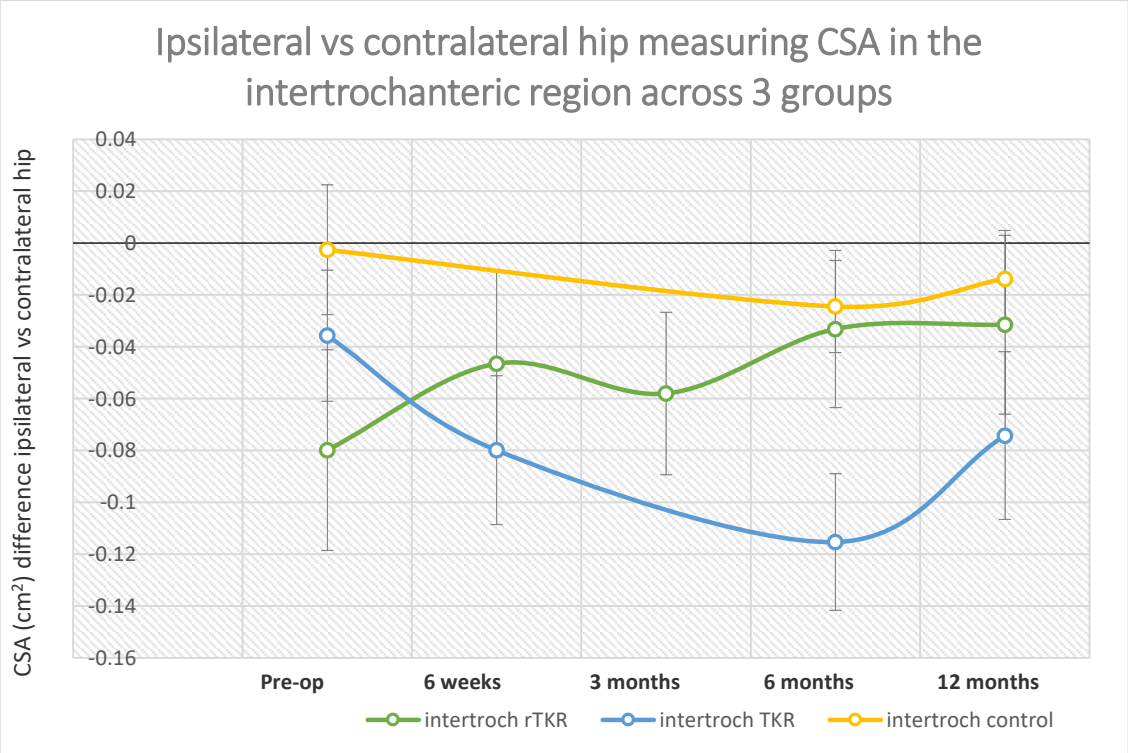


Figure 4.23. *Shows CSA differences between ipsilateral and contralateral in the intertrochanteric region hip for each of the three groups (error bars are SE) over 12 months*

Table 4.15. *Shows the difference in CSA between ipsilateral and contralateral data, including percentage difference, CI (95 %), t-test, and p-value (there was no data collected for 6 week and 3 month control data, and none for 3 month TKR data)*

PRE-OP (RTKR N=27, TKR N=23, CONTROL N=45)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.052	0.092	0.018	2.938 **(0.01)**	-4.190	-12.150	3.770
neck TKR (cm^2)	0.024	0.070	0.015	-1.689 (0.11)	2.328	-5.676	10.331
neck control (cm^2)	0.001	0.099	0.015	-0.087 (0.93)	0.124	-5.540	5.789
intertroch rTKR (cm^2)	-0.080	0.201	0.04	2.065 **(0.05)**	-3.701	-15.006	7.604
intertroch TKR (cm^2)	-0.036	0.121	0.03	1.412 (0.17)	-2.040	-10.437	6.357
intertroch control (cm^2)	-0.003	0.168	0.03	0.104 (0.92)	-0.153	-10.942	8.314
6 WEEK (RTKR N=17, TKR N=15)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.025	0.101	0.025	1.019 (0.32)	-1.933	-15.127	11.261
neck TKR (cm^2)	-0.013	0.080	0.021	0.624 (0.54)	-1.224	-11.000	8.551
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.047	0.146	0.035	1.312 (0.21)	-2.052	-17.123	13.020
intertroch TKR (cm^2)	-0.080	0.111	0.029	2.786 **(0.01)**	-4.676	-15.635	6.283
intertroch control (cm^2)	-	-	-	-	-	-	-
3 MONTH (RTKR N=17)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.062	0.129	0.031	1.973 (0.07)	-4.744	-17.927	8.440
neck TKR (cm^2)	-	-	-	-	-	-	-
neck control (cm^2)	-	-	-	-	-	-	-
intertroch rTKR (cm^2)	-0.058	0.165	0.040	1.451 (0.17)	-2.543	-18.476	13.391
intertroch TKR (cm^2)	-	-	-	-	-	-	-
intertroch control (cm^2)	-	-	-	-	-	-	-
6 MONTH (RTKR N=14, TKR N=17, CONTROL N=43)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.062	0.096	0.026	2.436 **(0.03)**	-5.122	-19.902	9.659
neck TKR (cm^2)	-0.016	0.068	0.017	0.968 (0.35)	-1.528	-9.479	6.422
neck control (cm^2)	-0.015	0.102	0.015	0.945 (0.35)	-1.419	-7.490	4.651
intertroch rTKR (cm^2)	-0.033	0.114	0.030	1.092 (0.29)	-1.606	-19.945	16.734
intertroch TKR (cm^2)	-0.115	0.109	0.026	4.379 **(0.00)**	-6.542	-15.627	2.542
intertroch control (cm^2)	-0.024	0.117	0.018	1.377 (0.18)	-1.440	-8.483	5.603
12 MONTH (RTKR N=7, TKR N=15, CONTROL N=36)							
	Mean change	SD	SE	T-Critical (P-value)	Mean % Change	95 % CI	
neck rTKR (cm^2)	-0.090	0.077	0.031	2.877 **(0.03)**	-7.079	-18.885	4.728
neck TKR (cm^2)	0.011	0.070	0.018	-0.621 (0.54)	1.075	-8.016	10.166
neck control (cm^2)	-0.011	0.077	0.013	0.858 (0.40)	-1.044	-6.830	4.743
intertroch rTKR (cm^2)	-0.031	0.084	0.034	0.913 (0.40)	-1.400	-16.398	13.597
intertroch TKR (cm^2)	-0.074	0.125	0.032	2.298 **(0.04)**	-4.222	-14.479	6.034
intertroch control (cm^2)	-0.014	0.112	0.019	0.738 (0.47)	-0.778	-7.393	5.836

Figures 4.22, 4.23 and table 4.15 show the difference in CSA between ipsilateral and contralateral hips, with the biggest difference of CSA reported in the rTKR group in the neck region reported as -7.079 % (p-value 0.03) at 12 months. In the pre-op in the neck of femur in the TKR group the difference is reported as 2.328 % (p-value 0.11) with further differences reported at six weeks (-1.224 %) and six months (-1.528 %) until reaching a final difference of 1.075 % at 12 months. Similar to the CSMI result when investigating the difference between the ipsilateral and contralateral hips the control group shows no statically difference (all overlap 0 with their SE), except the two reported scores at six months -1.440 % (p-value 0.18) at the neck and -1.419 % (p-value 0.35) at the intertrochanteric region, the same as in the CSA group.

4.6 DISCUSSIONS

4.6.1 CORTICAL SURFACE BMD

The cortical surface BMD (sBMD) results when compared to baseline hip data show minimal changes across all control participants; this is the same in the hip comparison data. One study involving the 3D-SHAPER software [380] used control participants, although these were a much younger cohort of controls (mean age 33+/-10 years) their cortical sBMD (164+/-22 g/cm^2) was similar to the control baseline scores reported in this study (163.86 g/cm^2), although no longitudinal changes were investigated. Further to this, a study investigating 3D-SHAPER and hip fracture association [381], reported controls of post-menopausal women aged 68.8+/-8.9 years, weight 62.6+/-7.9, height 153.2+/-6.4, BMI 26.7+/-3.3 (similar characteristics shared by our group, although our control group is taller). They reported a cortical sBMD of 138.1+/-19.9 mg/cm^2 which overlaps with the SD of our group 163.86+/-24.83 mg/cm^2, although these differences might be related to regional, ethnicity or other co-founding factors. Unfortunately, there is limited data on 3D-SHAPER software, and no studies investigating longitudinal changes.

Therefore, due to the limited 3D-SHAPER data, data investigating the BMD in the hip will be utilised (not directly cortical bone in this region). Changes reported in on study [23] described that the control group (who were matched to

participants undergoing TKR) reported a BMD loss of -0.89 % in the ipsilateral neck and -0.32 % in the total hip BMD over 12 months [23]. Additionally, research by Rao et al reports that there is no dominant hip, and that the left and right hip are highly correlated [382], this again supports the control comparison data showing minimal change.

These control results are supportive in what we would expect to see a control group, supporting the idea that the software is accurate. Furthermore, this is contributed by a 3D-SHAPER precision study, which showed similarities between the software and areal BMD reported in DXA scans [383].

The rTKR ipsilateral group data reported a large loss of cortical bone at six weeks (-1.249 %) with losses continuing at three, six and 12 months (-1.735 %). The contralateral hip comparator data show a similar trend with cortical sBMD loss reported in all visits. The TKR group baseline data show a comparable declination to the rTKR data, reporting an ipsilateral hip loss of -1.911 % at six weeks, with this gradually decreasing until reaching -2.139 % at 12 months. The hip comparator TKR data again show a similar trend.

Unfortunately there are no data reporting cortical BMD in the hips and rTKR, but there is research investigating TKA and BMD in the hip [26]. This research reported BMD losses of -2.7 % at 12 months post-surgery in the ipsilateral hip, and losses of -1.18 % in the contralateral hip [26]. Other research supports this loss, reporting a figure of -1.80 % [25] in the ipsilateral hip post TKR.

Both the rTKR and TKR group show analogous changes in the cortical sBMD. This change is especially important given that a lack of cortical bone can increase fracture risk in both groups [384, 385], as it has been reported that thicker cortices contribute to greater mechanical strength, and with both groups reporting a loss of cortical bone there is an increase in associated hip fracture risk [384]. It has also been reported that identifying cortical thinning which this software has done, could help address bone fragility and identify fracture risk [386].

Furthermore, this loss might be due to the reported changes in cortical bone compared to trabecular bone, where trabecular bone turnover is higher than in cortical bone [76]. This change might be due to cortical bone not being under the same direct stressors as trabecular bone due to its more brittle structure [387]; cortical bone can only withstand strains (the deformity the bone can undergo) of around 2 %, with trabecular bone withstanding strains of 30 % [388], and is highly metabolically active with a higher surface area to volume ratio than cortical bone [389, 390]. Thus the majority of bone remodelling and turnover is conducted by the trabeculae even though it only makes up 20 % of the skeletal bone mass [365]. Additionally, there is also the impact of the inflammatory response slowing BMD recovery [391]. Therefore, this loss at 12 months in both groups might be due to slower turnover of bone in the cortical area, with these participants possibly not recovering BMD until 24 months post-surgery, as shown in the systematic review and Soininvaara et al data [26].

4.6.2 TRABECULAR VOLUMETRIC BMD

The trabecular volumetric BMD (vBMD) for the controls again shows minimal to no change between baseline and subsequent visits and for the comparison data, although there is a loss reported at 12 months in both the ipsilateral and contralateral sides compared to baseline (-1.029 % and -1.032 %), these losses might be due to precision or positional errors, but are more likely due to natural changes in BMD in post-menopausal women, in which hip BMD is reported to decline 1–1.4 % per year [307]. This loss is reported in the trabecular vBMD which supports the idea of the impact of bone turnover. Furthermore, a study utilising the 3D-SHAPER software [379] reported controls of a similar age, height, weight, and BMI as our control group, reporting a trabecular vBMD of 136.1+/-38.5 mg/cm^3 with our control group reporting a score of 164.51+/-42.38, again as previously stated this differences may be regional, due to the impact of surgery, or other variations within the two control groups. Unfortunately, there is no follow up for this control group so it is unknown if these change are mimicked directly in other groups.

In the rTKR group recovery was seen immediately post-surgery in the ipsilateral hip, which continued throughout reporting a positive score by 12 months. The TKR group shows a post-surgery decline but reports some recovery between

six and 12 months. Investigating the comparison data, the BMD differences in the rTKR group are still shown, with a large positive difference at 12 months, showing an increase in trabeculae vBMD, the TKR group shows a steady loss throughout with a slight difference between six and 12 months, mimicking the baseline changes.

This slow recovery in the TKR group agrees with the systematic review knee data regarding a lack of a plateau effect until at 24 months [26], as oppose to 12 months. Although it is unclear if this was due to changes in cortical opposed to trabecular bone, especially as the TKR group showed a loss at 12 months in both the cortical and trabecular bone. Furthermore, the data gathered from the TKR group would agree with the data from the systematic review and the current available research [26] regarding the changes in BMD, which parallel the DXA data adding to the software's potential accuracy. Additionally, the changes in the rTKR group might be due to the influence of the new metaphyseal cone being tested as part of this study, promoting remodelling due to participant early weight bearing, leading to the ipsilateral hip undergoing mechanical loads promoting bone turnover. This is supported by research that shows trabecular bone has a higher turnover than cortical bone [76], thus increased weight bearing could be the reason for the increased trabecular vBMD. Furthermore, cone implantation has shown to increase BMD in rTKR [226, 392].

The trabecular volumetric data for the TKR group also aligns with current research regarding BMD loss, as reported in a small amount of hip data in TKR and DXA scans [26], as well as the BMD knee data in the systematic review, in which participants who underwent a TKR lost BMD consistently throughout the first 12 months around the knee implant, with data then suggesting that at 24 months there was a recovery and possible plateau effect.

Additionally, the physiotherapy regime which the rTKR participants underwent as part of their routine recovery pathway cannot be underestimated, and this might be the reason for the difference between the TKR and rTKR groups and the increased trabecular vBMD, as a study by Benedetti et al has shown that physiotherapy and exercise can increase BMD [393].

4.6.3 INTEGRAL VOLUMETRIC BMD

Integral vBMD again shows minimal change in the control data for the baseline or comparison figures. Furthermore, a study involving 3D-SHAPER software [380] had controls reporting an integral vBMD of 345+/-51, this is within the reported figures in this study (322.59+/-58.29 mg/cm^3), although this cohort is not matched to TKR participants and has an average age of 33+/-10 years. Another 3D-SHAPER study [379] with control reported scores of 279.3+/-54.3 mg/cm^3. As stated there is overlap between the SD, but the variations between our controls and these controls might be due to regional differences, medications, exercise (the control group did report high pedometer readings [23]), and other variables.

The rTKR ipsilateral baseline data show small losses and gains throughout the visits with a reported loss of -0.965 % (-2.997 mg/cm^3) at six months, and a gain of 0.358 % (1.159 mg/cm^3) at 12 months. This integral volumetric data are in the area where there is a unison of cortical and trabecular bone [357]**,** this result is reflected in the results so far, with the increases and decreases most likely due to the combination of the trabecular vBMD gains, and cortical sBMD losses. The rTKR comparison data show a large difference at pre-op of -3.055 % (-9.988 mg/cm^3) this difference gradually reduces throughout the months with a reported difference of -1.716 % (-5.670 mg/cm^3) at 12 months similar to the trabecular vBMD.

The TKR group reports an ipsilateral gradual loss throughout, with a loss of -2.344 % at 12 months. These results again are reflective of the combined trabecular vBMD loss and the loss in the cortical sBMD. The comparison data reported shows a similar trend in change with a difference of -2.461 % at six weeks, -3.861 % at six months, and then a difference of -3.110 % at 12 months.

Bringing all these data together, you can see that the cortical sBMD data for both the TKR and rTKR show that the cortical thickness is being reduced across the hip region without any implication of recovery compared to either baseline or contralateral hip, the cortical sBMD gradually decreases even at 12 months, as stated this might be due to slow cortical bone turnover [76].

The trabecular vBMD and integral vBMD show similar patterns in both the baseline and comparison data. The rTKR group data show a gradual increase throughout for both comparison and baseline data when reviewed against the previous months, even in one instance reporting a positive 12 month change having recovered from a large pre-op deficit. The TKR data show the opposite trend, with a starting equal or negative score and decreasing it further across each visit, resulting in a large negative at 12 months.

All control results across all three tests (cortical sBMD, trabecular vBMD and integral vBMD) show minimal change both the baseline changes and between the ipsilateral and contralateral hip data. As for the TKR and rTKR there is no comparison data for this software's use. These changes are important, as reductions in volumetric, cortical, and trabecular bone is associated with increased fracture risk [394] as well as being correlated with ageing. Furthermore, differences in volumetric BMD (total hip) were measured by 3D-SHAPER software in an article in press (November 2018 [379]), in which they reported that in Caucasian post-menopausal participants who had suffered a fractured hip within a six year period, had a cortical sBMD mg/cm^2 difference of -13.9 % (p-value <0.001), trabecular vBMD mg/cm^3 difference of -31.8 %, and an integral vBMD mg/cm^3 difference of -44.2 % all compared to the control group who did not have a fracture [379]. This shows a strong statistical association between fracture risk and cortical sBMD, trabecular BMD, and integral vBMD. Although it must be noted this was a retrospective case controlled study.

4.6.4 CROSS SECTIONAL MOMENT OF INERTIA

The CSMI control data show some change, there is a loss reported at 12 months in the intertrochanteric region, a baseline change of -4.734 % (-0.069 cm^4). Furthermore, the baseline data recorded for the CSMI control group reports losses at other time periods and regions; at six months there is a loss reported of -2.815 % (neck), and -2.542 % (intertrochanteric), at 12 months it is reported as -1.377 % (neck). As stated previously these losses might be due to natural BMD loss in the post-menopausal group [307], which is reflected in the ipsilateral vs contralateral control data which shows minimal difference between the two hips. Additionally, the CSA data show a similar trend of loss in the

control group, with this idea is further supported by the trabecular vBMD that shows a loss for the controls at 12 months compared to baseline, in both the ipsilateral and contralateral hips but minimal change between the two hips, which is supported by the he left and right hip being highly correlated [382].

Across both the neck and intertrochanteric there are losses reported in both groups at every visit (with only the neck in rTKR group at six weeks reporting an increase), this might be due to cortical thinning as supported by the cortical sBMD data, leading to reduced flexibility and bending stress, increasing the chances of buckling and fracture, this is supported by the literature that has shown that participants who have lower CSMI and lower cortical thickness have an increased association of hip fracture in both men and women [363, 395, 396]. It must also be noted that the TKR group baseline data show an increase in CSMI which is not reflected in the cortical sBMD, but this could be due to the cortical sBMD reporting the mean cortical surface of the entire hip and not individual regions which show these variations.

4.6.5 CROSS SECTIONAL AREA

The CSA shows minimal changes in the control group in both the baseline and comparison data changes, although at six months there is a loss at the femoral neck and the intertrochanteric region, with the reasoning behind these changes already discussed as part of the trabecular vBMD changes and CSMI data.

The CSA data show the loss at the femoral neck which is reported by the cortical bone loss in the cortical sBMD in the rTKR, this is shown in both the baseline and comparison data and shows the same trend of gradual loss throughout each visit. The pattern in the CSA is similar to the pattern in the CSMI for each group, the TKR group in the neck region has a loss at six weeks, and an increase at 12 months when compared to the 6 months score. For the same data the rTKR has a similar trend across the CSA and CSMI, with an increase at six weeks (in comparison to the pre-op) and then a continuing loss at 12 months, this trend is seen in both the baseline and comparison data.

In the intertrochanteric ipsilateral baseline data, the TKR group shows a loss throughout, but by 12 months there is an increase when compared to the six

month data, again this is shown in the baseline and comparison data. The rTKR group for the intertrochanteric data again shows a similar trend to the TKR group, reporting a loss throughout, although there is no increase at 12 months compared to six months.

Unfortunately, even after extensive searching there seems a limited amount of data reporting CSA or CSMI hip data and its relation to rTKR or TKR. A study from Özen et al [397] investigated hip CSA and CSMI in control participants, but their findings were recorded in a different format and provided no longitudinal data, so cannot be compared to this study. Although, Beck et al [398] found a decline of 5 % per decade in CSMI in both pre- and postmenopausal women. Furthermore, it must be note there are some software that has been developed for enhancing diagnostic precision in hip fracture risk by using CSMI and CSA [399].

Finally, as stated the CSMI and CSA show very similar trend lines and the losses reported might be due to cortical thinning, with this supported by the cortical sBMD data but also due to the CSA only investigating the cortical equivalent area of the cross section of the femoral neck, with all trabecular and cellular spaces eliminated.

4.7 LIMITATIONS

Across all three groups there are many variations, the rTKR group had an older mean age, as these participants have already undergone a TKR previously. Furthermore, only women were included in the TKR and control groups, This might impact the BMD changes reported, as women have reported to lose BMD of between 3.4-4.8 % over four years, with men losing 0.2-3.6 % over the same time period [400]**.** As noted this might have impacted the control group results within the study.

Furthermore, all participants were white, and it has been reported that black people have higher BMD, CSMI, and CSA when compared to white people, so these results cannot be generalised to other ethnicities or demographics [359]. Additionally, cortical, trabecular, and volumetric BMD loss appears to follow

different patterns amongst African participants [394], again reducing the generalisability of this data.

Further to this, the sample size was small, especially at 12 months were there was attrition of participants, this sample size impacted the results creating larger SD and SE margins in the 12 month data (seven, 15, and 36 participants across all three groups). This was due to the revision group being preliminary data due to time limitations on the software's licence.

The impact on the results of some participants having already undergone TKR prior to their rTKR, might have been exacerbated due to the participants having already had a TKR on their contralateral knee. Although this figure is not recorded several patients did have bilateral TKR, meaning possible deterioration in the contralateral knee might have hastened the BMD turnover changes seen in the ipsilateral hip due to exaggerated offloading.

4.8 CONCLUSION

For all control data there are minimal reported changes throughout for both the baseline and contralateral data, with some minimal changes reported as plausible natural bone changes.

The knowledge about these differences between trabecular and cortical bone, and the changes of their relation due to ageing has multiple potential implications for clinical practice in understanding and treatment of a TKR or rTKR. It might be advantageous to apply anti-resorptive medications or regimens that aim for modification of trabecular bone remodelling in TKR patients due to their slower recovery, or rTKR patients due to the quicker recovery might benefit more directly from modification of cortical bone remodelling. This has already been investigated with this software [394] which investigated different drug treatments in osteoporotic women and reported on their cortical and trabecular bone changes. This might also impact future ideas of surgical procedures in addressing either trabecular or cortical characteristics, for example bone cement, is strong in compression and weak in shear and tension forces, and is a useful tool the treatment of osteoporosis, in which it

imitates trabecular bone as shown in its treatment in osteoporotic vertebral fractures [401, 402]. With cortical modifications the focus could be on the use of cortical bone grafts [403, 404].

Overall the 3D-SHAPER software's ability to be applied to hip DXA imaging shows promise; this is reflected in the control participant's results showing minimal changes throughout. This is also supported by the trabecular vBMD data from the TKR group data agreeing with current DXA literature [26], and the CSA and CSMI data showing similar trends, due to their correlation in the femoral strength index.

Furthermore, it must be acknowledged that the separation of cortical from trabecular bone does give a deeper underpinning of the mechanical structures and effects bone undergoes as part of the recovery process pre and post total knee revisions and replacements, as well as showing the losses in CSA and CSMI suggesting that the spatial distribution of bone in the femoral neck is less able to resist greater loading, increasing fracture risk. This is supported by data from the Humbert et al study [379], which shows how this type of software could be integrated into predicting or identifying those at future fracture risk.

Finally, as stated this software is in its infancy and these results should be treated with caution, although 3D measurements could potentially provide additional indicators to improve patient monitoring in clinical practice. It is still unclear as to why these changes might be between the groups, and thus further investigated is required.

4.9 FUTURE WORK

Further development of the 3D-SHAPER software should be undertaken, with additional validation and testing. Additionally, investigation into the 24 month appointment scans and into the full clinical trial could provide additional evidence regarding the changes in both cortical and trabecular bone, in conjunction this dataset, if it could be expanded, would allow a stronger comparison between the groups. Especially if more data could be collected regarding other TKR and rTKR groups/studies. This would address issues that

both the data and the systematic review have raised regarding plateau effects of BMD. Additionally, there should be investigations into the changes perceived between the rTKR and TKR groups, and the root cause for this possible difference and investigations into post-care influences. Unfortunately, although the 3D-analysis software offers preliminary greater information into the characteristics of the BMD results, it is unlikely to be used in the full study due to the time and cost limitations of licencing the software. Although given as the main pilot study will cover a five year period and this software can be used retrospectively, it could still be utilised even after the research is nearing its end. This would still allow this data to be directly compared to the BMD results throughout the subsequent pilot study data.

CHAPTER 5: MAIN STUDY – BMD CHANGES IN TOTAL BODY, LUMBAR SPINE AND BILATERAL HIPS – A COMPARISON BETWEEN BASELINE, IPSILATERAL AND CONTRALATERAL FOR RTKR PARTICIPANTS

5.1 INTRODUCTION

This chapter will report the BMD results of the main study covering the total body, lumbar spine, and bilateral hips. It will outline the participant recruitment, DXA method and the analysis used in the main study (The knee DXA data is addressed separately in the subsequent chapters, as are the additional scans).

From the systematic review data, it has been shown that there are little data regarding ipsilateral and contralateral hip BMD and the subsequent changes throughout the revision and replacement process, with no reported data regarding BMD hip impact from total knee revisions (rTKR).

This chapter will report on the results of exploring the impact of rTKR on BMD on the bilateral hip regions (neck, wards, trochanter, shaft, and total) of cone and non-cone participants, as reported via DXA scans. Additionally, changes in the lumbar spine (L1, L2, L3, L4 and L1-L4) and total body BMD will be investigated between cone and non-cone participants as well as comparisons between visits at pre-op (baseline) and six weeks, three months, six months and 12 months.

It must be noted that due to the COVID-19 pandemic, I was unable to conduct the 12 month DXA scans on four participants due to lockdown, closure of the University campuses and a complete halt on all non-COVID-19 research both within the University and the hospital. Since many of the participants on this study are in the over 70 group and often have multiple co-morbidities, I was advised to write up without completing data collection in June 2020 because it was deemed unlikely that both the RD&E department, the University or the risk assessments on the individual participants would allow for scanning of these missed visits within the duration of my PhD.

Bone mineral density and the characteristics and architecture of bone have already been discussed in chapter 1 section 1.2.2. Although it must be stated that there is a direct link between hip strength and the influence of both cortical and trabecular bone as mentioned in the previous chapter; with cortical bone supporting flexibility in the distal regions of the femoral neck, and trabecular bone supporting the proximal loads the hip has to undergo [405]. With both bone types creating a complex relationship in supporting the hip function and load bearing.

Furthermore, the importance in defining exact areas of weaknesses or bone loss is important especially with the advent of atypical femoral fractures.

5.1.1 AIM

This study was a prospective randomised feasibility study to investigate BMD changes in patients with and without cone implants in rTKR at pre-determined time intervals over a one year period. In order to identify when these BMD changes occur, and in what regions and the differences between the groups. Therefore, the total body, lumbar spine and bilateral hips were investigated through DXA imaging. .

5.2 PARTICIPANT RECRUITMENT

This study focused on recruiting rTKR patients with an AORI type two defect, and included both men and women in the study. This group was selected for two reasons. The participants required a revision, and be viable to undergo cone implantation, this meant the participants had to have an AORI type two defect, thus having enough bone to support the additional implantation, but not too much as to deem the implant superfluous. Since the participants are having a knee revision rather than a primary knee replacement, the group on average would be older, and thus more likely to have poorer baseline BMD due to natural progression with age. Matched controls undergoing rTKR but who did not received a cone were also recruited (non-cone group), with all participants blinded to their group.

5.2.1 PARTICIPANT GROUPING AND RECRUITMENT

Participants were recruited for the cone testing through the knee research team at the RD&E hospital via one of two ways outlined below. These were matched against to the inclusion and exclusion criteria (see table 5.1 and 5.2). Firstly, patients that were listed for rTKR surgery whilst attending orthopaedic out-patient clinics at the RD&E Hospital were consulted and given the opportunity to participate in the study. They were given a copy of the participant information sheet (PIS) (appendix 5), and the consent form (appendix 6). Secondly, patients were identified from existing surgical waiting lists, contacted by telephone or in writing asking for their permission for one of the study team to approach them about the study. Patients interested in the study were then sent a copy of the PIS and a consent form. PGH or one of the research team at the RD&E then contacted the patient and obtained written consent for study participation. Consent in most cases was obtained at the pre-operative assessment clinic which occurred two-four weeks prior to the surgery.

Table 5.1. *Inclusion criteria list*

Inclusion Criteria:
· Patients undergoing first time revision knee replacement for aseptic loosening or wear of the components
· Patient has signed an ethics committee approved consent form
· rTKR to be performed at The Royal Devon and Exeter Hospital
· AORI class 2 defects of femur and/or tibia
· Skeletally mature male or female
· Patient is willing and able to comply with postoperative scheduled clinical and radiological evaluations and rehabilitation
· Patient must be suitable for a rTKR with the Triathlon TS system i.e. must not have gross collateral ligament laxity

Table 5.2. *Exclusion criteria list*

Exclusion Criteria:
· Refusal to consent to participate in the study
· Patients known to have an infected joint replacement prior to revision surgery
· Patients identified with an unexpected infected joint replacement identified per-operatively
· AORI class 1 defects of tibia or femur where metaphyseal cone fixation is not indicated
· AORI class 3 defects of tibia and femur where distal femoral replacement or proximal tibial replacement is required
· Cases of ligamentous instability where condylar knee revision is not indicated
· Patient is diagnosed with a systemic disease or metabolic disorder leading to progressive bone deterioration
· Patient has a neuromuscular or neurosensory deficiency
· Patients undergoing patella revision in isolation
· Pregnancy

5.2.2 REASONS FOR EXCLUSION

The exclusions were made due to the possible impact of confounding variables affecting the BMD results (e.g. long-term corticosteroid use) and thus were justified. This study had few exclusions, as it was felt that it was important to keep the patients in the study as close to those in real life clinical practice, in order to ensure that the results were more generalisable to the clinical population. Furthermore, extensive exclusions in the study would have resulted in a smaller pool of participants over the two years recruiting period making the results less statistically relevant.

5.2.3 GROUP ALLOCATION

Originally the aim of the study was to recruit 51 participants. The number 51 was calculated due to several factors (from the protocol). Firstly, there were no prospective studies to use as a basis for calculating sample size. The choice of 51 participants initially with the potential for further recruitment after preliminary

analysis, was determined by statistical advice who were confident that 51 will be sufficient to test the progression rules and to offer reasonable estimates of standard deviations of the intended outcome measures.

Pragmatically, (based on the 2015 figures) the RD&E undertook approximately 62 rTKR procedure per year and in 2015, 27 of these did not meet the inclusion criteria. Of the remaining 35 cases, with an assumed 20% unwilling to participate left 28 cases per annum. With a likely 56 potential participants in just under a two-year period. With the initial plan to recruit 51 subjects (17 to the no cone arm and 17 each to the cone with short or long stem arms respectively). With a preliminary analysis after 51 participants have been recruited. Due to time constraints, winter bed pressures, delays in surgery, and COVID-19, the results were a total of 37 participants who were recruited and consented for this study. Participants were then randomly allocated, with 24 assigned to undergo an implant with a Triathlon Cone and a new rTKR (cone group), and 13 to undergo just a new rTKR (non-cone group), with varying stem lengths used in both groups. The 13 participants who were assigned to the non-cone group (the control group), further to this each participant's contralateral knee was also scanned.

5.3 PARTICIPANT RECRUITMENT RESULTS

During the recruitment period of those who were eligible post screening 21 declined to enter the study, although this is actually a lower figure than the 50 % expected (37 (consented) + 21 (declined) = 58 (total) so 36.21 % declined).

The commonest reasons for declining study entry were:

- Too far to travel for extra appointments needed for study (six participants)
- Too many extra appointments (10 participants)
- Patient recently required oxygen therapy at home so felt it was too much (1 participant, although this participant could have been excluded rather than declined)
- Unhappy with concept of randomisation (two participants)
- No reason given (four participants)

From this list above there are 23 reasons, this was because two participants declined for multiple reasons.

A number of the participants initially stated yes, when they were sent the participant information sheet. Upon being phoned up by the research team at the RD&E regarding the study, and being given a date for the hospital admission (many months later), they then declined to go into the study.

Conclusively, this resulted in 37 participants being consented into the study between the dates of 03/07/2017 and 17/06/2019, they were randomly allocated into either the cone (24) or the non-cone (13) group, with 13 male and 11 female participants in the cone group, and eight male and five female participants in the non-cone group. Of the original 37, 35 participants completed the pre-op DXA scan (22 cone, 13 non-cone), a mean of 8.71 days prior to their surgery (range 1-62 days). Of the two who did not attend: one participant was consented then withdrew, due to revaluating the number of scans and questionnaires they would have to undertake, the second participant (although wanting to be part of the study) was withdrawn due to being prescribed alendronic acid (a bisphosphonate medication that increases BMD), and part of the study exclusion criteria.

At six weeks post-surgery 26 participants completed the DXA scan (18 cone, eight non-cone) at a six week mean of +4.58 (range -1 to +15) days. Of those who did not attend: one participant died prior to surgery, one participants husband had died, two participants cancelled their six week appointment on pre-existing health grounds unrelated to their rTKR, and five were for surgical reasons, so were withdrawn from the study. These surgical reasons meant the participants could not have the rTKR type originally proposed, this was due to two main reasons; three participants required a special type of hinge joint, and two participants did not have enough bone in their distal femur for this type of revision, both of these reasons were discovered whilst the participants were undergoing surgery.

At the three month visit, 26 participants completed the DXA scan (18 cone, eight non-cone) at a three month mean of +7.04 (range -1 to +32) days. One

participant could not attend the appointment, and the same two who failed to attend their six week due to health reasons, also could not attend their three month appointment due to ill health. At the six month visit, 25 participants completed the DXA scan (17 cone, eight non-cone) at a six month mean of +8.04 (range -13 to +29) days, four participants did not attend their appointment, one could not attend (no explanation was given), the same two who had previously missed their previous appointments due to ill health could unfortunately not attend their six month appointment either, and one participant had a myocardial infarction so missed their appointment.

At the 12 month visit, 22 participants completed the DXA scan (15 cone, seven non-cone) at a 12 month mean of +13.50 (range -7 to +81) days**.** One participant cancelled due to health reasons, one participant was withdrawn due to an infection in their knee revision, and four DXA scans could not be performed due to the emergence of the COVID-19 pandemic, and the university closedown procedures and health concerns. An entire synopsis of the participant attrition is shown in the CONSORT diagram in table 5.3.

Table 5.3. *CONSORT table showing participant attrition per visit*.

	Consented and randomised by research team at RD&E (N=37)	
cone group (N=24)		**non-cone group (N=13)**
24		13
	Pre-op DXA (N= 35)	
cone group (N=22)	2 withdrew prior to scanning	**non-cone group (N=13)**
22 (1 due to time commitment, and 1 due to medication exclusion)		13
	6 week DXA (N=26)	
cone group (N=18)	35 participants still available, 9 did not undergo a 6 week scan: 6 withdrawn (5 plus one died), 3 unable to attend	**non-cone group (N=8)**
18 (1 died, 1 due to poor health, 2 had surgical issues)		8 (1 due to poor health, 3 due to surgical issues, 1 cancelled the appointment due to an bereavement)
	3 month DXA (N=26)	
cone group (N=18)	29 participants still available, 3 did not undergo a 3 month scan 2 due to poor health, 1 could not attend	**non-cone group (N=8)**
18 (1 due to poor health)		8 (1 due to poor health, 1 could not attend appointment)
	6 month DXA (N=25)	
cone group (N=17)	29 participants still available, 4 did not undergo a 6 month scan 2 due to poor health, 1 could not attend, 1 had a myocardial infarction	**non-cone group (N=8)**
17 (1 due to poor health, 1 could not attend)		8 (1 due to poor health, 1 due to myocardial infarction)
	12 month DXA (N=22)	
cone group (N=15)	28 participants still available; 6 did not undergo a 12 month scan; 1 due to poor health, 1 withdrew due to knee infection, and 4 were cancelled due to the issues of COVID-19	**non-cone group (N=7)**
15 (3 due to COVID-19)		7 (1 due to poor health, 1 withdrew due to knee infection, 1 due to COVID-19)

5.3.1 PRE-OP BMD FOR SURGICALLY WITHDRAWN PARTICIPANTS

In total 35 participants completed a pre-op scan, of those, five participants had to be withdrawn post-surgery due to the standard rTKR not being a suitable option, and a different surgical procedure required (three required a hinge joint, and two lacked bone in the distal femur for this type of operation). Therefore, in order to investigate differences, the pre-op BMD results were separated into two groups (the five who withdrew post-op due to surgical reasons, and the 30 other participants who continued in the study).

Tables 5.4 and 5.5 report the pre-op BMD of each group, with an independent unpaired samples t-test and p-value performed.

Table 5.4. *Total body and lumbar spine mean BMD (g/cm^2) of the five withdrawn, and 30 included participants including t-test and p-value*

	TOTAL BODY	L1	L2	L3	L4	L1-L4
Average BMD g/cm^2 (N=30)	1.230	1.104	1.237	1.339	1.367	1.270
SD	0.147	0.234	0.260	0.283	0.306	0.262
SE	0.027	0.043	0.047	0.052	0.056	0.048
Average BMD g/cm^2 (N=5) (withdrawn group)	1.212	1.114	1.225	1.283	1.308	1.237
SD	0.081	0.065	0.056	0.142	0.205	0.098
SE	0.036	0.029	0.025	0.063	0.092	0.044
BMD difference between groups	0.017	-0.010	0.012	0.056	0.059	0.033
T-Critical	0.388	-0.193	0.227	0.685	0.548	0.512
P-Value	0.707	0.849	0.822	0.509	0.601	0.616

Table 5.5. *Ipsilateral hip and contralateral hip average BMD (g/cm^2) of the five withdrawn, and 30 included participants including t-test and p-value*

IPSILATERAL HIP					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
Average BMD g/cm^2 (N=30)	0.957	0.718	0.872	1.175	1.013
SD	0.142	0.181	0.212	0.206	0.183
SE	0.027	0.035	0.041	0.040	0.035
Average BMD g/cm^2 (N=5) (withdrawn group)	0.907	0.680	0.786	1.106	0.941
SD	0.101	0.096	0.220	0.142	0.136
SE	0.045	0.043	0.098	0.064	0.061
BMD difference	0.050	0.038	0.085	0.069	0.072
T-Critical	0.950	0.690	0.801	0.914	1.018
P-Value	0.317	0.506	0.460	0.387	0.342
CONTRALATERAL HIP					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
Average BMD g/cm^2 (N=30)	0.967	0.725	0.871	1.174	1.017
SD	0.170	0.168	0.201	0.203	0.181
SE	0.032	0.031	0.037	0.038	0.034
Average BMD g/cm^2 (N=5) (withdrawn group)	0.962	0.733	0.856	1.184	1.006
SD	0.108	0.097	0.209	0.113	0.127
SE	0.048	0.044	0.093	0.051	0.057
BMD difference	0.005	-0.008	0.015	-0.009	0.011
T-Critical	0.082	-0.158	0.148	-0.150	0.168
P-Value	0.937	0.878	0.888	0.884	0.872

Tables 5.4 and 5.5 show that the BMD difference show a larger average BMD in lumbar spine in the standard rTKR group, reporting a L1-L4 figure of 1.270 g/cm^2 compared to 1.237 g/cm^2. Otherwise there is minimal difference between the BMD reported scores in the total body and lumbar spine.

The contralateral hip differences between the groups is minimal, although the ipsilateral BMD average across all regions of the hip is smaller in the withdrawn group, with the total hip reported as 1.013 g/cm^2 from the 30 participants, and 0.941 g/cm^2 from the five participants in the withdrawn group, although there is no reported statistical significance reported.

5.4 METHOD, IMAGING

Those who were eligible and who had consented were sent a pre-op letter with the date and time for a physiotherapy appointment and DXA scan (appendix 7).

5.4.1 DXA IMAGING METHOD

Prior to their rTKR all 37 participants were invited to undergo a pre-operative BMD evaluation via a DXA scan (GE Lunar prodigy, Bedford, MA). This involved scanning the total body, bilateral hips, and lumbar spine.

TOTAL BODY POSITIONING

The patient should be situated in the supine position and placed within the boundaries of the white lined marks on top of the DXA bed; they should be straight and in the midline of the scanner table. The pelvis should not be rotated, and the anterior superior iliac spines (ASIS) should be equidistant. The legs should be separated via the midline and slightly internally rotated to make them straight, the arms are placed by the patient's side with palms of the hands resting against the side of the patient in the lateral position, with the thumbs closest to the scanner arm, positioning should be checked to make sure the hands are not obstructed or placed under the patient's buttocks [406].

If the patient was too tall to fit within the boundaries of the box then the patient would be placed outside the box at the superior aspect, as to include the feet and disregard the head. Furthermore, if the patient was obese it was difficult to

fit the patient within the boundaries, so support bands were placed to allow the elbows to be tucked in, if not then one side would be sacrificed, with repeated imaging following the same protocol and excluding the same anatomy, as this will affect the BMD result.

Scanning begins at the superior aspect of the scan field moving in sweeps towards the patient's feet, the scan may be stopped once the scanner arm has cleared the patient's feet [406].

LUMBAR SPINE POSITIONING

The patient lies supine on the scanner table with their arms either side, with no rotation, and their ASIS should be equidistant. They should be straight in order to make sure the spine is in the midline of the scanning field with equal amounts of soft tissue on either side of the spinal column. The knees are raised onto a supporting pad flexing them at 90° to reduce the lumbar lordosis and open the intervertebral spaces [406].

The laser positioning crosshair is centred in the midline 1.5 cm below the iliac crests as to include half of the fifth lumbar vertebrae [406]. Scanning starts at this level and goes towards the patient's head, ending at the top of twelfth thoracic vertebrae [406].

FEMORAL HIP POSITIONING

The patient is placed supine on the table; rotation is checked via the ASIS being equidistant from the tabletop. The patient's arms are placed on their chest away from the scanning area. The foot support is placed between the patient's legs, abducting the leg to be scanned approximately 15° away from the midline. The whole leg is then internally rotated through 15° and strapped into place [406].

This abduction of the leg separates the ischium of the pelvis from the lesser trochanter of the femur, as to not include it in the analysis. Furthermore, the internal rotation of the whole leg brings the lesser trochanter posterior and the greater trochanter anteriorly, with the femoral neck ending up parallel to the scanner table top, this avoids a foreshortening effect of the neck which can cause BMD measurements to be falsely elevated [406]. It must also be

acknowledged that in slender individuals, if necessary, rice bags should be placed either side of the upper femur to simulate soft tissue. This prevents edge detection artefacts that result in false measurements [406].

The laser positioning crosshair is then centred two inches below the greater trochanter and is on the medial side of the femoral shaft [407].

PATIENT PREPARATION

Prior to any DXA scans the patient should be asked if they have undergone any recent nuclear medicine scans, as gamma rays emitted by any remaining radionuclide will cause an additional erroneous signal in the detectors of the DXA scanner which might affect the accuracy of the BMD measurements [406]. Furthermore, any recent X-ray examination using contrast media should also be investigated [408], as a radiopaque contrast medium will most likely produce additional attenuation of the DXA scanner X-ray beam, affecting the accuracy of the BMD measurements. Any contrast media within the bone will falsely increase the reported BMD, while contrast media in any adjacent soft tissue will affect the soft tissue reference comparator, resulting in a falsely low BMD measurement [406].

All metal should be removed from the patient prior to scanning in order that no artefacts are in the regions of interest being scanned; this again is similar to contrast media in which the metal can falsely elevate the BMD causing spurious measurements as well as artefacts on the image.

DXA QA

Prior to, and throughout the study the DXA scanner underwent Quality Assurance (QA) via a daily precision BMD block and a manufacturer-supplied aluminium weekly spine phantom (number 15867). Over the period of the study the results of the daily QA are shown in figure 5.1 below (pre-COVID when the study stopped).

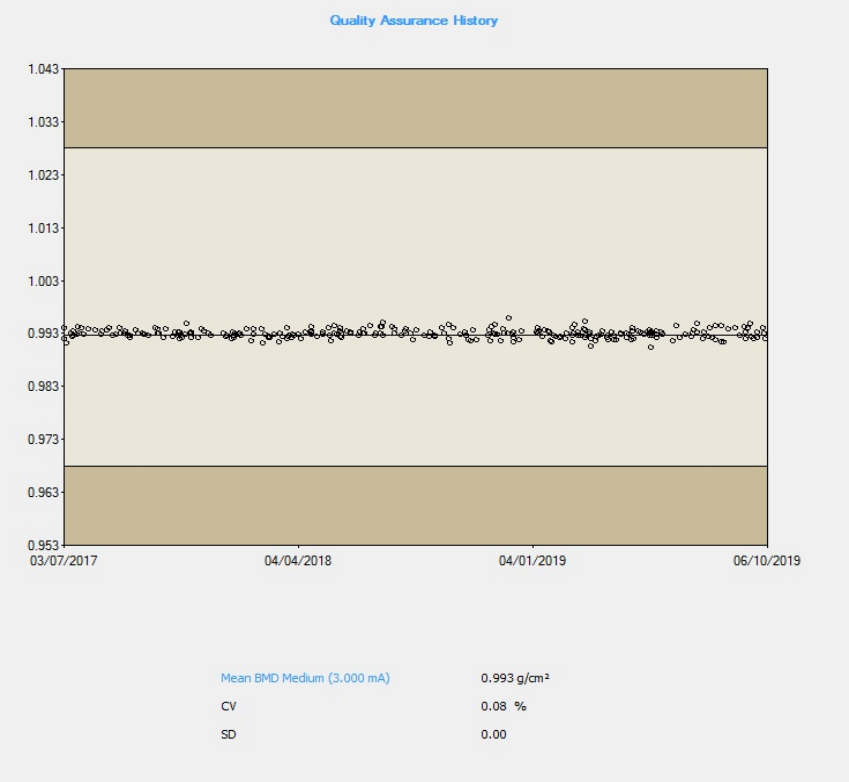


Figure 5.1. *Showing the QA precision BMD block deviation over the study period of 3/07/17 to 6/10/19 (pre-COVID).*

In addition to the QA block, a COV was calculated for the spine phantom over the same period (pre-COVID), with a reported score of 0.39 % COV this is shown in figure 5.2.

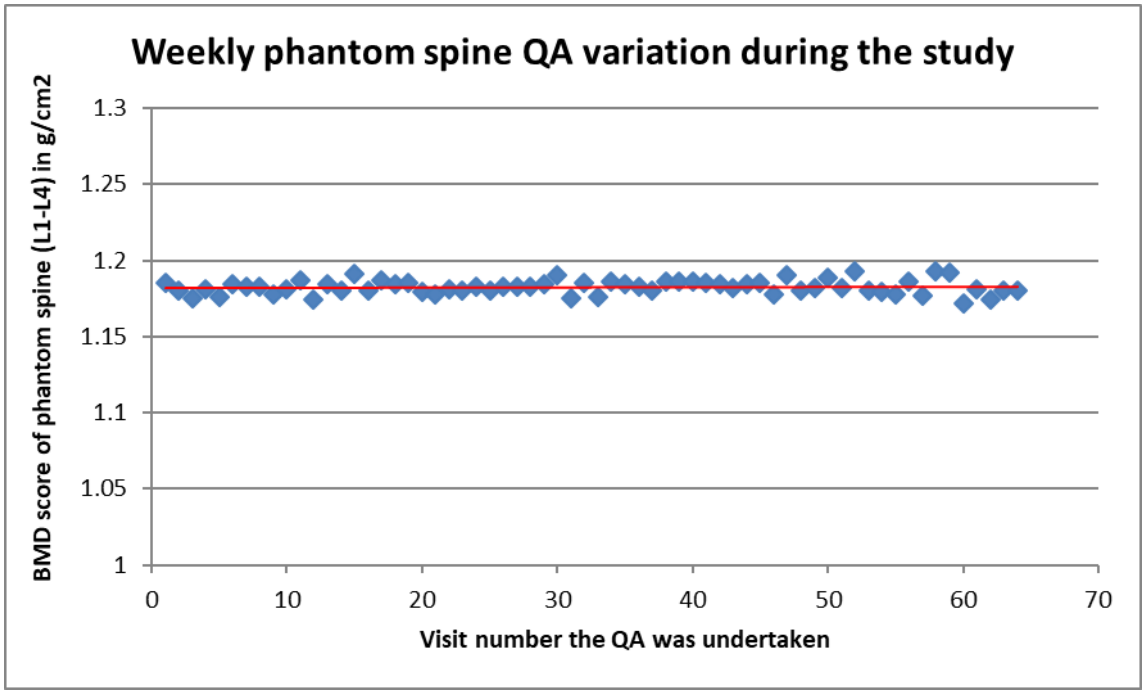


Figure 5.2. *Showing the phantom QA spine BMD for L1-L4 over the study period of 3/07/17 to 6/10/19 (Pre-COVID).*

The precision results from both QA tools are well within the reported precision errors and these ensured safe and accurate operation throughout the study. Once QA checks had been completed and a participant had arrived, their identity was checked utilising the checklist (appendix 8) and they were given a brief description of the scan and any issues/questions were addressed. Furthermore, their date of birth and ethnicity were inputted into the scanner as well as their height (Seca, Germany) to the nearest 0.1 m, and weight (Seca 877, Germany) to the nearest 0.1 kg, which was measured by the researcher prior to the scan.

APPOINTMENTS

Dual Energy X-ray Absorptiometry scans (this time includes the DXA knee scan as well, stated in chapter six) took approximately 90-120 minutes per session, with future scans arranged at dates and times that coincided with their physiotherapy, consultation, and other scans (x-ray and CT; which will be mentioned in subsequent chapters); this was done to reduce participant travel fatigue. All participants were provided parking, with the option of a wheelchair escort or crutches in order make their way to the scanner (approximately a five minute walk from the parking area).

5.4.2 TIME SCALE FOR SCANS

After rTKR surgery participants had follow up DXA and physiotherapy appointments at six weeks post operation (this was defined as one week before or one week after the exact six week post-op date), and then at three (defined as one week before and two weeks after the exact three month date), six (defined as one week before and two weeks after the exact six month date), and 12 months (defined as two weeks before and four weeks after the exact 12 month date).

5.5 ANALYSIS OF IMAGING

5.5.1 DXA TOTAL BODY, LUMBAR SPINE, AND BILATERAL HIPS ANALYSIS

All DXA scans followed the positioning protocol already stated in section 5.3.1, will all images were analysed using the GE Lunar enCORE™ 2005 software

(version 9.30.044). This software automatically detects the bone edges of the regions of interest (ROI), and subdivides those regions, in conjunction with categorising bone, soft tissue, air, and artefact. It must be noted that manual modification to the images was undertaken by the researcher (MG), in order that correct anatomy or artefact was classified. All BMD figures were recorded in a Microsoft Excel spreadsheet, and a DXA report with their T-score was created (an example is shown in appendix 9) by KK, which was sent to the referring physician AT as was the analysed data.

The DXA scan report utilised the data from the total body (figure 5.3), bilateral hips (figure 5.4), and lumbar spine (figure 5.5).

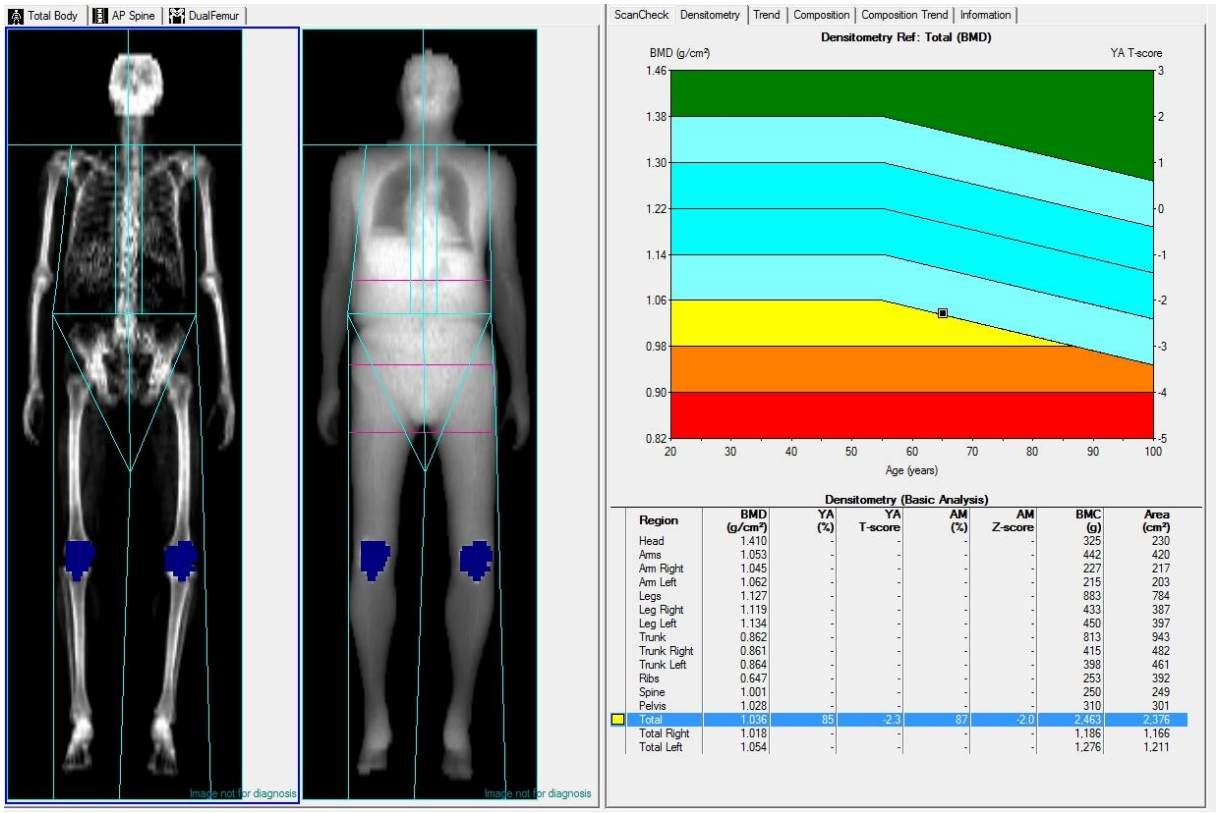


Figure 5.3. *Shows a standard total body DXA scan (the software has highlighted the knee replacements as artefacts in blue), the total body is divided into ROI with each region reporting a BMD (g/cm^2) as well as a total score for the body. These ROI can be moved or modified, as to more correctly represent the anatomy.*

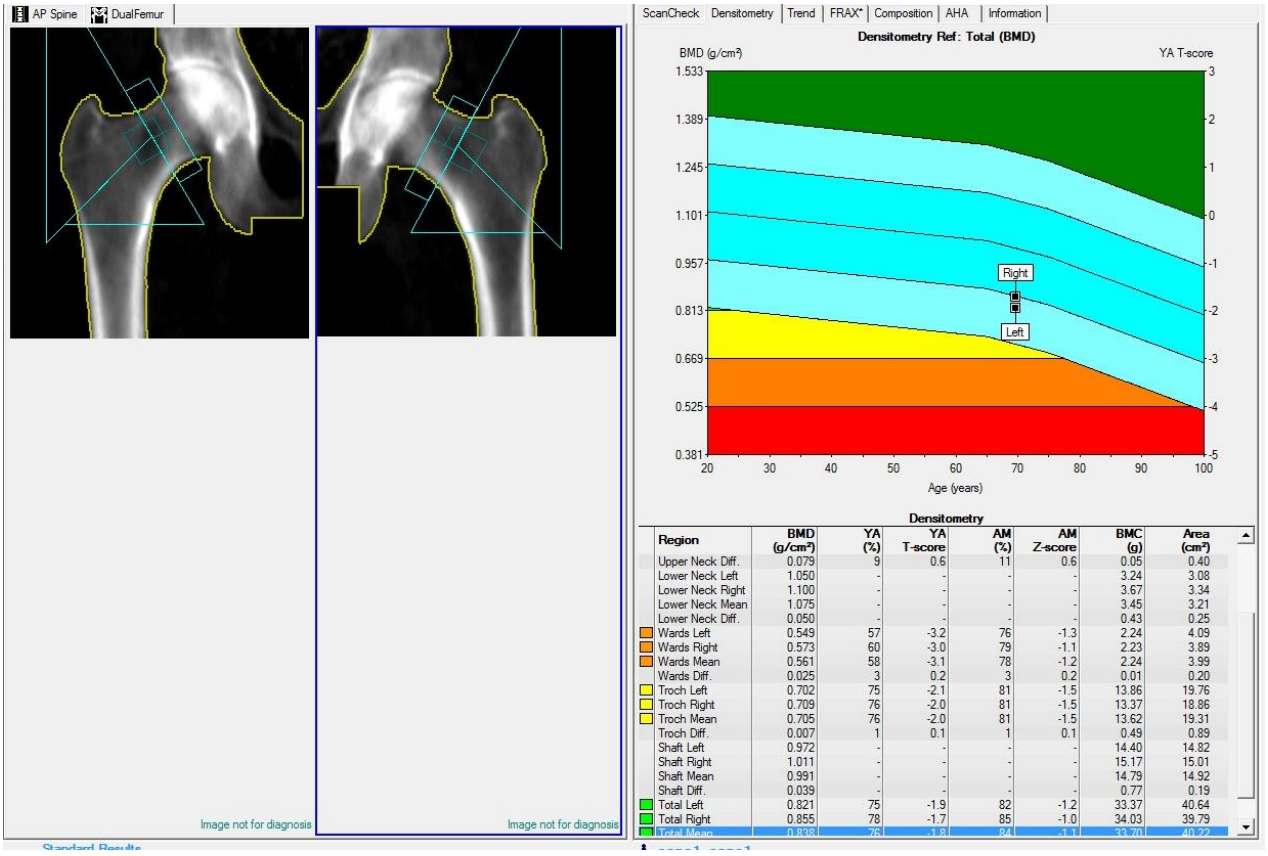


Figure 5.4. *DXA scan of standard bilateral hips. Each hip is divided into ROI with each region reporting a BMD (g/cm^2) as well as a total hip score. These ROI can be moved or modified, as to more correctly represent the anatomy.*

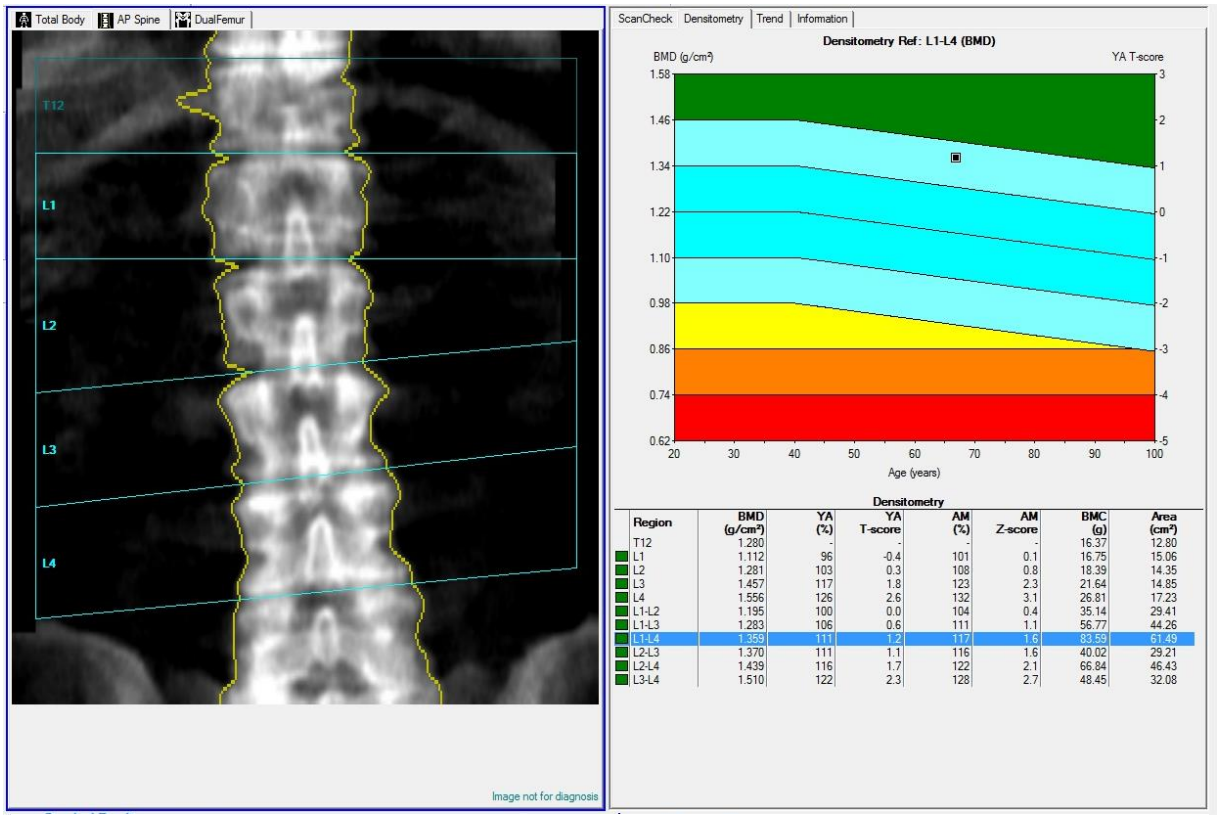


Figure 5.5. *DXA scan of a standard lumbar spine (PA). The lumbar spine is divided into ROI with each region reporting a BMD (g/cm2) and a total lumbar spine (L1-L4) calculated, these ROI can be moved or modified, as to more correctly represent the anatomy.*

The 37 participants DXA images across all five appointments were separated into their participant groups: with cones, and non-cones (24 and 13 respectively). The 24 participants with cones had their DXA images intracompared between the anatomical sites at the pre-op and each post-op visit. Total body scans were compared from each visit to their original pre-op baseline, and all BMD differences between each scan recorded in a Microsoft Excel spreadsheet. The hip BMD underwent the same comparison for both the ipsilateral and contralateral hip, with additional data collected via sub regions of the hip: the trochanter, neck of femur, wards triangle, femoral shaft, and the total hip BMD, again all compared to their pre-op scan. The lumbar spine scan was intracompared per lumbar vertebrae for L1, L2, L3, L4, and as a total of L1-L4. These differences in BMD were re-calculated as a percentage difference for each visit, either as a gain or a loss when compared to their pre-op data.

A mean, standard deviation (SD) and standard error (SE) was calculated for both the BMD difference and the calculated percentage difference as well as a

95 % CI. A paired samples t-test (assuming normal distribution as reported in similar studies [23]) was also undertaken to compare the differences, to see if the changes were statistically significant, and a p-value recorded.

All of these visit comparisons to the pre-op scan involved overlaying the original region data from the pre-op DXA scans and manually modifying (if needed) the ROI to correctly cover the anatomy of the latest scan, an example of this is shown in figures 5.6 and 5.7.

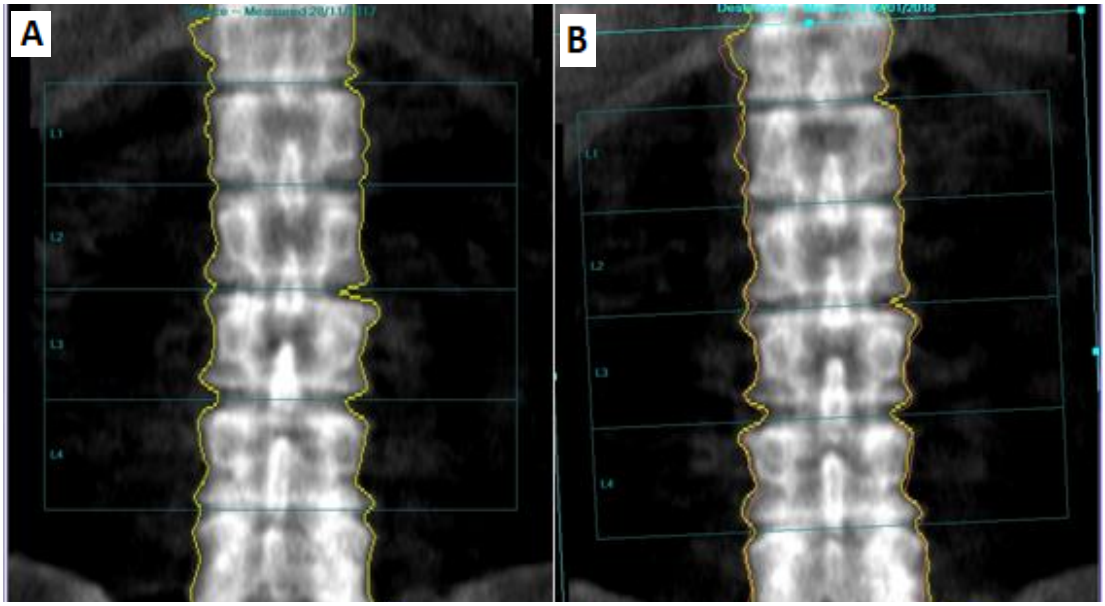


Figure 5.6. *DXA scan showing lumbar spine (PA) original pre-op ROI (A) overlaid on the six week post-surgery scan (B). This overlap is represented by a redish line seen in image B, the overlap is nearly perfect except for some slight variations at L1 and L4 where the two images do not quite overlap directly.*

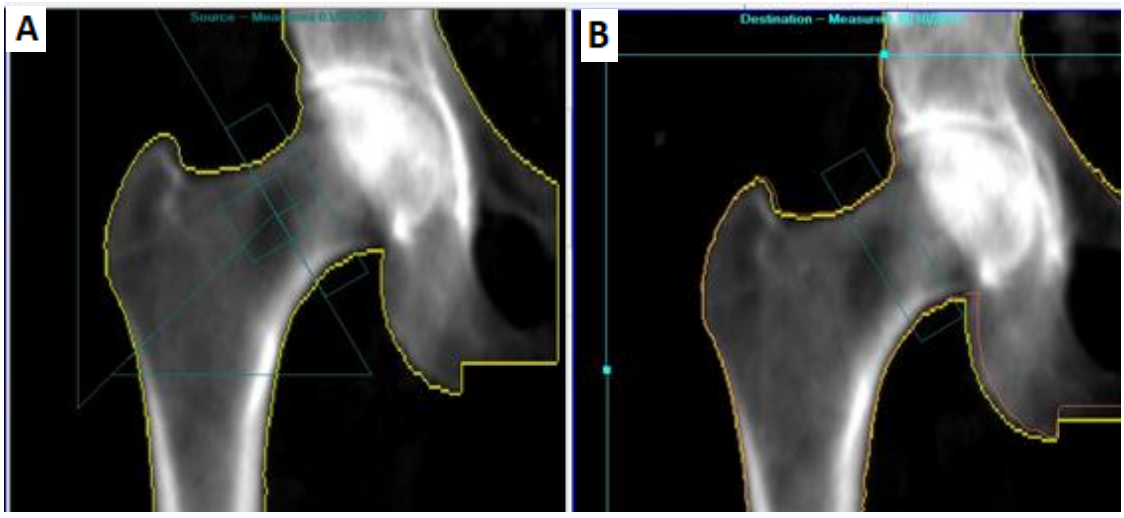


Figure 5.7. *DXA scan of the hip showing the original pre-op ROI (A) overlaid on the three month post-surgery scan (B). The redish outline on image B represents the ROI from image A i.e near the ischium of B the overlap is less accurate, but the femoral shaft and neck overlap perfectly.*

The 13 non-cone participants underwent the same intracomparison analysis, calculated mean, SD, SE, and the same statistical paired samples t-test and p-value.

Both groups also had this mean percentage difference compared between the ipsilateral and contralateral hip (with the contralateral hip acting as a control), at each of the appointments. Again, a SD, SE and a paired samples t-test was utilised and a p-value created. Any participants who had a THR on either side meant their other hip data were automatically excluded from this direct comparison between the ipsilateral and contralateral hip (due to no comparison being able to be made).

Additionally, as well as the comparisons of the percentage changes (when compared to baseline), the direct mean BMD results were reported and compared in the hip data between the ipsilateral and contralateral of each participant at each visit for both cone and non-cone participants with a mean BMD calculated, SD, SE and t-critical score and p-value.

The data analysis has so far compared the total body, lumbar spine, and bilateral hips to their pre-op baseline data, in addition to the ipsilateral hip data being compared to the contralateral hip data for each group, in both percentage change and BMD. A comparison between the cone and non-cone group for each appointment visit was also performed. Therefore at six weeks the mean percentage difference (compared to baseline) cone data for the total body, lumbar spine, ipsilateral and contralateral hip was compared to the non-cone percentage difference (compared to baseline) six week data for the same regions, this will be repeated for the three, six and 12 months with a SD, SE, as well as an independent t-test assuming unequal variance producing a t-critical score and p-value.

Furthermore, the reported mean BMD for each region was also compared between cone and non-cone including the pre-op score. This gave me additional data not just on the percentage changes but the actual absolute values that were involved, a SD, SE, as well as an independent t-test assuming unequal variance and p-value was again produced.

5.6 BMD DXA RESULTS OF THE TOTAL BODY AND LUMBAR SPINE

This section will now report the BMD results for the total body and lumbar spine (the hip results will follow on in section 5.7). The results follow the analysis stated previously, with data compared between each participant's visits (six week, three month, six month and 12 month) to their baseline (pre-op) scan, with an average difference in both g/cm^2 and percentage change calculated for both the cone and non-cone group, these results were then compared between the two groups.

Table 5.6. *Shows the average baseline (pre-op) BMD (g/cm^2) for the total body, and lumbar spine for the cone group (N=22) and non-cone group*

	TOTAL BODY (g/cm^2)	L1 (g/cm^2)	L2 (g/cm^2)	L3 (g/cm^2)	L4 (g/cm^2)	L1-L4 (g/cm^2)
			CONE (N=22)			
AVERAGE	1.225	1.147	1.273	1.349	1.375	1.292
SD	0.147	0.239	0.264	0.296	0.318	0.273
SE	0.031	0.051	0.056	0.063	0.068	0.058
			NON-CONE (N=13)			
AVERAGE	1.230	1.036	1.171	1.301	1.331	1.220
SD	0.128	0.161	0.186	0.218	0.251	0.188
SE	0.036	0.045	0.052	0.060	0.070	0.052

Table 5.6 shows the mean BMD in g/cm^2 baseline results of the 35 pre-op participants, it must be noted that the comparisons to baseline in the following results tables and figures involved comparing the participants BMD visit score with their own baseline score to report a direct percentage change.

5.6.1 BMD PERCENTAGE DIFFERENCE WHEN COMPARED TO PRE-OP FOR TOTAL BODY AND LUMBAR SPINE FOR CONE AND NON-CONE GROUPS

Table 5.7. *Shows the results for the cone group compared to baseline, for percentage change, confidence intervals (95 %), t-test, and p-value.*

6 WEEK (N=18)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.018	1.491	0.648	2.330	1.826	0.430	3.337	**0.004**
L1 (g/cm²)	-0.004	-0.195	-2.060	1.680	4.046	0.954	-0.417	0.682
L2 (g/cm²)	0.003	0.334	-2.110	2.770	5.285	1.246	0.188	0.853
L3 (g/cm²)	-0.010	-0.486	-2.070	1.090	3.427	0.808	-0.852	0.406
L4 (g/cm²)	0.007	0.610	-1.040	2.260	3.574	0.842	0.550	0.590
L1-L4 (g/cm²)	-0.001	0.060	-1.200	1.320	2.725	0.642	-0.083	0.935
3 MONTHS (N=18)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.016	1.220	0.790	1.220	1.709	0.403	3.063	**0.007**
L1 (g/cm²)	-0.015	-1.169	-3.690	1.350	5.448	1.284	-0.917	0.372
L2 (g/cm²)	-0.014	-1.006	-3.130	1.110	4.587	1.081	-1.000	0.331
L3 (g/cm²)	-0.006	-0.363	-1.430	0.707	2.309	0.544	-0.868	0.397
L4 (g/cm²)	-0.010	-0.641	-1.720	0.439	2.333	0.550	-1.248	0.229
L1-L4 (g/cm²)	-0.012	-0.810	-1.500	-0.123	1.487	0.351	-2.349	**0.031**
6 MONTHS (N=17)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.013	1.012	0.262	1.760	1.578	0.383	2.593	**0.020**
L1 (g/cm²)	-0.001	-0.086	-2.660	2.480	5.414	1.313	-0.070	0.945
L2 (g/cm²)	-0.009	-0.697	-2.570	1.170	3.926	0.952	-0.783	0.445
L3 (g/cm²)	-0.002	0.231	-1.480	1.940	3.599	0.873	-0.205	0.840
L4 (g/cm²)	-0.001	0.313	-1.920	2.540	4.685	1.136	-0.035	0.972
L1-L4 (g/cm²)	-0.003	-0.079	-1.250	1.090	2.456	0.596	-0.409	0.688
12 MONTHS (N=15)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.015	1.187	0.489	1.890	1.379	0.356	3.300	**0.005**
L1 (g/cm²)	0.003	0.544	-1.370	2.450	3.772	0.974	0.305	0.765
L2 (g/cm²)	0.006	0.671	-1.870	3.210	5.010	1.294	0.393	0.701
L3 (g/cm²)	-0.007	-0.207	-2.360	1.940	4.248	1.097	-0.484	0.636
L4 (g/cm²)	0.012	0.975	-0.645	2.600	3.195	0.825	0.980	0.344
L1-L4 (g/cm²)	0.004	0.440	-0.940	1.820	2.719	0.792	0.415	0.684

Table 5.7 reports the changes in the cone group when compared to their baseline measurement, BMD in the total body in the cone group increases at six

weeks, but starts to drop after this period, until at 12 months were there is a slight increase (1.187 % (p-value 0.005)) compared to six months (1.012 %). The lumbar spine reports small amounts of changes primarily BMD loss, with the highest loss in L1 and L2 at three months, with an overall L1-L4 change of -0.810 %, although this has recovered by six months to -0.079 % and is reported as a positive at 12 months of 0.440 %.

Table 5.8. *Shows the results for the non-cone group compared to baseline, for percentage change, confidence interval (95 %), t-test, and p-value.*

6 WEEK (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.008	0.567	-0.663	1.800	1.774	0.627	1.031	0.337
L1 (g/cm²)	0.005	0.385	-2.460	3.220	4.093	1.447	0.316	0.761
L2 (g/cm²)	0.040	2.984	-0.486	6.450	5.003	1.769	1.836	0.110
L3 (g/cm²)	0.031	1.987	-1.610	5.590	5.129	1.813	1.032	0.337
L4 (g/cm²)	0.028	1.863	0.043	3.680	2.631	0.930	1.650	0.143
L1-L4 (g/cm²)	0.026	1.752	-0.158	3.660	2.757	0.975	1.650	0.143
3 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.008	0.655	-0.575	1.890	1.772	0.626	1.052	0.333
L1 (g/cm²)	-0.004	-0.254	-4.380	3.880	5.953	2.105	-0.203	0.845
L2 (g/cm²)	0.018	1.158	-3.470	5.790	6.687	2.364	0.651	0.536
L3 (g/cm²)	0.009	0.543	-2.350	3.430	4.165	1.473	0.421	0.687
L4 (g/cm²)	0.038	3.212	-1.080	7.500	6.192	2.189	1.309	0.232
L1-L4 (g/cm²)	0.016	1.280	-0.610	3.170	2.734	0.967	1.261	0.248
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	0.002	0.155	-1.020	1.330	1.697	0.600	0.323	0.756
L1 (g/cm²)	-0.020	-1.916	-3.980	0.144	2.978	1.053	-1.847	0.107
L2 (g/cm²)	-0.002	-0.869	-6.170	4.430	7.654	2.706	-0.070	0.946
L3 (g/cm²)	0.020	1.543	-2.830	5.910	6.305	2.229	0.774	0.464
L4 (g/cm²)	0.029	2.038	-1.400	5.480	4.959	1.753	1.300	0.235
L1-L4 (g/cm²)	0.009	0.448	-1.460	2.360	2.757	0.975	0.719	0.495
12 MONTHS (N=7)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Total body (g/cm²)	-0.006	-0.458	-1.260	1.670	1.634	0.618	-0.740	0.487
L1 (g/cm²)	0.005	0.491	-2.260	3.240	3.715	1.404	0.331	0.752
L2 (g/cm²)	0.031	2.104	-1.780	5.980	5.236	2.013	1.229	0.684
L3 (g/cm²)	0.007	-0.019	-4.530	4.490	6.093	2.303	0.203	0.846
L4 (g/cm²)	0.019	1.391	-1.070	3.850	3.321	1.255	1.097	0.684
L1-L4 (g/cm²)	0.016	1.022	-1.240	3.280	3.051	1.153	1.009	0.352

Table 5.8 reports the changes in the non-cone group when compared to their baseline measurement, BMD in the total body increases at six weeks but by 0.567 %, resulting in a loss by 12 months of -0.458 %. The lumbar spine shows small amounts of changes primarily BMD increases, with the highest gain reported at L4 of 3.212 % (p-value of 0.232) at three months, although none of the changes are statistically significant.

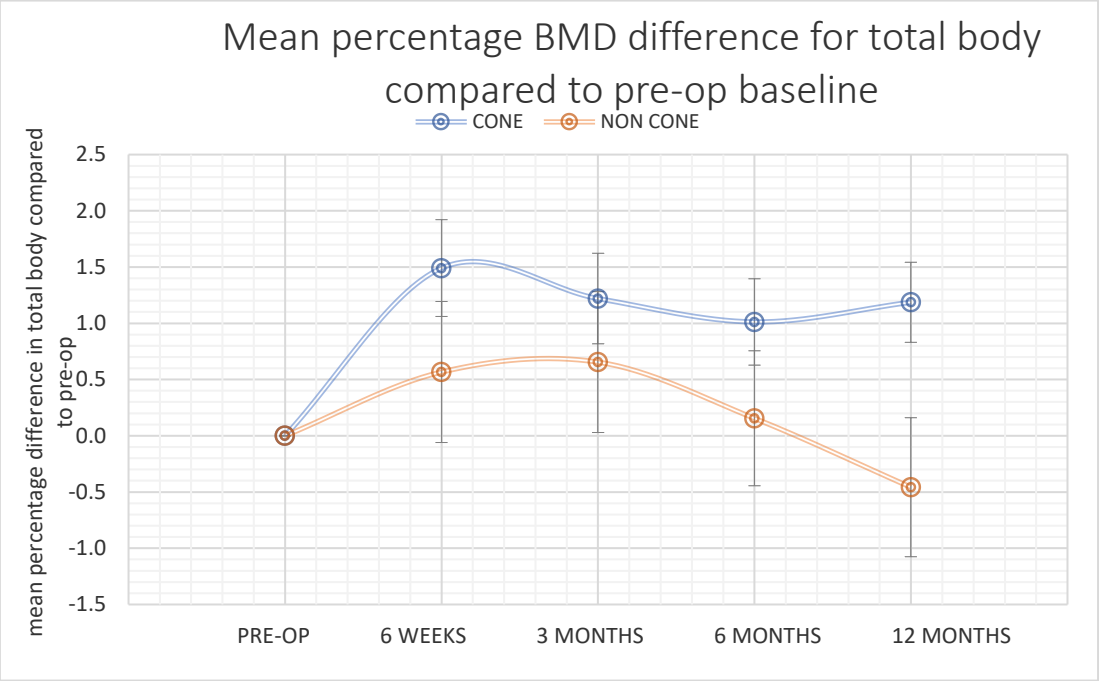


Figure 5.8. *Shows total body mean BMD changes across 12 months for cone and non-cone participants, error bars are SE*

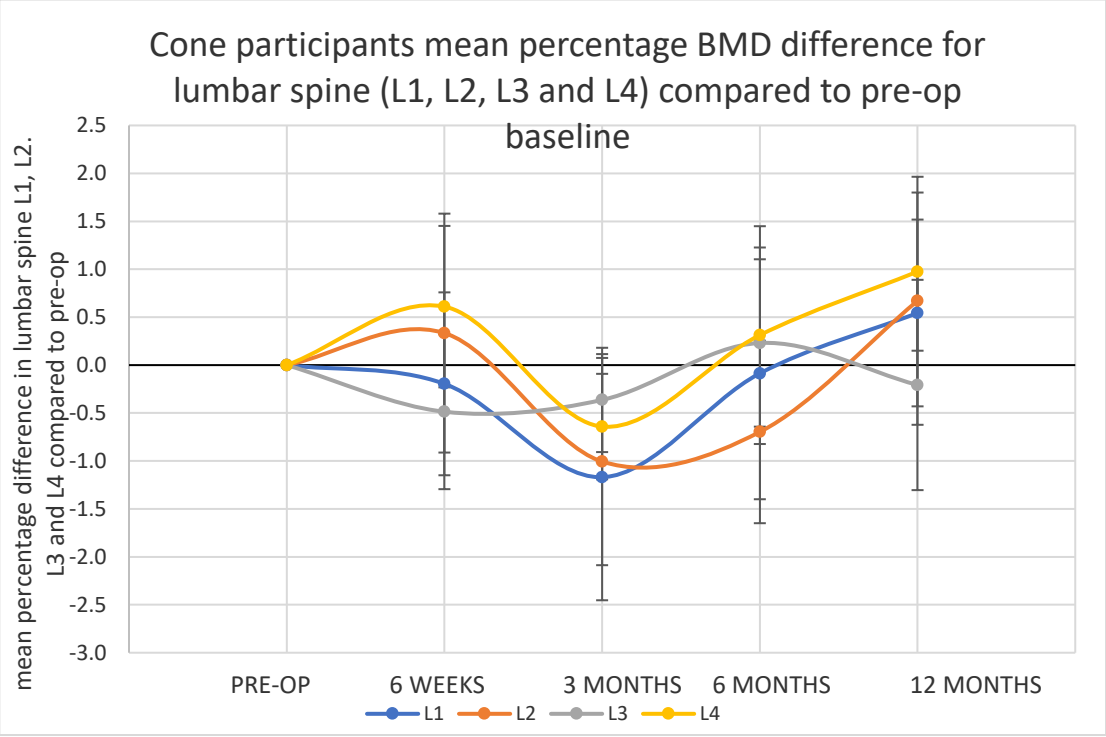


Figure 5.9. *Shows individual lumbar spine for cone participants as reported mean BMD changes over 12 months, error bars are SE*

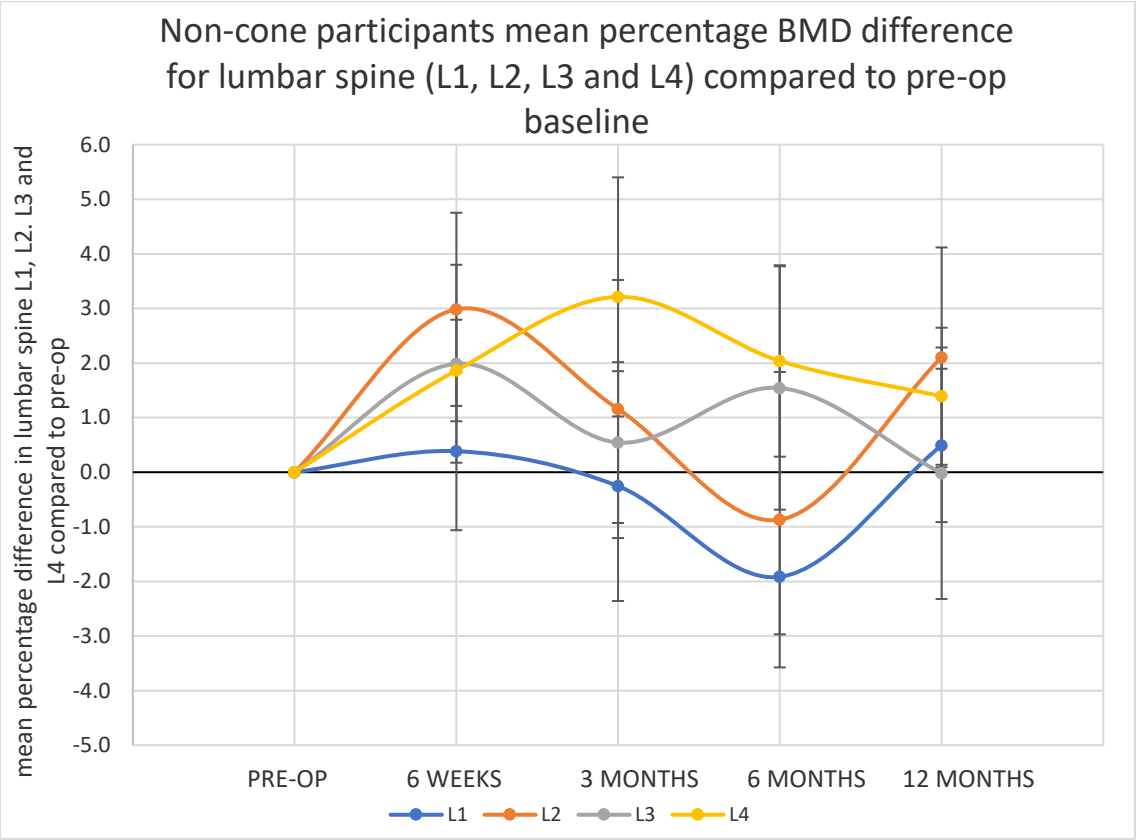


Figure 5.10. *Shows individual lumbar spine for non-cone participants as reported mean BMD changes over 12 months, error bars are SE*

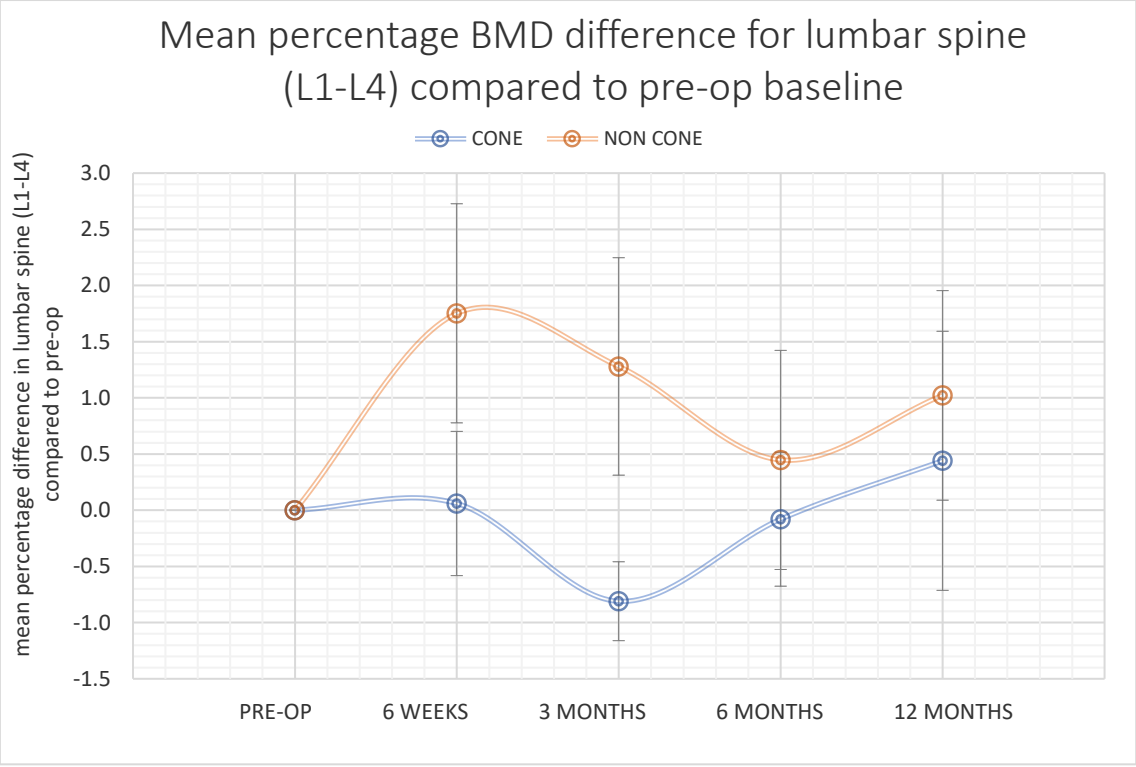


Figure 5.11. *Shows total lumbar spine mean BMD changes across 12 months for cone and non-cone participants, error bars are SE.*

The data shown in tables 5.7 and 5.8 is expressed visually in figures 5.8-5.11 to show the trends of BMD change in the cone and non-cone group over a 12 month period, for the total body and lumbar spine.

5.6.2 COMPARISON BETWEEN CONE AND NON-CONE GROUPS FOR BMD PERCENTAGE DIFFERENCE AND BMD MEAN, FOR TOTAL BODY AND LUMBAR SPINE

A direct comparison between the cone and non-cone group for BMD percentage change and absolute BMD difference is shown in tables 5.9 and 5.10.

Table 5.9*. Shows percentage differences between visits compared between cone and non-cone compared to their pre-op baseline*

6 WEEKS (% DIFFERENCE)	***CONE (N=18)***	***NON-CONE (N=8)***	***T-CRITICAL***	***P-VALUE***	***3 MONTHS (% DIFFERENCE)***	***CONE (N=18)***	***NON-CONE (N=8)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.491	0.567	-1.215	0.244	***TOTAL BODY***	1.220	0.655	-0.759	0.462
L1	-0.195	0.385	0.335	0.743	***L1***	-1.169	-0.254	0.371	0.717
L2	0.334	2.984	1.225	0.241	***L2***	-1.006	1.158	0.832	0.425
L3	-0.486	1.987	1.246	0.241	***L3***	-0.363	0.543	0.577	0.578
L4	0.610	1.863	0.998	0.332	***L4***	-0.641	3.212	1.707	0.126
L1-L4	0.060	1.752	1.450	0.171	***L1-L4***	-0.810	1.280	2.033	0.073
6 MONTHS (% DIFFERENCE)	***CONE (N=17)***	***NON-CONE (N=8)***	***T-CRITICAL***	***P-VALUE***	***12 MONTHS (% DIFFERENCE)***	***CONE (N=15)***	***NON-CONE (N=7)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.012	0.155	-1.204	0.250	***TOTAL BODY***	1.187	-0.046	2.307	**0.044**
L1	-0.086	-1.916	-1.087	0.289	***L1***	0.491	0.544	0.031	0.975
L2	-0.697	-0.869	-0.060	0.954	***L2***	2.104	0.671	-0.599	0.561
L3	0.231	1.543	0.548	0.597	***L3***	-0.019	-0.207	-0.074	0.943
L4	0.313	2.038	0.825	0.424	***L4***	1.391	0.975	-0.277	0.787
L1-L4	-0.079	0.448	0.461	0.653	***L1-L4***	1.022	0.440	-0.431	0.675

Table 5.10. *Shows the BMD differences at all visits compared between cone and non-cone group*

PRE-OP (MEAN BMD g/cm²)	***CONE (N=22)***	***SD***	***SE***	***NON-CONE (N=13)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.225	0.147	0.031	1.230	0.128	0.036	-0.005	-0.106	0.916
L1	1.147	0.239	0.051	1.036	0.161	0.045	0.112	1.653	0.108
L2	1.273	0.264	0.056	1.171	0.186	0.052	0.101	1.324	0.195
L3	1.349	0.296	0.063	1.301	0.218	0.060	0.048	0.550	0.586
L4	1.375	0.318	0.068	1.331	0.251	0.070	0.044	0.449	0.656
L1-L4	1.292	0.273	0.058	1.220	0.188	0.052	0.071	0.911	0.369
6 WEEKS (MEAN BMD g/cm²)	***CONE (N=18)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.254	0.146	0.034	1.247	0.162	0.057	0.007	0.098	0.924
L1	1.170	0.221	0.052	1.070	0.160	0.056	0.100	1.303	0.209
L2	1.301	0.269	0.063	1.232	0.241	0.085	0.069	0.652	0.524
L3	1.381	0.278	0.066	1.362	0.304	0.107	0.020	0.155	0.879
L4	1.433	0.295	0.070	1.376	0.322	0.114	0.057	0.428	0.676
L1-L4	1.328	0.257	0.061	1.268	0.254	0.090	0.060	0.558	0.585
3 MONTH (MEAN BMD g/cm²)	***CONE (N=18)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.251	0.153	0.036	1.247	0.147	0.052	0.004	0.071	0.945
L1	1.159	0.223	0.053	1.061	0.141	0.050	0.098	1.356	0.190
L2	1.284	0.263	0.062	1.210	0.245	0.086	0.074	0.692	0.500
L3	1.385	0.287	0.068	1.340	0.279	0.099	0.045	0.375	0.713
L4	1.415	0.289	0.068	1.386	0.282	0.100	0.029	0.243	0.811
L1-L4	1.317	0.257	0.061	1.258	0.226	0.080	0.059	0.587	0.566
6 MONTH (MEAN BMD g/cm²)	***CONE (N=17)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.254	0.157	0.038	1.209	0.145	0.051	0.046	0.715	0.486
L1	1.185	0.233	0.057	0.981	0.181	0.064	0.204	2.382	**0.028**
L2	1.303	0.266	0.065	1.114	0.267	0.094	0.189	1.654	0.120
L3	1.399	0.274	0.067	1.292	0.281	0.099	0.107	0.896	0.386
L4	1.434	0.286	0.069	1.344	0.309	0.109	0.090	0.692	0.501
L1-L4	1.338	0.256	0.062	1.197	0.244	0.086	0.141	1.326	0.206
12 MONTH (MEAN BMD g/cm²)	***CONE (N=15)***	***SD***	***SE***	***NON-CONE (N=7)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
TOTAL BODY	1.251	0.159	0.041	1.247	0.155	0.059	0.004	0.061	0.953
L1	1.169	0.216	0.056	1.086	0.152	0.057	0.083	1.043	0.312
L2	1.298	0.276	0.071	1.248	0.250	0.094	0.050	0.427	0.677
L3	1.368	0.287	0.074	1.359	0.321	0.121	0.009	0.059	0.954
L4	1.434	0.316	0.082	1.376	0.319	0.121	0.058	0.399	0.697
L1-L4	1.325	0.266	0.069	1.298	0.256	0.097	0.050	0.418	0.683

Table 5.9 and 5.10 show the comparison between both groups for BMD and percentage changes, the results show that at six weeks the total body BMD results were very similar (1.225 g/cm^2 and 1.230 g/cm^2), showing a lack of difference in BMD even though the percentage change between six weeks and pre-op shows an increase of 1.491 % in the cone group and 0.567 % in the non-cone group. The difference in BMD between the groups shows the cone group having a mean BMD higher than the non-cone group at every visit and at every region (except total body pre-op), with two statistically significant, one at six months in the L1 region reporting a BMD difference of 0.204 g/cm^2, this concurs with the percentage change, that for the same region and visit reports a score of -0.086 % with the cone group (when compared to baseline) and the non-cone group reporting a score of -1.916 % (the highest loss of the non-cone group), especially as the majority of the lumbar spine data report an increase compared to baseline. The second is the total body score reported as a gain of 1.187 % in the cone group and a loss of -0.458 % in the non-cone group (p-value 0.04).

5.7 HIP DATA ANALYSIS

The results in the following section are from the hip DXA analysis BMD data, both compared to the baseline measure for the ipsilateral and contralateral hip and between the hips and groups. Table 5.11 show the reported BMD at the hip ipsilateral and contralateral for both cone and non-cone participants.

Table 5.11. *Shows the mean baseline/pre-op BMD for the rTKR ipsilateral and contralateral hip in rTKR cone (N=22) and non-cone (N=13) participants prior to surgery (N=22)*

CONE (N=22)						
DXA MEASUREMENTS (g/cm^2)	**Ipsilateral (mean)**	**SD**	**SE**	**Contralateral (mean)**	**SD**	**SE**
BMD Neck (g/cm^2)	0.953	0.123	0.028	0.985	0.155	0.034
BMD Wards (g/cm^2)	0.731	0.166	0.037	0.730	0.148	0.032
BMD Troch (g/cm^2)	0.882	0.197	0.044	0.878	0.197	0.043
BMD Shaft (g/cm^2)	1.169	0.187	0.042	1.163	0.185	0.040
BMD Total (g/cm^2)	1.013	0.171	0.038	1.016	0.170	0.037
NON-CONE (N=13)						
DXA MEASUREMENTS (g/cm2)	**Ipsilateral (mean)**	**SD**	**SE**	**Contralateral (mean)**	**SD**	**SE**
BMD Neck (g/cm2)	0.943	0.161	0.047	0.936	0.173	0.048
BMD Wards (g/cm2)	0.680	0.180	0.052	0.719	0.181	0.050
BMD Troch (g/cm2)	0.819	0.238	0.069	0.853	0.210	0.058
BMD Shaft (g/cm2)	1.156	0.221	0.064	1.195	0.206	0.057
BMD Total (g/cm2)	0.982	0.192	0.055	1.014	0.183	0.051

Baseline results of the 35 pre-op participants are shown in table 5.11, these show that on average the ipsilateral hip has an overall lower BMD compared to the contralateral, in both groups. It must be noted that the comparisons to baseline in the following results involved directly comparing the participants BMD with their baseline BMD as with the previous total body and lumbar spine analysis. Therefore, as participants dropped out at post-op intervals the overall baseline would reflect only the participants who remained.

5.7.1 RESULTS OF CONE PARTICIPANTS IPSILATERAL AND CONTRALATERAL HIP REGIONS

Table 5.12 and figure 5.12 show the results from the cone participants in the ipsilateral hip when compared to their baseline score, and the subsequent percentage changes reported between visits. It must be noted that one of the cone participants had a TKR in their contralateral knee between the six and 12 month visit, thus their contralateral hip data were excluded.

Table 5.12. *Shows the BMD ipsilateral cone results to 3 d.p. including percentage change, confidence intervals (95 %), t-test, and p-value*

6 WEEK (N=16, 18 COMPLETED BUT TWO HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.036	3.580	1.520	5.640	4.469	1.117	3.381	**0.004**
BMD Wards (g/cm²)	0.020	2.102	-0.078	4.280	4.727	1.182	2.167	**0.047**
BMD Troch (g/cm²)	-0.018	-2.043	-3.190	-0.893	2.496	0.624	-2.844	**0.012**
BMD Shaft (g/cm²)	-0.009	-0.864	-1.900	0.176	2.248	0.562	-1.360	0.194
BMD Total (g/cm²)	-0.004	-0.469	-1.200	0.265	1.589	0.397	-0.950	0.357
3 MONTHS (N=16, 18 COMPLETE BUT TWO HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.018	1.807	-0.583	4.200	4.884	1.221	1.612	0.128
BMD Wards (g/cm²)	0.003	0.333	-1.950	2.610	4.660	1.165	0.337	0.741
BMD Troch (g/cm²)	-0.018	-2.345	-3.880	-0.815	3.123	0.781	-2.848	**0.012**
BMD Shaft (g/cm²)	-0.012	-1.090	-2.290	0.110	2.446	0.611	-1.649	0.120
BMD Total (g/cm²)	-0.010	-1.068	-2.020	-0.112	1.952	0.488	-2.115	0.051
6 MONTHS (N=16, 17 COMPLETE BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.001	-0.125	-2.050	1.800	3.939	0.985	-0.073	0.943
BMD Wards (g/cm²)	-0.004	-0.652	-2.360	1.060	3.500	0.875	-0.617	0.547
BMD Troch (g/cm²)	-0.009	-1.025	-4.530	2.480	7.134	1.783	-0.681	0.506
BMD Shaft (g/cm²)	-0.019	-1.698	-2.980	-0.418	2.614	0.653	-2.564	**0.021**
BMD Total (g/cm²)	-0.015	-1.562	-2.760	-0.362	2.450	0.613	-2.567	**0.021**
12 MONTHS (N=14, 15 COMPLETE BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.001	0.097	-2.430	2.630	4.824	1.289	0.113	0.912
BMD Wards (g/cm²)	0.003	0.109	-2.820	3.040	5.591	1.494	0.282	0.783
BMD Troch (g/cm²)	-0.014	-1.890	-3.480	-0.300	3.027	0.809	-2.115	**0.054**
BMD Shaft (g/cm²)	-0.018	-1.582	-2.870	-0.292	2.465	0.659	-2.264	**0.041**
BMD Total (g/cm²)	-0.013	-1.365	-2.520	-0.205	2.224	0.594	-2.129	**0.053**

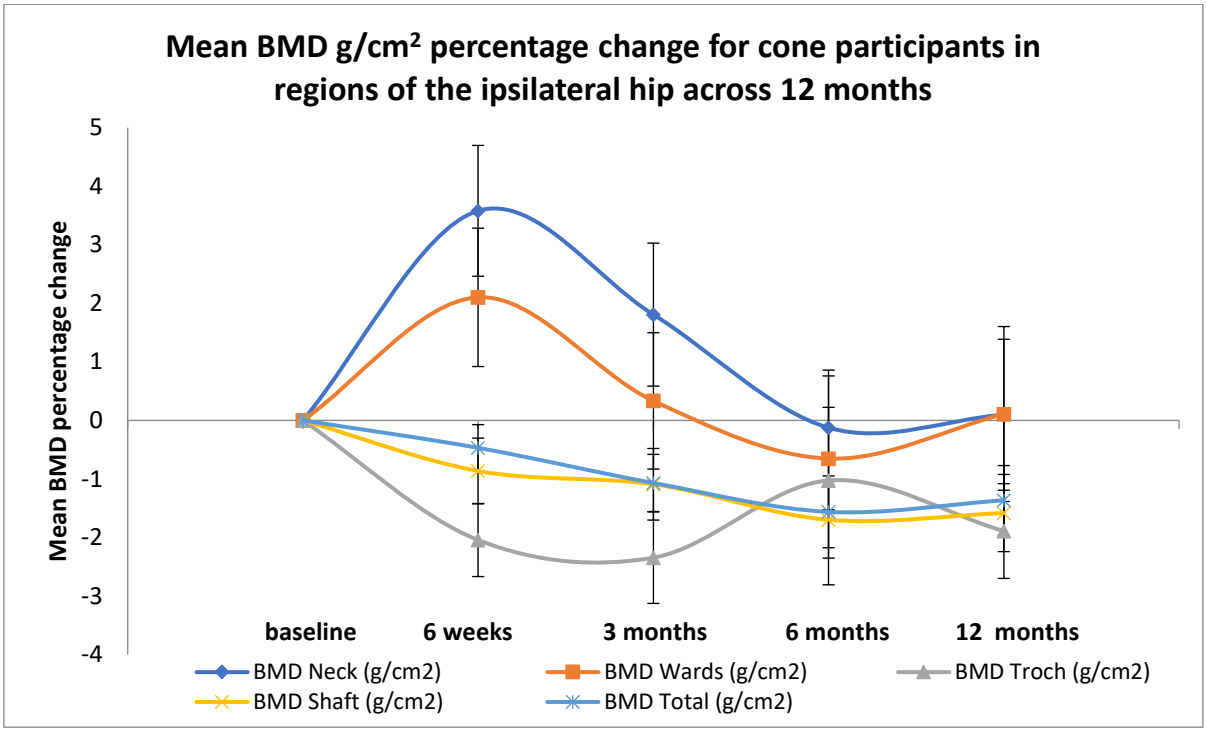


Figure 5.12. *BMD changes in the ipsilateral hip regions across 12 months (error bars are SE)*

The biggest BMD change is reported at six weeks with a reported increase of 3.58 % at the neck region, there is also a gain of 2.102 % in the wards region, at 3 months this is reduced to 1.807 % and 0.333 %, at six month this is a loss -0.125 % and -0.652 %., at 12 months there is an increase in these two regions of 0.097 % and 0.109 %. There is also a reported loss throughout the study in the trochanter at all visits, with statistically significant results at: six weeks, three months, and 12 months, reporting figures of -2.043 % (p-value 0.01), -2.345 % (p-value 0.01) and -1.89 % (p-value 0.05) respectively. The total BMD reports a gradual loss starting at six weeks (compared to baseline) -0.469 %, then -1.068 %, -1.562 % (p-value 0.02), then at 12 months this loss has recovered slightly reporting a change of -1.365 % (p-value 0.05). Both the neck and wards trends, and the shaft and total trends, follow similar patterns to each other, as shown in figure 101.

Table 5.13. *Shows the BMD contralateral cone results but to 3 d.p. including percentage change, confidence intervals (95 %) t-test, and p-value*

6 WEEK (N=17, 18 COMPLETED BUT ONE HAD A THR ON CONTRALATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.009	-0.647	-2.490	1.190	3.973	0.964	-0.833	0.417
BMD Wards (g/cm²)	-0.001	-0.520	-3.140	2.100	5.674	1.376	-0.075	0.941
BMD Troch (g/cm²)	0.010	1.290	-0.920	3.500	4.777	1.159	1.032	0.318
BMD Shaft (g/cm²)	0.007	0.561	-0.578	1.880	2.867	0.695	0.865	0.400
BMD Total (g/cm²)	0.006	0.551	-0.559	1.660	2.404	0.583	0.976	0.343
3 MONTHS (N=17, 18 COMPLETED BUT ONE HAD A THR ON CONTRALATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.007	0.919	-2.030	3.870	6.197	1.503	0.402	0.693
BMD Wards (g/cm²)	0.011	1.604	-1.470	4.670	6.463	1.568	1.030	0.318
BMD Troch (g/cm²)	0.003	0.150	-1.890	2.190	4.286	1.040	0.379	0.710
BMD Shaft (g/cm²)	0.012	1.017	-0.423	2.460	3.025	0.734	1.367	0.910
BMD Total (g/cm²)	0.009	0.808	-0.040	1.660	1.783	0.432	1.934	0.071
6 MONTHS (N=16, 17 COMPLETED BUT ONE HAD A THR ON CONTRALATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.010	1.272	-2.010	4.550	6.693	1.673	0.570	0.577
BMD Wards (g/cm²)	-0.001	0.001	-3.130	3.130	6.380	1.595	-0.061	0.952
BMD Troch (g/cm²)	-0.004	-0.665	-3.120	1.790	4.992	1.248	-0.355	0.728
BMD Shaft (g/cm²)	0.014	1.220	-0.570	3.010	3.660	0.915	1.250	0.231
BMD Total (g/cm²)	0.007	0.684	-0.596	1.960	2.607	0.652	0.981	0.342
12 MONTHS (N=13, 15 COMPLETED BUT ONE HAD A THR ON CONTRALATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.001	0.136	-3.970	4.250	7.566	2.098	-0.063	0.951
BMD Wards (g/cm²)	-0.003	-0.200	-2.750	2.350	4.697	1.303	-0.308	0.764
BMD Troch (g/cm²)	0.001	0.178	-1.920	2.280	3.856	1.069	0.116	0.910
BMD Shaft (g/cm²)	0.010	0.911	-0.829	2.650	3.193	0.885	0.960	0.356
BMD Total (g/cm²)	0.004	0.388	-1.280	2.060	3.078	0.854	0.440	0.668

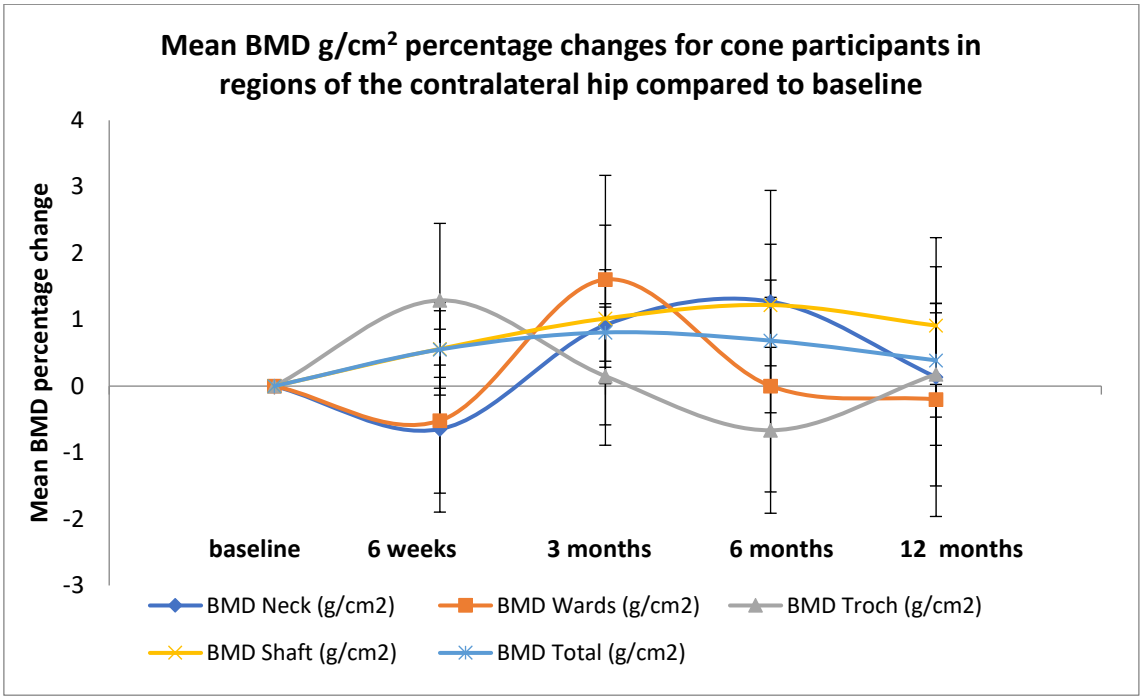


Figure 5.13. *BMD changes in the contralateral hip regions across 12 months (error bars are SE)*

Table 5.13 and figure 5.13 show the changes reported in the contralateral hip in the cone group. At six weeks the wards and neck region report a loss of -0.647 % and -0.520 % respectively. Although at three months there is an increase of 0.919 % in neck, and the largest change reported in the contralateral hip is reported in the wards region, with a reported gain of 1.604 %, at 12 months this change is reported as -0.200 % (wards) and 0.136 % (neck). The total BMD was reported as an increase in all visits, reporting figures of 0.551 %, 0.808 %, 0.684 % and 0.388 %, although it must be noted none of the results in the contralateral hip are statistically significant.

5.7.2 RESULTS OF NON-CONE PARTICIPANTS IPSILATERAL AND CONTRALATERAL HIP REGIONS

Table 5.14 and figure 5.14 show the results from the non-cone participants in the ipsilateral hip following the same analysis as previously stated. It must be noted that one of the non-cone participants had a rTKR on their contralateral knee between the six and 12 month visit, thus their contralateral hip data were excluded.

Table 5.14. *Shows the ipsilateral BMD non-cone results to 3 d.p. including percentage change, confidence intervals (95 %), t-test and p-value*

6 WEEKS (N=7, 8 COMPLETED BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.004	0.084	-1.870	2.030	2.813	1.063	0.401	0.702
BMD Wards (g/cm²)	0.023	4.213	-2.740	11.200	9.385	3.547	1.242	0.261
BMD Troch (g/cm²)	-0.002	0.043	-2.550	2.630	3.496	1.321	-0.145	0.889
BMD Shaft (g/cm²)	-0.004	-0.492	-2.010	1.030	2.050	0.775	-0.519	0.627
BMD Total (g/cm²)	0.002	0.135	-1.190	1.460	1.778	0.672	0.335	0.749
3 MONTHS (N=7, 8 COMPLETED BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.003	-0.043	-2.800	2.720	3.725	1.408	0.188	0.857
BMD Wards (g/cm²)	0.015	2.933	-4.360	10.200	9.842	3.720	0.814	0.447
BMD Troch (g/cm²)	0.010	1.013	-1.740	3.940	3.834	1.449	0.691	0.515
BMD Shaft (g/cm²)	0.001	-0.115	-1.990	1.760	2.528	0.956	0.085	0.935
BMD Total (g/cm²)	0.002	-0.021	-1.930	1.890	2.575	0.973	0.207	0.843
6 MONTHS (N=7, 8 COMPLETED BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.020	-1.944	-4.360	0.480	3.266	1.234	-1.473	0.191
BMD Wards (g/cm²)	0.010	1.727	-7.120	10.600	11.949	4.516	0.382	0.715
BMD Troch (g/cm²)	0.003	-0.500	-4.050	3.050	4.796	1.813	0.193	0.853
BMD Shaft (g/cm²)	-0.009	-0.916	-2.500	0.664	2.137	0.808	-1.016	0.349
BMD Total (g/cm²)	-0.003	-0.570	-2.280	1.140	2.314	0.875	-0.414	0.693
12 MONTHS (N=6, 7 COMPLETED BUT ONE HAD A THR ON IPSILATERAL SIDE)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.032	-3.363	-5.150	-1.570	2.237	0.913	-4.588	**0.006**
BMD Wards (g/cm²)	-0.003	-0.377	-6.910	6.150	8.159	3.331	-0.163	0.878
BMD Troch (g/cm²)	0.013	0.612	-3.840	5.060	5.567	2.273	0.041	0.969
BMD Shaft (g/cm²)	-0.009	-1.372	-4.140	1.400	3.465	1.415	-0.025	0.981
BMD Total (g/cm²)	-0.001	-0.572	-3.020	1.880	3.065	1.251	-0.003	0.998

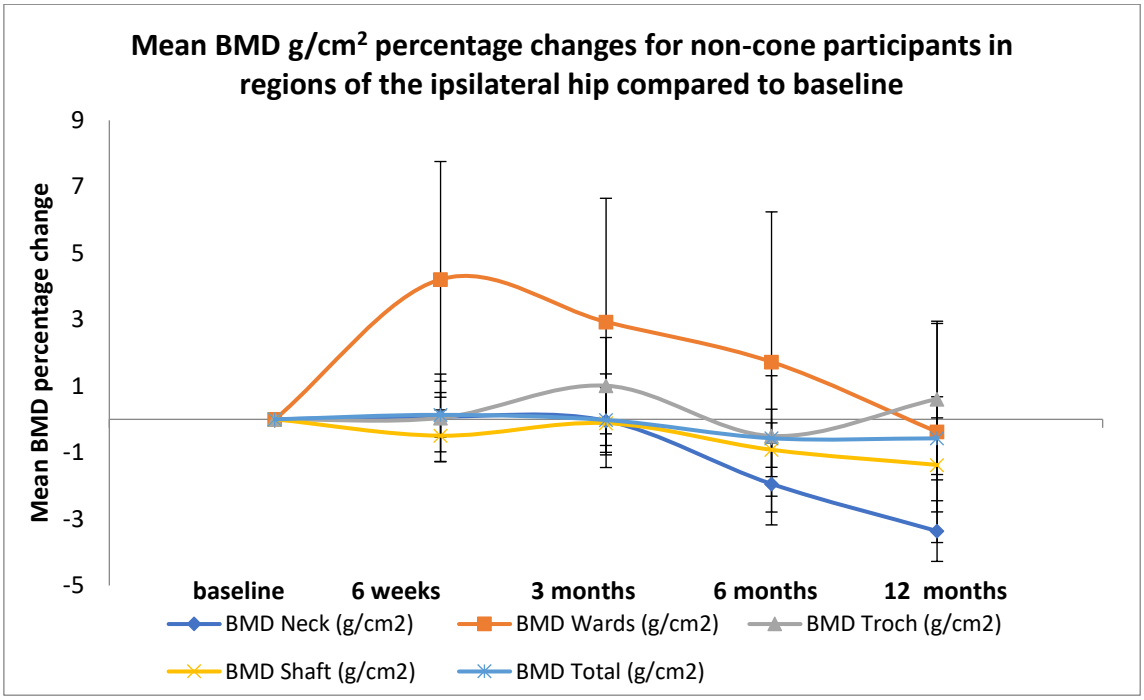


Figure 5.14. *BMD changes in the ipsilateral hip regions across 12 months (error bars are SE)*

The biggest BMD change was reported at six weeks with an increase of 4.2 % at the wards triangle region. There was also a reported loss at six and 12 months in the neck, reported as -1.944 % and 3.363 % (p-value 0.01) respectively. The total BMD shows a small gain at six weeks of 0.135 %, the rest of the visits report a loss in the total of the hip reporting -0.572 at 12 months.

Table 5.15 *Shows the contralateral BMD non-cone results to 3 d.p. including percentage change, confidence intervals (95 %), t-test and p-value*

	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
6 WEEK (N=8)								
BMD Neck (g/cm²)	0.019	2.057	0.847	3.270	1.750	0.619	2.953	**0.021**
BMD Wards (g/cm²)	-0.004	-0.580	-3.840	2.680	4.705	1.663	-0.361	0.729
BMD Troch (g/cm²)	0.014	1.694	-0.166	3.550	2.688	0.950	1.678	0.137
BMD Shaft (g/cm²)	0.003	0.019	-0.991	1.030	1.457	0.515	0.369	0.723
BMD Total (g/cm²)	0.008	0.760	-0.179	1.700	1.335	0.472	1.555	0.164
3 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.021	-2.160	-4.610	0.290	3.540	1.252	-2.079	0.076
BMD Wards (g/cm²)	-0.020	-3.047	-4.850	-1.250	2.595	0.917	-3.615	**0.009**
BMD Troch (g/cm²)	0.002	0.287	-2.140	2.720	3.505	1.239	0.176	0.865
BMD Shaft (g/cm²)	-0.002	-0.431	-1.980	1.120	2.242	0.793	-0.166	0.873
BMD Total (g/cm²)	-0.007	-0.694	-2.030	0.646	1.936	0.684	-1.072	0.319
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	0.015	1.718	-3.520	6.960	7.555	2.671	0.597	0.570
BMD Wards (g/cm²)	-0.003	-0.358	-4.760	4.040	6.354	2.246	-0.178	0.864
BMD Troch (g/cm²)	-0.005	-0.880	-3.680	1.920	4.042	1.429	-0.513	0.624
BMD Shaft (g/cm²)	-0.001	-0.177	-2.630	2.270	3.541	1.252	-0.063	0.951
BMD Total (g/cm²)	0.001	0.251	-1.640	2.140	2.728	0.964	0.178	0.864
12 MONTHS (N=6)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
BMD Neck (g/cm²)	-0.032	-3.232	-4.640	-1.820	1.760	0.719	-4.387	**0.007**
BMD Wards (g/cm²)	-0.023	-3.631	-7.810	0.549	5.225	2.133	-1.956	0.108
BMD Troch (g/cm²)	0.016	1.578	-1.900	5.060	4.354	1.777	1.082	0.328
BMD Shaft (g/cm²)	-0.005	-0.590	-2.060	0.880	1.842	0.752	-0.539	0.613
BMD Total (g/cm²)	-0.004	-0.536	-1.830	0.754	1.611	0.658	-0.527	0.592

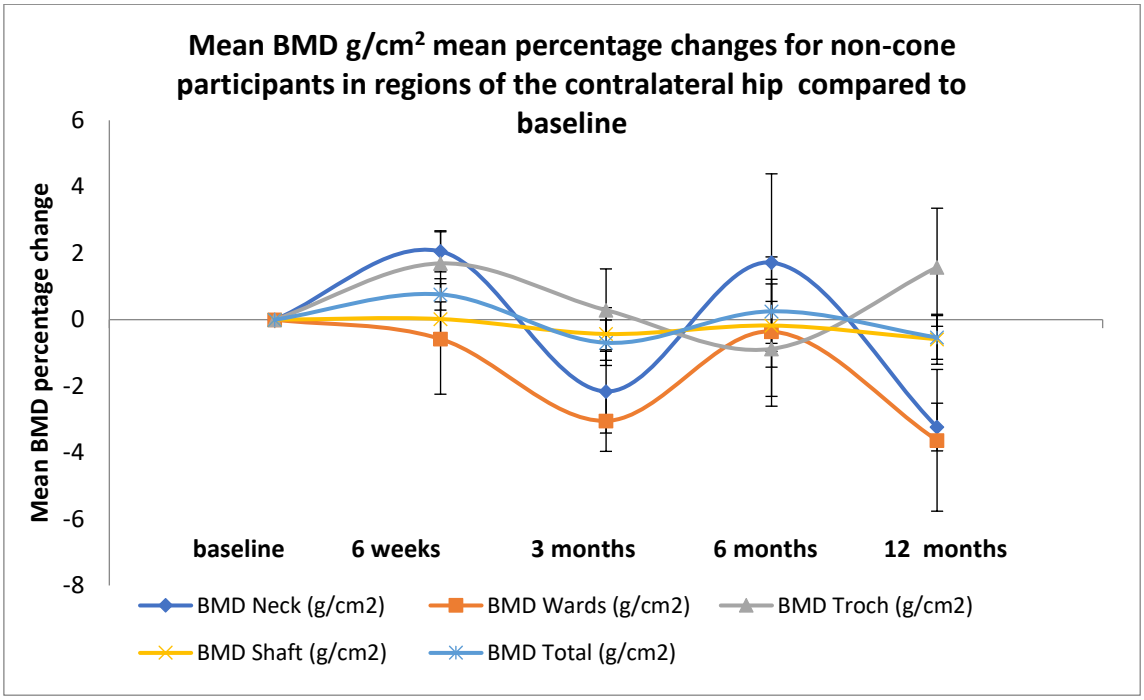


Figure 5.15. *BMD changes in the contralateral hip regions across 12 months (error bars are SE)*

Table 5.15 and figure 5.15 show the results from the non-cone participants in the contralateral hip. There is an increase percentage change at the neck of just over 2 % at six weeks compared to baseline, this increase was reported as a loss of just over -2 % at three months, although there was an increase at six months of 1.7 % and a loss of -3.232 % at 12 months (p-value 0.01). Wards triangle reports losses throughout all visits, with the highest loss at three months with a reported loss of just over 3 %. The total BMD reports a gain at six weeks a loss at three months and a gain at 12 months.

5.7.3 COMPARISON BETWEEN CONE VS NON-CONE IPSILATERAL AND CONTRALATERAL HIPS

The percentages created between comparisons of post-op visits to pre-op from tables 5.12, 5.13, 5.14 and 5.15, were themselves compared between the two groups, for the ipsilateral and contralateral hip differences. This comparison was done in the singular direction with the non-cone figure subtracted from the cone figure. A positive percentage meant the cone percentage figure was higher than the non-cone group, with a minus percentage figure reporting that the non-cone group had the higher value for that region.

Table 5.16 reports this comparison between the ipsilateral percentage changes (compared to baseline) in the cone group (table 5.12) compared against the ipsilateral percentages changes (compared to baseline) in the non-cone group (table 5.14).

Table 5.16. *Shows the mean BMD percentage difference compared to baseline at different visits, in the ipsilateral hip of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test, and p-value.*

6 WEEK BMD % DIFFERENCE IN IPSILATERAL HIP CONE (16) VS NON-CONE (7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	3.496	-2.111	-2.086	-0.371	-0.604
T-CRITICAL	2.267	-0.565	-1.427	-0.388	-0.774
P VALUE	**0.036**	0.590	0.187	0.704	0.457
3 MONTH BMD % DIFFERENCE IN IPSILATERAL HIP CONE (16) VS NON-CONE (7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	1.850	-2.600	-3.358	-0.975	-1.048
T-CRITICAL	0.992	-0.667	-2.040	-0.860	-0.962
P VALUE	0.337	0.526	0.069	0.408	0.361
6 MONTH BMD % DIFFERENCE IN IPSILATERAL HIP CONE (16) VS NON-CONE (7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	1.818	-2.379	-0.525	-0.782	-0.992
T-CRITICAL	1.152	-0.517	-0.206	-0.752	-0.929
P VALUE	0.269	0.624	0.839	0.464	0.371
12 MONTH BMD % DIFFERENCE IN IPSILATERAL HIP CONE (14) VS NON-CONE (6)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	3.460	0.486	-2.502	-0.210	-0.793
T-CRITICAL	2.190	0.133	-1.037	-0.135	-0.572
P VALUE	**0.042**	0.898	0.340	0.900	0.585

Table 5.16 shows the results of the comparison differences between ipsilateral hips of the two groups, there is a greater difference in the neck in the cone group and a greater difference in the wards area in the non-cone group at six weeks, although both groups had increases compared to baseline. The difference of 3.496 % was due to the larger increase in BMD in the neck in the cone group, likewise the -2.111 % reported in the wards triangle was due to the increase of 4.20 % (in the non-cone group) compared to the 2.10 % increase in the cone group. At 12 months the difference between cone and non-cone was reported as 3.460 % (p-value 0.04) in the neck and 0.486 % in the wards, this was due to the non-cone group data reporting a loss of -3.363 % and -0.377 % at 12 months, whilst the cone group reported slight increases of 0.097 % and 0.109 %. The trochanter difference is more prominent in the cone group

compared to the non-cone group, with the largest difference (excluding the neck) reported as -3.358 % at three months.

Table 5.17 shows the results of the contralateral percentage changes (compared to baseline) in the cone group (table 5.12) compared to the contralateral percentages changes (compared to baseline) in the non-cone group (table 5.15).

Table 5.17. *Shows the mean BMD percentage difference compared to baseline at different visits in the contralateral hip of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test, and p-value.*

6 WEEK BMD % DIFFERENCE IN CONTRALATERAL HIP CONE (17) VS NON-CONE (8)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-2.704	0.060	-0.404	0.542	-0.209
T-CRITICAL	-2.361	0.028	-0.269	0.626	-0.279
P VALUE	**0.027**	0.978	0.790	0.538	0.783
6 MONTH BMD % DIFFERENCE IN CONTRALATERAL HIP CONE (16) VS NON-CONE (8)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-0.446	0.360	0.215	1.397	0.434
T-CRITICAL	-0.142	0.131	0.113	0.901	0.373
P VALUE	0.890	0.898	0.911	0.382	0.715
3 MONTH BMD % DIFFERENCE IN CONTRALATERAL HIP CONE (17) VS NON-CONE (8)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	3.079	4.651	-0.137	1.448	1.502
T-CRITICAL	1.574	2.561	-0.085	1.341	1.855
P VALUE	0.130	**0.017**	0.933	0.197	0.086
12 MONTH BMD % DIFFERENCE IN CONTRALATERAL HIP CONE (13) VS NON-CONE (6)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	3.369	3.431	-1.399	1.501	0.924
T-CRITICAL	1.159	1.373	-0.674	1.292	0.857
P VALUE	0.150	0.203	0.517	0.215	0.403

Table 5.17 shows that the contralateral hips are similar, but the non-cone group reported a higher percentage difference at six weeks, with the difference being reported as -2.704 % although at three months both the neck and wards triangle report greater differences of 3.079 % and 4.651 % (with the wards difference being statistically significant, this is due to the 3.047 % increase in the cone group compared to the -1.604 % in the non-cone group see tables 5.12 and 5.14). Although at six months this change is negligible, at 12 months there is difference of 3.369 %, and 3.431 % in the neck and wards triangle respectively.

The total hip data also showed a difference of 0.924 % at 12 months, although strongly influenced by the neck and wards triangle differences. Again these figures are just reflecting the percentage changes compared to baseline in both groups, and these large differences in the wards are due to increases in BMD at three months in the cone group and a loss in the non-cone group.

5.7.4 IPSILATERAL VS CONTRALATERAL HIP PERCENTAGE DIFFERENCE IN CONE AND NON-CONE PARTICIPANTS

The percentages created between comparisons of post-op visits to pre-op baseline figures, were also compared between ipsilateral and contralateral hip within each group. This comparison, as with section 5.7.3 was done in the singular direction with the contralateral percentage figure subtracted from the ipsilateral figure. A positive percentage means the ipsilateral percentage figure was higher than the contralateral, with a minus percentage figure reporting that the contralateral hip region had the higher value.

Table 5.18 reports this ipsilateral vs contralateral hip percentage change (compared to baseline) (table 5.12 compared to table 5.13), with the same comparison done for the non-cone group (table 5.14 compared to table 5.15) reported in table 5.19.

Table 5.18. *Shows the mean BMD percentage difference between ipsilateral and contralateral percentage changes compared to baseline at different visits in the cone group 3 d.p. t-test, SD, SE and p-value.*

6 WEEK BMD % IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	4.775	2.340	-2.730	-1.464	-0.997
MEAN BMD DIFFERENCE (g/cm²)	0.050	0.019	-0.025	-0.016	-0.010
SD	5.324	5.952	4.088	4.399	2.947
SE	1.375	1.537	1.056	1.136	0.761
T-CRITICAL	3.474	1.523	-2.586	-1.289	-1.311
P VALUE	**0.004**	0.150	**0.022**	0.218	0.211
3 MONTH BMD % IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	1.736	-1.258	-2.602	-2.428	-1.973
MEAN BMD DIFFERENCE (g/cm²)	0.020	-0.008	-0.023	-0.027	-0.020
SD	4.767	7.619	4.971	4.840	2.733
SE	1.231	1.967	1.283	1.250	0.706
T-CRITICAL	1.410	-0.640	-2.027	-1.943	-2.797
P VALUE	0.180	0.533	0.062	0.072	**0.014**
6 MONTH BMD % IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-0.125	-0.347	-0.669	-2.722	-2.136
MEAN BMD DIFFERENCE (g/cm²)	0.001	-0.001	-0.008	-0.030	-0.021
SD	6.022	5.802	9.236	5.051	4.092
SE	1.555	1.498	2.385	1.304	1.056
T-CRITICAL	-0.080	-0.232	-0.281	-2.087	-2.021
P VALUE	0.937	0.820	0.783	0.056	0.063
12 MONTH BMD % IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=12)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	1.965	0.640	-2.559	-1.651	-1.222
MEAN BMD DIFFERENCE (g/cm²)	-0.014	0.015	-0.014	-0.007	-0.008
SD	8.900	5.134	4.747	3.879	3.761
SE	2.569	1.482	1.370	1.120	1.086
T-CRITICAL	0.765	0.432	-1.867	-1.474	1.126
P VALUE	0.461	0.674	0.089	0.168	0.284

Reviewing the difference between the ipsilateral and contralateral, the neck and wards both report differences of 4.775 % and 2.34 % at six weeks, and at 12 months the neck was reported as 1.965 % and wards 0.640 %. The trochanter at six weeks also reported the greatest difference of -2.730 %, with a percentage difference of -2.559 % at 12 months. The total was reported as a difference of nearly -1 %, changing to -1.973 % at three months (p-value 0.01), and -2.316 % at six months. Although by 12 months this had reduced to -1.222 %.

Table 5.19. *Shows the mean BMD percentage difference between ipsilateral and contralateral percentage changes compared to baseline at different visits in the non-cone group 3 d.p. t-test, SD, SE and p-value*

6 WEEK BMD % IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-1.798	5.911	-1.320	-0.551	-0.500
MEAN BMD DIFFERENCE (g/cm²)	-0.014	0.032	-0.013	-0.008	-0.005
SD	2.394	8.063	4.120	2.216	1.989
SE	0.905	3.048	1.557	0.838	0.752
T-CRITICAL	-1.987	1.940	-0.848	-0.658	-0.664
P VALUE	0.094	0.101	0.429	0.535	0.531
3 MONTH BMD % IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	2.228	5.805	0.819	0.716	0.945
MEAN BMD DIFFERENCE (g/cm²)	0.025	0.034	0.009	0.007	0.012
SD	5.990	9.528	2.608	2.596	2.223
SE	2.264	3.601	0.986	0.981	0.840
T-CRITICAL	0.984	1.612	0.831	0.730	1.125
P VALUE	0.363	0.158	0.438	0.493	0.304
6 MONTH BMD % IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-3.403	3.092	1.079	-0.350	-0.355
MEAN BMD DIFFERENCE (g/cm²)	-0.033	0.018	0.013	-0.004	-0.001
SD	10.138	14.083	3.966	4.358	4.560
SE	3.832	5.323	1.499	1.647	1.724
T-CRITICAL	-0.888	0.581	0.720	-0.212	-0.206
P VALUE	0.409	0.582	0.499	0.839	0.843
12 MONTH BMD % IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=5)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN PERCENTAGE DIFFERENCE	-0.493	-0.927	-2.993	-1.472	-1.036
MEAN BMD DIFFERENCE (g/cm²)	-0.002	-0.003	-0.019	-0.011	-0.006
SD	2.587	2.646	5.246	2.568	2.685
SE	1.157	1.183	2.346	1.148	1.201
T-CRITICAL	-0.462	-0.783	-1.276	-1.282	-0.863
P VALUE	0.692	0.477	0.271	0.269	0.437

Table 5.18 shows the difference between the ipsilateral and contralateral hip BMD in the non-cone group, wards triangle shows a large difference of 5.9 % at six weeks, although this drops at every visit (5.8 % at three months, 3.092 % at six months), finally reported as -0.927 % at 12 months. The neck data started at a difference of -1.798 % at six weeks and increases at three months (2.228 %), and then a loss of 3.403 % at six months, until at 12 months it was reported as -0.493 %. The trochanter reports a difference of -1.32 % at six weeks, although

this increases to 1.079 % by six months, and was reported as -2.993 % at 12 months. There is little change in the shaft throughout, and the total reports both losses and gains in difference, although at 12 months it reports a difference of -1.472 %.

5.7.5 BMD REPORTED IPSILATERAL HIP AND CONTRALATERAL HIP FOR THE CONE VS NON-CONE GROUPS

Tables 5.20 and 5.21 report the absolute BMD figures rather than the percentage change, this is in order to show the reported absolute BMD figures throughout the visits.

Table 5.20. *Shows the mean BMD for the ipsilateral hip with a comparison between cone and non-cone group at each visit, reported as to 3 d.p. t-test, SD, SE and p-value*

PRE-OP (MEAN BMD g/cm²)	***CONE (N=20)***	***SD***	***SE***	***NON-CONE (N=12)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.953	0.123	0.028	0.943	0.161	0.047	0.011	0.195	0.848
WARDS	0.731	0.166	0.037	0.680	0.180	0.052	0.050	0.788	0.439
TROCH	0.882	0.197	0.044	0.819	0.238	0.069	0.062	0.765	0.453
SHAFT	1.169	0.187	0.042	1.156	0.221	0.064	0.013	0.176	0.862
TOTAL	1.013	0.171	0.038	0.982	0.192	0.055	0.031	0.462	0.649
6 WEEKS (MEAN BMD g/cm²)	***CONE (N=16)***	***SD***	***SE***	***NON-CONE (N=7)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	1.010	0.138	0.035	0.975	0.217	0.082	0.035	0.393	0.705
WARDS	0.777	0.193	0.048	0.711	0.232	0.088	0.066	0.660	0.524
TROCH	0.895	0.200	0.050	0.876	0.255	0.096	0.019	0.172	0.867
SHAFT	1.187	0.204	0.051	1.155	0.277	0.105	0.032	0.273	0.791
TOTAL	1.037	0.181	0.045	1.011	0.241	0.091	0.025	0.247	0.811
3 MONTH (MEAN BMD g/cm²)	***CONE (N=16)***	***SD***	***SE***	***NON-CONE (N=7)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.993	0.133	0.033	0.974	0.214	0.081	0.019	0.214	0.836
WARDS	0.760	0.168	0.042	0.703	0.228	0.086	0.057	0.595	0.566
TROCH	0.895	0.213	0.053	0.887	0.271	0.102	0.007	0.063	0.951
SHAFT	1.184	0.199	0.050	1.160	0.283	0.107	0.023	0.197	0.848
TOTAL	1.031	0.181	0.045	1.011	0.250	0.095	0.019	0.183	0.859
6 MONTH (MEAN BMD g/cm²)	***CONE (N=16)***	***SD***	***SE***	***NON-CONE (N=7)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.974	0.130	0.032	0.941	0.183	0.069	0.033	0.434	0.675
WARDS	0.753	0.171	0.043	0.690	0.232	0.088	0.063	0.649	0.532
TROCH	0.904	0.207	0.052	0.827	0.256	0.097	0.077	0.702	0.499
SHAFT	1.177	0.203	0.051	1.125	0.267	0.101	0.052	0.459	0.657
TOTAL	1.026	0.184	0.046	0.972	0.228	0.086	0.054	0.549	0.595
12 MONTH (MEAN BMD g/cm²)	***CONE (N=14)***	***SD***	***SE***	***NON-CONE (N=6)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.956	0.127	0.034	0.964	0.205	0.084	-0.008	-0.090	0.931
WARDS	0.720	0.156	0.042	0.695	0.255	0.104	0.025	0.219	0.833
TROCH	0.885	0.220	0.059	0.904	0.305	0.124	-0.019	-0.137	0.895
SHAFT	1.159	0.203	0.054	1.173	0.325	0.133	-0.014	-0.101	0.922
TOTAL	1.010	0.187	0.050	1.026	0.274	0.112	-0.016	-0.132	0.899

Table 5.21. *Shows the mean BMD for the contralateral hip with a comparison between cone and non-cone group at each visit, reported as to 3 d.p. t-test, SD, SE and p-value*

PRE-OP (MEAN BMD g/cm²)	***CONE (N=21)***	***SD***	***SE***	***NON-CONE (N=13)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.985	0.155	0.034	0.936	0.173	0.048	0.049	0.836	0.412
WARDS	0.730	0.148	0.032	0.719	0.181	0.050	0.011	0.191	0.850
TROCH	0.878	0.197	0.043	0.853	0.210	0.058	0.025	0.346	0.732
SHAFT	1.163	0.185	0.040	1.195	0.206	0.057	-0.032	-0.461	0.649
TOTAL	1.016	0.170	0.037	1.014	0.183	0.051	0.002	0.024	0.981
6 WEEKS (MEAN BMD g/cm²)	***CONE (N=17)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.987	0.149	0.036	0.958	0.222	0.079	0.029	0.331	0.748
WARDS	0.740	0.174	0.042	0.713	0.237	0.084	0.027	0.288	0.779
TROCH	0.906	0.200	0.048	0.901	0.225	0.080	0.005	0.054	0.958
SHAFT	1.186	0.201	0.049	1.184	0.273	0.096	0.002	0.023	0.982
TOTAL	1.038	0.181	0.044	1.031	0.227	0.080	0.007	0.082	0.936
3 MONTH (MEAN BMD g/cm²)	***CONE (N=17)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	1.002	0.155	0.038	0.918	0.211	0.074	0.084	1.008	0.335
WARDS	0.752	0.156	0.038	0.697	0.235	0.083	0.056	0.607	0.557
TROCH	0.899	0.213	0.052	0.889	0.228	0.081	0.010	0.107	0.916
SHAFT	1.191	0.200	0.048	1.180	0.279	0.099	0.011	0.101	0.921
TOTAL	1.041	0.183	0.044	1.015	0.224	0.079	0.026	0.282	0.783
6 MONTH (MEAN BMD g/cm²)	***CONE (N=16)***	***SD***	***SE***	***NON-CONE (N=8)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	1.018	0.155	0.039	0.942	0.212	0.075	0.077	0.910	0.382
WARDS	0.742	0.157	0.039	0.700	0.223	0.079	0.043	0.486	0.637
TROCH	0.913	0.200	0.050	0.842	0.216	0.076	0.071	0.779	0.450
SHAFT	1.200	0.198	0.050	1.169	0.267	0.094	0.031	0.289	0.778
TOTAL	1.051	0.176	0.044	1.001	0.208	0.073	0.050	0.585	0.569
12 MONTH (MEAN BMD g/cm²)	***CONE (N=13)***	***SD***	***SE***	***NON-CONE (N=6)***	***SD***	***SE***	***BMD DIFFERENCE (g/cm²)***	***T-CRITICAL***	***P-VALUE***
NECK	0.991	0.137	0.038	0.968	0.215	0.088	0.023	0.243	0.815
WARDS	0.708	0.134	0.037	0.743	0.263	0.107	-0.035	-0.308	0.769
TROCH	0.921	0.201	0.056	0.919	0.271	0.111	0.002	0.019	0.986
SHAFT	1.180	0.212	0.059	1.221	0.303	0.124	-0.041	-0.298	0.774
TOTAL	1.038	0.188	0.052	1.054	0.259	0.106	-0.016	-0.136	0.896

The results in table 5.20 show the changes in BMD difference in the ipsilateral hip in the cone and non-cone group, the BMD differences report that the

ipsilateral cone side has a higher BMD than the non-cone group at every region in 20 out of 20 results, except at 12 months where the mean BMD is lower in four of the five regions, although none of results report a statistical significance p-value.

The results in table 5.21 show a similar trend, with 19 out of 20 regions and visits, reporting a higher BMD in the cone group than non-cone group. Except at 12 months where the BMD is lower in the cone group in three out of five regions, but again with no statistical significance.

5.7.6 BMD REPORTED IPSILATERAL HIP VS CONTRALATERAL HIP FOR THE CONE AND NON-CONE GROUPS

The data shown in tables 5.22 and 5.23 show the absolute BMD differences between the ipsilateral and contralateral hip regions, for the cone and non-cone groups. Due it being a comparison between ipsilateral and contralateral this meant all pre-op participants who underwent a DXA scans were included. Furthermore, the participants although allocated to cone and non-cone (at pre-op) had at pre-op not been allocated yet.

Table 5.22. *Shows the mean BMD difference between ipsilateral and contralateral changes at different visits in the cone group 3 d.p. t-test, SD, SE and p-value*

PRE-OP BMD IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=19)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.045	-0.004	-0.005	-0.001	-0.008
SD	0.078	0.063	0.042	0.056	0.041
SE	0.018	0.014	0.010	0.013	0.009
T-CRITICAL	-2.481	-0.245	-0.551	-0.099	-0.833
P VALUE	**0.023**	0.809	0.588	0.9225	0.416
6 WEEK BMD IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	0.012	0.030	-0.020	-0.009	-0.008
SD	0.051	0.064	0.029	0.059	0.033
SE	0.013	0.017	0.007	0.015	0.009
T-CRITICAL	0.938	1.777	-2.697	-0.586	-0.969
P VALUE	0.364	0.097	**0.017**	0.568	0.349
3 MONTH BMD IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.018	0.003	-0.018	-0.020	-0.019
SD	0.065	0.071	0.037	0.044	0.031
SE	0.017	0.018	0.009	0.011	0.008
T-CRITICAL	-1.056	0.138	-1.901	-1.735	-2.323
P VALUE	0.309	0.892	0.078	0.105	**0.036**
6 MONTH BMD IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=15)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.037	0.010	-0.003	-0.022	-0.019
SD	0.101	0.068	0.056	0.053	0.040
SE	0.026	0.017	0.014	0.014	0.010
T-CRITICAL	-1.405	0.581	-0.198	-1.628	-1.843
P VALUE	0.182	0.571	0.846	0.126	0.087
12 MONTH BMD IN CONE IPSILATERAL VS CONTRALATERAL HIP (N=12)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.014	0.015	-0.014	-0.007	-0.008
SD	0.071	0.080	0.042	0.051	0.041
SE	0.020	0.023	0.012	0.015	0.012
T-CRITICAL	-0.681	0.652	-1.148	-0.462	-0.676
P VALUE	0.510	0.528	0.275	0.654	0.513

Table 5.23. *Shows the mean BMD difference between ipsilateral and contralateral changes at different visits in the cone group 3 d.p. t-test, SD, SE and p-value*

PRE-OP BMD IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=12)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.005	-0.053	-0.043	-0.045	-0.041
SD	0.073	0.054	0.056	0.060	0.046
SE	0.021	0.016	0.016	0.017	0.013
T-CRITICAL	-0.226	-3.413	-2.633	-2.594	-3.086
P VALUE	0.826	**0.006**	**0.023**	**0.025**	**0.010**
6 WEEKS BMD IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE	-0.003	-0.022	-0.042	-0.036	-0.034
SD	0.071	0.066	0.075	0.079	0.065
SE	0.027	0.025	0.028	0.030	0.025
T-CRITICAL	-0.107	-0.887	-1.500	-1.187	-1.366
P VALUE	0.919	0.409	0.184	0.280	0.221
3 MONTH BMD IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	0.036	-0.020	-0.021	-0.021	-0.017
SD	0.099	0.071	0.070	0.060	0.053
SE	0.037	0.027	0.026	0.023	0.020
T-CRITICAL	0.973	-0.756	-0.776	-0.937	-0.857
P VALUE	0.368	0.478	0.467	0.385	0.425
6 MONTH BMD IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=7)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.018	-0.028	-0.025	-0.045	-0.037
SD	0.098	0.119	0.079	0.061	0.063
SE	0.037	0.045	0.030	0.023	0.024
T-CRITICAL	-0.493	-0.616	-0.830	-1.947	-1.532
P VALUE	0.640	0.561	0.439	0.100	0.176
12 MONTH BMD IN NON-CONE IPSILATERAL VS CONTRALATERAL HIP (N=6)					
	NECK	**WARDS**	**TROCH**	**SHAFT**	**TOTAL**
MEAN ABSOLUTE BMD DIFFERENCE (g/cm²)	-0.024	-0.089	-0.067	-0.049	-0.053
SD	0.086	0.043	0.077	0.074	0.056
SE	0.038	0.019	0.034	0.033	0.025
T-CRITICAL	-0.621	-4.641	-1.970	-1.500	-2.110
P-VALUE	0.568	**0.009**	0.120	0.209	0.102

The data in tables 5.22 and 5.23 report the absolute BMD rather than percentage change experienced by participants in the hip of the cone and non-cone groups. The cone group data in table 5.22 reports negative differences at pre-op between ipsilateral and contralateral, showing the contralateral hip to

have higher BMD, at six weeks there is a positive difference in the ipsilateral hip in the neck and wards, as is the ward region difference reported at 12 months. The trochanter reports a negative difference at six weeks which reduces throughout each visit. The total difference is reported as a difference of -0.008 g/cm^2 at pre-op and six weeks, increasing to -0.019 g/cm^2 at three months and six months, resulting in a BMD difference of -0.008 g/cm^2 at 12 months, similar to the percentage change reported in the previous section.

Table 5.23 reports the difference between the ipsilateral and contralateral hip BMD in the non-cone group, wards triangle shows a difference at six weeks of -0.022 g/cm^2 which is an increase on the pre-op of -0.053 g/cm^2, although this gradually decreases reporting a six month and 12 month difference of -0.028 g/cm^2 and -0.089 g/cm^2 (p-value 0.01) respectively, compared to the pre-op difference the trend fits the percentage change difference already reported.

The neck data reported also reflects the percentage change data, starting at a difference of a loss -0.003 g/cm^2 at six weeks and increases at three months (0.036 g/cm^2) and then a loss of -0.018 g/cm^2 at six months, until at 12 months it was reported as -0.024 g/cm^2. The trochanter again reports a similar trend to the percentage data already stated, a difference of -0.042 g/cm^2 at six weeks, is reported, along with -0.067 g/cm^2 at 12 months. The total reports a negative difference throughout, with a difference of -0.037 g/cm^2 at 12 months.

5.8 DISCUSSION

5.8.1 PARTICIPANTS

Considering the cohort of participants were elderly, often frail, and facing daunting revision surgery, the burden of the research requirements must not be over looked. Furthermore, there was often a long delay between initial contact regarding the study and admission (and thus study consent). Therefore, a repeat phone call nearer the time of admission for surgery might reduce those who agreed, and then ultimately declined from the study.

In total 37 participants were consented for the study as per the CONSORT diagram in Table 5.3, although only 22 completed the 12 month scan (four participants could not undergo their 12 month scan due to COVID-19 and thus the DXA scanner being inaccessible (two did not undergo a pre-op scan; one changed their mind due to the amount of scans after consenting, and one was discovered to be on bisphosphonates after consenting), and was withdrawn. Issues with attrition post consent were addressed prior to the commencement of the study, appointments were organised in advance and in the majority of cases organised on a single day (i.e. participants would undergo the DXA scan, physiotherapy appointment, and knee x-rays, on the same day), which we believed helped address these potential attrition issues. Unfortunately, this did mean that appointments were not always precisely at six weeks or three, six or 12 months, especially due to participant holidays, work, and other commitments. Therefore, an approximation was used to define each period; six weeks was defined as within a week either side, three months was one week prior two weeks post, six months was one week prior two weeks post, and 12 months two weeks prior four weeks post. So the results gathered are not perfect and represent a range.

Further to this, five participants who attended the pre-op had to undergo a different surgical procedure and be withdrawn from the study, which is reflected in the results in tables 5.4 and 5.5. The comparison data between those who under a standard rTKR and those who were withdrawn, reported minimal differences in the total body and contralateral hip, although a difference is reported in the lumbar spine (an increase in the standard rTKR group), this could be simply due to the osteophytes and degenerative changes impacting BMD [409].

Interestingly the ipsilateral BMD average is higher in the group of participants who underwent the standard rTKR compared to the withdrawn group, with results across all regions of the hip reporting higher values. These hip BMD differences could be related to the withdrawal of the participants, with low BMD in the ipsilateral hip regions at pre-op correlating to their subsequent lack of BMD in the distal femur [410], and ultimately not being suitable to undergo the cone surgical procedure (lack of BMD in the distal femur was one of the

reasons two participants were withdrawn). Although, it is important to note that differences between the groups are not statically significant, involve a very small sample size, and contain a wide SD, therefore the results are more likely to just be standard variations within the groups.

5.8.2 TOTAL BODY AND LUMBAR SPINE DISCUSSION

The total body percentage in the cone group increases at six weeks (1.491 % compared to baseline) but then gradually decreases throughout each visit until 12 months reported as 1.187 % (p-value 0.01). This change could be a result of the cement used in the knee revision process falsely elevating the BMD, although we addressed this by classifying the rTKR (including the stems) and the surrounding area as artefact (excluding it from BMD calculations), it is possible not all the cement was not directly classified due to poor visualisation of it on the image.

Furthermore, this gain in BMD could be because the revised knee is no longer included as part of the BMD figures (as stated it was classified as artefact), as with the pre-op score, only the TKR replacement part was excluded (no stems had been implanted yet), and the BMD along the mid shaft of the tibia and femur were included in the total body calculation, having now undergone the revision, the stem (classified as artefact) is now situated in this region, excluding the region from being part of the overall BMD, which previously might have been reducing the overall mean BMD. Although, if this were the case we would expect to see similar increases in the BMD of the non-cone group (having undergone the same cement revision and varying stem lengths), and although there is an increase, this is demonstrated as just over 0.5 % (compared to the cone reporting nearly 1.5 %), and at six months this figure is 0.16 % (the cone group reporting 1.012 %), at 12 month it is -0.458 % (non-cone) (with the cone group reporting 1.187 %). With a statistical significance at 12 months when the two groups were compared (p-value of 0.04).

Therefore, it is worth considering that the changes in BMD in the cone group might be related to stabilisation and weight bearing, cone implantation has shown to demonstrate good stabilisation [229], which might result in the participants being more active post-surgery due to the possible stabilising

factors of the cone implant, thus increasing weight bearing and BMD [404]. This is further supported by the total body results reporting a statistically significant increase at every visit in the cone group (whereas the non-cone group reported no statistically significant changes when compared to pre-op). Additionally, it must be noted no activity monitoring or pedometers were recorded in this study, and although both groups were given the same physiotherapy regime it is unknown if the participants adhered to these instructions, with a systematic review reporting that non-adherence to physiotherapy has been stated between 14-70 % [411]. This adherence is not reported in this study, but participants from both groups did have physiotherapy appointments post-op as part of their standard patient pathway.

Unfortunately, there is a lack of comparison evidence reporting changes in total body BMD post rTKR, as well as a lack of TKR or TKA data, so it is unknown if the trend in the non-cone group is reflective of participants clinically who also undergo a revision. There is some control data, for instance 36 post-menopausal Greek women aged between 55 and 65 years old were studied over a 12 month period for changes in their total body BMD. At 12 months they reported losses of 0.008 g/cm^2 (-0.71 %) compared to baseline figures [412]. A study involving 99 men aged 57+/-10 were also studied over a 12 month period, reported total body BMD loss of approximately -0.1 % compared to baseline [413].

For the lumbar spine data the cone group changes are small compared to baseline, although at three months the cone group does report a statistically significant change (p-value 0.03) at the L1-L4 region of - 0.810 %, although at six months this has returned to a baseline levels. In the non-cone group the lumbar spine changes were mainly increases, although none with statistically significance. The differences reported in the lumbar spine of both groups might be due to either osteophytes or sclerotic changes within individual participants elevating their BMD, with extensive literature reporting this link [409]. This is why clinically in DXA reporting, two vertebral bodies free from osteophytes or degenerative disease are required for a bone density diagnosis [414].

When directly comparing the two groups percentage difference, there was no statistically significant result, although the absolute BMD differences does report one at L1 at six months with the cone group reporting a higher BMD than the non-cone group (a difference of 0.204 g/cm^2 (p-value of 0.028)). This is reflected in the percentage change with the non-cone reporting its highest lumbar spine loss of -1.916 % when compared to baseline.

For the overall total spine (L1-L4) the cone group reports a loss of 0.08 % at six months and a gain of 1 % at 12 months, in the non-cone group they report an increase of 1.3 % at six and 12 months. Other research investigating changes in L1-L4 over 12 months have shown decreases [23] (compared to baseline/pre-op) in both TKR and control groups, with a reported change of -0.013 g/cm^2 at six months (-1.07 %) and -0.011 g/cm^2 at 12 months (-0.91 %) in the TKR group, and -0.005 g/cm^2 (-0.44 %) and -0.004 g/cm^2 (-0.35 %) in the control group [23]. Although these differences might be for the degenerative disease reasons already stated, especially as this study included revision participants who were an older age group, and thus more likely to develop osteophytes and degenerative disease [415].

HIP BMD CHANGES IN CONE GROUP

The ipsilateral hip in the cone group compared to the baseline figures show statistically significant changes from the start, at six weeks there is an increase in BMD in the neck and wards (0.036 g/cm^2 or 3.580 %, and 0.020 g/cm^2 or 2.102 %), but a loss in the trochanter of -2.043 % (-0.018 g/cm^2), resulting in an overall total hip loss. The increases in the wards triangle and neck region might be due to the high concentration of trabecular within the wards triangle which makes up the majority of bone remodelling and turnover [416]**.** It is also highly metabolically active and has a high surface area to volume ratio [389, 390]. This turnover might be the reason there is an increase at 6 weeks in these regions, as the participants become more stable and weight bear more, it promotes more remodelling. Although the total hip data report a loss (-0.469 %), this figure is possibly due to the losses in the slower cortical bone turnover especially as the trochanter has a greater ratio of cortical to trabecular bone [417].

At three month the increases in the wards and neck, have diminished (compared to six weeks) reporting gains of 1.807 % (0.018 g/cm^2) and 0.333 % (0.003 g/cm^2), this might be due to more equal weight bearing and a more balanced gait, with the trochanter still reporting a statistically significant loss (-2.345 % or -0.018 g/cm^2). Overall the total loss has also increased from just under 0.5 % (-0.004 g/cm^2) to just over 1 % (0.010 g/cm^2) most likely due to the increased loss in the trochanter.

At six months there are losses reported by every region, with the shaft and total hip reporting statistically significant losses of -1.698 % (-0.019 g/cm^2) and -1.562 % (-0.015 g/cm^2) respectively. At 12 months the total loss was reported as -1.365 % (-0.013 g/cm^2) (p-value 0.05), and there is minimal change in the wards and neck (compared to baseline), and a loss in the trochanter of just under 2 % (p-value 0.05).

These changes in the baseline comparison data are supported by the literature: Soininvaara et al [26] reported at 12 months a loss of -0.012 g/cm^2 in the femoral neck (compared to baseline), -0.023 g/cm^2 in the trochanter, and a loss of -0.013 g/cm^2 in the total hip, and Hopkins et al [23] reported a loss of -0.016 g/cm^2 in the neck, and -0.015 g/cm^2 in the total hip. As stated our data report a similar 12 month figure in the trochanter -0.014 g/cm^2 (-1.890 %), and matches the reported figure from Soininvaara et al [26] of -0.013 g/cm^2 in the total (-1.365 %).Although in our data there are minimal changes in the neck and wards of 0.001 g/cm^2 (0.097 %) and 0.003 g/cm^2 (0.109 %).

For the contralateral hip data there is a reported loss at six weeks compared to baseline in the wards and neck, and an increase in the total hip, this is complimentary to the ipsilateral data, in that there is an increase in the ipsilateral and loss in the contralateral (in the wards and neck), and a decrease in total hip in the ipsilateral and an increase in the contralateral. Overall the total hip changes in the contralateral are just over 0.5 % (six weeks 0.006 g/cm^2), to 0.8 % (three months 0.009 g/cm^2), to just over 0.6 % (0.007 g/cm^2) at six months, and 0.388 % at 12 months (0.004 g/cm^2). These results in the cone group reported throughout the visits could be because of dominant use post-op in the ipsilateral hip especially in the first six weeks maybe due to modified gait,

and then reverting back to the contralateral with weight bearing becoming a more equal. Unfortunately, Soininvaara et al [26] did not record six week data, and Hopkins et al [23] did record femoral neck data (a loss 0.07 g/cm^2), and total hip (-0.011 g/cm^2) there was no recorded wards or trochanter.

If we look at the comparisons directly between the ipsilateral and contralateral hips in the cone group, there are three regions of statistical significance: at six weeks the neck difference is 4.78 % (p-value 0.004) in support of the ipsilateral hip and -2.730 % in the trochanter (p-value 0.02), the reasons for these possible changes have already been stated. At three months the total hip is a difference of -1.973 % this is due to the accumulation of BMD losses in the hip regions, as all four visits report total hip losses of between 1 and 2 %. At 12 months the reported differences were neck 1.965 % (-0.014 g/cm^2), wards 0.64 % (0.015 g/cm^2), trochanter -2.56 % (-0.014 g/cm^2), shaft -1.651 % (-0.007 g/cm^2) and total -1.222 % (-0.008 g/cm^2).

Due to the reported change in BMD and the absolute figures, it is argued that at 12 months in the cone group the BMD has not started to plateau yet.

This is supported by the literature that has shown that in control groups the ipsilateral and contralateral hips have similar BMD figures, as Rao et al [418] stated that there was a highly significant correlation between the BMD of the two hips at the femoral neck, trochanter, and wards triangle. This is further supported by Soininvaara et al in 2004 [26] who reported BMD changes in TKA participants between the ipsilateral and contralateral at 12 months post-operation, reporting a loss of -0.029 g/cm^2 (femoral neck), -0.039 g/cm^2 (trochanter), -0.030 g/cm^2 (shaft) and -0.032 g/cm^2 in the total hip (although they also report -0.026 g/cm^2 (wards), which does not match these data). This trend is similar in Hopkins et al study [23] investigating TKR reported a difference between the ipsilateral and contralateral total hip at 12 months was reported as -0.027 g/cm^2, although an increase of 0.002 g/cm^2 was reported at the femoral neck at 12 months.

HIP BMD CHANGES IN THE NON-CONE GROUP

In the non-cone ipsilateral data there is a similar trend to the cone data, with an increase in the neck (0.08 %) and wards (4.2 %) at six weeks, and gradually decreasing at every visit, until reporting -3.363 % (neck, p-value 0.01) and -0.377 % (wards) at 12 months.

The total hip BMD figures show a similar trend again to the cone group, with the highest difference reported at six weeks (0.135 % (0.002 g/cm^2) and this figure continuing to drop throughout, reporting a 12 month figure of -0.572 % (-0.001 g/cm^2). The total hip BMD has most likely been influenced by the wards results of 4.2 % for the six week visit, with the changes in the neck and wards triangle paralleling the total hip changes, which is mimicked in the cone data, so is probably for the same reasons i.e. increased weight bearing post-op on the ipsilateral hip, and thus increased turnover in those hip regions.

The non-cone ipsilateral trochanter data reports only one minus figure at all visits (unlike in the cone group), although at six months there are losses reported by every region (except one) showing a similar trend to the six month cone ipsilateral data. It must be noted that the non-cone group figures are not statistically significant.

For the contralateral comparison data between cone and non-cone there is more variation; in the wards triangle at six weeks there is a loss (-0.580 % (-0.004 g/cm^2)) this would agree with the cone contralateral data, although the non-cone contralateral femoral neck data report a statistically significant increase of just over 2 % (0.019 g/cm^2) compared to the negative result of the cone group. At three months there is a reported statistically significant loss of BMD in the wards triangle at three months (-3.047 % -0.020 g/cm^2) in the contralateral hip. Although, at six months the neck figure reports a positive of 0.015 g/cm^2 (non-cone) (as does the same region in the cone group, 0.010 g/cm^2), with the 12 month data both contralateral hip totals reporting a loss (although more severe in the non-cone data).

The trochanters show a similar a pattern to the contralateral cone group, reporting an increase of just less than 1.7 % at six weeks, reducing to an

increase of 0.287 % at three months, a loss reported at six months, and an increase at 12 months**.** The total hip data follow a similar trend to the contralateral hip cone data, at six weeks and six months there is an increase (0.76 % (0.08 g/cm^2), and 0.251 % (0.001 g/cm^2)). Furthermore, it must be stated that at 12 months the total for the contralateral non-cone hip was -0.536 % (-0.004 g/cm^2) compared to the 0.388 % (0.004 g/cm^2) in the cone contralateral group, although there was no statistical significance between these two groups, except in the two regions mentioned.

Investigating the comparison between the ipsilateral and contralateral in the non-cone data, again there a similar traits, at six weeks there is a difference of 5.9 % (0.032 g/cm^2) in the wards (like in the cone group) but there is a negative difference in the neck reporting just under -1.8 % (-0.014 g/cm^2) were the cone group reported a positive, the total reported for the difference was -0.5 % (-0.005 g/cm^2) (with the cone group reporting -1 %). By six months the neck is reported as a difference of -3.4 % (-0.033 g/cm^2) in the neck and 3.09 % 0.018 g/cm^2) in the wards, this trend is similar in the cone group as in comparison to the six week figures both the neck and wards have been reduced. At 12 months the neck has increased (compared to six months) with a reported difference of -0.493 % (-0.002 g/cm^2), although the wards has decreased further (-0.927 % or -0.003 g/cm^2), the trochanter regions have dropped to its highest difference at 12 months reporting a difference of -2.993 % -0.019 g/cm^2). Finally, the total is reported as -1.036 % (-0.006 g/cm^2). Looking at the 12 month absolute BMD (so the reported BMD not the change) as we did with the cone group the differences between ipsilateral and contralateral is reported as: -0.024 g/cm^2 (neck), -0.089 g/cm^2 (wards), -0.067 g/cm^2 (trochanter), -0.049 g/cm^2 (shaft) resulting in a total BMD difference of -0.053 g/cm^2. These absolute figures would again agree with the data already mentioned from Soininvaara et al [26] and Hopkins et al study [23]. Although none of the ipsilateral vs contralateral non-cone data were statistically significant and did include large SD and a small sample size.

Overall, when comparing the cone and non-groups; at six weeks the non-cone group had a greater increase in the wards triangle 4.20 % vs 2.10 %, but the cone group had a greater increase in the neck 3.58 % vs 0.08 %, with the neck

result difference reported as statistically significant between the two ipsilateral hip groups. Both groups show a gain at six weeks of BMD in the wards triangle region, and then a loss from that six week position, with the neck trend again being similar between the two groups, the shaft reports a loss compared to baseline for every visit in both groups. The total BMD shows similar trends as well, both reporting their most positive figure at six weeks, then starting to decrease at three months and six months until 12 months were the cone group changes from -1.50 % to -1.36 %, and the non-cone group go -0.570 % at six months to -0.572 % at 12 months.

These changes reported in the total hip in both groups could be the beginning of the hip BMD starting to return to a plateau, and that by the 24 months both groups could be back at their baseline figures. This would correlate with the TKR knee BMD data reported from the systematic review data across several studies [178, 292, 300, 305]. Furthermore, the four papers that investigated the lumbar spine [23, 301] and hip changes [23, 26, 301] in TKR, all reported BMD losses at 12 months when compared to baseline both for the hip and lumbar spine, although it must be noted these data are extremely limited.

5.9 LIMITATIONS OF THE STUDY

5.9.1 LIMITATIONS TO TOTAL BODY AND LUMBAR SPINE

Limitations in the total body analysis was the inability to visualise the cement fully on the image making artefact classification an issue, to address this the revision implant and some of the area around it were manually classified as artefact.

For the lumbar spine data, it was originally proposed to remove those lumbar vertebrae which had pre-op reported sclerotic bodies or degenerative change (via the DXA radiographers report), and re-analyse the data. Unfortunately, a high majority of participants (most likely due age) had sclerotic or osteophytic issues with their lumbar spine (with some participants having their entire lumbar spine excluded from the report), thus exclusion and re-analysis of the data was deemed impractical due to the small number of participants to start with, being

diluted further, this would have resulted in excluding approximately half of the lumbar spine vertebrae. Furthermore, this would also have required each scan from each visit to be re-reported on due to the possibility of future sclerotic changes impacting those additional scans, with further vertebrae excluded throughout the visits. Therefore, as the issue was across both groups it was concluded to include all vertebral bodies of the participants individually, and as a whole, especially as this was comparing changes to their own baseline. With a larger cohort exclusions could be implemented and a more robust result could have been attained.

5.9.2 LIMITATIONS OF HIP STUDY

Unfortunately, there are no data for rTKR participants from DXA scans, so it is unknown if the trends reported in both groups was consistent, as there is no direct data to correlate this. Furthermore, the comparisons to the additional studies are of a small sample size, especially with this study only having 22 complete the 12 month appointment (Hopkins et al [23] N=19) (Soininvaara et al [26] N=69).

Moreover, the participants involved underwent different procedures, Hopkins et al recruited TKR participants, and Soininvaara et al [26] recruited TKA patients. Although it must be noted that the participants from the Hopkins et al [23] study where from the same area and scanned on the same DXA equipment, although additionally. Hopkins et al study did not include male participants, and Soininvaara et al [26] study did, but only 29 % were male of the 69 participants.

It is unknown if the differences reported in the cone group compared to the TKR and TKA studies are simply due to revision participants recovering sooner due to previous experience of having a TKR, or the impact of the physiotherapy changes, so it is possible participants had a greater understanding, and less apprehension about limitations and functionality, and those who were more actively engaged in the physiotherapy may have thus recovered their BMD more quickly. Although this change is not entirely seen in the non-cone group, who received the same physiotherapy instructions (although as stated it is unclear which participants were completely compliant in adhering to the physiotherapy instructions).

Furthermore, it must be acknowledged that the non-cone groups sample size was much smaller, and possibly with greater numbers would result in similar figures and trends reported. Unfortunately, the loss of five participants due to bone loss, could not be predicted, and there was no reported difference between their group and the group that continued, and only the advent of additional visual inspection by other orthopaedic surgeons creating a consensus during AORI classification could possibly reduce this attrition. The reported changes are also subject to precision errors as discussed in a previous chapter, although this would mean the total hip result is more prominent due to its lower precision error and its utilisation in reporting on outcomes of BMD figures when investigating osteopenia and osteoporosis.

5.10 CONCLUSION

The lumbar spine data although higher in the non-cone group than the cone group, is unlikely to be definitively influenced by the cone vs non-cone comparison, this is due to the influence of sclerotic and degenerative changes in the lumbar spine most likely falsely elevating the BMD. The total body BMD data show an association to the cone group reporting increases across all visits; this is even in conjunction with the increased BMD results of the lumbar spine across multiple visits in the non-cone group. This would support the idea that those in the cone group are undergoing weight bearing exercise earlier, although without knowledge of adherence to physiotherapy, this cannot be definitive.

This BMD data as reported via the DXA scans would suggest that there is early remodelling in rTKR patients at six weeks in the wards and neck, and that by 12 months, although there were still reported losses, there was the beginning of a move towards a plateau, and that by 24 months equilibrium might be reached. This is supported by the absolute change in the cone group and the total hip cone data. This is less clear in the non-cone group, and it is unknown if this is due to the impact of the cone on stabilisation or the small numbers in the non-cone group, based on the six week data also support the remodelling increase in the wards and hip, I would conclude it is more likely the latter.

Finally, these data for the total body, lumbar spine, and bilateral hips should be treated with reservations due to the limitations of the small sample size in both groups, and the lack of comparative rTKR BMD DXA hip data.

5.11 FUTURE WORK

Moving forward towards the full trial, the DXA modality has produced strong evidence of BMD change, with comparisons between groups and appointments due to the overlap ROI function providing accurate evidence. Therefore, it would be recommended as the main tool for determining BMD change during the study. That being said, consistent positioning is still required and caution should be used when interpreting the lumbar spine changes due to the osteophytic and sclerotic changes reported in this cohort.

CHAPTER 6: MAIN STUDY – BMD CHANGES IN PA AND LATERAL KNEES– A COMPARISON BETWEEN BASELINE, IPSILATERAL AND CONTRALATERAL, AND CONE VS NON-CONE FOR RTKR PARTICIPANTS

6.1 INTRODUCTION

This chapter will outline the methods utilised, and the analysis used in the main study. This study utilised the same participants as the chapter five with the addition of DXA knee imaging and knee regional analysis. This was in order to identify BMD changes in the ipsilateral and contralateral knees in and around the implant at certain time intervals over a period of one year.

From the systematic review data, it has been shown that there are minimal studies investigating ipsilateral BMD change in rTKR surgery via DXA imaging. Although there are some reported data regarding replacements and arthroplasties. In the systematic review there were only two papers that investigated rTKR and BMD in DXA imaging, and both were from Jensen et al [178, 179]. Furthermore, no study involving this new type of Stryker cone has been investigated, although Jensen et al 2012 [178] did investigate their own type of cone and its impact in rTKR on BMD; this was a different construction and style of cone.

6.1.1 AIM

To investigate the BMD changes in rTKR participants in and around regions of the distal femur and proximal tibial areas at post-op intervals, with comparisons between baseline measurements (defined as six weeks post-op) and their subsequent visits. Percentage changes throughout the visits were calculated in the DXA data, and differences between cone and non-cone groups were also investigated.

6.2 PARTICIPANTS

Participants, grouping, randomisation and recruitment are exactly the same group as mentioned in chapter five section 5.2. This resulted in 37 participants recruited and consented (24 cone, 13 non-cone).

6.3 METHOD, IMAGING

6.3.1 DXA IMAGING METHOD

Prior to their rTKR all 37 participants were invited to undergo a pre-operative BMD evaluation via a DXA scan (GE Lunar prodigy, Bedford, MA). This involved scanning their ipsilateral and contralateral knees in the PA and lateral projection.

DXA KNEE POSITIONING

Knee positioning in DXA is relatively new but follows the densitometric analysis positioning protocol [255]. For the PA knee scan this requires the patient to be supine and straight, with the scan done with the knee in full extension with 15° internal rotation, this is maintained via the foot scan device used in hip DXA imaging which maintains internal rotation for repeated imaging by strapping the foot in place. Lateral DXA knee scans are done with the patient on their right or left lateral decubitus, with the knee in 20° flexion checked via a goniometer [255], a pad is placed under the ankle to superimpose the femoral condyles more easily. Furthermore, both the PA and lateral are supported with rice bags due to the need for a soft tissue substitute around the knee area [255] due to edge detection artefacts. Additionally, all DXA knee scans are produced on the spine “thin” mode setting, as there is no pre-defined knee setting.

Laser crosshair positioning in both the PA and lateral is dependent on stem or replacement length under investigation, as the whole implant should be included. Please note patient preparation and DXA QA are the same as the previous chapter. DXA knee scans with total body, lumbar spine, and bilateral hips were conducted at pre-op, six weeks post operation (this was defined as one week before or one week after the exact six week post-op date), and then at three (defined as one week before and two weeks after the exact three month date), six (defined as one week before and two weeks after the exact six month date), and 12 months (defined as two weeks before and four weeks after the exact 12 month date).

6.4 ANALYSIS OF KNEE DXA IMAGING

6.4.1 DXA KNEE ANALYSIS

The DXA knee scans were done on a PA thin spine setting (which is the standard setting as previously stated), due to this setting the DXA analysis on the PA and lateral knee scans resulted in some miscategorisations by the DXA software (encore GE Healthcare version 14.10.22), (as shown in figure 6.1).

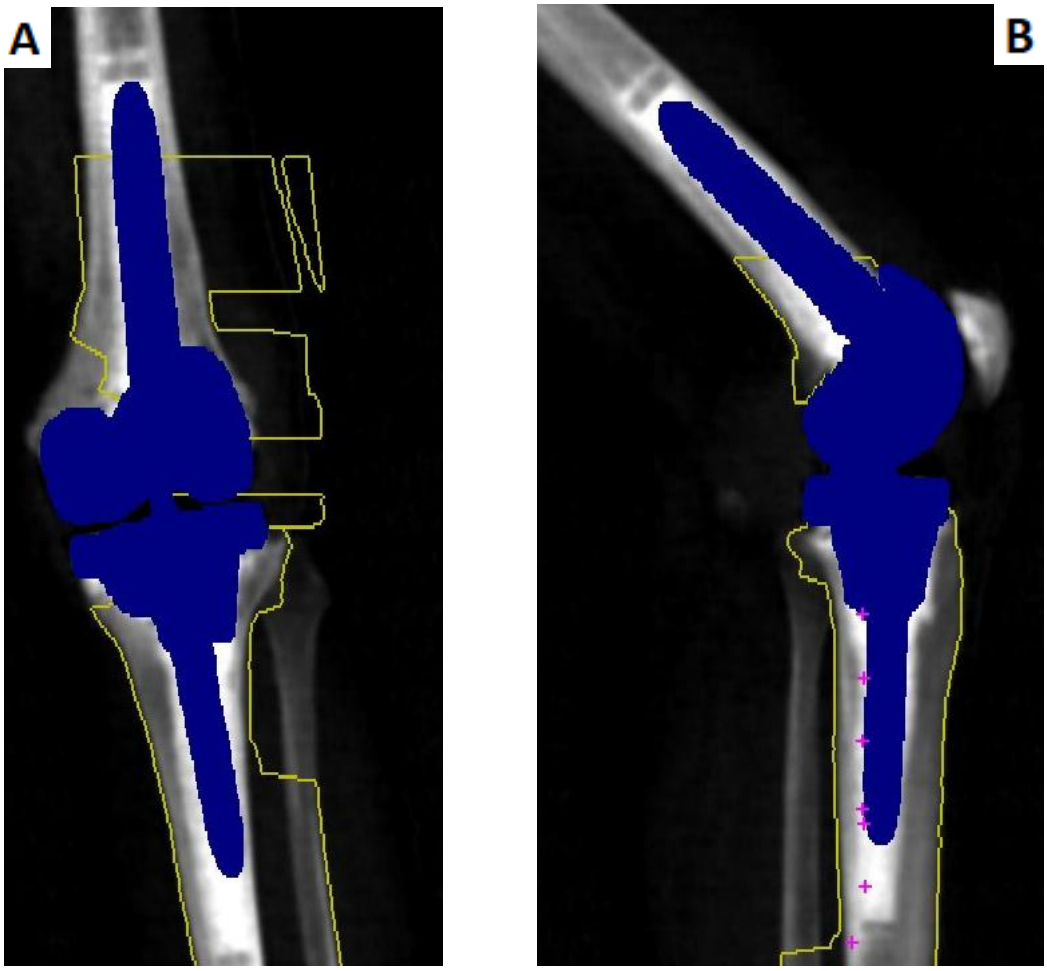


Figure 6.1 *PA (A) and lateral (B) knee DXA image, with the software defining the bone (yellow on the image), artefact (blue) and soft tissue (not coloured)*

Therefore, modifications were required to manually alter the classifications of soft tissue and bone, the definition of the artefact (the blue in the image in figure 6.1) was not altered as it highlighted the implants within the patient, the lateral images were annotated and classified in the same way (figure 6.2 and 6.3 show an annotated set with ROI).

Due to this manual classification of soft tissue and bone on the lateral and PA images, a COV was calculated to determine variation in the researcher's (MG)

ability to define soft tissue and bone on multiple identical images. Therefore 10 random PA revision knee images, and 10 random lateral revision knee images were chosen, the bone and soft tissue were then manually classified on the individual image and BMD result recorded, the image was wiped of the classification and this was repeated for 10 times resulting in a calculated COV for classification of bone and soft tissue, this precision score is reported in the subsequent sections.

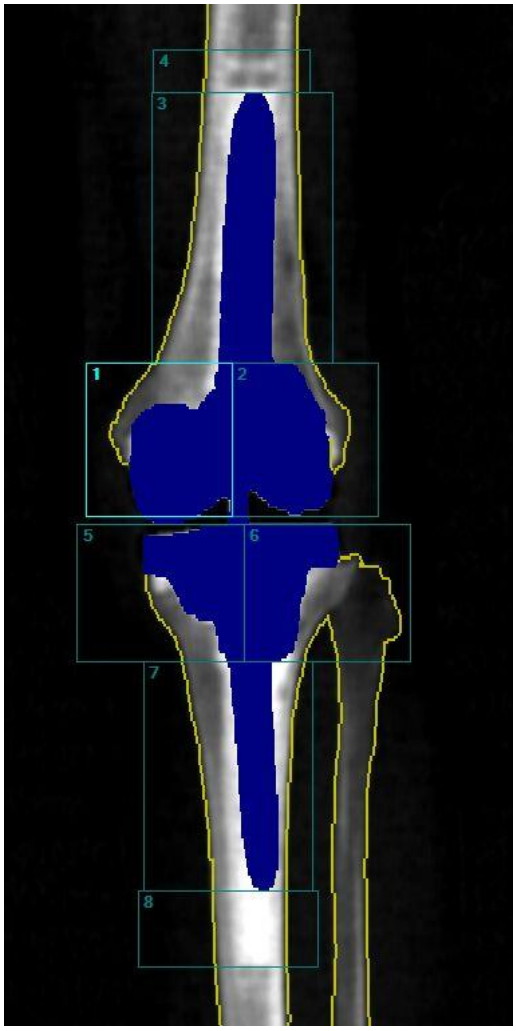


Figure 6.2. *DXA PA knee image, showing ROI (blue boxes) for DXA analysis*

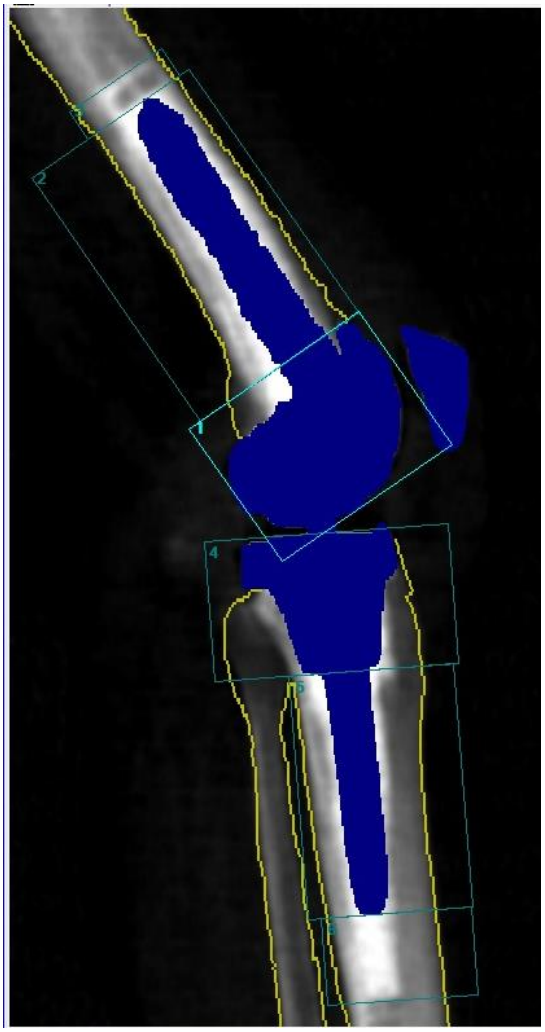


Figure 6.3. *DXA lateral knee image, showing ROI (blue boxes) for DXA analysis*

After correct classification of the PA and lateral knee images, the knees were subdivided into ROI as shown in figures 6.2 and 6.3. This ROI subdivision knee analysis was based on standard format which has been shown in previous BMD knee research [178, 255, 260, 419].

The region selections were kept consistent between each individual participants scans, with the ROI maps saved from the original scan, reloaded onto future appointments and then slight modifications applied to allow correct overlap of the anatomy. The regions were kept anatomically consistent across all regions (table 6.1).

Table 6.1. *Region selection for PA and lateral knee images*

PA (figure 6.2)	**Lateral (figure 6.3)**
Region 1 –Femoral medial condyle	Region 1 – Superimposed femoral condyles
Region 2 – Femoral lateral condyle	Region 2 – Femoral stem
Region 3 – Femoral stem	Region 3 – After stem
Region 4 – After femoral stem	Region 4 – Superimposed tibial condyles
Region 5 – Tibial medial condyle	Region 5 – Tibial stem
Region 6 – Tibial lateral condyle	Region 6 – After tibial stem
Region 7 – Tibial stem	
Region 8 - After tibial stem	

It must be noted these regions were kept consistent regardless of PA left or PA right, with the ROI flipped when needed.

For the lateral data the regions were kept consistent, but were rotated to become parallel with the patients femur and tibia, with further minor adjustments made to fit the correct recorded regions.

After application of the ROI in both the PA and lateral images, the fibula in both the PA and lateral images were classified as artefact if it was in any ROI box, this did not affect any overall BMD, and was applied so it would not interfere with the true BMD of the tibia (an example of this is shown in figure 6.4), this was seen as a more optimum solution than modifying each ROI individually and still reported the same BMD.

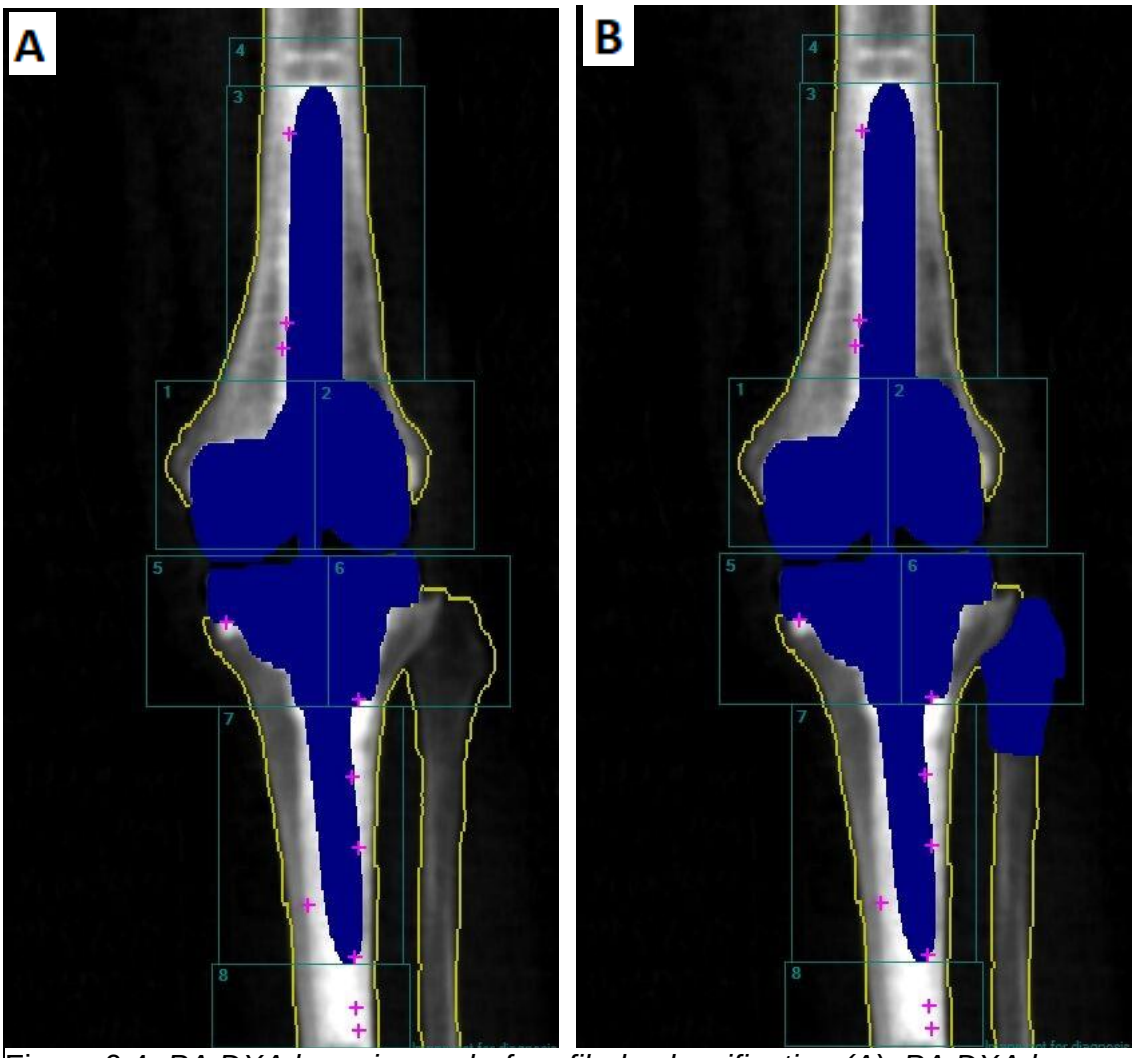


Figure 6.4. *PA DXA knee image before fibula classification (A), PA DXA knee image of after fibula classification (B).*

All regions (both PA and lateral) were kept consistent across all images when intra comparing patient visits; although these regions were slightly modified to always reflect the correct anatomical region. Thus, patients with short stems would have a smaller region seven but this would be consistent when intra comparing between their visits. It must be acknowledged that post processing of the knee scans was administered in the form of checking the correct classification of soft tissue, bone and artefact within the image, although this processing was done prior to any regional analysis in order to reduce bias of selection.

The BMD of the regions for the ipsilateral knee were compared to the six week post-op rather than the pre-op, this was done for several reasons, firstly due to there being no definitive regions in the pre-op scan until the implant was in place, and thus would have provided erroneous data. Secondly, we were

primary investigating the impact of the cone on BMD post-surgery in the knee, thus for all knee BMD data the six week scan was utilised.

As with the other anatomical regions, the ipsilateral knee per region was intracompared at each visit to the baseline six week post-op. This BMD change was recorded on a Microsoft Excel spreadsheet as an absolute change as well as calculated percentage change for each visit, an overall mean difference, SD and 95 % CI was calculated for each region and a paired samples t-test and p-value created for each comparison. This analysis was repeated for the contralateral knee as well, again compared to its six week post-op BMD regional result.

This analysis was repeated for the non-cone group, including scans of both the ipsilateral and contralateral knee for all 12 month visits, this allowed comparisons between the ipsilateral BMD changes in the cone group and ipsilateral changes in the non-cone group at each visit, as well as changes in the contralateral knee. This was in order to investigate if contralateral knee changes in both groups were also similar. In comparing groups an independent t-test assuming unequal variance, p-value, SD, SE was calculated.

Furthermore, mean BMDs between the ipsilateral and contralateral were not compared directly (unlike in the hip analysis), and only compared as a percentage change compared to baseline, this was simply due to the ipsilateral containing the revision and fixation cement so having a more highly elevated BMD.

Due to the nature of repeated t-tests leading to increased probability of type one errors a statistician was consulted (Dr Obi Ukoumunne) who suggested using a linear regression analysis. This was performed on the absolute BMD figures per region from the PA and lateral knee data. Participant ID was used as the random effect, obtaining maximum likelihood estimate score per region. Any data missing (due to lack of attendance) was left blank. Data were coded as such; participant ID number, group (cone group 1, non-cone group 0), and time period (6 week baseline = 0, three months = one, six months = two, 12 months

= three). With the STATA (version 16) used to analyse the figures resulting in a coefficient, 95 % CI and overall p-value.

6.4.2 INTRAOPERATOR REGIONAL ANALYSIS OF THE KNEE

Due to the selective nature of the ROI over the DXA images, especially in the PA and lateral DXA knee images, it was decided to calculate a COV for the ROI selected, thus an intraoperator repeated ROI study was conducted. This involved five PA and five lateral ipsilateral knee DXA images, five PA and five lateral non-cone ipsilateral images, and five PA and five lateral random contralateral knee images. Each image was analysed as per the method stated in section 6.5.1.1 with the regions utilised in table 6.1, with these images re-analysed, this was repeated until 10 repeats were created for each group and orientation with a COV created for each ROI.

6.5 RESULTS

6.5.1 INTRAOPERATOR RESULTS - COV FOR COLOURISATION OF DXA KNEE IMAGES

The method involved collecting 10 random PA knee images and 10 random lateral knee images (post standard software application), any corrections to soft tissue or bone was then applied and the BMD recorded for that image, this was to be repeated 10 times over several weeks. A COV was to be calculated to create a precision score for the manual modifications/classifications of bone and soft tissue (although it must be noted that some images required only slight modification). Unfortunately, due to COVID-19 and campus lockdown, access to the DXA room was suspended, thus classifications and repeated visits could not be undertaken, and thus no COV precision for manual modification could be calculated. It must be acknowledged that DXA software is unique and only on the DXA computer (following compliance with the General Data Protection Act), remote access was trialled, but this was not successful, due to the restrictions.

6.5.2 INTRAOPERATOR RESULTS- COV ROI ANALYSIS FOR PA AND LATERAL KNEE IN DXA IMAGES

The method was to create a COV for the ROI on the PA ipsilateral and lateral cone images, the PA ipsilateral and lateral non-cone images and for PA and lateral contralateral knee images. This (similar to the COV colourisation) was to involve several visits and repeats over several weeks. Unfortunately, as per 6.5.1, COVID-19 restricted access to the campus and the DXA room, not only stopped participant recruitment, but meant that a COV ROI precision could not be completed due to inaccessibility of the facilities.

6.6 BMD DXA RESULTS OF THE PA KNEE

In total 37 participants consented to pre-op, 26 completed six weeks, 26 at three months, 25 at six months, with 22 participants completing 12 months (15 cone, seven non-cone). As stated previously, one participant received a femoral cone (so not a tibial cone like the other “cone” participants), therefore their DXA knee data was treated as non-cone data for the tibial regions (having had no implant in the tibia, other than the revision), with the femoral data were excluded from the analysis altogether. Furthermore, two participants underwent knee operations prior to their 12 month visit, both on their contralateral knee (a revision and replacement), therefore their contralateral BMD data for the PA and lateral knee data were excluded. Due to the impact on the participant numbers the cone group was not divided into the long and short stems, and instead was kept together as the “cone” group. In total the cone group reported 15 short stems and eight long stems (one cone group participant withdrew prior to receiving either length making 24 cone participants), the non-cone group reported four short stems nine long stems making 13 non-cone participants at pre-op (37 total).

This section will now report the BMD results for the PA knee in DXA images, with the lateral knee DXA data following in the next section. The data was compared between each participant’s visits (three month, six month, and 12 month) to their baseline (six week post-op) score, with a mean percentage change calculated for both the cone and non-cone group, with these percentage results then compared between the two groups.

Table 6.2. *Shows the mean baseline (6 week) BMD (g/cm^2) for the PA knee, for the cone group (N=17) and non-cone group (N=9)*

N=17 (CONE GROUP)	**6 WEEKS (BASELINE) IPSILATERAL**			**6 WEEKS (BASELINE) CONTRALATERAL**		
	Mean (g/cm^2)	**SD**	**SE**	**Mean (g/cm^2)**	SD	SE
Medial femoral condyle	**0.834**	0.208	0.050	**1.116**	0.487	0.118
Lateral femoral condyle	**0.916**	0.257	0.062	**1.015**	0.244	0.059
Femoral stem	**1.455**	0.181	0.044	**1.084**	0.281	0.068
Beyond stem	**1.974**	0.333	0.081	**1.501**	0.485	0.118
Medial tibial condyle	**1.167**	0.298	0.072	**1.027**	0.242	0.059
Lateral tibial condyle	**1.193**	0.283	0.069	**1.012**	0.228	0.055
Tibial stem	**1.955**	0.222	0.054	**1.399**	0.249	0.060
Beyond stem	**2.449**	0.189	0.046	**1.689**	0.352	0.085
N=9 (NON-CONE GROUP)						
Medial femoral condyle	**0.835**	0.198	0.070	**0.959**	0.292	0.097
Lateral femoral condyle	**0.708**	0.242	0.086	**0.835**	0.277	0.092
Femoral stem	**1.515**	0.243	0.086	**1.024**	0.418	0.139
Beyond stem	**2.139**	0.561	0.212	**1.525**	0.601	0.200
Medial tibial condyle	**1.150**	0.318	0.106	**0.840**	0.318	0.106
Lateral tibial condyle	**1.266**	0.260	0.087	**0.951**	0.380	0.127
Tibial stem	**1.911**	0.185	0.062	**1.398**	0.309	0.103
Beyond stem	**2.351**	0.381	0.127	**1.828**	0.447	0.149

Table 6.2 show the mean BMD in g/cm^2 baseline (six week) results of the 26 (17 cone, nine non-cone) participants who underwent a DXA scan at six weeks. It must be noted that the comparisons to baseline in the following results tables and figures, involved comparing the participants BMD visit score with their own baseline score to report a direct change with this BMD change converted into a percentage for each participant, with an overall mean percentage calculated for that group. It must also be acknowledged that the high baseline figures in the stem and beyond stem sections of both the tibia and femur are primarily due to the addition of fixation cement in these areas, hence why there will be no direct BMD comparisons, only the reported percentage changes.

6.6.1 BMD PERCENTAGE DIFFERENCE IN PA KNEE WHEN COMPARED TO BASELINE, FOR IPSILATERAL AND CONTRALATERAL CONE GROUP

These data compare the BMD percentage results compared to baseline in the PA knee, and are shown in the table below.

Table 6.3. *Shows the ipsilateral PA knee compared to baseline (6 week) BMD (g/cm^2) for the cone group*

3 MONTHS (N=17)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	-0.002	0.612	-6.24	7.46	14.425	3.499	0.08	0.93
Lateral femoral condyle (g/cm^2)	0.043	4.931	0.71	9.11	8.825	2.140	-2.11	**0.05**
Femoral stem (g/cm^2)	0.003	0.118	-2.27	2.51	5.026	1.219	-0.19	0.85
Beyond femoral stem (g/cm^2)	0.046	2.411	0.62	4.20	3.760	0.912	-2.63	**0.02**
Medial tibial condyle (g/cm^2)	-0.046	-4.101	-8.36	0.16	8.953	2.171	1.88	0.08
Lateral tibial condyle (g/cm^2)	0.026	2.461	-2.1	7.00	9.542	2.314	-1.01	0.32
Tibial stem (g/cm^2)	0.007	0.535	-2.36	3.44	6.099	1.479	-0.25	0.81
Beyond tibial stem (g/cm^2)	-0.012	-0.486	-3.39	2.41	3.116	0.756	0.63	0.54
6 MONTHS (N=16)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.018	2.560	-5.01	10.10	15.082	3.771	-0.64	0.53
Lateral femoral condyle (g/cm^2)	-0.040	-3.084	-10.70	4.49	15.451	3.863	1.02	0.32
Femoral stem (g/cm^2)	-0.013	-0.979	-4.24	2.28	6.653	1.663	0.55	0.59
Beyond femoral stem (g/cm^2)	0.009	0.625	-2.06	3.31	5.460	1.365	-0.33	0.75
Medial tibial condyle (g/cm^2)	-0.059	-5.336	-13.50	2.84	16.687	4.172	1.15	0.27
Lateral tibial condyle (g/cm^2)	0.007	0.538	-5.19	6.27	11.688	2.922	-0.21	0.83
Tibial stem (g/cm^2)	-0.021	-1.112	-4.84	2.62	7.622	1.906	0.59	0.56
Beyond tibial stem (g/cm^2)	0.016	0.650	-1.74	3.04	4.876	1.219	-0.53	0.60
12 MONTHS (N=14)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.010	2.114	-7.89	12.10	19.107	5.107	0.23	0.83
Lateral femoral condyle (g/cm^2)	-0.010	0.132	-8.46	8.72	16.931	4.525	-0.23	0.82
Femoral stem (g/cm^2)	-0.041	-2.847	-6.67	0.97	7.285	1.947	-1.46	0.17
Beyond femoral stem (g/cm^2)	0.089	4.495	2.10	6.89	4.575	1.269	3.54	**0.00**
Medial tibial condyle (g/cm^2)	-0.099	-8.979	-19.50	1.520	19.999	5.345	-1.59	0.14
Lateral tibial condyle (g/cm^2)	0.054	3.695	-3.15	10.50	13.057	3.490	1.42	0.18
Tibial stem (g/cm^2)	-0.050	-2.930	-6.21	0.35	6.256	1.672	-1.52	0.15
Beyond tibial stem (g/cm^2)	-0.038	-1.653	-4.21	0.907	4.885	1.305	-1.22	0.25

Table 6.4. *Shows the contralateral PA knee compared to baseline (6 week) BMD (g/cm^2) for the cone group*

3 MONTHS (N=17)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.019	2.767	-1.47	7.01	8.925	2.165	-1.04	0.31
Lateral femoral condyle (g/cm^2)	0.007	1.398	-4.66	7.46	12.753	3.093	-0.28	0.78
Femoral stem (g/cm^2)	0.017	1.178	-1.07	3.43	4.735	1.148	-1.37	0.19
Beyond femoral stem (g/cm^2)	0.004	0.102	-1.42	1.62	3.189	0.773	-0.38	0.71
Medial tibial condyle (g/cm^2)	-0.001	-0.123	-2.35	2.11	4.687	1.137	0.12	0.91
Lateral tibial condyle (g/cm^2)	0.009	0.408	-2.07	2.89	5.214	1.265	-0.77	0.46
Tibial stem (g/cm^2)	0.024	1.515	-0.38	3.40	3.981	0.966	-1.63	0.12
Beyond tibial stem (g/cm^2)	0.033	1.978	-0.84	4.80	5.923	1.436	-1.24	0.23
6 MONTHS (N=16)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.002	0.798	-3.02	4.62	7.798	1.949	-0.12	0.90
Lateral femoral condyle (g/cm^2)	0.014	0.855	-4.37	6.07	10.645	2.661	-0.50	0.63
Femoral stem (g/cm^2)	-0.007	-0.729	-3.33	1.87	5.297	1.324	0.50	0.62
Beyond femoral stem (g/cm^2)	-0.018	-1.554	-3.84	0.74	4.681	1.170	1.24	0.23
Medial tibial condyle (g/cm^2)	-0.010	-1.098	-3.85	1.65	5.620	1.405	0.75	0.46
Lateral tibial condyle (g/cm^2)	0.021	1.597	-1.16	4.36	5.627	1.407	-1.50	0.16
Tibial stem (g/cm^2)	-0.001	0.082	-1.78	1.94	3.790	0.948	0.08	0.94
Beyond tibial stem (g/cm^2)	0.002	0.424	-1.69	2.53	4.306	1.076	-0.08	0.93
12 MONTHS (N=13) 1 PARTICIPANT UNDERWENT TKR ON CONTRALATERAL KNEE SO THESE DATA HAS BEEN EXCLUDED								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.013	3.931	-4.39	12.30	15.311	4.246	0.41	0.69
Lateral femoral condyle (g/cm^2)	-0.012	-1.498	-9.17	6.17	14.118	3.916	-0.30	0.77
Femoral stem (g/cm^2)	0.000	-0.196	-2.80	2.40	4.781	1.326	-0.02	0.98
Beyond femoral stem (g/cm^2)	0.002	-0.060	-2.50	2.38	4.482	1.243	0.09	0.93
Medial tibial condyle (g/cm^2)	0.003	0.496	-7.51	6.51	12.897	3.577	0.11	0.92
Lateral tibial condyle (g/cm^2)	-0.001	-0.333	-4.52	3.86	7.175	1.990	-0.05	0.96
Tibial stem (g/cm^2)	0.001	0.217	-2.95	3.39	5.831	1.617	0.04	0.97
Beyond tibial stem (g/cm^2)	-0.006	0.049	-3.16	3.26	5.900	1.636	-0.22	0.83

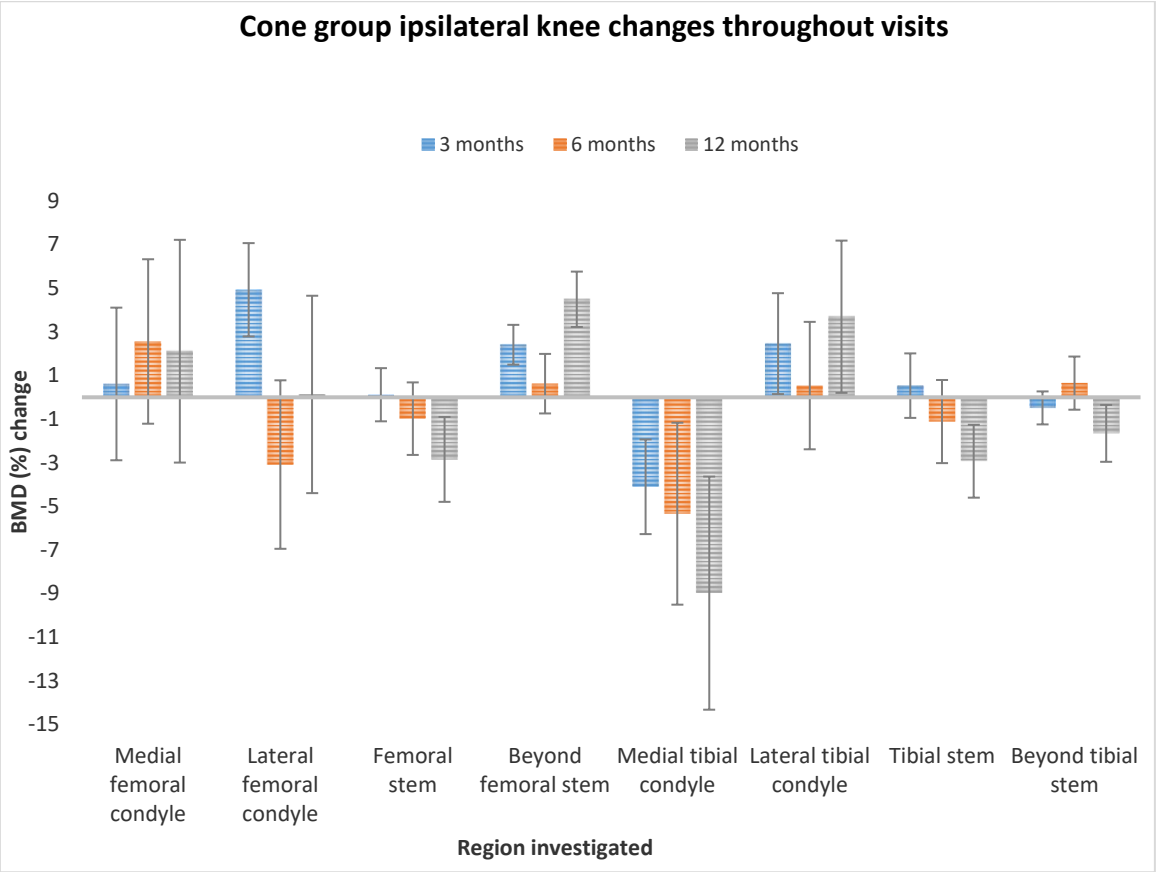


Figure 6.5. *Shows bar graph for BMD (%) changes in the cone group ipsilateral knee in different ROI throughout visits, error bars are SE*

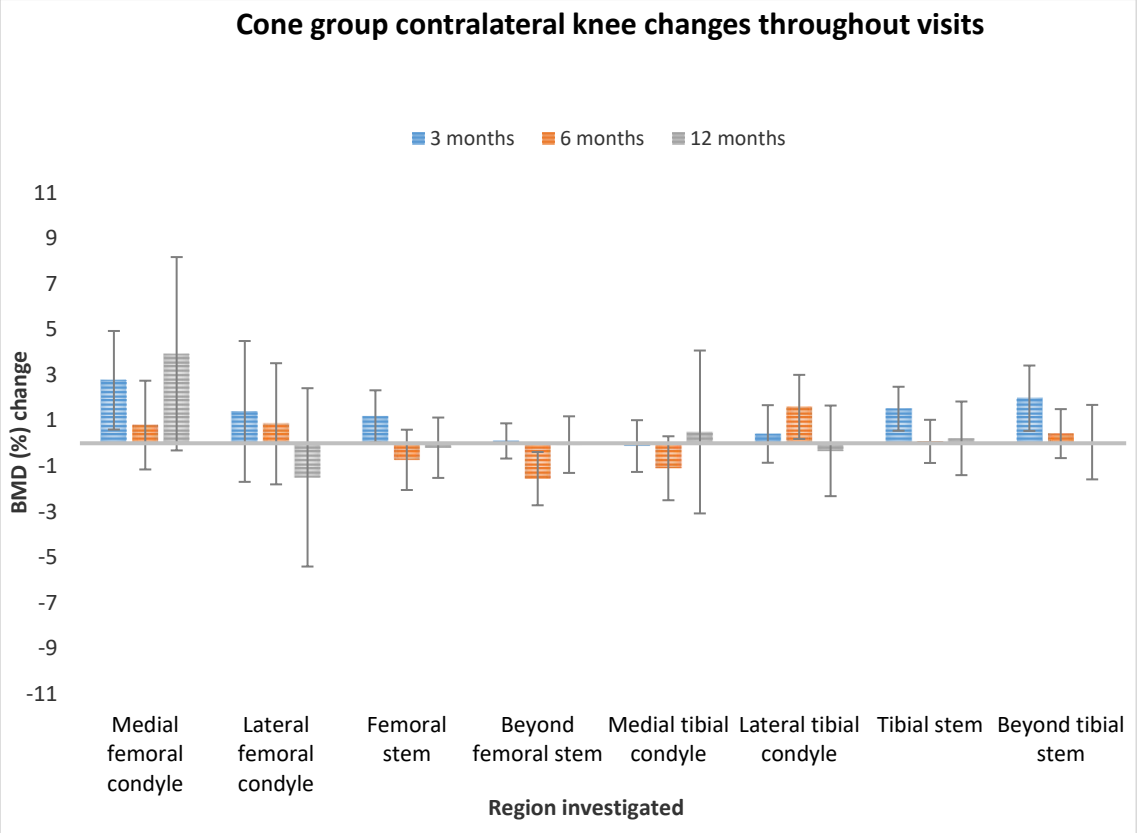


Figure 6.6. *Shows bar graph for BMD (%) changes in the cone group contralateral knee in different ROI throughout visits, error bars are SE*

Table 6.3 and figure 6.5 show the ipsilateral cone group changes throughout the visits. The medial femoral condyle shows increases at all three visits, with the highest reached at six months with a reported score of 2.56 %, the lateral femoral condyle has the greatest gain of all regions, with a reported increase at three months of 4.9 % (with a p-value of 0.05) (although this is a loss at six months and a slight gain by 12 months). The femoral stem shows very little change across all visits, beyond the femoral stem shows an increase across all visits with a large score of 4.495 % at 12 months (0.00 p-value).

The tibial ipsilateral data involve the two regions around the cone, the medial and lateral tibial condyles. In the tibial medial condyle, the loss in BMD is seen throughout each visit, gradually getting worse; -4.1 % (three months, p-value 0.08), -5.3 % (six months, p-value 0.27), -8.979 % at 12 months (p-value 0.14). In the lateral tibial condyle, the BMD reports the opposite, reporting increases at every visit; 2.5 % (three months) 0.5 (six months), and 3.695 % at 12 months**.** In the tibial stem there is a small increase at three months, and then gradually decreases reporting a loss of -2.93 % at 12 months. Beyond the tibial stem reports a small decrease at three months, a gradual increase at 6 months, with a final change of -1.653 % at 12 months. Although it must be noted only three figures reported a statistical significant p-value: the lateral femoral condyle at three months (4.931 %, p-value 0.05), beyond femoral stem also at three months (2.411 %, p-value 0.02), and again at the femoral stem at 12 months (4.495 % (p-value 0.00)).

Table 6.4 and figure 6.6 report the contralateral cone group changes throughout the visits. The medial femoral condyle shows increases throughout each visit, with a reported figure of 2.77 % at three months, and an increase of 3.39 % at 12 months. The lateral femoral condyle shows increases at three and six months (1.4 % and 0.86 % respectively) and a decrease at 12 months of -1.498 %. The femoral stem and beyond the femoral stem, show small increases and decreases throughout with a reported 12 month figure of -0.196 % (femoral stem), -0.060 % (beyond the femoral stem).

In the tibial regions the medial tibial condyle reports small changes throughout, reporting just over -1 % at six months, but -0.1 % and 0.496 % for three and 12

month respectively. In the lateral tibial condyle region, there are also small changes reported as 0.41 % at three months, and -0.333 % at 12 months, with the six month reported as a gain of 1.60 %. The tibial stem again is similar in the changes it reports, disclosing small changes at six and 12 months (0.08 % and -0.217 % respectively), with a reported increase of 1.5 % at three months. Under the tibial stem there was a small increase of 0.42 % (six months), with large increases of just under 2 % at three months, and at 12 months as 0.049 %.

It must be stated that none of the contralateral knee cone data reported a statistically significant change of a p-value of 0.05.

6.6.2 BMD PERCENTAGE DIFFERENCE IN PA KNEE WHEN COMPARED TO BASELINE, FOR IPSILATERAL AND CONTRALATERAL FOR THE NON-CONE GROUP

These data compare the BMD percentage results compared to baseline in the PA knee, and are shown in the table below.

Table 6.5. *Shows the ipsilateral PA knee compared to baseline (6 week) BMD (g/cm^2) for the non-cone group*

3 MONTHS (N=9)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	-0.022	-3.391	-9.39	2.61	9.183	3.247	0.77	0.47
Lateral femoral condyle (g/cm^2)	0.005	0.976	-6.22	8.18	11.019	3.896	-0.17	0.87
Femoral stem (g/cm^2)	-0.013	-0.808	-4.04	2.42	4.950	1.750	0.51	0.62
Beyond femoral stem (g/cm^2)	-0.011	-1.119	-4.31	2.07	4.889	1.848	0.32	0.76
Medial tibial condyle (g/cm^2)	-0.052	-3.061	-12.80	6.70	14.938	4.979	0.99	0.35
Lateral tibial condyle (g/cm^2)	-0.035	-3.717	-8.86	1.42	7.875	2.625	1.05	0.32
Tibial stem (g/cm^2)	-0.100	-5.219	-9.36	-1.08	6.339	2.113	2.42	**0.04**
Beyond tibial stem (g/cm^2)	-0.021	-0.398	-3.60	2.80	4.901	1.634	0.58	0.58
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	-0.020	-2.962	-13.90	7.94	15.800	5.972	0.40	0.70
Lateral femoral condyle (g/cm^2)	0.008	0.912	-3.99	5.81	7.065	2.670	-0.38	0.72
Femoral stem (g/cm^2)	-0.041	-2.913	-5.57	-0.25	3.832	1.448	1.83	0.12
Beyond femoral stem (g/cm^2)	0.041	2.055	-1.25	5.37	4.777	1.950	-0.85	0.43
Medial tibial condyle (g/cm^2)	-0.034	-1.373	-11.90	9.13	15.183	5.368	0.52	0.62
Lateral tibial condyle (g/cm^2)	0.009	-0.783	-9.23	7.67	12.200	4.313	-0.14	0.89
Tibial stem (g/cm^2)	-0.028	-1.310	-5.96	3.34	6.704	2.370	0.60	0.56
Beyond tibial stem (g/cm^2)	0.048	2.429	-2.23	7.09	6.722	2.377	-0.92	0.39
12 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.017	2.189	-13.10	17.50	22.020	8.323	0.28	0.79
Lateral femoral condyle (g/cm^2)	0.008	2.733	-5.49	11.00	11.856	4.481	0.38	0.72
Femoral stem (g/cm^2)	-0.028	-1.619	-5.12	1.88	5.047	1.908	-0.89	0.41
Beyond femoral stem (g/cm^2)	0.010	0.223	-1.14	1.58	1.961	0.801	0.60	0.58
Medial tibial condyle (g/cm^2)	-0.066	-3.856	-13.50	5.79	13.920	4.921	-1.18	0.28
Lateral tibial condyle (g/cm^2)	-0.010	-2.015	-8.14	4.12	8.853	3.130	-0.19	0.85
Tibial stem (g/cm^2)	-0.074	-3.496	-8.21	1.21	6.793	2.402	-1.48	0.18
Beyond tibial stem (g/cm^2)	-0.013	-0.252	-3.52	3.02	4.720	1.669	-0.31	0.77

Table 6.6. *Shows the contralateral PA knee compared to baseline (6 week) BMD (g/cm^2) for the non-cone group*

3 MONTHS (N=9)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	-0.075	-7.686	-11.90	-3.51	6.397	2.132	3.29	**0.01**
Lateral femoral condyle (g/cm^2)	0.037	5.810	-6.19	17.80	18.388	6.129	-0.85	0.42
Femoral stem (g/cm^2)	-0.009	-0.662	-3.27	1.95	3.998	1.333	0.66	0.53
Beyond femoral stem (g/cm^2)	-0.063	-2.907	-5.70	-0.12	4.277	1.426	1.73	0.12
Medial tibial condyle (g/cm^2)	0.027	2.088	-1.37	5.55	5.295	1.765	-1.29	0.23
Lateral tibial condyle (g/cm^2)	0.008	0.953	-2.92	4.82	5.927	1.976	-0.44	0.67
Tibial stem (g/cm^2)	-0.009	-0.868	-5.01	3.27	6.330	2.110	0.33	0.75
Beyond tibial stem (g/cm^2)	-0.025	-1.975	-6.11	2.15	6.324	2.108	0.69	0.51
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	0.007	2.679	-7.52	12.90	14.648	5.179	-0.16	0.88
Lateral femoral condyle (g/cm^2)	0.015	3.154	-5.51	11.80	12.495	4.418	-0.47	0.65
Femoral stem (g/cm^2)	0.014	1.152	-1.80	4.10	4.255	1.505	-1.16	0.28
Beyond femoral stem (g/cm^2)	-0.018	-1.681	-4.42	1.06	3.956	1.399	1.22	0.26
Medial tibial condyle (g/cm^2)	0.035	4.894	0.514	9.27	6.320	2.234	-2.06	0.08
Lateral tibial condyle (g/cm^2)	0.009	0.409	-4.24	5.06	6.706	2.371	-0.44	0.67
Tibial stem (g/cm^2)	-0.007	-0.827	-5.94	4.28	7.377	2.608	0.20	0.85
Beyond tibial stem (g/cm^2)	-0.031	-2.378	-7.01	2.25	6.681	2.362	0.89	0.40
12 MONTHS (N=7) 1 PARTICIPANT UNDERWENT TKR ON CONTRALATERAL KNEE SO THESE DATA HAS BEEN EXCLUDED								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Medial femoral condyle (g/cm^2)	-0.062	-5.997	-14.1	2.14	10.993	4.155	-1.60	0.16
Lateral femoral condyle (g/cm^2)	0.048	5.825	-4.14	15.80	13.456	5.086	1.04	0.34
Femoral stem (g/cm^2)	-0.024	-2.577	-8.35	3.19	7.783	2.942	-0.59	0.58
Beyond femoral stem (g/cm^2)	-0.016	-2.636	-8.24	2.96	7.566	3.089	-0.38	0.72
Medial tibial condyle (g/cm^2)	0.060	4.547	-1.75	10.80	8.500	3.213	1.50	0.18
Lateral tibial condyle (g/cm^2)	-0.031	-2.380	-8.39	3.63	8.114	3.067	-0.75	0.48
Tibial stem (g/cm^2)	0.006	-0.590	-7.19	6.01	8.916	3.370	0.13	0.90
Beyond tibial stem (g/cm^2)	-0.011	-2.256	-9.80	5.28	10.182	3.848	-0.17	0.87

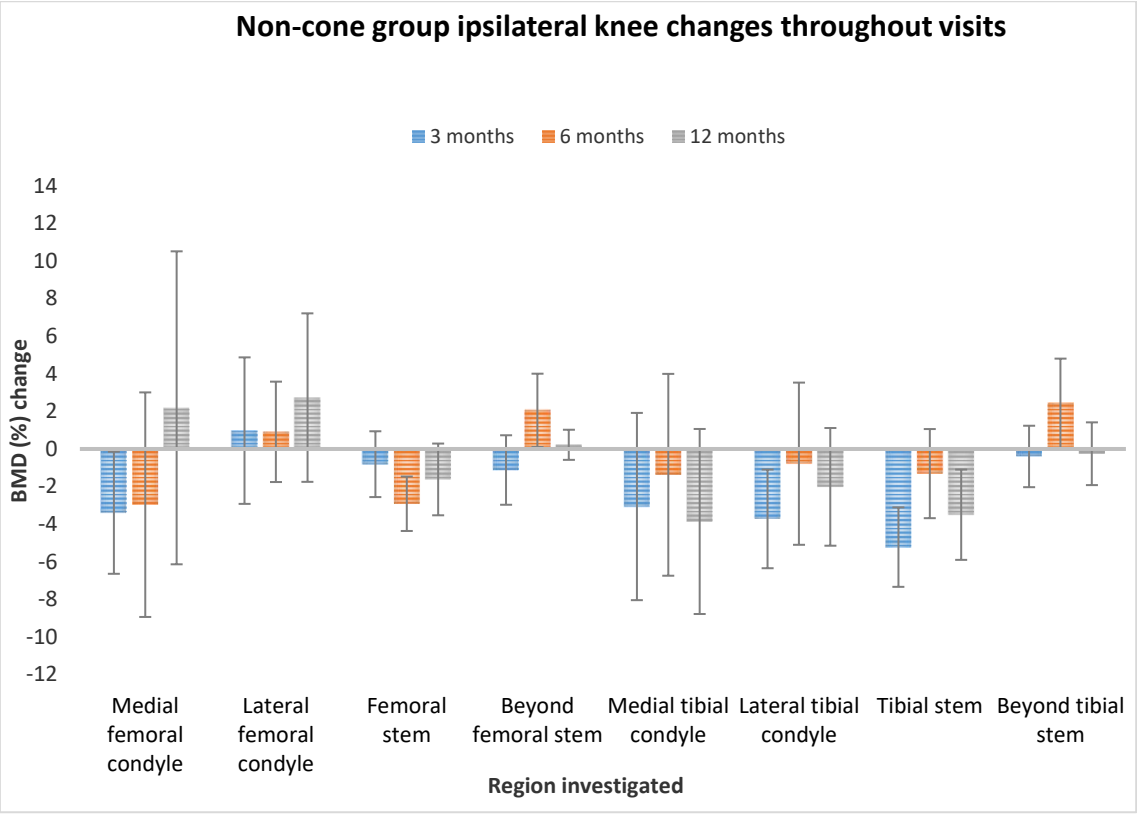


Figure 6.7. *Shows bar graph for BMD (%) changes in the non-cone group ipsilateral knee in different ROI throughout visits, error bars are SE*

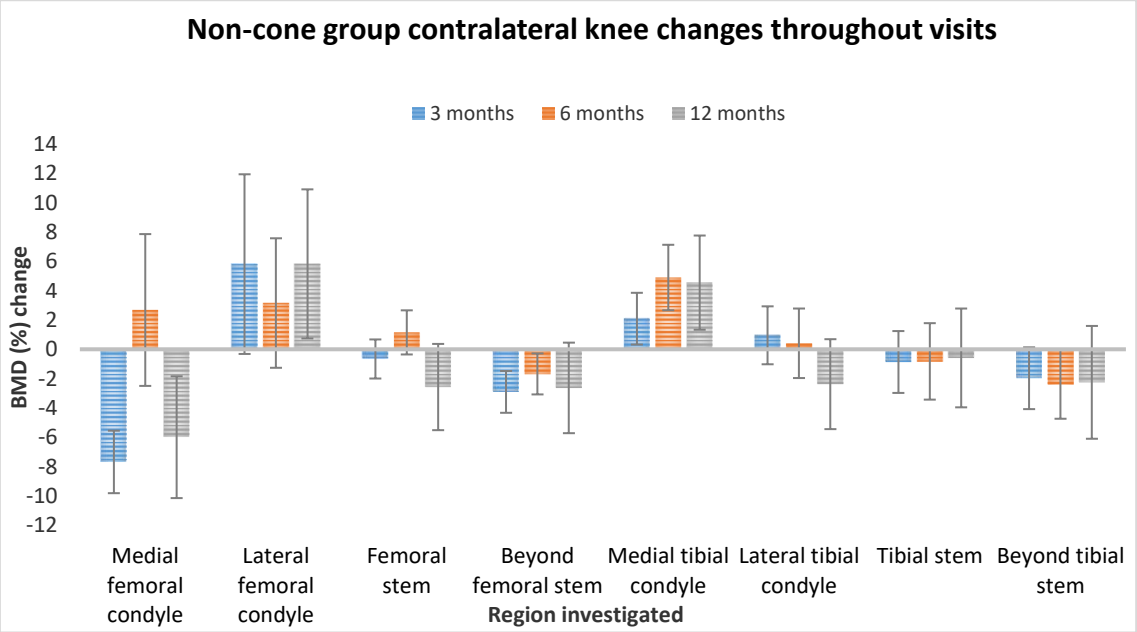


Figure 6.8. *Shows bar graph for BMD (%) changes in the non-cone group contralateral knee in different ROI throughout visits, error bars are SE*

Tables 6.5 and figure 6.7 report the changes between visits of the ipsilateral knee in the non-cone group. The medial femoral condyle reported -3.4 % at three months, -2.96 % at six months, and an increase of 2.189 % at 12 months.

In the lateral femoral condyle there is an increase at three and six months of just under 1 %, increasing to 2.733 % at 12 months. The femoral stem shows decreases at all visits (-0.81 %, -2.9 % at six months p-value 0.12, and -1.619 % at 12 months). Beyond the femoral stem, reports a loss of just over -1 % at three months then an increase of 2 % at six months, finishing on a change of just over 0.2 % at 12 months.

For the tibial ipsilateral non-cone data, the medial tibial condyle shows losses throughout all visits with a maximum of -3.856 % (0.28 p-value) at 12 months (-1.37 % at six months, and -3.06 % at three months). The lateral tibial similarly shows losses throughout each visit (-3.7 % at three months, -0.78 % at six months, and -2.015 % 12 months). The tibial stem also reported losses at every visit: -5.2 % at three months (p-value 0.04), -1.31 % at six months, and -3.496 % at 12 months. Beyond the tibial stem showed variations throughout (-0.4 % at three months, 2.4 % at six months, and -0.252 % at 12 months).

Only the tibial stem reported as -5.2 % (p-value 0.04) at three months stated a statistically significant p-values of 0.05 or under.

Table 6.6 and figure 6.8 show the changes between visits of the contralateral knee in the non-cone group. The Medial femoral condyle reported -7.69 % (p-value 0.01) at three months, increasing to 2.68 % at six months, with a final increase of just under 6 % at 12 months (0.16 p-value). The lateral femoral condyle is reported as an increase at every visit (5.81 % at three months, 3.15 % at six months and 5.83 % at 12 months). The femoral stem shows increases and decreases, reported as -0.67 % at three months, 1.15 % at six months, and -2.58 % at 12 months. Beyond the femoral stem reported losses throughout all visits reporting the highest at three months of -2.91 %.

For the tibial contralateral non-cone knee data, the medial tibial condyle shows increases at all visits, with a reported increase of 2.09 % at six weeks, 4.89 % (p-value 0.08) at six months, and 4.55 % at 12 months. The lateral tibial shows small differences at three and six months (+0.95 % at three months, -0.4 % at six months), and a loss of -2.38 % at 12 months. The tibial stem also reported losses at every visit (-0.87 % at three months, -0.83 % at six months, and -0.59

% at 12 months). Beyond the tibial stem showed decreases throughout (-1.98 % at three months, -2.38 % at three months, and -2.26 % at 12 months).

Only the medial femoral condyle reported as -7.69 % (p-value 0.01) at three months, states a p-value of statistical significance (0.05 or under).

6.6.3 BMD PERCENTAGE DIFFERENCE IN PA IPSILATERAL KNEE WHEN COMPARED BETWEEN CONE AND NON-CONE GROUP

Table 6.7 conveys the ipsilateral percentage changes (compared to baseline) in the cone group when compared directly to ipsilateral percentages changes (compared to baseline) in the non-cone group. If there is no difference between groups the two figures should be similar, and thus report a 0 % difference, a positive difference is in support of the cone group and negative difference is in support of the non-cone group.

Table 6.7. *Shows the mean BMD percentage difference compared to baseline at different visits, in the ipsilateral knee of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test and p-value*

3 MONTHS CONE (N=17) AND NON-CONE (N=9)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	4.003	-0.84	0.41
Lateral femoral condyle (g/cm²)	3.955	-0.89	0.39
Femoral stem (g/cm²)	0.926	-0.43	0.67
Beyond femoral stem (g/cm²)	3.53	-1.71	0.12
Medial tibial condyle (g/cm²)	-1.04	0.19	0.85
Lateral tibial condyle (g/cm²)	6.178	-1.77	0.09
Tibial stem (g/cm²)	5.754	-2.23	**0.04**
Beyond tibial stem (g/cm²)	-0.088	0.05	0.96

12 MONTHS CONE (N=14) AND NON-CONE (N=7)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	-0.075	0.01	0.99
Lateral femoral condyle (g/cm²)	-2.601	-0.41	0.69
Femoral stem (g/cm²)	-1.228	-0.45	0.66
Beyond femoral stem (g/cm²)	4.272	2.85	**0.01**
Medial tibial condyle (g/cm²)	-5.123	-0.71	0.49
Lateral tibial condyle (g/cm²)	5.711	1.22	0.24
Tibial stem (g/cm²)	0.566	0.19	0.85
Beyond tibial stem (g/cm²)	-1.402	-0.66	0.52

6 MONTHS CONE (N=16) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	5.522	-0.78	0.45
Lateral femoral condyle (g/cm²)	-3.996	0.85	0.40
Femoral stem (g/cm²)	1.934	-0.88	0.39
Beyond femoral stem (g/cm²)	-1.430	0.60	0.56
Medial tibial condyle (g/cm²)	-3.964	0.58	0.57
Lateral tibial condyle (g/cm²)	1.321	0.40	0.80
Tibial stem (g/cm²)	0.199	-0.07	0.95
Beyond tibial stem (g/cm²)	-1.779	0.67	0.52

Table 6.7 reports the comparison between the cone and non-cone group for the ipsilateral knee percentage difference at each visit. In the femoral condyle the difference at three months is +4.00 %, and +5.52 % at six months, but a negative difference at 12 months of -0.075 %. In the lateral femoral condyle it is reported as: +3.96 % (three months), -4.00 % (six months) and -2.601 % (12 months). The difference reported in the femoral stem is greater in the cone

group at three and six months, and then is greater in the non-cone group at 12 months. Beyond the femoral stem reports +3.53 % (three months) and then -1.43 % (six months), and then +4.27 % at 12 months.

The tibial medial condyle reported -1.04 % at three months, -3.96 % (six months), -5.123 % (12 months). The lateral tibial condyle at three months reports the highest difference across all visits and regions, reporting a difference between cone and non-cone of +6.18 % (p-value 0.09). Although this was reported as +1.32 % at six months, and a score of +5.71 % at 12 months. The tibial stem shows a difference of +5.75 % (p-value 0.04) at three months, but reports small differences at six and 12 months (0.20 % and 0.56 % respectively). Beyond the tibial stem shows a small difference at three months, and larger ones at six and 12 months, reported as -1.78 % and 1.402 % respectively.

Table 6.7 reports only two statistically significant values, and that is at the tibial stem with an increase of +5.75 % at three months (p-value 0.04), and beyond the femoral stem at 12 months reporting a score of +4.27 (p-value 0.01).

6.6.4 BMD PERCENTAGE DIFFERENCE IN PA CONTRALATERAL KNEE WHEN COMPARED BETWEEN CONE AND NON-CONE GROUP

Table 6.8 reports the contralateral knee percentage changes (compared to baseline) in the cone group, now directly compared to the contralateral percentages changes (compared to baseline) in the non-cone group. Again, if there is no difference between groups, it should be reported as 0 % with positive figures in support of the cone group and negative figures in support of the non-cone group.

Table 6.8*. Shows the mean BMD percentage difference compared to baseline at different visits, in the contralateral knee of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test and p-value*

3 MONTHS CONE (N=17) AND NON-CONE (N=9)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	10.453	-3.44	**0.00**
Lateral femoral condyle (g/cm²)	-4.412	0.64	0.53
Femoral stem (g/cm²)	1.839	-1.01	0.31
Beyond femoral stem (g/cm²)	3.009	-1.86	0.09
Medial tibial condyle (g/cm²)	-2.211	1.05	0.31
Lateral tibial condyle (g/cm²)	-0.545	0.23	0.82
Tibial stem (g/cm²)	2.383	-1.03	0.33
Beyond tibial stem (g/cm²)	3.953	-1.55	0.14

12 MONTHS CONE (N=13) AND NON-CONE (N=7)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	9.928	1.67	0.11
Lateral femoral condyle (g/cm²)	-7.323	-1.14	0.27
Femoral stem (g/cm²)	2.382	0.74	0.48
Beyond femoral stem (g/cm²)	2.576	0.77	0.46
Medial tibial condyle (g/cm²)	-4.051	-0.84	0.41
Lateral tibial condyle (g/cm²)	2.047	0.56	0.59
Tibial stem (g/cm²)	0.807	0.42	0.83
Beyond tibial stem (g/cm²)	2.305	0.55	0.60

6 MONTHS CONE (N=16) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Medial femoral condyle (g/cm²)	-1.881	0.34	0.74
Lateral femoral condyle (g/cm²)	-2.299	0.45	0.66
Femoral stem (g/cm²)	-1.881	0.94	0.36
Beyond femoral stem (g/cm²)	0.127	-0.07	0.95
Medial tibial condyle (g/cm²)	-5.993	2.27	**0.04**
Lateral tibial condyle (g/cm²)	1.188	-0.43	0.67
Tibial stem (g/cm²)	0.909	-0.33	0.75
Beyond tibial stem (g/cm²)	2.802	-1.08	0.31

Table 6.8 shows the comparisons between contralateral cone and contralateral non-cone knee percentages. The femoral medial condyle reports the biggest difference in the contralateral knee region of +10.45 % with a p-value of 0.00, but reporting a difference of -1.88 % at six months, and increasing again to a figure of +9.928 % at 12 months (p-value 0.11). The lateral femoral condyle shows the opposite with negative differences at all visits (-4.41 %, -2.30 % and -

7.32 % at 12 months respectively). The femoral stem shows +1.84 % three month, -1.88 % at six months, +2.6 % at 12 months. Beyond the femoral stem there is a difference of +3.01 % (p-value 0.09) at three months, -1.88 % at six months and +2.58 % at 12 months.

The medial tibial condyle shows negative differences; reporting -2.11 % at three months, -5.99 % at six months with a p-value of 0.04, and -4.05 % at 12 months. Lateral tibial condyle -0.55 % at three months, six months +1.19 %, 12 months this was reported as +2.047 %. The tibial stem shows positives across all visits, reporting +2.38 % at three months, 0.91 % at six months and 0.81 % at 12 months. Beyond the tibial shows positive differences across all visits reported as 3.95 % at three months, 2.80 % at six months, and 2.31 % at 12 months.

Table 6.8 reports two statistically significant values, one is at the medial femoral condyle reporting a difference of +10.45 % at three months (p-value 0.00), and the other is medial tibial condyle -5.99 % at six months (p-value 0.04).

6.6.5 STATISTICAL ANALYSIS OF THE PA KNEE USING A RANDOM EFFECTS LINEAR REGRESSION MODEL

The data from both groups for both the ipsilateral and contralateral PA knee is shown in table 6.9.

Table 6.9. *Shows the coefficient score comparing both groups across all visits via linear regression model.*

IPSILATERAL KNEE

Region	Coefficient at 3m (CI in brackets)	Coefficient at 6m (CI in brackets)	Coefficient at 12m (CI in brackets)	Overall p-value
Medial femoral condyle	0.0197 (-0.072 to 0.111)	0.0367 (-0.059 to 0.132)	-0.0166 (-0.118 to 0.085)	0.77
Lateral femoral condyle	0.0597 (-0.038 to 0.157)	-0.0287 (-0.130 to 0.073)	0.0026 (-0.105 to 0.110)	0.38
Femoral stem	0.0110 (-0.059 to 0.0812)	0.0178 (-0.055 to 0.091)	-0.0149 ('-0.093 to 0.063)	0.87
Beyond femoral stem	0.0342 (-0.159 to 0.227)	-0.0586 (-0.261 to 0.144)	0.0382 (-0.179 to 0.2554)	0.81
Medial tibial condyle	0.0086 (-0.107 to 0.124)	-0.1897 (-0.139 to 0.101)	-0.0202 ('-0.147 to 0.107)	0.96
Lateral tibial condyle	0.0564 (-0.032 to 0.145)	-0.0061 (-0.098 to 0.0857)	0.0458 (-0.051 to 0.143)	0.45
Tibial stem	0.1131 (0.019 to 0.207)	0.0134 (-0.840 to 0.111)	0.0481 (-0.055 to 0.151)	0.10
Beyond tibial stem	0.0164 (-0.065 to 0.098)	-0.0177 ('-0.102 to 0.067)	-0.0139 (-0.103 to 0.076)	0.87

CONTRALATERAL KNEE

Region	Coefficient at 3m (CI in brackets)	Coefficient at 6m (CI in brackets)	Coefficient at 12m (CI in brackets)	Overall p-value
Medial femoral condyle	0.1172 (-0.061 to 0.296)	0.0316 (-0.153 to 0.217)	0.0415 (-0.157 to 0.240)	0.63
Lateral femoral condyle	-0.0132 ('-0.104 to 0.077)	0.0055 (-0.088 to 0.099)	-0.0390 ('-0.139 to 0.061)	0.84
Femoral stem	0.0341 (-0.101 to 0.169)	-0.0005 ('-0.141 to 0.139)	0.0409 (-0.109 to 0.191)	0.92
Beyond femoral stem	0.0641 (0.127 to 0.255)	0.0119 (-0.187 to 0.211)	0.0314 (0.190 to 0.252)	0.92
Medial tibial condyle	-0.0224 ('-0.082 to 0.037)	-0.0499 ('-0.112 to 0.012)	-0.0468 (-0.113 to 0.0191)	0.36
Lateral tibial condyle	0.0091 ('-0.113 to 0.131)	0.0341 (-0.093 to 0.161)	0.0270 (-0.109 to 0.163)	0.95
Tibial stem	0.0335 (-0.055 to 0.122)	0.0108 ('-0.081 to 0.103)	0.0069 ('-0.091 to 0.106)	0.90
Beyond tibial stem	0.0508 (-0.054 to 0.156)	0.0255 (-0.083 to 0.134)	0.0091 (-0.107 to 0.125)	0.80

Table 6.9 indicates the sample mean change between baseline and visits at three, six and 12 months. The majority of ipsilateral data indicate the intervention group is greater, 24 data points 15 show the difference is greater in the cone group. The highest being 0.0597 (lateral femoral condyle, three months) and 0.0564 (lateral tibial condyle, months), and -0.1897 (medial tibial condyle, six months). For the contralateral data 18 data points indicate that the difference is greater in the cone group, with a difference of 0.1172 in the medial femoral condyle at three months. Although none of this data (from either side) is statistically significant.

6.7 BMD DXA RESULTS OF THE LATERAL KNEE

This section will report the lateral knee DXA data, and go through the same comparisons and analysis as in the PA data (as stated in section 6.6).

Table 6.10. *Shows the average baseline (6 week) BMD (g/cm^2) for the lateral knee, for the cone group (N=17) and non-cone group (N=9)*

CONE GROUP (N=17)						
6 WEEKS (BASELINE) IPSILATERAL				**6 WEEKS (BASELINE) CONTRALATERAL**		
	Mean (g/cm^2)	**SD**	**SE**	**Mean (g/cm^2)**	**SD**	**SE**
Femoral condyle	**2.026**	0.347	0.084	**1.408**	0.537	0.130
Femoral stem	**1.842**	0.318	0.077	**1.274**	0.299	0.073
Beyond femoral stem	**2.163**	0.422	0.102	**1.596**	0.424	0.103
Tibial condyles	**1.163**	0.394	0.096	**1.164**	0.286	0.069
Tibial stem	**1.710**	0.285	0.069	**1.166**	0.245	0.059
Beyond tibial stem	**1.874**	0.215	0.052	**1.336**	0.270	0.065
NON-CONE GROUP (N=9)						
Femoral condyle	**2.028**	0.537	0.190	**1.174**	0.401	0.134
Femoral stem	**1.802**	0.391	0.148	**1.224**	0.438	0.146
Beyond femoral stem	**2.157**	0.582	0.220	**1.560**	0.538	0.179
Tibial condyles	**1.398**	0.307	0.102	**1.027**	0.353	0.118
Tibial stem	**1.663**	0.200	0.067	**1.107**	0.307	0.102
Beyond tibial stem	**1.830**	0.291	0.097	**1.429**	0.432	0.144

Table 6.10 shows the mean BMD in g/cm^2 baseline (six week) results of the 26 six week participants from their lateral DXA knee data. It must be noted that the comparisons to baseline in the following results tables and figures involved comparing the participants' knee BMD visit data directly to their own six week baseline data, in order to report a direct change. It must also be acknowledged that the high BMD figures in some of the regions have been addressed in the PA section of this chapter.

6.7.1 BMD PERCENTAGE DIFFERENCE IN THE LATERAL KNEE WHEN COMPARED TO BASELINE, FOR IPSILATERAL AND CONTRALATERAL CONE GROUP

Table 6.11. *Shows the ipsilateral lateral knee compared to baseline (6 week) BMD (g/cm^2) for the cone group*

	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
3 MONTHS (N=17)								
Femoral condyles (g/cm^2)	-0.085	-3.702	-9.72	2.32	12.663	3.071	1.30	0.21
Femoral stem (g/cm^2)	-0.062	-3.136	-7.26	0.98	8.675	2.104	1.79	0.09
Beyond femoral stem (g/cm^2)	-0.017	-0.748	-4.10	2.60	7.045	1.709	0.47	0.65
Tibial condyles (g/cm^2)	-0.004	0.526	-4.03	5.09	9.599	2.328	0.15	0.88
Tibial stem (g/cm^2)	0.007	0.446	-1.83	2.73	4.790	1.162	-0.32	0.75
Beyond tibial stem (g/cm^2)	0.053	2.895	1.16	4.63	3.653	0.886	-3.02	**0.01**
6 MONTHS (N=16)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	0.069	3.715	-1.91	9.34	11.473	2.868	-1.27	0.22
Femoral stem (g/cm^2)	0.006	0.295	-4.33	4.92	9.429	2.357	-0.16	0.87
Beyond femoral stem (g/cm^2)	0.061	2.619	-0.218	5.52	5.913	1.478	-2.21	**0.04**
Tibial condyles (g/cm^2)	0.009	0.718	-3.66	5.10	8.932	2.233	-0.38	0.71
Tibial stem (g/cm^2)	0.004	0.335	-1.79	2.46	4.331	1.083	-0.22	0.83
Beyond tibial stem (g/cm^2)	0.056	2.928	0.798	5.06	4.344	1.086	-2.88	**0.01**
12 MONTHS (N=14)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	0.085	5.462	-0.32	11.20	11.037	2.950	1.51	0.15
Femoral stem (g/cm^2)	-0.062	-3.314	-8.27	1.65	9.478	2.533	-1.36	0.20
Beyond femoral stem (g/cm^2)	0.019	0.982	-2.58	4.54	6.789	1.814	0.54	0.60
Tibial condyles (g/cm^2)	-0.014	0.164	-5.68	6.00	11.150	2.980	-0.39	0.70
Tibial stem (g/cm^2)	-0.017	-0.662	-3.15	1.83	4.758	1.272	-0.69	0.50
Beyond tibial stem (g/cm^2)	0.022	1.190	-0.88	3.26	3.943	1.054	1.04	0.32

Table 6.12. *Shows the contralateral lateral knee compared to baseline (6 week) BMD (g/cm^2) for the cone group*

	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
3 MONTHS (N=17)								
Femoral condyles (g/cm^2)	0.008	0.914	-0.70	2.52	3.384	0.821	-0.59	0.57
Femoral stem (g/cm^2)	0.032	2.402	0.44	4.36	4.113	0.998	-2.31	**0.03**
Beyond femoral stem (g/cm^2)	0.037	2.050	0.24	3.86	3.804	0.923	-2.17	**0.05**
Tibial condyles (g/cm^2)	0.021	1.869	0.55	3.19	2.785	0.675	-2.61	**0.02**
Tibial stem (g/cm^2)	0.011	1.080	-0.21	2.37	2.719	0.659	-1.32	0.21
Beyond tibial stem (g/cm^2)	0.000	0.003	-1.52	1.52	3.198	0.776	0.00	1.00
6 MONTHS (N=16)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.008	-0.152	-1.77	1.47	3.302	0.826	0.52	0.61
Femoral stem (g/cm^2)	0.023	1.796	-0.21	3.81	4.110	1.027	-2.16	**0.05**
Beyond femoral stem (g/cm^2)	0.005	0.274	-1.03	1.57	2.653	0.663	-0.55	0.59
Tibial condyles (g/cm^2)	0.003	0.212	-1.41	1.83	3.298	0.824	-0.37	0.72
Tibial stem (g/cm^2)	0.009	0.773	-0.75	2.29	3.100	0.775	-1.14	0.27
Beyond tibial stem (g/cm^2)	0.006	0.397	-1.15	1.95	3.154	0.789	-0.61	0.55
12 MONTHS (N=13) 1 PARTICIPANT UNDERWENT TKR ON CONTRALATERAL KNEE SO THESE DATA HAS BEEN EXCLUDED								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.004	0.286	-2.68	3.26	5.466	1.516	-0.15	0.88
Femoral stem (g/cm^2)	0.042	3.271	-0.05	6.59	6.103	1.693	2.23	**0.05**
Beyond femoral stem (g/cm^2)	0.039	2.138	0.04	4.24	3.854	1.069	2.05	0.06
Tibial condyles (g/cm^2)	0.010	1.104	-1.85	4.05	5.422	1.504	0.62	0.55
Tibial stem (g/cm^2)	0.000	-0.020	-2.52	2.12	4.274	1.185	-0.01	1.00
Beyond tibial stem (g/cm^2)	-0.003	-0.405	-3.08	2.28	4.929	1.367	-0.20	0.85

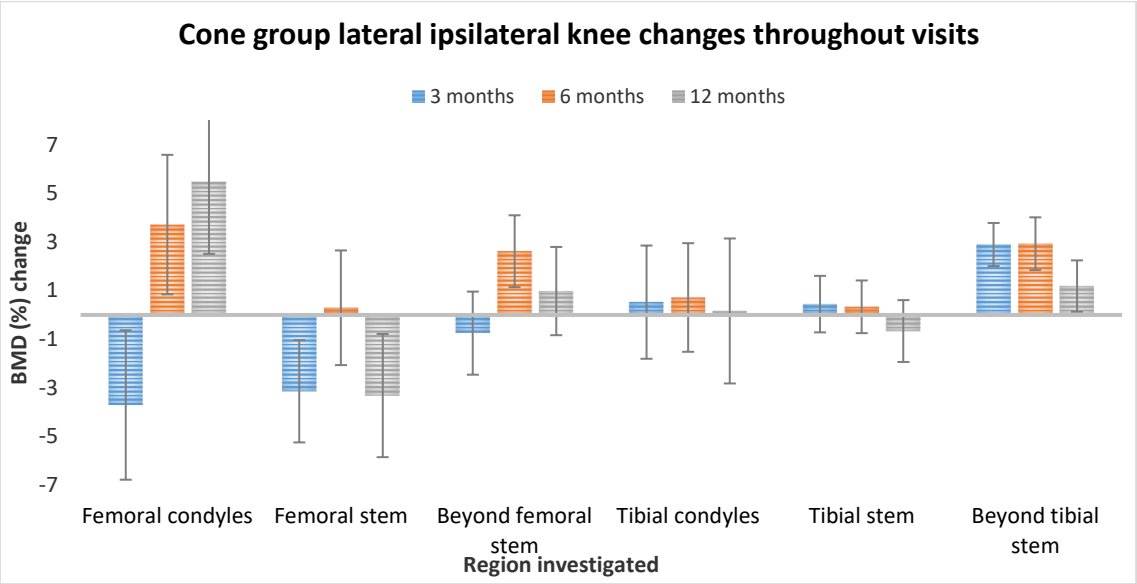


Figure 6.9. *Shows bar graph for BMD (%) changes in the cone group lateral ipsilateral knee in different ROI throughout visits, error bars are SE*

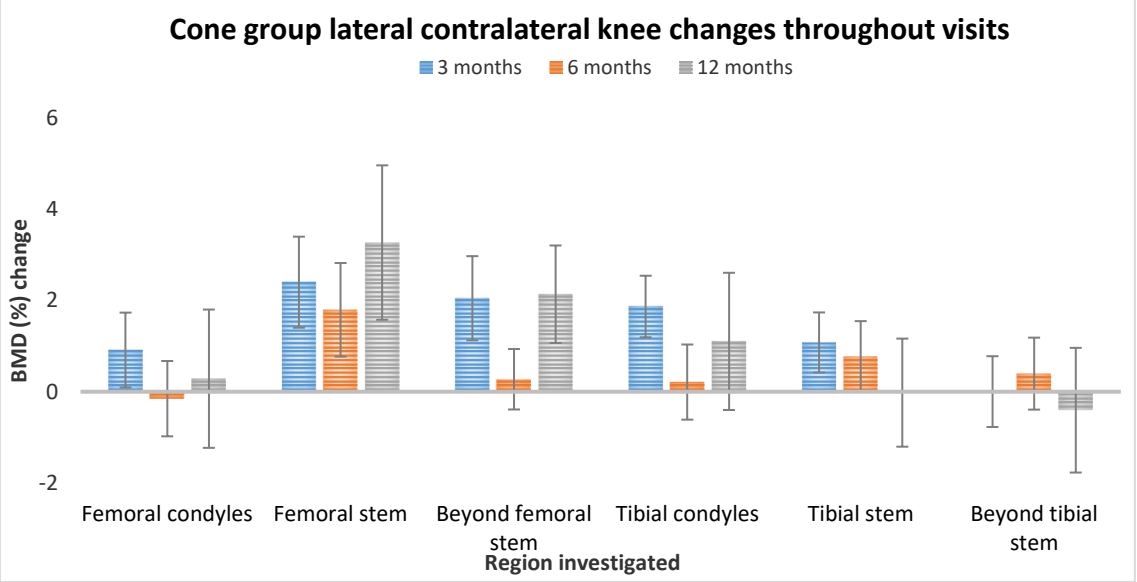


Figure 6.10. *Shows bar graph for BMD (%) changes in the cone group lateral contralateral knee in different ROI throughout visits, error bars are SE*

Table 6.11 and figure 6.9 show the ipsilateral knee lateral BMD in the cone group compared to their baseline score, with percentage changes calculated.

Femoral changes reported a condyle change of -3.70 % at three months, although this increases to a positive of 3.72 % at six months, increasing to 5.462 % at 12 months. The femoral stem reports similar losses at three and 12 months (-3.314 %), with a 0.30 % increase at six months. Beyond the femoral stem reports a small decrease at three months, and then increases at six and

12 months, with the highest increase reported as 2.62 % at six months (p-value of 0.04).

The tibial condyles show increases at all visits although nothing of significance, with the highest difference reported as 0.72 % (p-value 0.71). The tibial stem reports small increases at three and six months, and a loss at 12 months of just under -1 %. Beyond the tibial stem is where the biggest change in the tibia is reported, all visits report an increase at beyond the tibial stem; reported as 2.90 % (p-value 0.01) at three months, 2.93 %, at six months (p-value 0.01), and 1.19 % at 12 months. Table 6.12 and figure 6.10 show the contralateral knee lateral BMD in the cone group compared to their baseline score, with percentage changes calculated.

For the femoral data the condyles report minimal changes with both increases and decreases, with the highest difference reported as 0.91 %. The femoral stem reports the most statistical change of the contralateral lateral knee, with an increase of 2.40 % (p-value 0.03) at three months, and 1.80 % (p-value 0.05), with an increase of 3.271 % (0.05 p-value) at 12 months. Beyond the femoral stem there were increases at all visits, with large increases at three (2.05 % p-value 0.05) and 12 months (2.14 %, 0.06 p-value).

For the tibial data, at the condyles there is an increase of 1.87 % (p-value 0.02), although this reduces at six months returning to just over 1 % by 12 months. The tibial stem data report an increase at three months of just over 1 %; this is reduced to 0.77 % at six months, reaching a near baseline level by 12 months. For beyond the tibial stem there is very little change in percentage at three, six, and 12 months, with the highest difference reported as just under -0.405 %.

Across both figures and tables there are a few statistically significant results. The most consistent in the ipsilateral knee appears to be the increases beyond the tibial stem in the ipsilateral knee reported at three and six months (2.90 % and 2.93 %). although beyond the femoral stem also reports a statistically significant figure at six months (2.62 %). In the contralateral knee there are increases reported at all three visits in the femoral stem (2.40 %, 1.80 % 3.27 %). There are a further two statistically significant results in the contralateral

data, both at 3 months; one in beyond the femoral stem (2.05 %) and the other reported in the tibial condyles (1.87 %).

6.7.2 BMD PERCENTAGE DIFFERENCE IN THE LATERAL KNEE WHEN COMPARED TO BASELINE, FOR IPSILATERAL AND CONTRALATERAL FOR THE NON-CONE GROUP

Table 6.13. *Shows the ipsilateral lateral knee compared to baseline (6 week) BMD (g/cm^2) for the non-cone group*

3 MONTHS (N=9)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.102	-5.127	-8.90	-1.36	5.773	2.041	2.25	0.06
Femoral stem (g/cm^2)	-0.079	-3.614	-7.92	1.60	7.284	2.753	1.58	0.16
Beyond femoral stem (g/cm^2)	-0.005	0.540	-4.09	5.17	7.080	2.676	0.09	0.93
Tibial condyles (g/cm^2)	-0.004	0.155	-5.96	6.27	9.346	3.115	0.10	0.92
Tibial stem (g/cm^2)	-0.019	-1.163	-3.98	1.66	4.324	1.441	0.78	0.46
Beyond tibial stem (g/cm^2)	-0.003	0.152	-3.61	3.91	5.753	1.918	0.07	0.94
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.113	-3.215	-12.40	6.00	13.927	5.264	1.18	0.28
Femoral stem (g/cm^2)	-0.044	-1.416	-5.69	2.85	6.166	2.517	1.27	0.26
Beyond femoral stem (g/cm^2)	0.066	3.204	1.43	4.97	2.551	1.041	-2.56	**0.05**
Tibial condyles (g/cm^2)	-0.026	-1.349	-8.46	5.76	10.257	3.626	0.56	0.59
Tibial stem (g/cm^2)	-0.053	-3.058	-8.09	1.97	7.252	2.564	1.27	0.24
Beyond tibial stem (g/cm^2)	0.003	0.554	-4.30	5.40	6.992	2.472	-0.07	0.95
12 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.097	-5.213	-14.30	3.88	13.114	4.957	-1.00	0.36
Femoral stem (g/cm^2)	-0.079	-3.983	-8.71	0.75	6.832	2.789	-1.40	0.22
Beyond femoral stem (g/cm^2)	0.057	2.960	-1.55	7.47	6.507	2.656	0.93	0.40
Tibial condyles (g/cm^2)	-0.100	-7.547	-15.60	0.513	11.631	4.112	-1.83	0.11
Tibial stem (g/cm^2)	-0.090	-5.425	-8.07	-2.77	3.818	1.350	-4.09	**0.00**
Beyond tibial stem (g/cm^2)	0.008	0.533	-3.34	4.40	5.580	1.973	0.21	0.84

Table 6.14. *Shows the contralateral lateral knee compared to baseline (6 week) BMD (g/cm^2) for the non-cone group*

3 MONTHS (N=9)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.020	-1.530	-4.00	0.94	3.777	1.259	1.19	0.27
Femoral stem (g/cm^2)	-0.010	-1.129	-3.90	1.64	4.247	1.416	0.52	0.62
Beyond femoral stem (g/cm^2)	-0.001	-0.710	-3.53	2.11	4.322	1.441	0.04	0.97
Tibial condyles (g/cm^2)	-0.022	-2.584	-5.21	0.05	4.031	1.344	1.80	0.11
Tibial stem (g/cm^2)	-0.025	-2.668	-5.60	0.26	4.485	1.495	1.99	0.08
Beyond tibial stem (g/cm^2)	-0.039	-2.601	-6.62	1.42	6.152	2.051	1.52	0.17
6 MONTHS (N=8)								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	0.001	0.370	-2.72	3.46	4.466	1.579	-0.08	0.93
Femoral stem (g/cm^2)	-0.004	-0.669	-4.13	2.79	4.992	1.765	0.31	0.76
Beyond femoral stem (g/cm^2)	-0.034	-2.904	-5.74	-0.06	4.099	1.449	2.44	**0.05**
Tibial condyles (g/cm^2)	0.005	0.253	-3.37	3.87	5.226	1.848	-0.35	0.74
Tibial stem (g/cm^2)	-0.010	-1.043	-3.45	1.37	3.478	1.230	0.99	0.35
Beyond tibial stem (g/cm^2)	-0.025	-1.455	-4.50	1.59	4.407	1.558	1.06	0.33
12 MONTHS (N=7) 1 PARTICIPANT UNDERWENT TKR ON CONTRALATERAL KNEE SO THESE DATA HAS BEEN EXCLUDED								
	BMD Change	% Change	95 % CL		SD	SE	T-Critical	P-Value
Femoral condyles (g/cm^2)	-0.082	-6.122	-14.20	1.97	10.919	4.127	-1.31	0.24
Femoral stem (g/cm^2)	-0.022	-2.646	-7.67	2.37	6.774	2.560	-0.71	0.51
Beyond femoral stem (g/cm^2)	-0.032	-3.059	-7.65	1.53	6.195	2.341	-1.06	0.33
Tibial condyles (g/cm^2)	-0.022	-2.881	-6.84	1.08	5.351	2.023	-1.12	0.30
Tibial stem (g/cm^2)	-0.016	-2.514	-7.05	2.03	6.123	2.314	0.78	0.47
Beyond tibial stem (g/cm^2)	-0.038	-3.468	-9.44	2.50	8.060	3.046	-1.06	0.33

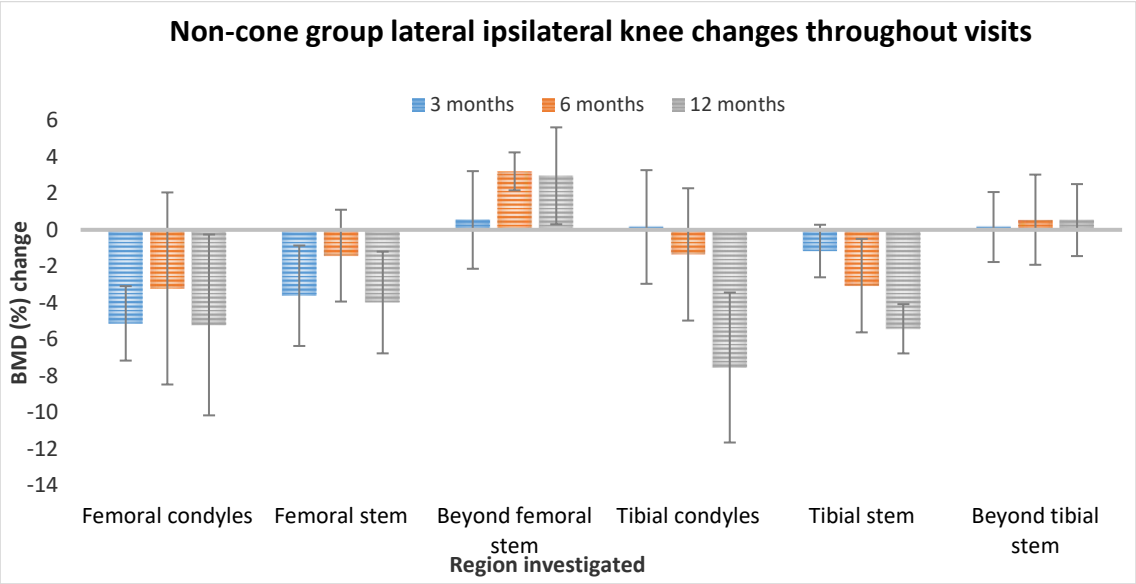


Figure 6.11. *Shows bar graph for BMD (%) changes in the non-cone group lateral ipsilateral knee in different ROI throughout visits, error bars are SE*

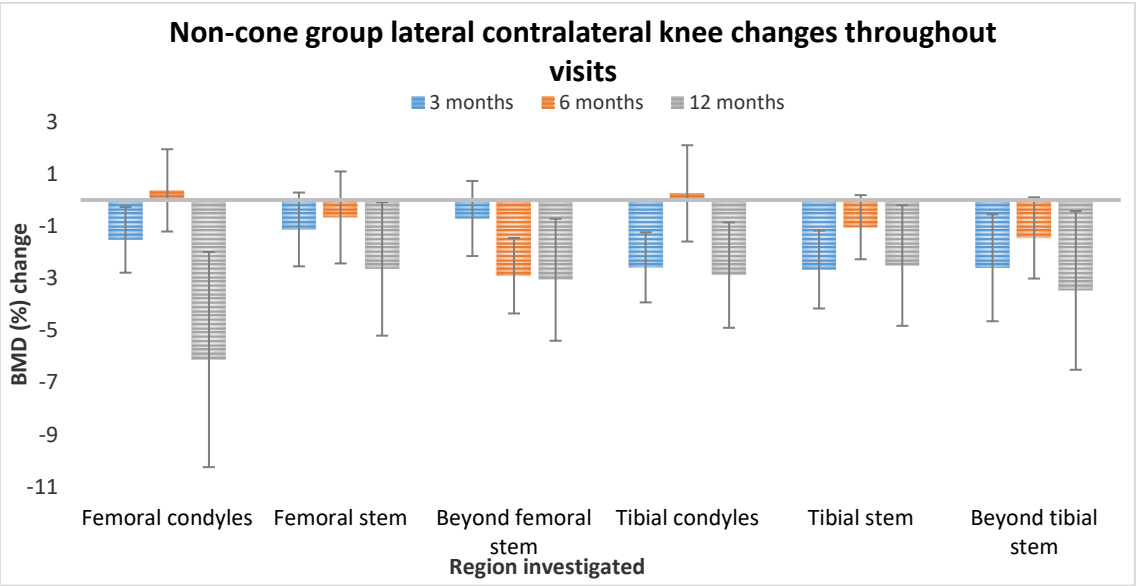


Figure 6.12. *Shows bar graph for BMD (%) changes in the non-cone group lateral contralateral knee in different ROI throughout visits, error bars are SE*

Table 6.13 and figure 6.11 shows the ipsilateral knee lateral BMD data in the non-cone group compared to their baseline score, with percentage changes calculated.

The femoral condyles report losses throughout each visits, reported as -5.13 % at three months (p-value 0.06), -3.22 % (p-value 0.28), -5.21 % at 12 months (p-value 0.36). The femoral stem also reports losses at every visit -3.61 % at three

months, -1.42 % and -3.98 % (for six and 12 months respectively). Beyond the femoral stem reports increases at all visits, with a statistically significant score at six months, reporting an increase of 3.20 % (p-value 0.05), with a reported 12 month score of 2.96 %.

The tibial condyles report an increase at three months of 0.16 %, as a loss of -1.35 % at six months, and with the largest difference of all the lateral tibial data reporting a loss of -7.547 % (0.11 p-value) at 12 months. As for the tibial stem this region reports large losses across all visits (-1.16 %, -3.06 % and -5.43 % (0.00 p-value) respectively). Beyond the tibial stem there is little to no change, with the largest difference reported as 0.55 %.

Table 6.14 and figures 6.12 shows the non-cones group contralateral knee lateral BMD compared to their baseline score, with percentage changes calculated. For the femoral data the condyles show both increases and decreases at three and six months, with a large loss of -6.12 % (p-value 0.24) at 12 months. The femoral stem reports decreases at every visit, with the biggest decrease reported as -2.65 % at 12 months. Beyond the femoral stem also reported decreases at all visits, reporting -0.710 (three months) -2.90 % (six months p-value 0.05), -3.06 % (12 months).

For the tibial data, at the condyles there is a decrease at three months of -2.58 %, as 0.25 at six months, and -2.88 % by 12 months. The tibial stem and beyond the tibial stem each show decreases across all visits. With both reporting -2.67 % and -2.60 % at three months, reducing to -1.04 % and -1.46 % at six months, increasing back to -3.47 % and -2.51 % at 12 months.

Across both figures and tables there are a few statistically significant results, the most consistent appears to be the femoral stem at 12 months 3.27 %, and there are increases beyond the femoral stem in the ipsilateral knee reported at 6 (3.20 %), and beyond the femoral stem in the contralateral, reporting a decrease of -2.90 %.

6.7.3 BMD PERCENTAGE DIFFERENCE IN LATERAL IPSILATERAL KNEE WHEN COMPARED BETWEEN CONE AND NON-CONE GROUP

Table 6.14 shows the ipsilateral percentage changes (compared to baseline) in the cone group now compared to the ipsilateral percentage's changes (compared to baseline) in the non-cone group and reporting the difference. If there is no difference between groups the two figures should be similar, and report a 0 % difference, a positive difference is in support of the non-cone group.

Table 6.15.*Shows the mean BMD percentage difference compared to baseline at different visits, in the ipsilateral knee of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test and p-value*

3 MONTHS CONE (N=17) AND NON-CONE (N=9)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	1.425	-0.39	0.7
Femoral stem (g/cm²)	0.478	-0.14	0.89
Beyond femoral stem (g/cm²)	-1.288	-0.53	0.61
Tibial condyles (g/cm²)	0.370	-0.01	0.93
Tibial stem (g/cm²)	1.609	-0.87	0.40
Beyond tibial stem (g/cm²)	2.742	-1.30	0.22

6 MONTHS CONE (N=16) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	6.930	-1.16	0.27
Femoral stem (g/cm²)	1.711	-0.50	0.63
Beyond femoral stem (g/cm²)	-0.585	0.32	0.75
Tibial condyles (g/cm²)	2.067	-0.49	0.64
Tibial stem (g/cm²)	3.392	-1.22	0.25
Beyond tibial stem (g/cm²)	2.373	-0.88	0.40

12 MONTHS CONE (N=14) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	10.675	1.85	0.09
Femoral stem (g/cm²)	0.670	0.18	0.86
Beyond femoral stem (g/cm²)	-1.978	-0.62	0.55
Tibial condyles (g/cm²)	7.711	1.52	0.15
Tibial stem (g/cm²)	4.764	2.57	**0.02**
Beyond tibial stem (g/cm²)	0.658	0.29	0.77

Table 6.15 reports the comparison between the cone and non-cone group for the ipsilateral knee percentage difference at each visit in the lateral DXA view. In the femoral condyle there is a reported positive difference between the two

groups at every visit; reporting +1.43 % at three months, +6.93 % (p-value 0.27), and +10.68 % (0.09 p-value) at 12 months. In the femoral stem all visits report a positive difference, with the highest reaching +1.71 % at six months. Beyond the femoral stem reported a negative difference at every visits when comparing the two groups directly, with the highest difference being -1.98 % at 12 months.

The tibial condyle showed a positive difference at each visit, reaching the largest difference of +7.71 % at 12 months (0.15 p-value). The tibial stem reports a similar pattern with positive differences at each visit, reaching its largest at 12 months reported as +4.76 % (p-value 0.02). Beyond the tibial stem also reports a positive difference at all visits, although not as dramatic, it reports +2.74 % (three months), +2.37 % (six months), and +0.658 % at 12 months.

Table 6.15 shows one statistically significance in the 12 month data, which is in the tibial stem, reported as a difference of +4.76 %.

6.7.4 BMD PERCENTAGE DIFFERENCE IN LATERAL CONTRALATERAL KNEE WHEN COMPARED BETWEEN CONE AND NON-CONE GROUP

Table 6.15 shows the contralateral percentage changes (compared to baseline) in the cone group now compared to contralateral percentages changes (compared to baseline) in the non-cone group again following the same format as stated previously.

Table 6.16*. Shows the mean BMD percentage difference compared to baseline at different visits, in the contralateral knee of the cone group vs the non-cone group to 3 d.p. including percentage difference (between groups), t-test and p-value*

3 MONTHS CONE (N=17) AND NON-CONE (N=9)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	2.444	-1.63	0.12
Femoral stem (g/cm²)	3.531	-2.04	0.06
Beyond femoral stem (g/cm²)	2.760	-1.61	0.13
Tibial condyles (g/cm²)	4.453	-2.96	**0.01**
Tibial stem (g/cm²)	3.748	-2.29	**0.04**
Beyond tibial stem (g/cm²)	2.604	-1.19	0.26

6 MONTHS CONE (N=16) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	-0.522	0.29	0.78
Femoral stem (g/cm²)	2.465	-1.21	0.25
Beyond femoral stem (g/cm²)	3.179	-1.99	0.07
Tibial condyles (g/cm²)	-0.041	0.02	0.98
Tibial stem (g/cm²)	1.816	-1.25	0.23
Beyond tibial stem (g/cm²)	1.851	-1.06	0.31

12 MONTHS CONE (N=14) AND NON-CONE (N=8)

	% Difference	T-Critical	P-Value
Femoral condyles (g/cm²)	6.408	1.46	0.18
Femoral stem (g/cm²)	5.917	1.93	0.08
Beyond femoral stem (g/cm²)	5.198	2.02	0.07
Tibial condyles (g/cm²)	3.985	1.58	0.14
Tibial stem (g/cm²)	2.495	0.96	0.36
Beyond tibial stem (g/cm²)	3.063	0.92	0.39

Table 6.16 shows the comparisons between contralateral cone and contralateral non-cone knee lateral data. The femoral condyles report a difference at three months of +2.44 % (p-value 0.12), as -0.52 % at six months, and is again a positive at 12 months (+6.41 %). The femoral stem shows positive differences at all visits, with the highest at 12 months reporting +5.917 % (p-value 0.08). Beyond the femoral stem also showed this trend also, with positive difference at all visits, the highest again being recorded at 12 months reporting +5.198 % (p-value 0.07).

The tibial condyle data show positive differences at three and 12 months reported as +4.45 % (p-value 0.01) and +3.99 % (p-value 0.14) respectively, although there is a difference of -0.04 % at six months. The tibial stem again shows positive difference, this time across all visits, reporting +3.75 % (p-value 0.04) at 3 months, +1.82 % at six months, and +2.495 % at 12 months. Beyond the tibial again also shows positive differences across all visits reported as +2.60 % at three months, +1.85 % at six months, +3.063 % at 12 months. In contralateral lateral DXA data there are reported statistically significant results in the tibial condyles and tibial stem at three months (+4.45 % and +3.75 %).

6.7.5 STATISTICAL ANALYSIS OF THE LATERAL KNEE USING A RANDOM EFFECTS LINEAR REGRESSION MODEL

The data from both groups for both the ipsilateral and contralateral lateral knee is shown in table 6.17.

Table 6.17. *Shows the coefficient score comparing both groups across all visits via linear regression model.*

IPSILATERAL KNEE

Region	Coefficient at 3m (CI in brackets)	Coefficient at 6m (CI in brackets)	Coefficient at 12m (CI in brackets)	Overall p-value
Femoral condyles	0.0163 (-0.184 to 0.217)	0.1748 (-0.034 to 0.384)	0.1208 (-0.103 to 0.344)	0.32
Femoral stem	0.0281 (-0.180 to 0.236)	0.0726 (-0.146 to 0.291)	-0.1344 ('-0.353 to 0.085)	0.37
Beyond the femoral stem	-0.0107 (-0.300 to 0.278)	0.0178 (-0.286 to 0.322)	-0.2673 ('-0.572 to 0.374)	0.28
Tibial condyles	-0.0355 ('-0.202 to 0.131)	-0.0020 ('-0.174 to 0.170)	0.0457 (-0.137 to 0.229)	0.87
Tibial stem	0.0326 (-0.082 to 0.147)	0.0593 ('-0.059 to 0.178)	0.0642 (-0.0616 to 0.191)	0.71
Beyond tibial stem	0.0596 (-0.140 to 0.133)	0.0468 (-0.030 to 0.123)	0.0258 (-0.055 to 0.107)	0.42

CONTRALATERAL KNEE

Region	Coefficient at 3m (CI in brackets)	Coefficient at 6m (CI in brackets)	Coefficient at 12m (CI in brackets)	Overall p-value
Femoral condyles	0.0587 (-0.137 to 0.254)	0.0411 (-0.161 to 0.243)	0.0962 (-0.120 to 0.313)	0.85
Femoral stem	0.0475 (-0.093 to 0.188)	0.0440 (-0.102 to 0.190)	0.0698 (-0.086 to 0.226)	0.83
Beyond the femoral stem	0.0426 (-0.143 to 0.228)	0.0465 (-0.146 to 0.239)	0.0771 (-0.129 to 0.284)	0.90
Tibial condyles	0.0605 (-0.067 to 0.188)	0.0204 (-0.112 to 0.152)	0.0387 (-0.103 to 0.180)	0.82
Tibial stem	0.0433 (-0.060 to 0.147)	0.0289 (-0.079 to 0.136)	0.0184 (-0.097 to 0.133)	0.87
Beyond tibial stem	0.0272 (-0.103 to 0.157)	0.0248 (-0.110 to 0.160)	0.0205 (-0.124 to 0.165)	0.98

Table 6.17 indicates the sample mean change between baseline and visits at three, six and 12 months. The majority of ipsilateral data indicate the

intervention group is greater, 18 data points 13 show the difference is greater in the cone group. The highest being 0.1748 (femoral condyle) and -0.2673 (beyond the femoral stem). For the contralateral data all 18 data points indicate that the difference is greater in the cone group. Although none of this data (in either side) is statistically significant.

6.8 DISCUSSION

6.8.1 FEMORAL AND TIBIAL IPSILATERAL BMD CHANGES IN THE CONE GROUP

In the cone ipsilateral group, nine from a total of 12 BMD data points (four regions across three visits) of the femoral regions reported increases, with some reporting consistent results across visits. The reported changes in the medial femoral condyle and beyond the femoral stem each show increases at every visit. The lateral femoral condyle reported a statistically significant increase at three months although this is just over -3 % by six months and is similar to baseline by 12 months (0.13 %). The femoral stem shows a loss at six and 12 months.

The lateral DXA image data in the ipsilateral cone group, supports these changes reported on the PA image, reporting five of none data points as increases (three regions across three visits), for example the femoral condyles (superimposed on the lateral image) report increases at six and 12 months (although not statistically significant), the lateral data show losses at the femoral stem at 12 months, and increases at beyond the femoral stem, similar to the PA result. The main difference between the lateral and PA data is at the three month visit; the lateral data reports losses at all three regions, yet the PA data report increases at those corresponding sites, it must be noted that all three regions at three months in the lateral data report non statistical significance, and precision errors are greater in the lateral data series than the PA, due to issues of rotation and flexion affecting the femoral position, and thus BMD [420].

The tibial PA regions report six increases across 12 data points. In the main two regions around the cone (the lateral and medial tibial condyles) there is

consistency throughout the visits. The medial tibial condyle reports large losses increasing at every visit (-8.98 % at 12 months). With the opposite in the lateral tibial condyle, which reported increases at every visit (+4.495 % at 12 months p-value 0.00). The tibial stem also reports losses at six month and at 12 months, with beyond of the stem reporting increases at six and 12 months.

The tibial lateral data changes report eight of the nine data points as BMD increases, with the one loss reported in the tibial stem at 12 months. The lateral DXA data matches the reported PA data, the tibial condyles show a slight increase in the lateral DXA data, which supports the idea from the PA image that reports an increase in lateral tibial condyle and decrease in medial tibial condyle, thus when superimposed would report an averaged small increase (0.53 %, 0.72 %, and 0.16 % at three, six and 12 months respectively). The tibial stem, and beyond the tibial stem data also supports the changes reported in the PA data, reporting increases at three months, a decrease at 12 months in the tibial stem, and increases at six and 12 months beyond the tibial stem.

The figures and changes reported in both the femoral regions and tibial regions could be due to several influences, the increases shown in all three visits beyond the femoral stem as reported in the PA data could be due to altered WB forces being channelled through the joint along the stem to beyond the stem, this would increase early bone turnover in the beyond the stem region due to adaptive bone remodelling. This remodelling of the periprosthetic bone is well known and is described in Wolff's law [421], in which the bone remodels to adapt to altered mechanical loads.

In 2010 Jensen et al [179] investigated femoral BMD changes in rTKR patients (a cemented revision with either a constrained condylar prosthesis (N=12) or a posterior stabilised implant (N=4)). They investigated BMD changes along the stem and beyond the stem; unfortunately they did not investigate the femoral condyles. For the stem data they reported increases of +3.4 %, +4.7 % and +4.0 %, at three, six, and 12 month visits, although we reported decreases at six and 12 months**.** With beyond the stem reported an increase at 12 months of +0.4 % which is similar to our data, although we report a greater number (4.495

%), (although Jensen et al [179] did report small losses of -0.7 % and -0.8 % at three and six months respectively) were we reported increases.

It must be acknowledged that there is a lack of rTKR BMD DXA data, as reported the systematic review search. Jensen et al 2010 [179] even states within their paper **"***to our knowledge there exists no published studies on BMD changes in the distal femur after rTKR. With most studies evaluating BMD around the femoral component after a TKR and not a rTKR***".** So there is a lack of femoral BMD data, the differences reported in Jensen et al 2010 [179] might be due to both studies having low number of participants (16 for Jensen 2010 [179], 17 cone participants in our research) and/or variations between our two groups of participants.

Although the change beyond the stem has been reported in another revision study albeit a simulated study [422], in which they studied bone remodelling patterns of four femoral components: two primary TKAs and two stemmed revision prostheses. They found that in the ROI beyond the stem (comparable with the ROI we used in this study); there was a predictable increase in BMD in the most proximal ROI beyond the stem [422]. Although it must be noted this was a simulated study and they did report increases along the stem as well as beyond the stem.

The increases in the femoral condyle regions could be due to alignment issues in the knee and reformed gait, or due to increased activity post operation increasing bone turnover, especially given as these participants had already undergone TKR and understand the recuperation and physiotherapy demands, it must be acknowledged that Jensen et al 2010 [179] did not investigate alignment in the hip or knees. Furthermore, a systematic review investigating BMD change in the distal femur in TKR in 2019 investigated changes in the femoral intracondylar, supracondylar and combined regions, across several studies – at three months -9.32 % combined (11 studies), supracondylar -5.98 % (eight studies) intracondylar -11.68 % (seven studies), at six months combined -13.19 % (10 studies), supracondylar -11.01 % (eight studies), intracondylar -16.93 % (seven studies), and at 12 months -15.75 % combined (11 studies), supracondylar -13.18 % (nine studies) and intracondylar -18.43 %

(eight studies) [423]**.** Our data do not conform to the TKR data gathered via the systematic review, as stated this could simply be due to these being revision participants having greater understanding of recovery, or due to the cones effects of stabilisation. Furthermore, this systematic review data, although useful did not include rTKR, and included studies using dual photon absorptiometry. Moreover, the studies utilised different ROI from our study [423], making comparisons difficult.

The tibial condyle changes could be due to the influences of the cone in and around that area, and the subsequent integration of BMD, although the lateral condyle increase is not complemented by the medial condyle BMD loss. This BMD change could be a result of alignment of the hip and/or knee and thus exacerbating load bearing within the tibial plateau, or due to stress shielding, with the medial tibial condyle under less stress than previously so have significantly reduced bone turnover [163, 165]. The possible issue of alignment will be discussed in the next chapter were we investigated this further.

Currently there is only one other paper (Jensen et al 2012 [178]) that investigated cone implantation in rTKR in the tibial region using DXA BMD data. In their study at three months they reported a loss of -3.7 % in the lateral tibial region, at six months this had increased to +2.1 % but by 12 months was a reported loss of -1.0 %. In the medial tibial region it was reported as -3.5 % at three months, -3.0 % at six months, and -2.3 % at 12 months. The data from Jensen et al (2012 [178]) in the tibial medial region mimics what we have reported in our study, although our data report a larger loss than Jensen et al (2012) [178], both studies were a similar group number (N=17). As for the lateral tibial region there is a reported increase at six months with Jensen et al (2012) [178] (although there is a decrease at three and 12 months which do not match our data reporting all increases). This difference could be due to the type of cone implanted, or the variations in the small sample sizes.

Prior to Jensen et al 2012 study, Jensen et al in 2010 [179] investigated rTKR and BMD changes in the tibia, reporting figures of -2.5 % at three months, -4.4 % at six months and -1.3 % at 12 months although with high SD (9.5, 5.6 and 7.7 respectively). The regions themselves are not comparable to this study

(reported as distal tibial region which was just above the ankle joint) although it does show the losses reported after a rTKR.

Investigating changes in the tibial regions in TKR/A studies show decreases at both condyle regions, under the component and combined regions, across all three visits (three, six and 12 months) [17, 29, 287, 291, 296, 306]. Although a study by Winther et al [226] reported increases in the condyles throughout all visits (three, six and 12 months) across two different types of implant group, reported as 1.9 %, 1.12 % (three months medial condyle), 4.1 %, 8.2 % (three months lateral condyle), six months 2.2 % and 8.6 % (medial condyle), 2.1 % 6.6 % (lateral condyle), 12 months 2.4 % and 8.1 % (medial condyle), 3.1 % and 6.5 % (lateral condyle). This study used novel porous titanium construct Regenerex and the PPS style implants, in which the periprosthetic BMD changes was attributed by the author to the novel implants utilised, which might be the case with our study.

Additionally, these are TKR and not revision studies, and as stated there are only Jensen et al studies, whose results, including the ones within this research, are from a small sample size, and only include a few statistically significant differences.

6.8.2 FEMORAL AND TIBIAL IPSILATERAL BMD CHANGES IN THE NON-CONE GROUP

The femoral PA data from the non-cone group reports five increases across 12 data points. Reporting a consist decrease in the femoral stem. The lateral femoral condyle shows increases across all visits. The medial femoral condyle reports decreases at three and six months then an increase at 12 months. Beyond the stem has a similar baseline score at 12 months after undergoing a decrease and an increase.

The lateral femoral DXA data, show similar trends, reporting increases in three of nine data points (all from beyond the stem), although the femoral condyles show losses at every visit, (most likely due to a combination of the superimposition of the lateral and medial condyles and the precision errors of lateral DXA scans). The lateral femoral stem shows similar data to the PA data,

with both reporting losses at every visit; with the beyond the femoral stem reporting increases in the lateral data, a similar score at six months, and both show an increase at 12 months.

The tibial data from the non-cone group reports only one increase across all 12 data points, with it reported at beyond the tibial stem region, the tibial medial and lateral condyles all report losses at every visit, the highest reported at 12 months of -3.86 % in the medial tibial condyle, the tibial stem all report losses as well.

The lateral tibial DXA data report increases in four out of nine data points (although none of these are over 0.55 %, and three are in the beyond the tibial region). The tibial condyles show losses throughout very similar to the medial and lateral PA data, reporting the biggest difference in the non-cone lateral data at 12 months of -7.55 % which is supports the reported medial tibial condyle -3.86 % in the PA data. The lateral data reporting the tibial stem almost matches the same values as the PA data, with both reporting losses at every visit; beyond the stem has a similar pattern reporting increases at six and 12 months in both the lateral and PA data.

This increase from three months to 12 months in the PA DXA images in lateral and medial femoral condyles could be due to more weight bearing activities and thus higher turnover of bone remodelling [424]. Both the femoral and tibial stem report losses, which agree with the cone data and lateral and PA data for both groups. The losses reported in the non-cone group around the tibial condyles might be due to differential load bearing or alignment issues, or the cone implantation, as in the non-cone group there are losses reported in both tibial condyles at every visit, so if they were favouring a side due to alignment, we would expect to see an increase on one side [425].

In the only other cone rTKR study investigating BMD via DXA (Jensen et al (2012) [178], they included non-cone participants (N=19) in their data, they reported the lateral tibial condyle as -0.4 % (three months), +0.3 % (six months), +0.5 % (12 months), and the medial tibial aspect was reported as -1.1 % (three months) -1.4 % (six months) -1.8 % (12 months). These share similar losses

reported in our study in the medial tibial aspect, although it does not account for the increases reported in Jensen et al's study compared to the losses reported in our study in the lateral tibial condyle.

6.8.3 COMPARISONS BETWEEN CONE AND NON-CONE

In the cone group the PA tibial and femoral stem changes both show almost identical trends, both reporting a small increase at three months, and then decreases that gets worse at six and 12 months. This stem trend is also seen in the non-cone data as well, with decreases reported at every visit for both the femoral and tibial stems (no increase at three months like the cone data), with the tibial stem in the cone group reporting a difference of +5.75 % at three months, this is due to a high loss in the non-cone group and a slight increase in the cone group.

For beyond the femoral stem data both the cone and non-cone group report increases, although in the cone group there is a great increase in BMD change resulting in a difference between the groups of 4.27 %. For the beyond the tibial stem both groups show the same trend (decrease at three months, increase at six and decrease at 12 months) with no statistical difference between the groups.

As stated these trends in both the tibial and femoral stem and beyond data might be due to bone remodelling and transference of loading through the stem to beyond it. Furthermore, the differences between the two groups might be due to the stabilisation of the tibial cone resulting in the cone group load bearing earlier, although there is only one statistically significant figure comparing groups, thus the difference may be due to the small group in the non-cone data.

Interestingly the similarities between the tibia and femur is not seen in the medial and lateral aspects as clearly, both groups report increases in the lateral femoral condyles, with both groups having similar increases in the medial femoral condyle at 12 months.

The most notable difference between both groups is in comparing the lateral and medial tibial condyles, both groups show large decreases in the medial

tibial condyle region, with both groups reaching their highest loss at 12 months, the difference between the groups is 5.12 %, with the cone group having reported higher losses in the medial tibial condyle (this agrees with the Jensen et al data [178], which reports losses in both their cone and non-cone participants in the medial tibial condyle.

This similarity between the two studies and the change in BMD in the medial tibial condyle is most likely due to the alignment positioning (which will be explored in the next chapter), as stated over 90 % of OA patients have a varus position deformity [163]. This results in higher BMD in the medial aspect due to load bearing [163], once this deformity is corrected (with a rTKR), there is no longer this stress on the medial area, with stress shielding involved this reduces the BMD in the medial tibial aspect of both cone and non-cone participants across both studies, with this alignment data investigated in the next chapter, although unfortunately Jensen et al [178] did not state the alignment of their participants, so this cannot be concluded.

In the lateral tibial condyle the cone group reports increases at all visits, whilst the non-cone group report losses at all visits, accumulating in a difference of 5.71 % in support of the cone group. In the Jensen et al study this is harder to ascertain, as both groups report losses and increases, when comparing the groups directly Jensen et al showed there was no difference between groups, with the author concluding the bone remodelling pattern to be almost identical at two years post-surgery [178, 426].

As stated, both of these changes could be due to knee alignment issues, in the tibial medial condyle the loss is similar (although more severe in the cone group), with these losses reported extensively in the TKR literature [17, 29, 287, 291, 296, 306]. Furthermore, this possible difference in alignment might be the reason for the increases in the lateral tibial condyle, as stated tibial BMD changes are influenced by knee alignment [425**,** 427]. Additionally, these could be due to the variations due to the sample cohort, especially given as the non-cone group is even smaller than the cone group.

Additionally, it must be noted that the linear regression data showed no statistical difference between the groups when compared across all visits to baseline, although the cone (intervention) group did report a higher coefficient.

6.9 LIMITATIONS

The main limitation was recruitment and attrition, with participants withdrawing post- surgery due to requiring a different type of implant, and with several participants not completing the 12 month follow-up. Further to this one participant in the study attended their six month DXA appointment but had failed to attend their others (excluding pre-op), eventually withdrawing at 12 months, this six month knee data could not then be used in the comparison to baseline (six week) data due to this participant not having a baseline figure.

The advent of COVID-19 resulted in cancelled DXA imaging resulting in four participants 12 month imaging to be cancelled, and the inability for me to complete the COV analysis. Additionally, due to such a small sample size the separation between the stem lengths was not addressed, which in itself might influence the BMD changes. As of the 26 who attended at six weeks, four had a cone and a long stem, 13 had a cone and a short stem, five non-cone and long and four non-cone and short. So it is unknown if the short stem group being more prominent in the cone group is influencing the BMD changes.

Additionally, the baseline data for the DXA knee scores were the six week scans; this was due to the issues of cementation used in the revision process, falsely elevating BMD, and the inability to separate it from bone. Therefore, there is no comparison data between pre-op and six weeks, yet there is research in TKR (where no fixation cement was used) studies that state there is large BMD loss between two and five weeks post-op [16]. So it is unknown what BMD decreases may have happened within this early time period in our revision participants.

6.10 CONCLUSION

For the knee BMD data, it is shown that along the tibial stem there are decreases throughout the visits in both groups, in the beyond the femoral stem data there are increases throughout the visits, and this is seen in the PA and lateral DXA data in both groups. The medial tibial condyles are similar with both groups reporting losses at every visit which agrees with the minimal literature. Although there are increases in the tibial lateral condyle in the cone group which is paralleled by losses in the non-cone group.

The combination of the tibial BMD increase changes in the lateral region, I would conclude that there is a sign of osteointegration in and around the cone region with increased BMD. The increases in BMD around the knee might be due to the stabilisation of the cone, thus earlier WB exercising. Additionally, it must be noted that none of the cone group required further surgery, although one participant in the non-cone group did require a further revision due to a knee infection.

Data across all the DXA imaging shows no negative impact, although not significant, it is in support of cone implantation. However, this study contained a very small sample size, which makes the results less generalisable, resulting in a lack of statistical significance; add to this the issue of a lack of comparative cone BMD studies and rTKR DXA data in the research, means these data should be interpreted with caution.

6.11 FUTURE WORK

Recommendations for the full study, the DXA knee scanning and regional analysis shows promise as a viable methodology and analysis technique in determining BMD change. In order to address the issues of the possible plateau effect raised by the literature, the addition of 24 month data would have to be acquired. Addressing attrition, the use of possible public and patient involvement focus groups might communicate some of the attrition issues. Also widening the defined terms of appointment dates would allow for a much larger range for scanning participants, meaning cancelled or missed appointments could still be rearranged and completed, rather than losing that data.

CHAPTER 7: X-RAY IMAGING – PIXEL DENSITY DIFFERENCES AND ALIGNMENT

7.1 INTRODUCTION

This chapter will build upon the DXA knee data results, outlining and utilising x-ray imaging, investigating pixel values of several regions within the knee (via long leg x-rays), and alignment of the ipsilateral knee (via long leg x-rays). This will involve data from both the distal femur and proximal tibial areas, with comparisons between baseline measurements (defined as three months post-op for when exploring the pixel values, and pre-op scans in the alignment data) and their subsequent visits. Percentage changes throughout the visits were calculated in the DXA data, and differences between cone and non-cone groups were also investigated.

7.1.1 AIM

To investigate pixel value changes and hip knee ankle alignment within x-ray imaging, comparing the difference between visits and between cone and non-cone groups.

7.2 PARTICIPANTS

The participants who underwent DXA imaging also underwent x-ray imaging, with the majority scanned on the same day. So the same cohort was utilised, although it must be noted that some patients missed their appointments or their data were incomplete and could not be included.

7.3 METHOD, IMAGING

Those who were eligible and who had consented were sent a pre-op letter with the date and time for a physiotherapy appointment, DXA scan and x-ray (appendix 7).

7.3.1 X-RAY IMAGING METHOD

KNEE POSITIONING

Patient is erect, with their leg internally rotated 3-5 degrees [428]. The centring point for the AP knee is 2.5 cm below the apex of the patella [324], the distal third of femur and proximal third of tibia and fibula are included with outer skin margins laterally and medially, done at a distance of 100 cm with a kVp and mAs of 60 and 4 (as per Royal Devon and Exeter hospital (RD&E) protocols) on a cassette size of 18 x 24 cm in the portrait orientation.

The lateral is a similar set up with the patient side on to the cassette. Rotation of the patient should be checked by reviewing that the femoral condyles are laterally superimposed, with the patient flexing their knee. Additionally, the horizontal beam lateral might also be performed if the patient is unable to weight bear, as such the positional set up follows the same rules but with the patient lying supine.

X-RAY LONG LEG POSITIONING

These are normally produced to assess limb alignment prior to and after a TKR/A, or rTKR [429]. Long leg radiographs are normally obtained using a long length vertical cassette holder containing three to four 14×17 inch cassettes [429, 430], with the X-ray beam centred at the knee at a distance of 72- 94 inches [429, 430]. The beam is parallel to the floor and the machine's settings are at between 100-200 mAs (for approximately 0.05 second exposure) and a kVp of between 90 and 115 [429, 430], although this depends on tissue characteristics and limb size [430]. The patient is made to weight bear on both feet whilst in the erect position with the back of their knee against the cassettes; their legs should be rotated until their patellas are in the midline of the femoral condyles [429].

PATIENT PREPARATION

Patient preparation in x-ray imaging is similar to DXA, as artefacts can produce streaking effects on the image, thus any metal within the image must be removed.

Prior to surgery the patient attended an x-ray appointment and underwent a long leg x-ray scan as part of routine care using one cassette that acquired three images, and then the three radiographs were stitched together to create one image. A pre-set kVp of 85 but no mAs setting was utilised, in order to employ the automatic exposure controls (AEC). A working distance set at a consistent 260 cm for all long leg imaging was set for all participants.

Although there is no specific centring point for a long leg view (as this varies based on height of the patient), consistence was maintained via same repeatable set up between patient imaging. Additionally, due to possibilities in variations in exposures in the x-ray image, each radiograph contained an aluminium step wedge of a known density (1-12 mm per step), in order to allow standardisation and thus intercomparison across images. Aluminium step wedges are used both daily and annually in QA of x-ray equipment [431], and this type of technique has been used in knee x-ray imaging before [269] as well using similar standardisations [326, 432]. Additionally, the position of the step wedge does affect the correlation to density [269].

7.4 ANALYSIS OF X-RAY IMAGES

7.4.1 ANALYSIS OF PIXEL DENSITY CHANGES IN LONG LEG X-RAY IMAGES

Images were identified via patient information by the Picture Archive and Communications System (PACS) team at the RD&E and burnt onto CD. All images were in the Digital Imaging and Communications in Medicine (DICOM) format and imported into imageJ (version 1.53a) via the Bioformats importer (version 6.5.0). The canvas was standardised across all x-ray images to 3000 pixels wide to 7500 pixels in height (so all pixels were the same size). The window width and widow level were constant for each image, recorded as WW4095 and WL 2048, and each image was converted to 8 bit, this process builds upon the one mentioned previously in the bovine model (chapter three). Region selection was utilised to investigated pixel changes and osteointegration. These regions were chosen to cover the three zones of fixation from Morgan-Jones et al [433]**,** the epiphysis, the metaphysis, and the

diaphysis in order to investigate growth into the implant (figure 7.1). Therefore, ROI was set up covering five regions as shown in figure 7.2 (with a further region over the step wedge; in order to standardise the density across all images (as stated all x-ray images included a step wedge). Region four represented the joint surface, regions two and three the metaphysis of the femur and tibia (where in the tibial image in the cone group the metaphyseal cone resides) and regions five and six the diaphysis (region one was the step wedge).

These ROI were saved within a ROI manager program within imageJ at their three month visit, and applied and modified to subsequent images as per the DXA images, the ROI were modified to fit the pre-determined anatomy and regions.

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Figure 7.1. S*hows the zones of fixation from Morgan-Jones et al [376]*

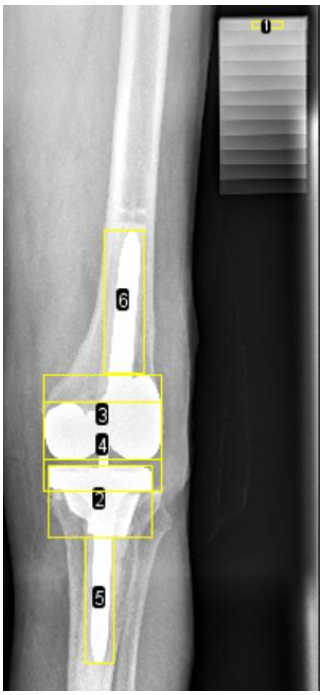

Figure 7.2. *Long leg showing all regions including step wedge*

Each pixel density score was recorded in a Microsoft Excel spreadsheet and an average pixel density of the step wedge region one for each participant was calculated, the regional data (two-six) then had a normalisation coefficient applied to each figure based off the step wedge data. This new standardised pixel density figure was then subtracted from the calculated average pixel

density and this difference was recorded for that participant, region, and visit. Thus for each visit, region, and participant there was a pixel density figure, the participant data were then separated into groups (cone and non-cone) and the mean pixel density difference calculated for each visit and region (along with a SD). Those data were then intracompared between three months and six months, and three months and 12 months post–op, a paired samples t-test was also applied. Furthermore, the mean differences between three and six months, and six and 12 months, were compared between the cone and non-cone group and an unpaired samples t-test of unequal variance applied.

This was repeated for all cone and non-cone participants, a mean (and SD) was calculated for each group (cone and non-cone participants), at each visit, and the mean differences compared, a mean change was recorded as was a SD.

Consistent placement of region of interest were also investigated in the long leg pixel analysis x-rays, this involved five random cone and five random non-cone six month long leg x-rays having their three month regions placed over them and modified to fit the specific regions, the pixel density score of each region was recorded in a Microsoft Excel spreadsheet, and then the process repeated 10 times for each group, a COV precision score was calculated for each participant and then a mean figure calculated for the COV for each region for the five cone participants, and the five non-cone participants.

7.4.2 ANALYSIS OF ALIGNMENT OF KNEE AND HIP IN LONG LEG X-RAY IMAGES

Using the same long leg x-ray DICOM images taken at pre-op and three, six and 12 months post-op. It was decided to calculate the ipsilateral alignment of the overall hip knee ankle (HKA) angle, the lateral distal femoral angle (LDFA), and the medial proximal tibial angle (mPTA) (see figure 7.3). This was undertaken to determine any alignment differences between the visits, and between cone and non-cone groups as this has been reported to impact BMD via weight bearing variations due to varus and valgus deformities [164]. The alignment and angulation was determined utilising a piece of software called MicroDicom viewer (version 3.1.4 [434]), following the same measurement technique as stated in previous research [435, 436], with the use of a 180°

alignment system being very familiar to all orthopaedic surgeons [436]. Each long leg x-ray was loaded into the viewer and using the MicroDicom measurement angulation tool, the HKA, LDFA, and mPTA were measured, as shown in figures 7.4 and 7.5.

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Figure 7.3. *Positions of the LDFA, mPTA and HKA angle is the line through them both [435]*

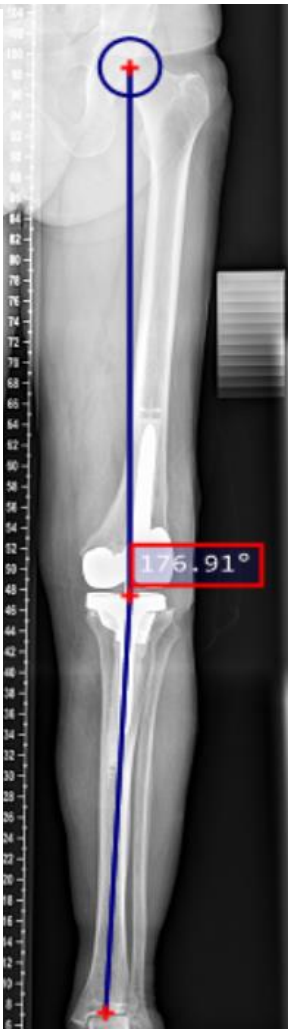


Figure 7.4. *Shows long leg x-ray with overall hip knee ankle angle calculated as 180-176.91 =3.09*

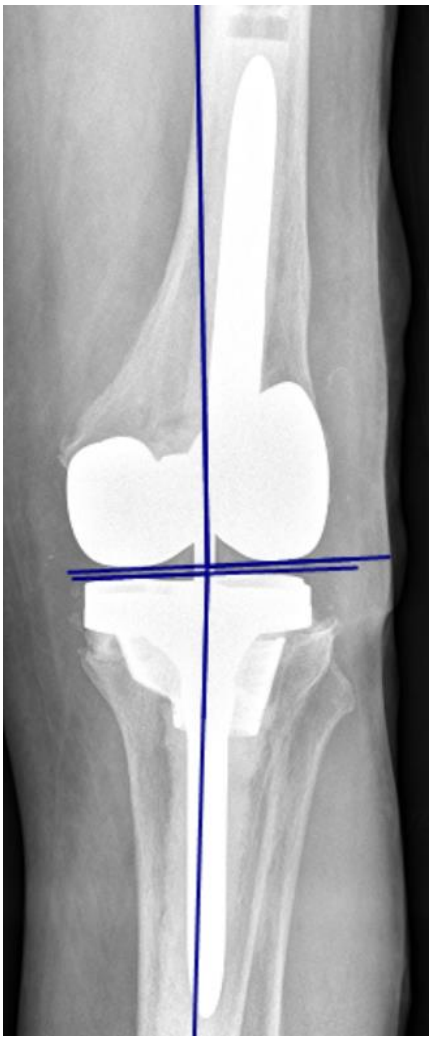


Figure 7.5. *Shows long leg x-ray with lateral distal femoral angle and medial proximal tibial angle applied (zoomed in)*

These measurements were performed for all cone participants and non-cone participants at pre-op, three, six and 12 months, a mean angulation for each visit was calculated for all cone and non-cone participants (as was a SD), and a comparison was made between pre-op and three months, pre-op and six months, pre-op and 12 months, as well as comparisons made between three and six months, and three and 12 month (with these three month comparisons

to create direct post-op changes), with a paired samples t-test performed for the intracomparison, and a t-test of unequal variance performed for the comparison between groups for their data at pre-op, three, six and 12 months.

7.4.3 INTRAOPERATOR ANALYSIS OF THE KNEE

Consistent placement of pixel density regions and placement of alignment lines was also investigated in the x-ray long leg data. For the pixel density data this involved 10 repeats of five random cone long leg images and 10 repeats from five non-cone participants, with the ROI placed over the correct areas. For the alignment data this involved loading five random six month cone participants and five random six month non-cone participants long leg x-rays, applying alignment angulation as demonstrated in figure 7.4 and 7.5, and repeating this 10 times for each participant. For both COV calculations the result recorded were recorded in a Microsoft Excel spreadsheet, a COV precision score was calculated for each participant, and then a mean figure calculated for the COV for the HKA, LDFA, and mPTA, for the cone group, and the non-cone group.

7.5 RESULTS

7.5.1 COV ROI ANALYSIS FOR PIXEL DENSITY ROI LONG LEG X-RAY IMAGES

The COV for ROI placement in long-leg x-ray pixel density analysis involved 10 repeats (of five random x-ray images), for the cone and non-cone groups was conducted over a mean separation of 1.44 days (range 1-4 days), with a COV calculated for each region per participant and then these figures averaged as shown in table 7.1

Table 7.1. *COV for pixel difference in the cone and non-cone group*

COV FROM 10 REPEATS OF 5 RANDOM CONE PARTICIPANTS						
Region number	**1**	**2**	**3**	**4**	**5**	**6**
Participant 06 COV (%)	0.21	0.08	0.14	0.26	0.05	0.21
Participant P08 COV (%)	0.27	0.13	0.11	0.17	0.09	0.29
Participant P13 COV (%)	0.33	0.20	0.40	0.15	0.30	0.07
Participant P15 COV (%)	0.46	0.29	0.24	0.16	0.33	0.08
Participant P19 COV (%)	0.48	0.21	0.19	0.57	0.25	0.15
AVERAGE (COV %)	**0.35**	**0.18**	**0.22**	**0.26**	**0.21**	**0.16**
SD	**0.12**	**0.08**	**0.11**	**0.18**	**0.13**	**0.09**
COV FROM 10 REPEATS OF 5 RANDOM NON-CONE PARTICIPANTS						
REGION number	**1**	**2**	**3**	**4**	**5**	**6**
Participant P04 (COV %)	0.51	0.49	0.23	0.31	0.11	0.46
Participant P12 (COV %)	0.11	0.21	0.20	0.18	0.21	0.03
Participant P24 (COV %)	0.12	0.25	0.18	0.16	0.11	0.02
Participant P27 (COV %)	0.21	0.36	0.34	0.23	0.29	0.02
Participant P37 (COV %)	0.18	0.28	0.16	0.10	0.12	0.09
AVERAGE (COV %)	**0.23**	**0.32**	**0.22**	**0.20**	**0.17**	**0.12**
SD	**0.16**	**0.11**	**0.07**	**0.08**	**0.08**	**0.19**

Table 7.1 shows the COV for the region placement in the long leg x-rays for the pixel density data. The cone groups highest COV precision percentage is 0.35 % in region one (the step wedge), and the lowest precision figure of 0.16 % in region six (the femoral diaphysis). In the non-cone data, the highest COV precision percentage is in region two (tibial metaphysis) reported as 0.32 %, the lowest is reported in region six the femoral diaphysis (0.12 %). From the reported data both groups report very low COV precision scores, across all regions, showing reliable and repeatable ROI placement, especially in the femoral diaphysis. Interestingly the tibial metaphysis reported as the highest in the non-cone data (0.32 %) which might be due to cone placement influencing region placement consistency (that region in the cone group was reported as 0.18 %), thus meaning that ROI placement might be more consistent in the cone group. Although as stated all COV precision scores are very low, with no real stated difference between the two groups.

7.5.2 COV ROI ALIGNMENT ANALYSIS FOR LONG LEG X-RAY IMAGES

The COV for alignment placement in long-leg x-ray analysis involved 10 repeats (of five random x-ray images), for the cone and non-cone groups over a mean separation of 1.44 days (range one to four days), with a COV calculated for

each alignment measurement, per participant and then these figures averaged as shown in table 7.2.

Table 7.2. *COV for alignment in the cone and non-cone group*

COV FROM 10 REPEATS OF 5 RANDOM CONE PARTICIPANTS				**COV FROM 10 REPEATS OF 5 RANDOM NON-CONE PARTICIPANTS**			
Participant number	**HKA**	**LDFA**	**mPTA**	Participant number	**HKA**	**LDFA**	**mPTA**
P06 COV (%)	0.29	0.46	0.60	P04 (COV %)	0.24	0.38	0.54
P08 COV (%)	0.09	0.35	0.42	P12 (COV %)	0.21	0.57	0.67
P13 COV (%)	0.24	0.58	0.52	P24 (COV %)	0.32	0.56	0.56
P15 COV (%)	0.26	0.60	0.59	P27 (COV %)	0.16	0.56	0.44
P19 COV (%)	0.23	0.41	0.81	P37 (COV %)	0.29	0.58	0.34
AVERAGE (COV %)	**0.22**	**0.48**	**0.59**	**AVERAGE (COV %)**	**0.25**	**0.53**	**0.51**
SD	**0.08**	**0.11**	**0.14**	**SD**	**0.06**	**0.08**	**0.13**

Table 7.2 reports the COV for the alignment values in the hip knee ankle (HKA) angle, the lateral distal femoral angle (LDFA), and the medial proximal tibial angle (mPTA. For the cone group the highest COV precision percentage is 0.59 % for the mPTA alignment, and the lowest precision is 0.22 % for the HKA. In the non-cone data the highest COV precision percentage is reported as 0.53 % in the LDFA, the lowest is reported in the HKA. From the reported data both groups report very low COV precision scores, across all alignment, reporting repeatable alignment positioning, especially in the overall HKA reported as the lowest in both groups of 0.22 % and 0.25 %.

7.5.3 X-RAY PIXEL DENSITY RESULTS IN LONG LEG X-RAY IMAGES

All participants who underwent a long leg x-ray had per the protocol a step wedge included in the image. This was used to standardise the pixel densities (using a normalisation coefficient as stated in the method), the three month long leg data was used as a comparator to the six and 12 month data, therefore only participants who had a three month long leg x-ray and had subsequent long leg scans (at either six or 12 months) were included in the analysis. Therefore, only long leg images which contained the step wedge were included, therefore eight long leg x-ray images were excluded from the analysis due to not including a step wedge, as the pixel values could not be standardised. Additionally, four participants could not attend their 12 month appointment due to the COVID-19 pandemic. The participant who had a femoral cone implanted had their long leg femoral data excluded with the tibial data classified as non-cone data, just as

with the DXA data. In total the number of participants who attend their long leg x-ray scan, who also had three month data, and had step wedges included was: three months 18 participants (11 cone and seven non-cone), six month 17 participants (11 cone and six non-cone) and 12 months six participants (four cone and two non-cone).

Table 7.3. *Cone and non-cone group pixel density differences on long leg x-rays at 3 and 6 month visits, including t-test and p-value*

CONE GROUP	**2 Tibial metaphysis**	**3 Femoral metaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
3 month (N=11) (mean pixel value)	19.12	34.79	39.19	43.13	33.81
SD	23.34	24.02	26.39	27.63	26.38
6 month (N=11) (mean pixel value)	19.24	37.14	40.67	44.36	31.43
SD	16.84	16.25	18.03	18.94	16.52
T-Critical between 3 and 6 months (p-value)	-0.02 (0.98)	-0.39 (0.70)	-0.23 (0.82)	-0.18 (0.86)	0.48 (0.64)
NON-CONE GROUP	**2 Tibial metaphysis**	**3 Femoral metaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
3 month (N=6)(N=5 femoral data) (mean pixel value)	22.16	34.14	37.93	39.83	39.39
SD	33.48	29.35	34.53	34.44	36.43
6 month (N=6) (N=5 femoral data) (mean pixel value)	14.61	31.26	34.94	31.97	34.29
SD	28.90	20.90	27.14	33.83	29.66
T-Critical between 3 and 6 months (p-value)	0.73 (0.50)	0.21 (0.85)	0.20 (0.85)	0.63 (0.56)	0.33 (0.76)

The results in table 7.3 report that for the cone group at six months there is an increase across all regions (except the femoral diaphysis); the greatest difference was an increase of 2.35 in mean pixel density in the femoral metaphyseal region. In the non-cone group, there is a loss in mean pixel density across all regions, with the highest being in the tibial regions pixel density loss of 7.86 (tibial metaphyseal) and 7.55 (tibial diaphyseal).

Table 7.4. *Cone and non-cone group pixel density differences on long leg x-rays of those who completed 3 and 12 month visits, including t-test and p-value*

CONE GROUP	**2 Tibial metaphysis**	**3 Femoral metaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
3 month (N=4)	37.02	48.43	58.01	63.14	50.78
SD	27.82	31.95	34.99	33.14	33.91
12 month (N=4)	18.00	28.83	34.49	39.18	30.66
SD	20.76	23.65	25.28	23.04	25.31
T-Critical between 6 and 12 months (p-value) (paired to only those 4)	3.30 (0.05)	2.48 (0.09)	2.49 (0.09)	2.46 (0.09)	2.62 (0.08)
NON-CONE GROUP	**2 Tibial metaphysis**	**3 Femoral metaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
3 month (N=2)(N=1 femoral data)	24.83	56.52	68.55	47.69	71.75
SD	40.57	-	-	43.84	-
12 month (N=2)(N=1 femoral data)	19.88	57.23	72.11	47.99	79.13
SD	44.50	-	-	54.38	-
T-Critical between 6 and 12 months (p-value) (paired to only those 2)	1.78 (0.33)	-	-	0.04 (0.97)	-

For the 12 month data (table 7.4), there was a very small sample size (four on the cone group and two in the non-cone group, which is only one participant for the femoral data) and large SDs, the p-values reported are a misnomer due to such small group sizes i.e. four participants (cone) report a 12 month pixel density score increase of 61.79 compared to another participants increase score of 1.49 (both for the same region).

Table 7.5. *Cone vs non-cone group pixel density differences between 3 and 6 months on long leg x-rays, including t-test and p-value*

CONE GROUP	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Average difference in mean pixel value between 3 and 6 months (N=11)	0.12	2.35	1.48	1.23	-2.38
SD	18.11	19.94	21.21	22.66	16.53
NON- CONE GROUP	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Average difference in mean pixel value between 3 and 6 months (N=6)(N=5 femoral data)	-7.55	-2.88	-2.99	-7.86	-5.10
SD	25.49	31.15	33.62	30.48	34.23
DIFFERENCE BETWEEN GROUPS	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Difference in mean pixel value	7.67	5.23	4.46	9.09	2.72
T-Critical (P-value)	-0.65 (0.53)	-0.34 (0.74)	-0.27 (0.79)	-0.64 (0.54)	0.44 (0.87)

Comparing the two groups in table 7.5, shows that even on the one region in the cone group that a loss was reported (femoral diaphysis), the loss was larger in the non-cone group (-2.38 compared to -5.10). The biggest difference between the two groups is in the tibial regions (metaphysis and diaphysis) reporting a difference of 7.67 and 9.09 respectively. Although it must be noted there is no statistical significance between the two groups.

Table 7.6. *Cone vs non-cone group pixel density differences between 3 and 12 months on long leg x-rays, including t-test and p-value*

CONE GROUP	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Average difference between 3 and 12 months (N=4)	-6.38	-8.84	-9.03	-8.36	-7.71
SD	7.87	14.40	17.98	13.00	10.11
NON- CONE GROUP	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Average difference between 3 and 6 months (N=2) (N=1 femoral data)	-2.17	0.71	3.56	7.76	7.38
SD	7.74	-	-	7.16	-
DIFFERENCE BETWEEN GROUPS	**2 Tibial metaphysis**	**3 Femoral diaphysis**	**4 Joint surface**	**5 Tibial diaphysis**	**6 Femoral diaphysis**
Difference	-4.21	-9.55	-12.59	-16.12	-15.08
T-Critical (P-value)	0.30 (0.78)	1.32 (no data)	1.40 (no data)	0.45 (0.88)	2.98 (no data)

Table 7.6 reports the 12 month data; this has been included for completion of the data, but as stated due to the lack of participant numbers making comparisons between the two groups difficult. Further to this, some of the comparison data does not report a p-value due to there only being one data point in the non-cone femoral data.

7.5.4 ALIGNMENT RESULTS FOR CONE AND NON-CONE PARTICIPANTS

This section will now report the alignment results for the knee in the long leg x-ray images. The data was recorded at each participant's visits (pre-op, three month, six month, and 12 month), with a mean angulation calculated for overall hip knee ankle (HKA) angle, the lateral distal femoral angle (LDFA), and the medial proximal tibial angle (mPTA), these figures were then compared between the two groups. It must be noted the participant who had a femoral

cone but not a tibial cone was placed into the non-cone group, and their femoral and overall HKA data excluded (so only their tibial angle was included), this matches the same method used in the DXA results and x-ray pixel analysis; with the femoral BMD/pixel density excluded, but the tibial data included as non-cone.

28 participants (18 cone participants and 10 non-cone participants) in total attended at least one long leg x-ray appointment, for pre-op it was: 17 cone participants and nine non-cone (26 total), at three months it was 15 cone and nine non-cone (24 total), at six months it was 13 cone and six non-cone (19 total) and 12 months seven cone and four non-cone (11 total).

As for appointments; the average three month visit was a mean +6.75 days away from the exact three month post-op date (range -16 to +32), for six months the mean was +5.16 days (range -30 to +28), and for 12 months the mean was +5.92 days (range -92 to +42).

Datasets were compared between the pre-op figure and the three, six and 12 month visits, and between three months to six, and three months to 12 months to investigate post-op changes. Furthermore, the data were compared between cone and non-cone to discern differences between the two groups.

Table 7.7. *Pre-op angulation for the overall hip knee angle (HKA), lateral distal femoral angle (LDFA) and medial proximal tibial angle (mPTA)*

	PRE-OP		
	CONE GROUP (N=17) (ONLY TIBIAL DATA FOR 1 PARTICIPANT)		
	HKA (°)	LDFA (°)	mPTA (°)
AVERAGE	2.48	-0.44	1.03
SD	4.94	2.74	2.63
	NON-CONE GROUP (N=9) (ONLY TIBIAL DATA FOR 1 PARTICIPANT)		
	HKA (°)	LDFA (°)	mPTA (°)
AVERAGE	-1.18	0.70	-0.76
SD	4.72	3.09	2.73
T-CRITICAL (P-VALUE)	1.778 (0.010)	-0.885 (0.39)	1.611 (0.13)

Table 7.7 reports the pre-op angles of the HKA, LDFA, and mPTA, on average the HKA in the cone group was 2.48° (177.52° varus) with the non-cone group

reporting -1.18° (181.18°), valgus alignment, so there is a difference in the pre-op data (although not statistically significant, but one of the eight non-cone participants has a reported HKA of 188.14°). Interestingly this is agreed upon in additional data, in the LDFA the cone group this is reported as 0.44° varus (90.44°), but with the non-cone group it was reported as 0.70° valgus (89.30°), with the tibial data mPTA reporting 1.03° varus (88.97°) for the cone group, and 0.76° valgus (90.76°) in the non-cone group.

CONE PRE-OP ALIGNMENT COMPARED TO OTHER VISITS

In this section the cone group compared the pre-op long leg x-ray with each visits long leg x-ray (three, six and 12 months), and then the cone group was also compared from the three month visit to the six and 12 month visit.

Table 7.8. *Cone group long leg compared to pre-op at each visit for HKA, LDFA and mPTA, including t-test and p-value*

CONE GROUP (N=14) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 3 MONTH VISIT

	PRE-OP	3 MONTH	DIFFERENCE	T-CRITICAL (P-VALUE)
HKA (mean °)	2.88	-2.16	-5.04	2.642 **(0.01)**
SD	5.43	4.23	6.45	
LDFA (mean °)	-0.53	1.39	1.92	-1.930 (0.08)
SD	2.99	1.87	3.59	
mPTA (mean °)	0.80	-1.15	-1.96	2.000 (0.07)
SD	2.68	2.53	3.66	

CONE GROUP (N=12) 6 MONTH VISIT

	PRE-OP	6 MONTH	DIFFERENCE	T-CRITICAL (P-VALUE)
HKA (mean °)	3.53	-2.28	-5.80	2.994 **(0.01)**
SD	5.13	4.33	6.15	
LDFA (mean °)	-0.93	1.33	2.26	-2.256 (**0.05**)
SD	2.74	1.71	3.47	
mPTA (mean °)	1.26	-1.62	-2.88	3.072 (**0.01**)
SD	2.46	3.31	3.24	

CONE GROUP (N=7) 12 MONTH VISIT

	PRE-OP	12 MONTH	DIFFERENCE	T-CRITICAL (P-VALUE)
HKA (mean °)	3.63	-1.65	-5.28	1.826 (0.09)
SD	6.14	4.57	5.70	
LDFA (mean °)	-1.65	1.43	3.08	-2.602 (**0.04**)
SD	3.05	1.71	3.14	
mPTA (mean °)	1.20	-0.64	-1.84	1.089 (0.32)
SD	2.87	3.62	4.46	

Data from table 7.8 reports changes in the cone group between pre-op and the subsequent visits, the HKA reports a reduction in degrees at each visit, with the largest difference in the HKA reported at six months with a figure moving from 3.53° to -2.28° (p-value 0.01). LDFA reports increases throughout each visit, the most significant difference is -0.93° at pre-op and 1.33° at six months this was reported as a p-value of 0.05, at 12 months this was reported as going from a pre-op of -1.65° to 1.43° (p-value 0.04). For the mPTA data reported a consistent pattern as well at each visit, this time reporting the opposite i.e. a positive score into a negative, e.g. 1.26° at pre-op to a six month score of -1.62° (p-value 0.01), this was seen in the 12 month data as well, reporting 1.20° at pre-op to -0.64° at 12 months

Table 7.9. *Cone group long leg compared to 3 month at each visit for HKA, LDFA and mPTA, including t-test and p-value*

CONE GROUP (N=13) 3 MONTH COMPARED TO 6 MONTH DATA				
	3 MONTH	**6 MONTH**	**DIFFERENCE**	**T-CRITICAL (P-VALUE)**
HKA (mean °)	-1.45	-1.90	-0.45	0.027 (0.79)
SD	4.30	4.36		
LDFA (mean °)	1.25	1.24	-0.01	0.043 (0.97)
SD	1.89	1.68		
mPTA (mean °)	-0.86	-1.45	-0.59	0.925 (0.37)
SD	2.59	3.23		

CONE GROUP (N=7) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 3 MONTH COMPARED TO 12 MONTH DATA				
	3 MONTH	**12 MONTH**	**DIFFERENCE**	**T-TEST (P-VALUE)**
HKA (mean °)	-2.11	-1.65	0.46	-0.176 (0.86)
SD	5.10	4.57		
LDFA (mean °)	1.36	1.43	0.07	-0.143 (0.89)
SD	1.48	1.71		
mPTA (mean °)	-1.19	-0.64	0.55	-0.739 (0.49)
SD	3.35	3.62		

Table 7.9 data report changes in the cone group between three month post-op and the subsequent six and 12 month visits, there is no statistically significant difference, the HKA reports a difference of -0.45° at six months to 0.46° at 12 months. LDFA figure shows no real change at six or 12 months when compared to three months**,** mPTA reports differences at six and 12 months of -0.59° and 0.55° respectively, this is reflected in the HKA data.

NON-CONE PRE-OP ALIGNMENT COMPARED TO OTHER VISITS

In this section the non-cone group compared the pre-op long leg x-ray to each subsequent visit (three, six and 12 months), and then the cone group was also compared from the three month visit to the six and 12 month visit.

Table 7.10. *Non-cone group long leg compared to pre-op at each visit for HKA, LDFA and mPTA, including t-test and p-value*

NON-CONE GROUP (N=8) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 3 MONTH DATA

	PRE-OP	3 MONTH	DIFFERENCE	T-CRITICAL P-VALUE
HKA (mean °)	-2.26	-2.11	0.15	-0.079 (0.94)
SD	3.87	2.95	5.05	
LDFA (mean °)	1.13	1.37	0.24	-0.338 (0.75)
SD	3.06	1.78	1.87	
mPTA (mean °)	-0.81	-0.87	-0.06	0.041 (0.97)
SD	2.92	1.74	4.15	

NON-CONE GROUP (N=5) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 6 MONTH DATA

	PRE-OP	6 MONTH	DIFFERENCE	T-CRITICAL P-VALUE
HKA (mean °)	-2.79	-1.31	1.49	-2.02 (0.11)
SD	4.18	3.71	1.35	
LDFA (mean °)	1.09	1.26	0.17	-0.118 (0.91)
SD	4.07	1.96	2.81	
mPTA (mean °)	-0.34	-1.46	-1.13	1.09 (0.34)
SD	3.03	1.04	2.32	

NON-CONE GROUP (N=4) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 12 MONTH DATA

	PRE-OP	12 MONTH	DIFFERENCE	T-CRITICAL P-VALUE
HKA (mean °)	1.86	-1.33	-3.19	1.277 (0.33)
SD	2.93	4.22	4.32	
LDFA (mean °)	0.01	1.03	1.02	-0.934 (0.45)
SD	2.29	1.96	1.89	
mPTA (mean °)	0.88	-1.08	-1.96	1.444 (0.24)
SD	1.82	2.58	2.71	

Data from table 7.10 report changes in the non-cone group between pre-op and the subsequent visits, the HKA reports a pre-op of -2.26° to -2.11° at three months, at 12 months this is reported as -1.33° from 1.86°). For the LDFA it reports an increase at each visit starting from a positive pre-op score, with the greatest difference reported at 12 months of 1.01° (0.01° to 1.03°). For the mPTA there is the same pattern at every visit resulting in a negative score at each visit, reporting the greatest difference of -0.34° to -1.46° at six months.

Table 7.11. *No-cone group long leg compared to 3 month at each visit for HKA, LDFA and mPTA, including t-test and p-value*

NON-CONE GROUP (N=6) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 3 MONTH COMPARED TO 6 MONTH DATA

	3 MONTH	6 MONTH	DIFFERENCE	T-CRITICAL P-VALUE
HKA (mean °)	-1.04	-1.00	0.04	-0.022 (0.98)
SD	2.25	3.29		
LDFA (mean °)	0.73	0.93	0.21	-0.578 (0.59)
SD	1.71	1.84		
mPTA (mean °)	-0.57	-1.29	-0.71	2.220 (0.08)
SD	0.83	1.03		

NON-CONE GROUP (N=3) (ONLY TIBIAL DATA FOR 1 PARTICIPANT) 3 MONTH COMPARED TO 12 MONTH DATA

	3 MONTH	12 MONTH	DIFFERENCE	T-CRITICAL P-VALUE
HKA (mean °)	-2.82	-2.16	0.66	-0.125 (0.91)
SD	4.80	5.61		
LDFA (mean °)	1.23	1.25	0.02	-0.468 (0.94)
SD	2.43	2.72		
mPTA (mean °)	-1.26	-0.80	0.46	-0.178 (0.89)
SD	1.44	3.08		

Table 7.11 data report changes in the non-cone group between three month and the subsequent six and 12 month visits, giving a comparison to post-op changes the results show. The difference reported in the HKA increases compared to three months with the greatest difference reported as 0.66° (-2.82° to -2.16°, the LDFA reports both positive changes, reported as 0.73° pre-op to 0.93° at six month, and 1.23° to 1.25° at 12 months**.** The mPTA data also report differences at each visit, for six months (pre-op -0.57 to -1.29°) and at 12 months of -1.26° to -0.80°.

ALIGNMENT COMPARISON BETWEEN CONE AND NON-CONE DATA

In this section the cone group was compared to non-cone group at three, six and 12 months.

Table 7.12. *Cone vs non-cone group long leg at each visit for HKA, LDFA and mPTA, including t-test and p-value*

CONE (N=14) AND NON CONE (N=8) (ONLY TIBIAL DATA FOR 2 PARTICIPANTS 1 CONE 1 NON-CONE) 3 MONTH DATA

	CONE PRE-OP	CONE 3M	NON-CONE PRE-OP	NON-CONE 3M	DIFFERENCE BETWEEN GROUPS AT 3M	T-CRITICAL P-VALUE
HKA (mean °)	177.12	182.16	182.26	182.11	0.05	0.029 (0.98)
SD	5.43	4.23	3.87	2.95		
LDFA (mean °)	90.53	88.61	88.87	88.63	-0.02	0.027 (0.98)
SD	2.99	1.87	3.06	1.78		
mPTA (mean °)	89.20	91.15	90.81	90.87	0.29	-0.312 (0.76)
SD	2.68	2.53	2.92	1.74		

CONE (N=12) AND NON CONE (N=5) (ONLY TIBIAL DATA FOR 1 PARTICIPANTS 1 NON-CONE) 6 MONTH DATA

	CONE PRE-OP	CONE 6M	NON-CONE PRE-OP	NON-CONE 6M	DIFFERENCE BETWEEN GROUPS AT 6M	T-TEST P-VALUE
HKA (mean °)	176.47	182.28	182.80	181.31	0.97	0.431 (0.68)
SD	5.13	4.33	3.98	3.71		
LDFA (mean °)	90.93	88.67	88.91	88.74	-0.08	0.069 (0.95)
SD	2.74	1.71	4.07	1.96		
mPTA (mean °)	88.74	91.62	90.34	91.46	0.16	-0.146 (0.89)
SD	2.46	3.31	3.03	1.04		

CONE (N=7) AND NON CONE (N=4) (ONLY TIBIAL DATA FOR 1 PARTICIPANTS 1 NON-CONE) 12 MONTH DATA

	CONE PRE-OP	CONE 12M	NON-CONE PRE-OP	NON-CONE 12M	DIFFERENCE BETWEEN GROUPS AT 12M	T-TEST P-VALUE
HKA (mean °)	176.37	181.65	178.14	181.33	0.32	0. 108 (0.92)
SD	6.14	4.57	3.97	4.22		
LDFA (mean °)	91.65	88.57	89.99	88.97	-0.40	0.310 (0.78)
SD	3.05	1.71	2.29	1.96		
mPTA (mean °)	88.80	90.64	89.12	91.08	-0.44	0.231 (0.82)
SD	2.87	3.62	1.82	2.58		

Table 7.12 reports the comparison data between the two groups, there is no reported statistical significance between the groups. Pre-op the cone group are in the varus position and the non-cone group in the valgus (177.12° and

182.26°), but by three months both groups report very similar figures (182.16° and 182.11°), at six month for the HKA both groups have again are closer to the 180° ideal than at pre-op, the cone group now reporting 182.28° and the non-cone reporting 181.31°. At 12 months the cone group reports 181.65° and the non-cone group reports a figure of 181.33°.

The LDFA comparison data at three months reports the cone and non-cone group are nearly identical reporting 88.61° and 88.63°, at six months 88.67° and 88.64° and at 12 months it is reported as 88.57° and 88.97°. It must be noted that the pre-op alignment in the cone group is over 90° reporting a varus alignment, the non-cone group pre-op is always as valgus alignment (under 90°) and is similar to the pre-op at each visit.

The mPTA data reported the cone at three months of 91.15°, 1.15° into valgus alignment; this was with a reported 89.20° at pre-op. The non-cone data show little change between pre-op and three months post-op reporting 90.87° from a pre-op score of 90.81°. At six months the cone group has increased, as has the non-cone group to 91.62° and 91.46°. At 12 months this is reported as 90.64° in the cone group and 91.08° in the non-cone group.

7.6 DISCUSSION

7.6.1 X-RAY PIXEL DENSITY CHANGES

Examining the six month data compared to the three month data, the cone group reports an increase in all regions (except one), and the non-cone group reporting losses at each region, the greatest deficient between the two groups was in the non-cone group in the tibial region, with reported losses of 7.67 (metaphyseal) and 9.09 (diaphyseal) in mean pixel density.

These changes could be due to the cone osteointegration and stabilisation around the joint at six months, thus increasing BMD within and around it (which is not seen in the non-cone group), especially as in the DXA results from the previous chapter the cone implant is classified as artefact, so cannot report the

BMD changes penetrating the cone or directly around it, only the changes in the surrounding area.

This idea of cone osteointegration is further supported due to the data demonstrating that the second greatest loss in the non-cone is in the tibial metaphyseal region, which is where the cone is situated (in the cone group), which as already stated was reported as an increase in pixel density in the cone group. This increase in pixel density could be due to osteointegration. Research has reported osteointegration of cones demonstrated on radiographs [218, 437, 438, 439], with no radioluciencies identified [218, 222, 440, 441]. Unfortunately, the reported literature do not report pixel densities, but rather state: "*cones show osteointegration as defined radiographically as absence of radiolucent lines*" [218] or "*absence of radiolucency lines between the cone and the host*" [442] or *"as absence of a lucent line between the bone and cone"* [443], with a high majority of cone studies showing good osteointegration after one year. Due to these issues, there is limited correlation data on BMD scores and pixel density changes. Kinds et al [269] did investigate this with cadavers, showing that accurate BMD measurements were possible from standard x-ray images (radiographs) with a step wedge. Although correlation between the two is used a lot in dentistry, a study by Nackaerts et al [444] investigated the correlation between mandibular BMD and pixel values on intra-oral radiographs using an aluminium step wedge and reported good observer agreement between the two. Concluding that the pixel values are likely representing the BMD changes in some capacity, although without robust correlation, this cannot be truly concluded in our study.

Regrettably, although there is 12 month data it only involves four participants (cone group), additionally, these four participants had losses at six months compared to the three month as well, so without 12 month data from the rest of the participants it is unknown osteointegration has happened overall. Furthermore, only two non-cone participants completed 12 months, with only one of those having femoral data, so there is a lack of direct comparison data.

It must be noted these pixel density changes may be for other reasons, although the region placement was accurate, with a reported COV precision

range of 0.09 % to 0.35 %, there is the possibility of rotation of the joint and other variations in positioning of the long leg x-ray, which may also be influencing the reported figures. For example, foot rotation in long leg x-rays has been reported to affect long leg x-rays and alignment results [445].

As stated previously there was at least eight long leg x-rays that could not be included due to not containing the step wedge in the image. Four participants could also not complete the 12 month long leg x-ray due to the COVID-19 pandemic. Additionally, no lateral data were used due to variations and a lack of consistency in the x-ray settings and positioning, in addition to this we did not have six week long leg comparisons, although this would have given us a more accurate baseline, and allowed direct comparisons to the DXA data**.** So it is unknown if there is an increase between pre-op and three months. It must be noted that a six week long leg was not part of routine care, and would have added to the issues of attrition, due to the need for additional scanning.

7.6.2 ALIGNMENT ANALYSIS CONE AND NON-CONE GROUP

As with the DXA data some participants missed their three, six and/or 12 month appointments, with only seven cone and four non-cone participants completing 12 months.

The average pre-op scores for the HKA in the cone (177.52° SD 4.94, 2.48°) and non-cone group (181.18° SD 4.72, -1.18°) both are similar to the reported 5° variation from 180**°** reported in the literature as defined as normal mechanical alignment [436]**,** although some do state it should be 180° ± 3° [446, 447]. With both groups reporting figures closer to 180° at three, six and 12 months, than at pre-op, showing a parallel to normal alignment. This is in agreement with a report by Mizu-Uchi et al who reported their HKA as 178.2° ± 1.5° (173.9° to 181.8°) in TKR patients [448], although one study involving cone implantation in rTKR patients the reported HKA was 178° ± 6° (163° to 194°) preoperatively, and 180° ± 4° (172° to 191°) at two year post-op [443]. Moreover, some have reported a greater difference in alignment in pre-op revision patients, with one report stating a mean difference of 7.3° valgus in pre-op revision patients [449]. Furthermore, research has shown that alignment within the range of 3° varus/valgus is associated with better survival of the prosthesis [450, 451, 452,

453, 454]. Additionally, although protocols were followed, there is the possibility of rotation in positioning, which can produce greater perceived varus alignment, and increased mechanical axis deviation from the knee joint centre [445].

In comparing this rTKA data to other studies it must be noted that a high majority of papers only define the degrees as valgus or varus, and do not stipulate exact degrees, a paper by Kamath et al [221] reviewed all articles published in Clinical Orthopaedics and Related Research, The Journal of Arthroplasty, and The Journal of Bone and Joint Surgery (American edition) from January 2008 to December 2009. Their results after exclusion/inclusion reported 96 articles involving alignment from radiographs, of which over 90 % of the papers (90 articles) used a variation on the varus/valgus system without a strict definition often using terms like ‘‘X degrees from/of varus’’ or ‘‘Y degrees from/of valgus” [221], with only 2 % of papers stating the degrees from 180°.

The LDFA data are reported in the cone group as -0.44° (90.44°) at pre-op, and 0.70° (89.30°) in the non-cone group (reported (when comparing to three month data) as 90.53° and 88.78°). This is within the same alignment as TKR patients, reporting 89.0° ± 1.4° (85.5° to 92.8°) [448]. Reviewing the changes at three, six and 12 months, all changes in the cone group resulted in a varus to valgus degree change. In the non-cone group there is a similar pattern but the alignment was already starting in a valgus position.

Data for the mPTA in TKR research reports similar alignment scores, with the mPTA reported in the tibial component as 89.2° ± 1.0° (87.4° to 91.6°) [448], with a reported pre-op of 88.97° (1.03°) in the cone group and 90.76° (-0.76°) in the non-cone group. For the cone group trend, the pre-op is in the varus and ends in the valgus position at each visit, with the 12 month data reporting a pre-op 1.20° to 12 month of -0.64°. For the non-cone the mPTA data the pattern is similar.

Both the LDFA and mPTA in the cone and non-cone data show both groups ending up in negative position (over 90°) in the LDFA, and in the positive position in the mPTA (under 90°), the main difference being their starting alignment position. Thus, the cone group seems to start in a more varus

misaligned position at pre-op, but by their first long leg x-ray at three months due to surgery this seems to have been rectified, this is the same in the mTPA data.

When directly comparing the two groups as stated there is little difference between them across all three visits, and no statistical significance with a high majority of p-values reported, although the difference at pre-op is noticeable (although not statistically significant) by three month the reported HKA is nearly identical. This is lack of statistical significance is most likely due to the issues of reduced data, and the problems already discussed in the DXA and pixel density data regarding recruitment and attrition exacerbated by the COVID-19 pandemic. This lack of difference between groups supports that the cone is not impacting alignment, and that the data demonstrated supports the importance of correct alignment in rTKR patients, as correction of malalignment via surgery has resulted in similar results between cone and non-cone data at three, six, and 12 months. It must be noted that these similarities between alignment measurements is very important, as malalignment can lead to implant failure, joint instability, and the need for further surgery [455, 456, 457, 458, 459].

Other revision alignment research has also supported reduced malalignment post-surgery, a study by Nakasone et al reported a pre-op tibiofemoral angle was 7.3° of valgus, and the average post-op tibiofemoral angle was 6.7° of valgus [460]. This change was reported in the femoral and tibial components as well; the femoral component angle reported 8.6° of valgus pre-op, with the average post-op angle being 6.5° valgus. The average pre-op tibial component angle was 1.4° of varus and the average post-op tibial component angle was 0.5° of valgus [460].

7.7 LIMITATIONS

Across the methods (pixel density, and alignment), as with the DXA imaging, the main limitation was recruitment and attrition, with participants withdrawing post- surgery due to requiring a different type of implant, and with several participants not completing the 12 month follow-up. In the pixel density method there was the issue of the step wedge not being included in the imaging,

although it was in the protocol I was not in the department, and a busy department combined with possibly new staff and long gaps between scans (i.e. six month to 12 month) meant this might have been overlooked during the imaging. This resulted in data that could not be included in the pixel density analysis, although this data could still be used in the alignment method. Moreover, the advent of COVID-19 resulted in cancelled x-ray and DXA imaging resulting in four participants 12 month imaging to be cancelled, and the inability for me to complete the COV analysis. Additionally, due to such a small sample size the separation between stem lengths was not addressed, which in itself might influence the pixel changes. So it is unknown if the short stem group being more prominent in the cone group influencing the BMD changes.

For the alignment analysis a different measurement such as anatomical alignment could have been used; although both mechanical and anatomical will always have variation in measurements, the mechanical axis has reported variations in the central axis of the knee [460], and in anatomical alignment there are inaccuracies in identifying the true centre of the intramedullary canal [460]. However, these variables will exist in any measuring system and possibly may be reduced by recording true angular measurements [360].

Finally, there was a lack of comparison baseline census, having a baseline of six weeks post-op across all methods would make the possibility of intercomparision easier; unfortunately the long-leg data was recorded at three months post-op. Given the large amount of scans, a six week long leg scan is not feasible and is outside of the normal routine care of patients with knee revisions.

7.8 CONCLUSION

Given the alignment results reporting a lack of difference between the cone and non-cone groups at three, six and 12 months, I would conclude that the alignment is only affecting the BMD difference minimally. That being said the difference between pre-op and three months in alignment cannot be ignored, and it is unknown if those changes may have influenced BMD early on. Unfortunately, there is no alignment data for the six week post-op long leg to

compare these changes directly to, so comparisons between modalities is difficult.

The lack of alignment impact in the data, and the supportive pixel density changes reported via the long leg x-rays in the tibial diaphysis, I would conclude that there is a sign of osteointegration in and around the cone region which coincides with the previous BMD reported figures.

The increases in pixel density around the knee might be due to the stabilisation of the cone, thus earlier WB exercising, and less about the alignment of the revision. Although it must be noted there is no complete overlap of those participants that attended DXA and those who attended the long leg x-ray.

Data across all these two methods shows no negative impact in the pixel, or alignment data, and that the data demonstrated, although not significant, is in support of cone implantation. However, this study contained a very small sample size, which makes the results less generalisable, resulting in a lack of statistical significance; add to this the issue of a lack of comparative data in the research, means these data should be interpreted with caution.

7.9 FUTURE WORK

Finally, moving into recommendations for the future full study, the pixel density changes show promise as a method and parallel the DXA BMD data. Although this data is limited, with two main issues, a lack of correlation data directly linking the pixel changes to BMD changes, and a lack of useable scan data as not all long leg images contained a step wedge. To address this, a phantom of known BMD could be utilised and imaged via DXA and x-ray and a more direct correlation created between these two modalities. Furthermore, and more importantly during the full study the research should be presented to the radiography department, to show the importance of the step wedge being within the images. This might help engage the radiography community and reduce this issue. Additionally, as with the DXA imaging, the addition of 24 month long leg pixel and alignment data would help address the reported plateau changes.

CHAPTER 8: CT IMAGING

8.1 INTRODUCTION

This chapter will outline the methods used in the CT imaging. This was in order to investigate bone in-growth into the implant using Dual Energy CT (DECT). This was chosen due to its ability to suppress beam hardening, scatter, and metal artefacts [278]. The conal implants being studied are composed of titanium so the degradation should be less pronounced and there should be reduced streaking [279, 280]. Computed Tomography has also been used via micro-CT investigating bone ingrowth in porous implants [271, 272, 273, 274] with some directly testing bone ingrowth in TKR in CT images [275].

8.1.1 AIM

To investigate CT imaging as a method for the potential bone in-growth into cone implantation in rTKR patients.

8.2 PARTICIPANTS

Only those who had a cone inserted were eligible for a CT scan. Of the 37 participants who consented (24 in the cone group) 13 attended the six month CT scan. As previously stated some participants had already left the study prior to the six month scans.

8.3 METHOD CT IMAGING

Those who were eligible and who had consented were sent a letter in time for their six month appointment, with the date coinciding with the six month physiotherapy appointment, x-ray, and DXA scan. This allowed, where possible, all scans to be done on the same day.

PATIENT PREPARATION

The CT patient preparation was similar to x-ray and DXA, with patients removing all metal artefacts, this was due to metal producing streaking artefacts on the image [461].

KNEE POSITIONING IN CT

The patient was placed in the supine position with their feet first, with their knee in the centre, in some cases the feet were taped together to stabilise the knee in place [416]. The area was collimated to the distal femoral metadiaphysis to the proximal tibial metadiaphysis [416], including the entire stem length and implant component [416]. Slices were taken at approximately 2 mm intervals [416], using the CT cone study knee protocol for dual energy CT (see appendix 11). This was performed in order to provide information regarding bone in-growth into the cone implant itself, and compare it against the DXA and x-ray data.

8.3.1 CT ANALYSIS AND RESULTS

Upon reviewing several CT images, it was decided that due to burst artefact and no baseline CT images as a comparator, it was determined that bone in-growth would be too inconclusive on the images produced in this study. They are however being utilised by engineering colleagues using advanced shape modelling to help model the biomechanical implications of the different types of rTKR.

8.4 LIMITATIONS

Only those who had cone implantation were invited as part of the six month CT scan, meaning although participants were blinded to their group, participants could potentially deduce their group from this appointment. Furthermore, this limited the pool, and meant there was no non-cone group comparison.

8.5 CONCLUSION

The data are not useable in this instance, due to too much artefact on the image making in-growth unable to be determined.

8.6 FUTURE WORK

Recommendations for the full trial would be to not include the six month CT scan, although models are being developed utilising the CT data compared to the DXA data. For this particular study there is no definitive ingrowth.

CHAPTER 9: RESULTS OF QUESTIONNAIRES

9.1 INTRODUCTION

This chapter will help investigate the psychological and physiological metrics pre and post rTKR in the form of questionnaires, as well as addressing possible variables between groups such as medications and pathological diseases. This included the Bone Health questionnaire (appendix 10), mental health wellbeing via the Hospital Anxiety and Depression Score (HADS) questionnaire (appendix 12), lower leg functionality investigated via the Lower Extremity Functionality Scale (LEFS) questionnaire (appendix 13), quality of life through the EQ-5D-3L questionnaire (appendix 14) and knee pain was assessed through the Oxford Knee Score (OKS) (appendix 15).

9.1.1 AIM

To investigate mental health and functionality changes in rTKR patients, at different stages post surgery. Additionally investigating differences between the cone and non-cone group, including medicines and pathological diseases.

9.2 PARTICIPANTS

As stated previously 37 participants were consented, with a total of 35 participants who attended their pre-op DXA appointment (two participants consented then withdrew prior to the pre-op, hence 37 registered but 35 attended). As per randomisation 22 received cone implantation as part of their rTKR, and 13 received no cone (non-cone control group).

Please note that some participants missed DXA appointments but were sent the questionnaires separately via the post with this data included in the analysis.

9.3 METHOD

Five questionnaires were utilised in this study, these were selected for their precision, reliability, and relevance in addressing different aspects of the study parameters such as pain and depression, quality of life, functionality and

manoeuvrability. Certain questionnaires were completed at home for ease of time, especially in cases where the participant could not attend their appointment.

9.3.1 BONE HEALTH QUESTIONNAIRE

This was un-validated questionnaire, although it had been administered in previous TKR research studies [23]. This questionnaire (appendix 10) covered questions regarding previous or current diseases (e.g. OA, RA, cancer) ethnicity, current medications, previous fracture, previous falls, history of other disease in the family, history of orthopaedic surgery, and other medical and social variables that might impact participants' bone quality. The questionnaire sent to participants as part of the pre-op DXA appointment letter and filled in by the participant at their leisure. It was then brought with them to their pre-op (first) DXA scan appointment. After pre-op subsequent appointments only asked follow-up bone health questions (e.g. falls and fractures since last appointment, changes in medication, and any additional orthopaedic surgery). Throughout the study the questionnaire was reviewed, with any ambiguity in language or information addressed with the researcher (MG) prior to starting the scan.

This provided important co-variables that might influence or impede BMD development with the links between disease, medication and social factors already established in chapter one. It also addressed the issue of variables between the two groups (cone and non-cone).

9.3.2 LOWER EXTREMITY FUNCTIONAL SCALE (LEFS)

The LEFS (appendix 13) is a validated and precise questionnaire developed by Binkley et al in 1997 and published in 1999 [462], it is used to asses recovery and functionality of the lower extremity. It is made up of 20 activity questions each with a difficulty score of zero to four (four being no pain or issue, and zero being unable to perform the task). Participants can rate each activity on the scale, with a total score calculated; a score of 80 indicates someone who is fully functional in all activities. This questionnaire was administered at each DXA visit, although in certain cases the participant was unable to attend the DXA scan and thus was sent the questionnaire separately to be completed at home.

9.3.3 HOSPITAL AND ANXIETY SCORE (HADS)

The HADS (appendix 12) was administered to determine depression and anxiety directly, this was both due to the potential impact of mood disorders on BMD and the impact the rTKR might have. The HADS questionnaire has been used in several other studies [463, 464]. It is a brief, reliable and validated metric [463, 465], and has even been translated and validated in other languages [466]. The questionnaire contains 14 questions divided into seven statements for both anxiety and depression, each item on the questionnaire is given a response between zero and three, and this means that a participant can score between zero and 21 for either anxiety or depression, with a higher score depicting a worse psychological condition [461].

9.3.4 QUALITY OF LIFE (EQ-5D-3L)

The EQ-5D-3L (appendix 14) was administered to assess difficulties with self-care, mobility, usual activities, pain, discomfort, and anxiety and depression. A score out of hundred was provided by each participant at each visit based on their perceived quality of life, with a hundred being the best possible state of health (as they perceive it) and zero being the worst.

9.3.5 OXFORD KNEE SCORE (OKS)

The OKS (appendix 15) is a reliable, widely used and valid self-administered patient questionnaire that enables assessment of knee quality after a TKR or rTKR [462, 463]. The OKS contains 12 questions on activities of daily living. The OKS was developed and validated specifically to assess function and pain after a TKR [464]. A score between 0 (worst outcome) and 48 (best outcome) can be reported, with divided sub sections linked to knee severity:

00 to 19 - May indicate severe knee arthritis
20 to 29 - May indicate moderate to severe knee arthritis
30 to 39 - May indicate mild to moderate knee arthritis
40 to 48 satisfactory joint function.
The lower the total score the more severe the problems the participant has with their knee.

9.4 ANALYSIS

9.4.1 BONE HEALTH QUESTIONNAIRE

Bone health questionnaire data were given no weighting for duration or level of medications, treatments or medical conditions therefore the data were recorded and converted into categorical data, any participant who had previous medical issues were recorded as 1, with any without recorded as 0. The data recorded were expressed in as a percentage of those who had the condition in question. The cone group data were compared to the non-cone group data via a chi square test for categorical data and a t-test of unequal variance was performed for the comparisons of weight, height, BMI and age. Resulting in percentage differences and p-vales between participants for each co-morbidity.

9.4.2 LEFS, EQ-5D-3L, OKS AND HADS

Data from the LEFS, HADS, OKS and EQ-5D-3L were intercompared between each of the participant's visits (pre-op, six weeks post, three months, six months 12 months), with a graph plotted to show the functionally, quality of life, knee pain, and depression and anxiety changes at each visit with the mean differences (and SD) between visits, a paired t-test was applied for each visit comparison, with results reported via a p-value, and median scores.

Comparisons were also made between the cone and non-cones at each visit score, with the calculated mean difference for each visit (compared to their pre-op score) compared between the cone and non-cone group via an unpaired t-test assuming unequal variance and p-value.

9.5 RESULTS FROM QUESTIONNAIRES

Most questionnaires were done in person at either the physiotherapy appointment or the DXA appointment. So those who attended their DXA also completed their LEFS questionnaire or updated details on their bone health questionnaire.

Those who failed to attend their appointment but were still happy to be part of the research and continue were posted the questionnaires. Unfortunately, in

some instance's participants failed to return these questionnaires or possibly they were lost within the postal system, either upon being sent or on return to the research team. In total 17 questionnaires from the cone group data were lost for this reason; a percentage of 1.05 % (372 questionnaires, 355 completed). Five questionnaires of the non-cone group also were not completed, a percentage of 1.03 % (192 of 197 questionnaires completed). It must be noted that due to this some data were gathered via the phone, these data were included in the "completed questionnaires" section, even though the participant did not manually fill in the questionnaire themselves.

9.5.1 BONE HEALTH QUESTIONNAIRE RESULTS

Table 9.1 below present the participants characteristics from the bone health questionnaire, at both pre-op and at six weeks, both results were included due to the drop out between pre-op and six weeks. Table 9.2 and table 9.3 reports the participants history of medical conditions and medications at pre-op (table 9.2) and at six weeks (table 9.3).

Table 9.1. *Participant's characteristics at pre-op and 6 weeks DXA scans*

Pre-op				6 weeks		
	Cone group (N=22)	**Non-cone group (N=13)**	**P-value**	**Cone group (N=18)**	**Non-cone group (N=8)**	**P-value**
Age mean (years) (SD)	69.82 (4.16)	71.00 (7.63)	0.94	69.56 (7.72)	70.88 (9.01)	0.73
weight (kg) (SD)	85.96 (17.32)	89.25 (21.51)	0.64	84.67 (16.68)	93.39 (26.02)	0.40
Height (m) (SD)	1.69 (0.10)	1.69 (0.11)	0.51	1.69 (0.09)	1.72 (0.10)	0.42
Body mass index (BMI) mean (SD)	29.82 (4.16)	31.19 (6.64)	0.67	29.34 (4.43)	30.86 (6.60)	0.57
Sex percentage male	59.09	61.54	-	55.56	75	-
Ethnicity percentage white	100	100	-	100	100	-
Alcohol consumption %						
Never	31.82	23.08	-	33.33	25	-
Less than weekly	27.27	0	-	22.22	0	-
1-5 units	13.64	46.15	-	16.67	50	-
6-10 units	13.64	23.08	-	11.11	25	-
11-15 units	0	0	-	0	0	-
16-20 units	4.55	0	-	5.56	0	-
more than 20 units	9.09	7.69	-	11.11	0	-
Caffeine consumption %						
None	13.64	0	-	16.67	0	-
1-5 cups/cans	63.64	61.54	-	66.67	37.5	-
6-10 cups/cans	22.73	38.46	-	16.67	62.5	-
11-15 cups/cans	0	0	-	0	0	-
More than 15 cups/cans	0	0	-	0	0	-
Previous fracture %	40.91	46.15	-	38.89	37.5	-
Falls in last year %	36.36	30.77	-	38.89	12.5	-
Previous orthopaedic surgery per participant on average	3.55	2.62	-	3.33	2.88	-
Average length in years since original TKR	13.67	12.23	-	13.94	12.50	-
% who had TKR on other side	50.00	30.77	0.27	61.11	37.50	0.27
Smoking %						
Ex-smoker	54.55	46.15	-	55.56	50	-
current smoker	0	7.69	-	0	12.5	-
Never smoked	45.45	46.15	-	44.44	37.5	-
Time spent exercising %						
None	9.09	23.08	-	5.56	25	-
Some but less than half an hour	40.91	23.08	-	44.44	25	-

Half to one hour	31.82	30.77	-	27.78	37.5	-
More than one hour	18.18	23.08	-	22.22	12.5	-

Table 9.2. *Participant's history of medical conditions and medications, at pre-op DXA P-values from Chi-square*

	Cone group (N=22)	Non-cone group (N=13)	P-value
Rheumatoid arthritis (%)	18.18	7.69	0.39
Average disease duration in years	15.75	7.00	-
Osteoarthritis (%)	59.09	46.15	0.46
Average disease duration	19.67	16.75	-
Ankylosing spondylitis (%)	0	0	-
Diabetes -type 1 – insulin dependent (%)	0	0	-
Diabetes – type 2 (%)	18.18	7.69	0.39
Overactive thyroid (%)	0	0	-
Underactive thyroid (%)	22.73	15.38	0.60
Breast cancer (%)	4.55	0	0.44
Other cancer (%)	0	7.69	0.20
Paget's disease of bone (%)	0	0	-
Liver disease (%)	0	0	-
Kidney disease (%)	4.55	7.69	0.70
Gastric surgery (%)	9.09	7.69	0.89
Lactose intolerance (milk allergy) (%)	0	0	-
Crohn's disease (%)	0	0	-
Coeliac disease (%)	0	0	-
Irritable bowel syndrome (%)	22.73	7.69	0.25
Malabsorption syndrome (%)	4.55	7.69	0.70
Osteomalacia (rickets) (%)	0	0	-
Osteogenesis Imperfecta (%)	0	0	-
Hypogonadism (%)	0	0	-
Chronic malnutrition / malabsorption (%)	0	0	-
Eating disorder e.g. anorexia nervosa (%)	0	0	-
Corticosteroids (%)	27.27	23.07	0.78
Anticonvulsants (%)	9.09	0	0.27
Diuretics (%)	4.55	15.38	0.27
Chemotherapy (%)	4.55	7.69	0.70
Immunosuppressive agents (%)	0	7.69	0.18
Heparin (%)	4.55	7.69	0.70
Thyroxine (%)	22.73	15.38	0.60
Fosamax (Alendronate) (%)	0	0	-
Actonel (Risidronate) (%)	4.55	0	0.44
Teriparatide (PTH) (%)	0	0	-
Protelos (Strontium Ranelate) (%)	0	0	-
Pamidronate (infusions) (%)	0	0	-
Zoledronate (injection) (%)	0	0	-
Ibandronate (%)	0	0	-
Arimidex (anastrozole) (%)	0	0	-
Androgen deprivation therapy (%)	0	0	-
Multivitamins (%)	9.09	0	0.26
Calcium (%)	13.64	7.69	0.59
Vitamin D medication (%)	13.64	0	0.16

Table 9.3. *Participant's history of medical conditions and medications, at six weeks, DXA P-values from Chi-square*

	Cone group (N=18)	Non-cone group (N=8)	P-value
Rheumatoid arthritis (%)	22.22	12.50	0.56
Average disease duration in years	15.75	7.00	-
Osteoarthritis (%)	61.11	25.00	0.09
Average disease duration in years	20.11	22.50	-
Ankylosing spondylitis (%)	0	0	-
Diabetes -type 1 – insulin dependent (%)	0	0	-
Diabetes – type 2 (%)	11.11	12.50	0.92
Overactive thyroid (%)	0	0	-
Underactive thyroid (%)	16.67	12.50	0.79
Breast cancer (%)	5.56	0	0.48
Other cancer (%)	0	0	-
Paget's disease of bone (%)	0	0	-
Liver disease (%)	0	0	-
Kidney disease (%)	5.56	12.50	0.54
Gastric surgery (%)	5.56	0	0.48
Lactose intolerance (milk allergy) (%)	0	0	-
Crohn's disease (%)	0	0	-
Coeliac disease (%)	0	0	-
Irritable bowel syndrome (%)	27.78	0	0.10
Malabsorption syndrome (%)	5.56	0	0.48
Osteomalacia (rickets) (%)	0	0	-
Osteogenesis Imperfecta (%)	0	0	-
Hypogonadism (%)	0	0	-
Chronic malnutrition / malabsorption (%)	0	0	-
Eating disorder e.g. anorexia nervosa (%)	0	0	-

	Cone group (N=18)	Non-cone group (N=8)	P-value
Corticosteroids (%)	27.78	25.00	0.88
Anticonvulsants (%)	11.11	0	0.33
Diuretics (%)	11.11	12.50	0.92
Chemotherapy (%)	11.11	0	0.33
Immunosuppressive agents (%)	0	0	-
Heparin (%)	11.11	0	0.33
Thyroxine (%)	16.67	12.50	0.79
Fosamax (Alendronate) (%)	0	0	-
Actonel (Risidronate) (%)	0	0	-
Teriparatide (PTH) (%)	0	0	-
Protelos (Strontium Ranelate) (%)	0	0	-
Pamidronate (infusions) (%)	0	0	-
Zoledronate (injection) (%)	0	0	-
Ibandronate (%)	0	0	-
Arimidex (anastrozole) (%)	0	0	-
Androgen deprivation therapy (%)	0	0	-
Multivitamins (%)	11.11	0	0.33
Calcium (%)	11.11	12.50	0.92
Vitamin D medication (%)	16.67	0	0.22

Table 9.1 and 9.2 show the original pre-op bone health questionnaire results gathered prior to their DXA scan (35 participants). Compared between groups they share several homogeneous qualities, for instance: height (average of 1.69 m for both), age (reported as 69.82 and 71 years), BMI (29.82 and 31.19), and with no statistically significant between the two groups for characteristics or medical conditions.

Table 9.1 and 9.3 report the bone questionnaire results of the 26 participants who underwent the six DXA week scan, these results are a more accurate reflection upon the participants involved in the study as they do not include the ones who were withdrawn after pre-op, these six weeks results also are useful for the knee BMD comparison data which utilised six week scans as baselines. These six week results are similar again to the pre-op, and there are no statistically significant differences between the groups, although with the smaller sample sizes they are more prominent; the non-cone group is made up of 75 % male participants (six out eight) whilst the cone group is 55.56 % (10 out of 18), more of the cone group have had a fall in the last year, and difference in weight between groups shows that the non-cone group is nearly nine kg heavier (although with similar BMI due to the non-cone group being taller on average). All participants were white and from the south west area representing the type of participants undergoing a rTKR in the Exeter area.

There is one medical condition that shows some difference between the groups (but is not statistically significant), the medical condition osteoarthritis with 61.11 % (11 out of 18 had the disease for an average of 20.11 years) and 25 % (two out of eight had the disease for an average of 22.50 years) in the non-cone group. It must be noted for RA in the cone group it was reported as 22 % (four out of 18) who on average had the disease for 15.75 years, and for the non-cone group was 12.5 % (one out of eight) who had had the disease for seven years.

Regarding participants who previously underwent a TKR, 61.11 % of cone participants had previously had a TKR on their contralateral knee, with this occurring in 37.50 % in the non-cone group, with a reported p-value of 0.27 when comparing the two groups.

BONE HEALTH QUESTIONNAIRE CHANGES REPORTED BETWEEN VISITS

Participants were asked at each following visit if there were any changes in their bone health questionnaire answers since the pre-op. Therefore, questions regarding additional orthopaedic surgery, any changes in medication or supplements, any fractured bones, and any falls were recorded.

During the 12 months one participant believed they fractured their toe (no treatment was administered); otherwise no other participants sustained any fractures. Four participants underwent orthopaedic surgery (one for an aspiration of their knee, one as a joint replacement in their right hand, one had a TKR in their contralateral knee and one had a rTKR in their contralateral knee - resulting in the 12 month contralateral knee data not being included of those two participants). There were also no medication changes reported throughout the study that potentially influenced the BMD as selected within the bone health questionnaire.

Regarding falls, at six weeks two cone participants reported three falls in total (two falls from one participant), in the non-cone group one participant reported one fall. At three months a total of four cone participants reported five falls (one participant reported two falls); with the non-cone group this was reported as two falls from two participants. At six months there were a reported five falls from four participants in the cone group, and five falls from one participant in the non-cone group (this participant was discovered to have an infection prior to their 12 month scan and was withdrawn after six months). At 12 months the cone group reported five falls from four participants, in the non-cone group there were two falls (one participant).

9.5.2 LEFS QUESTIONNAIRE RESULTS

At pre-op 35 participants completed the LEFS questionnaire, of those 35, 28 completed at least one follow up LEFS questionnaire. Therefore those seven who did not complete any questionnaire data post-op were withdrawn from the analysis due to lacking comparison data (as stated previously these participants were mainly due to surgical reasons for their withdrawal post-surgery).

The data recorded both the absolute mean scores, and more importantly the mean changes between pre-op and post-op visits, with the latter being used for comparison t-test data (both paired for pre-op comparison data, and t-test assuming unequal variance between groups), to compare both to the baseline and between the two groups to investigate statistical significance, with the LEFS form stating that the minimal level of detectable change was 9 +/- points for 90 % confidence. Please note the maximum score that could be reported with LEFS was 80.

At pre-op the mean cone group score was 30 (SD 14.67, N=18) with a non-cone group score of 25 (SD 12.17, N= 10), at six weeks the mean cone group score was 34.06 (SD 15.81, N =18) with the non-cone group reporting a score of 33.20 (SD 16.21, N=10). At three months the score was 42.39 (SD 16.00, N=18) for the cone group and 39.10 (SD 17.37, N=10) for the non-cone group. At six months the cone group reported a score of 48.29 SD 17.47, N=17) the non-cone group score was 41.10 (SD 17.37, N=10), finally at 12 months the cone group score was reported as 45.47 (SD 19.81, N=17), with the non-cone group reported as 47.38 (SD 15.66, N=8).

The results are shown in figure 9.1 and table 9.4 which state the difference between visits (six weeks, three months, six months or 12 months) compared to each participants original pre-op score, alongside a final comparison between groups.

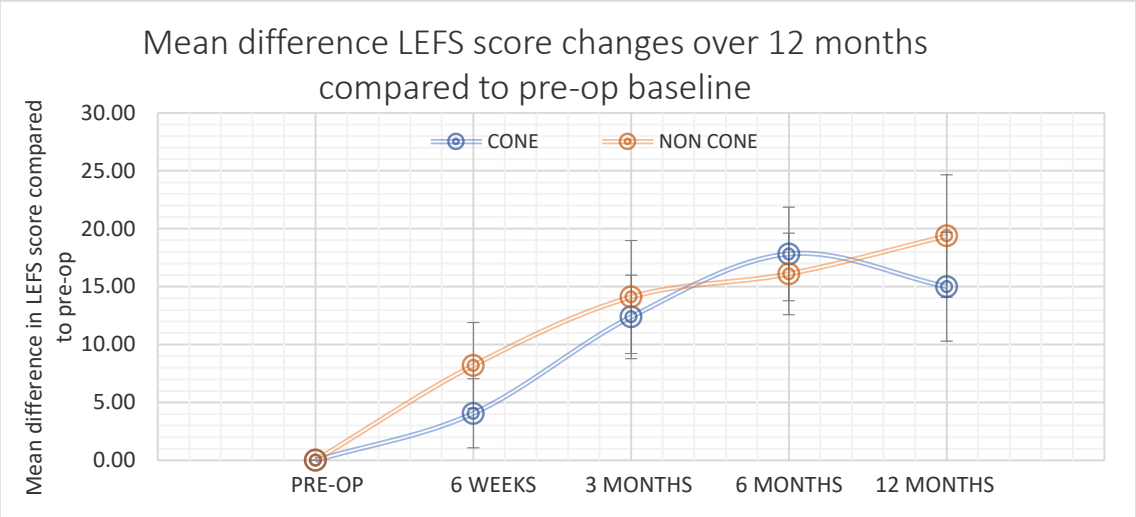


Figure 9.1. *LEFS mean changes throughout the visits for cone and non-cone data (error bars are SE)*

Table 9.4. *Shows the results expressed in figure 9.1, and also the comparison data between the two groups.*

	BASELINE	6 WEEK POST	3 MONTH POST	6 MONTH POST	12 MONTH POST
CONE MEAN SCORE DIFFERENCE	0.00	4.06	12.39	17.82	15.00
CONE SE	0.00	2.98	3.61	4.05	4.70
CONE SD	0.00	12.66	15.34	16.68	19.36
P-VALUE	-	0.19	**0.003**	**0.001**	**0.002**
NON CONE MEAN SCORE DIFFERENCE	0.00	8.20	14.10	16.10	19.38
NON CONE SE	0.00	3.70	4.88	3.53	5.27
NON CONE SD	0.00	11.69	15.42	11.16	14.91
P-VALUE	-	**0.05**	**0.017**	**0.001**	**0.004**
MEAN DIFFERENCE CONE VS NON-CONE	-	-4.14	-1.71	1.72	-4.38
P-VALUE	-	0.39	0.78	0.75	0.54

Data from figure 9.1 and table 9.4 show large differences between their pre-op scores and post-op throughout, with a gradual increase throughout the visits until six months which demonstrates the greatest mean improvement in the cone group, reporting an increase of 17.82 (16.10 in the non-cone group), at 12 months the non-cone group is highest reported as 19.10. Nearly all comparisons to pre-op data points showed statistical significance (only the cone six week data was not significant). Comparisons between the groups showed

no statistical significance, with both groups reporting similar improvements to their pre-op scores, with the non-cone group reporting the higher figure.

9.5.3 HADS QUESTIONNAIRE RESULTS

Similar to the LEFS questionnaire, participant data that only included pre-op with no further visits were excluded in the analysis, this was due to the lack of comparison data between visits. For these results the HADS questionnaire data were divided into its two sub sections of anxiety and depression scores, with a paired samples t-test used for the comparisons to pre-op and a t-test of unequal variance used for comparisons between groups.

ANXIETY RESULTS

A participant can score a maximum of 21 for anxiety, with a higher score relating to a more anxious participant.

The mean anxiety score overall was at its highest at pre-op in the cone group with a score of 5.53 (SD 4.59 N=19), at six weeks the reported mean was 4.83 (SD 3.62 N=18), at three months demonstrated as a mean of 3.78 (SD 3.96 N=18), at six months this is demonstrated as 3.13 (SD 3.98 N=16), at 12 months it is reported as 4.47 (SD 4.03 N=17). For the non-cone group, the mean pre-op score was 6.10 (SD 3.38 N=10), at six weeks it was 4.90 (SD 2.69 N=10) and at three months it was reported as 6.89 (SD 5.40 N=9), at six months it was 5.8 (SD 3.39 N=10) and finally at 12 months it was reported as 5.44 (SD 2.83 N=9).

The results shown in figure 9.2 and table 9.5 show the mean difference between the visits (six weeks, three months, six months or 12 months) and the pre-op score, alongside a paired t-test p-value.

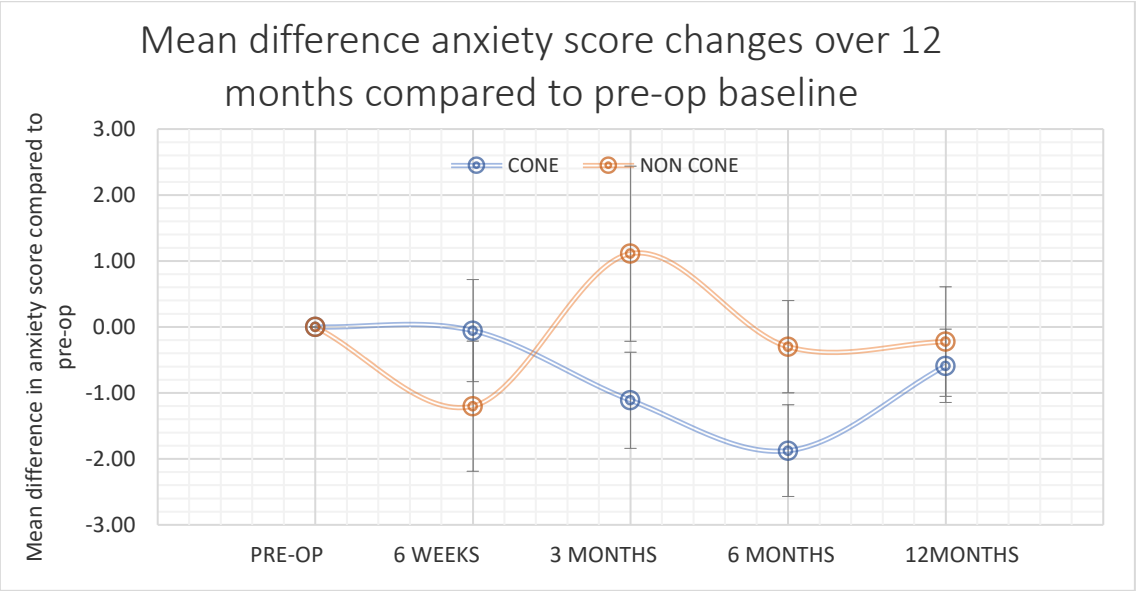


Figure 9.2. *Shows the anxiety mean score changes post-surgery for cone and non-cone data (error bars are SE)*

Table 9.5. *Shows the anxiety score data from figure 9.2 but with the inclusion of p-value comparison data.*

	BASELINE	6 WEEK POST	3 MONTH POST	6 MONTH POST	12 MONTH POST
CONE MEAN SCORE DIFFERENCE	0.00	-0.06	-1.11	-1.88	-0.59
CONE SE	0.00	0.74	0.74	0.71	0.56
CONE SD	0.00	3.13	3.16	2.85	2.29
P-VALUE	-	0.94	0.15	**0.02**	0.31
NON CONE MEAN SCORE DIFFERENCE	0.00	-1.20	1.11	-0.30	-0.22
NON CONE SE	0.00	1.07	1.33	0.70	0.83
NON CONE SD	0.00	3.38	3.98	2.21	2.49
P-VALUE	-	0.25	0.43	0.68	0.80
MEAN DIFFERENCE CONE VS NON-CONE	-	1.14	-2.22	-1.58	0.24
P-VALUE	-	0.36	0.17	0.18	0.72

Data from figure 9.2 and table 9.5 show reductions in mean anxiety for both groups, interestingly the cone group has a gradual reduction in anxiety throughout the first three visits, with the greatest difference reported at six months with a mean of -1.88, at 12 months this difference has been reduced. The non-cone group shows a slightly different change, with the greatest difference reported at six weeks post-op, reporting a mean of -1.20, and at six months participants average anxiety has actually increased by 1.11, although

by six months there is a reduction again, similarly at 12 months. When comparing both groups together there is no statistical significance.

DEPRESSION RESULTS

A participant can score a maximum of 21 for depression, with a higher score relating to a more depressed participant.

Mean depression scores were at their highest pre-op in the cone group with a score of 6.89 (SD 4.74 N=19), at six weeks as a mean of 4.89 (SD 3.77 N=18), at 3 months as a mean of 4.28 (SD 3.63 N=18), at six months as 4.13 SD (4.03 N=16), at 12 months it is reported as 5.41 (SD 5.48 N=17). For the non-cone group, the mean pre-op score was 6.20 (SD 3.33 N=10), at six weeks it was 4.8 (SD 3.12 N=10) and at three months it was reported as 6.33 (SD 5.83 N=9), at six months it was 6.30 (SD 38 N=10) and finally at 12 months it was reported as 5.67 (SD 4.18 N=9).

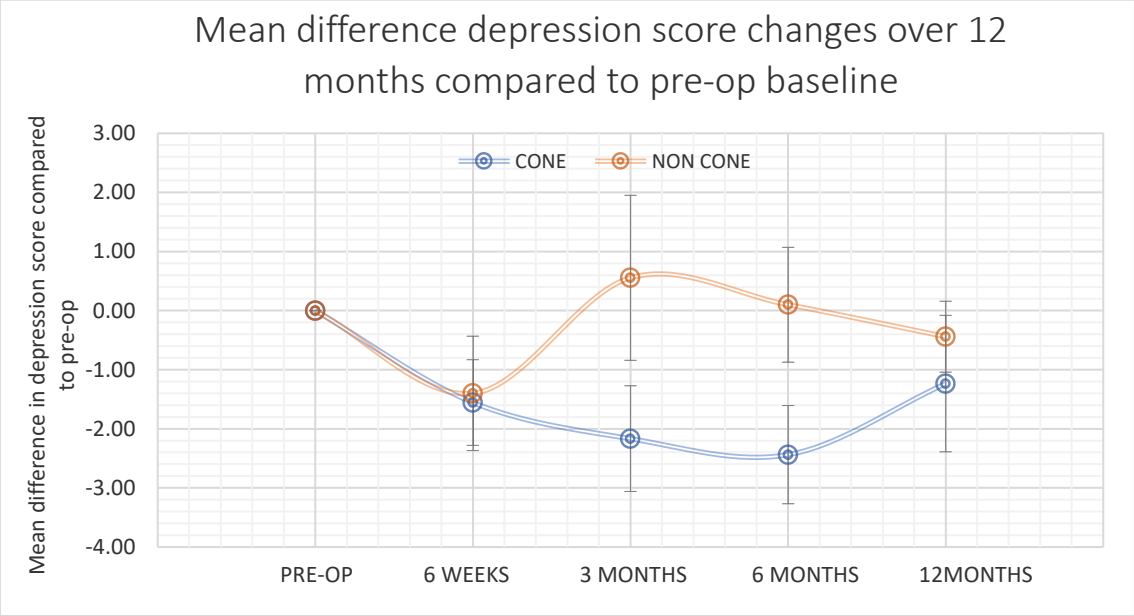


Figure 9.3. *Shows the depression mean score changes post-surgery for cone and non-cone data (error bars are SE)*

Table 9.6. *Shows the depression score data from figure 9.3 but with the inclusion of p-value comparison data.*

	BASELINE	6 WEEK POST	3 MONTH POST	6 MONTH POST	12 MONTH POST
CONE MEAN SCORE DIFFERENCE	0.00	-1.56	-2.17	-2.44	-1.24
CONE SE	0.00	0.72	0.89	0.83	1.16
CONE SD	0.00	3.07	3.79	3.33	4.76
P-VALUE	-	**0.046**	**0.026**	**0.01**	0.30
NON CONE MEAN SCORE DIFFERENCE	0.00	-1.40	0.56	0.10	-0.44
NON CONE SE	0.00	0.97	1.40	0.97	0.60
NON CONE SD	0.00	3.06	4.19	3.07	1.81
P-VALUE	-	0.18	0.70	0.92	0.48
MEAN DIFFERENCE CONE VS NON-CONE	-	-0.16	-2.73	-2.54	-1.68
P-VALUE	-	0.90	0.12	0.06	0.55

The depression mean numbers shown in figure 9.3 and table 9.6 report a reduction in depression for the cone group throughout the visits with gradual reduction in depression until reaching its lowest at six months (-2.44), with all these results being statistically significant with a p-value of 0.01. The non-cone group has a reduction in depression at six weeks (-1.40) but then starts to increase at three and six months, finally reporting a mean difference score of -1.68 at 12 months, although none of these data are statistically significant.

Comparing the two groups together there was no statistically significance, although the six month data are close, reporting a p-value of 0.06, due to the high loss in the cone group and the increase in the non-cone group.

9.5.4 EQ-5D-3L QOL RESULTS

Quality of life was scored by the participant between 0 and 100 (100 being the highest possible quality of life and 0 being the lowest).

Mean QOL scores were at their lowest pre-op in the cone group with a score of 63.87 (SD 25.05 N=19), at six weeks as a mean of 71.32 (SD 17.19 N=17), at three months as a mean of 73.94 (SD 19.57 N=17), at six months as 75.00 (SD

19.61 N=16), at 12 months as 71.56 (SD 18.93 N=18). For the non-cone group, the mean pre-op score was reported at its lowest with a score of 52.50 (SD 29.46 N=10), at six weeks it was 65.20 (SD 25.65 N=10) and at three months it was reported as 69.06 (SD 25.89 N=9), at six months it was 66.20 (SD 24.63 N=10) and finally at 12 months it was reported as 73.11 (SD 17.84 N=9).

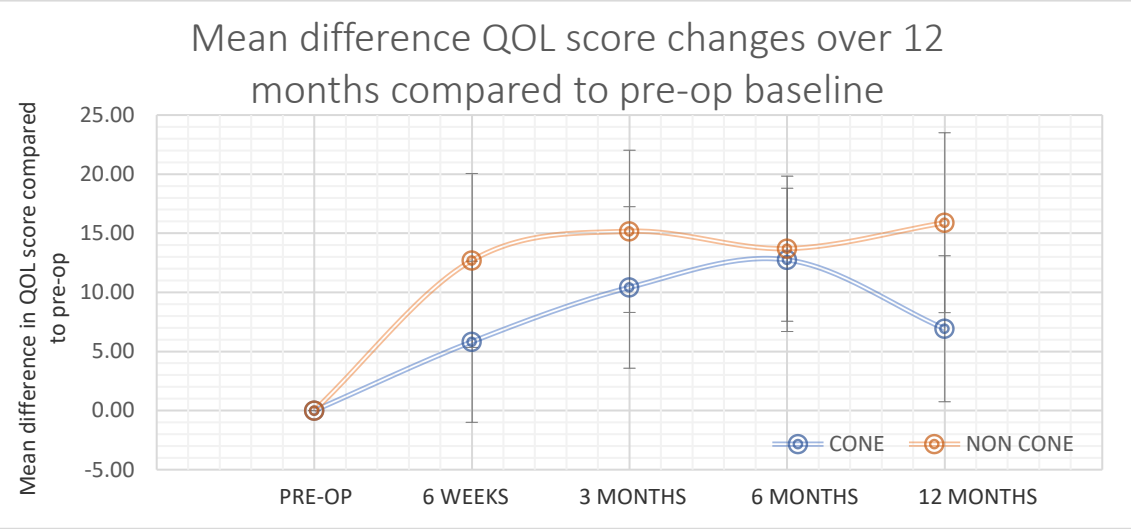


Figure 9.4. *QOL mean score changes for cone and non-cone data (error bars are SE)*

Table 9.7. *Shows the depression score data from figure 9.4 but with the inclusion of p-value comparison data.*

	BASELINE	6 WEEK POST	3 MONTH POST	6 MONTH POST	12 MONTH POST
CONE MEAN SCORE DIFFERENCE	0.00	5.82	10.42	12.75	6.92
CONE SE	0.00	5.75	6.82	6.06	6.18
CONE SD	0.00	28.10	28.96	24.25	26.21
P-VALUE	-	0.41	0.15	**0.05**	0.28
NON CONE MEAN SCORE DIFFERENCE	0.00	12.70	15.17	13.70	15.89
NON CONE SE	0.00	7.36	6.86	6.14	7.61
NON CONE SD	0.00	23.27	20.59	19.41	22.82
P-VALUE	-	0.12	0.06	**0.05**	0.07
MEAN DIFFERENCE CONE VS NON-CONE	-	-6.88	-4.75	-0.95	-8.97
P-VALUE	-	0.50	0.63	0.91	0.37

The EQ5D3L QOL mean value in figure 9.4 table 9.7 reported an increase for the cone group throughout the visits with a gradual increase until reaching its highest difference at six months (12.75), with this six month figure reporting a p-value 0.05, this figure was then reported as an increase of 6.92 at 12 months. Similarly the non-cone group has an increase across all visits, reporting higher figures than the cone group, with the six month figure also being statistically significant (13.70) and the final 12 month figure (15.89) being the highest difference reported throughout all visits, although not statistically significant (p-value 0.07).

Comparing the differences between cone and non-cone, both groups show increases, although at six weeks the score is a difference of -6.88 in support of the non-cone group, and at three months the difference is -4.75, and at six months of -0.95, and at 12 months was -8.97. Although there was no significant difference between the two groups.

9.5.5 OKS QUESTIONNAIRE RESULTS

As with all previous questionnaire results, only the data which had at least one post-op OKS questionnaire result were included. This questionnaire consisted of a series of 12 questions about issues and pain within their knee, resulting in a total score, with a lower total score being related to more severe function and pain issues within the knee.

Mean OKS scores were at their lowest pre-op in the cone group with a score of 20.42 (SD 9.70 N=19), at six weeks as a mean of 22.79 (SD 8.30 N=19), at three months as a mean of 29.33 (SD 11.16 N=18) at six months this is reported as 34.94 (SD 8.23 N=16), at 12 months as 31.17 (SD 11.37 N=18). For the non-cone group, the mean pre-op score was also at its lowest with a score of 17.70 (SD 6.09 N=10), at six weeks it was 24.10 (SD 10.15 N=10) and at three months it was reported as 27.33 (SD 11.69 N=9), at six months it was 30.30 (SD 11.46 N=10) and finally at 12 months it was reported as 34.89 (SD 11.73 N=9).

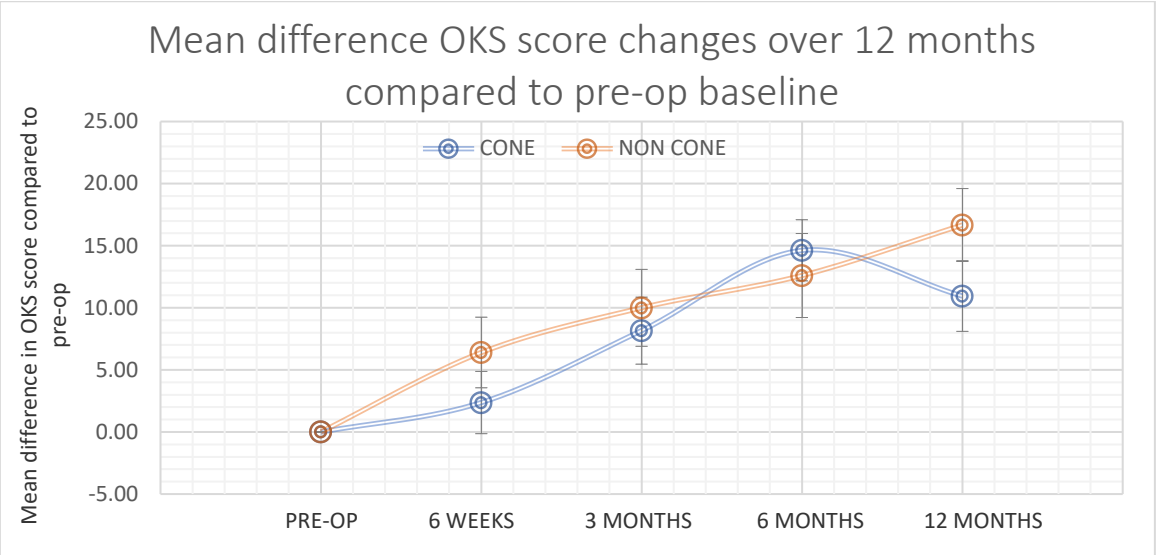


Figure 9.5. *OKS mean score changes for cone and non-cone data (error bars are SE)*

Table 9.8. *Shows the OKS data from figure 9.5 but with the inclusion of p-value comparison data.*

	BASELINE	6 WEEK POST	3 MONTH POST	6 MONTH POST	12 MONTH POST
CONE MEAN SCORE DIFFERENCE	0.00	2.37	8.17	14.63	10.94
CONE SE	0.00	2.51	2.70	2.46	2.84
CONE SD	0.00	10.94	11.44	9.85	12.05
P-VALUE	-	0.36	**0.01**	**0.00**	**0.00**
NON CONE MEAN SCORE DIFFERENCE	0.00	6.40	10.00	12.6	16.67
NON CONE SE	0.00	2.85	3.10	3.38	2.93
NON CONE SD	0.00	9.01	9.29	10.70	8.80
P-VALUE	-	**0.05**	**0.01**	**0.00**	**0.00**
MEAN DIFFERENCE CONE VS NON-CONE	-	-4.03	-1.83	2.03	-5.73
P-VALUE	-	0.30	0.66	0.63	0.18

Figure 9.5 and table 9.8 show similar trends with increases in the OKS throughout the visits, with both groups reporting a statistical significant change, the highest difference in the cone group was reported at six months of 14.63 (p-value 0.00), with the non-cone data reporting a mean difference of 16.67 at 12 months.

When compared together both groups show no statistical significance, so although both show a statistical gradual improvement in the OKS, there is no statistical difference between the two groups.

9.6 DISCUSSION OF QUESTIONNAIRE DATA

9.6.1 BONE HEALTH QUESTIONNAIRE

Both groups showed similar characteristics but with no statistically significant differences that would influence the data. One important piece of data were reported at six weeks with 11 out of 18 participants (61 %) in the cone group reporting OA, with the non-cone group reporting only 25 % (two out of eight participants), when compared, these figures were reported as a p-value of 0.09 (six weeks). Although it must be acknowledged that the participants stated if they had been diagnosed with OA, and no check to corroborate or contradict that information was addressed, therefore the reported OA disparity between the groups may be due to miscategorising the disease or being unaware of the condition (possibly stating RA instead). This is supported by the literature that reports OA as the primary cause of TKR in 80-90 % of cases [125, 126, 127, 128]. Additionally, this difference might simply be due to the small sample size.

It must be also be noted that RA was reported by 22 % (four out of 18) in the cone group, and 12.5 % (one out of eight) in the non-cone group. Although this difference like with OA was not statistically significant between the two groups. Furthermore, due to the true randomisation of the study, and the limited numbers between the groups these sections were not further subdivided. Although it must be noted that unlike OAs association with increase BMD, RA has associated bone loss with the disease [465], and that the severity of either OA or RA could influence the results, this severity was also not recorded.

An issue with this self-reporting in this study was that we had no access to the patients' medical records, and like the patient's disease history their prescriptions were also self-reported, therefore it is likely medication and disease histories are incomplete and this could be reason for variations presented in the data

9.6.2 LEFS QUESTIONNAIRE

Both groups showed improvements throughout the visits reaching a height at six months, with a change in excess of the nine point difference required for a 90 % confidence level, with the six month figure reported as an increase of 17.82 (cone group) and 16.10 (non-group), both statistically significant figures. At 12 months the cone group reported a 15 point increase, and the non-cone group a 19.38 increase (again both statistically significant). When the groups were compared against each other, there was no reported statistically significant difference, with the lowest p-value reported as 0.39.

The trend reported in both groups is similar in the Hopkins et al study [23] that reported a LEFS baseline score of 30, at six weeks 33, six months of 51 and 12 months 52.

Another study investigated TKA and also showed an increased LEFS score trend, with the greatest improvement at three months, with little improvement beyond the six month visit [466]. Although, these two studies investigated TKR and TKA, and not revisions. Studies dealing with cone implants in revisions have been investigated with these utilising similar robust rating systems regarding functionality. These studies reported increased scores in functionality the cone group (37 to 73 for cone compared to 24 to 58 in non-cone [178], and 52 to 85 in another study [467] (a higher number means greater functionality). This increase in functionality would parallel the data in our study, of increased functionality post-surgery.

Results of the LEFS questionnaire show that rTKR are successful and helpful in regaining mobility and functionality in the lower extremity, with both groups reporting statistically significant changes between visits. But it is unclear of the positive impact that cones have on these figures, as these trends are also seen in the non-group, and as stated there is no statistical significance between the two groups.

9.6.3 HADS QUESTIONNAIRE

ANXIETY

The cone group anxiety score decreased at each visit, and significantly at six months (a loss of 1.88 reporting a p-value 0.02) reporting a reduction in anxiety amongst this cohort. The non-cone group reports a slightly different trend, with an increase in anxiety by three months and their highest reduction being at six weeks (both with non-statistical significance).

Comparing the two groups, at six weeks both show a reduction, although at three months the cone value is -1.11 with non-cone 1.11 (a p-value of 0.17 when compared), at six months this difference is -1.88 cone and -0.3 non-cone (p-value 0.18), at 12 months both show a loss, but It must be noted there is no statistical difference between the groups across all visits.

The trend in both groups of a reduction in anxiety matches the pattern reported in the TKR literature [466, 468] with one study reporting a decline of 10.48 pre-op to 2.36 at three months. Although this difference is less dramatic in the rTKR group, with the TKR participants reporting a higher starting anxiety score (5.53 and 6.10 in this research, compared to 10.48 in the TKR study), this might be due to participants undergoing a revision and not a replacement, with those undergoing replacements reported as experiencing high levels of anxiety before surgery because of the possibility of surgery-related complications or death [469] as the revision group has experienced a TKR so may have allayed such fears.

Additionally, it must be acknowledged that the mean pre-op anxiety score was 6.10 in the non-cone group, and 5.56 in the cone group, meaning the starting score should not have influenced the change i.e. if the cone group had a score of 20 it would be easier to reduce this figure, yet both scores were similar.

Results of the HADS report both groups have a reduction in anxiety post-surgery, with the cone group more prominent (with one figure significant at six months); although at 12 months both groups report a similar reduction.

DEPRESSION

The depression score parallels the anxiety score both with decreases throughout, reaching its lowest at six months in the cone group (-2.44), with each figure showing statistical significance except 12 months. The non-cone group reports decreases only at six weeks and 12 months (although none of the figures are statistically significant).

There is also no statistical significance between groups in the depression results, although at six months the p-value is 0.06 with a reduction of depression in the cone group reported as -2.44, compared to the increase in depression of 0.10 reported by the non-cone group. Additionally, just like with the anxiety score data the pre-op mean figures are also similar between the two groups – although again the small sample size of nine (who completed 12 months) in the non-cone group cannot be ignored.

This reduction is similar to reported data, with a study by Shalaby et al who showed that at three months post-op the reported scores went from 9.60 to 4.72 [466]. Other studies investigating HADS in TKA showed a mean reduction at six months and 12 months; reporting a reduction of -1.16 and -1.08 [470] respectively, a further study also supports this decrease in depression rates at six weeks and 12 months [468].

The results from the depression scores show rTKR can reduce post-op depression scores, although the cone group is more prominent across all visits, the non-cone group does report reductions at six weeks and 12 months. Although it is unknown if these changes are due to a greater sample size in the cone group, or the possible influences of the cone increasing confidence in the joint and thus reducing depression.

These anxiety and depression changes are especially important given their association with heightened pain in TKR [471, 472]. A systematic review investigating anxiety, depression, and knee pain, reported that depression has a significant impact in knee pain [473]. If participants are in less pain they might be more active, which in itself might lower their anxiety and depression further [474, 475]. Although it must be noted no pedometer readings were gathered

during this study, and although the physiotherapy protocols were the same for each participant, it was not recorded if these sessions were undertaken by all participants.

Additionally, studies by Blalock et al and Hauser et al have shown there is an association between joint instability and pain [476, 477], thus the cone fixation or the knee revision itself might be increasing stabilisation of the knee joint leading to less pain, resulting in less anxiety and depression about the joint. This stabilisation is especially important as in a systematic review of TKA and balance, they reported that proprioception and knee extension strength have not fully recovered post-TKA and directly influence balance performance for up to one year post-surgery [478].

These differences might be due to the small sample size who completed 12 months; nine (non-cone) and 16 (cone), which is also reflective in the SD scores, and the lack of significant difference between the groups.

9.6.4 EQ-5D-3L QOL QUESTIONNAIRE

In the quality of life data, the results show a gradual increase over all visits, with two statistical significant results in both group reported at six months, with the cone group reporting an increase of 12.75, and 13.70 for the non-cone. For the 12 month data there is an increase in the non-cone group to 15.89 and an increase of 6.92 in the cone group.

Comparing the two groups, there is no statistical significance. Although both groups showed statistical significance when compared to baseline. This change in quality of life is supported by other studies, with a systematic review investigating quality of life (QOL), showed that patients who underwent TKA improved in their QOL [424]. Although, some data show that 30 % of participants are still unsatisfied after their knee replacement [479].

In this case the results show that it can be concluded that quality of life improves post knee revision, although the impact of cone implantation on quality of life is difficult to discern.

9.6.5 OKS QUESTIONNAIRE

Both the cone and non-cone group show statistically significant improvements at each visit, reaching the largest difference at six months for the cone group reported as an increase of 14.63, for the non-cone it was an increase of 16.67 at 12 months.

The difference between the groups was not statistically significant, but both show an increase in the OKS with statistically significant results, with results of the OKS questionnaire showing that rTKR are successful and helpful in regaining joint functionality, this is supported by the research that shows increases of between 14.5 and 22 points six months post TKR [480, 481, 482, 483], as well as reporting similar starting OKS pre-op [481]. This is further supported by revision research that reported a pre-op score of 20.1 and a post-op score of 30.2 [484]. There is no statistical difference between the two groups, so it is unclear of the impact that cones have on these figures, as these trends are also seen in the non-group. Additionally, it must be noted there have been cone studies utilising similar questionnaires reporting similar functionality improvements and reduced pain post-op [216, 218, 221, 437].

9.7 LIMITATIONS OF STUDY

As previously stated, the sample size was small due to attrition, recruitment issues and COVID-19, which most likely impact the statistical significance of certain groups. Additionally, due to the repeated measures of statistical tests via the questionnaire comparison data, this increases the likelihood of type one errors. Therefore, interpretation of any statistical significant results should be treated with caution.

Moreover, it must be stated that there were pieces of missing data; this was due to several reasons. Firstly, some participants could not attend their appointments, but they still completed the questionnaires, as these were sent via the post. Although small the compliance of those who failed to return their questionnaire data could have been followed up or an electronic option provided, although it must be noted the average age was 70 and some of these participants did not have phones or email contacts.

Additionally, it was recorded that all participants in the study were white, and all from the south west area, this limited generalisability of the study, it must be noted that as black women have a reported higher BMD, these results cannot be generalised to other ethnicities or demographics [98]. Furthermore, it must be stated this was not due to exclusion, but simply a reflection upon the demographics of the recruitment area available.

All questionnaires were based on self-administration which might reflect the issues discussed regarding the reported OA diagnosis, access to the patients' medical records could have addressed this issue or directly comparing medications to medical conditions. Although misinformation due to self-administration on the questionnaire regarding their medication would not be helped by the NHS database. Moreover, participants may have been subject to demand characteristics, although participants were blinded to the type of implant they received, and the data demonstrated does align with reported literature.

9.8 CONCLUSION

The trends show reductions in depression and anxiety scores, with statistical significance reported in the depression data between the cone group and baseline figures, the non-cone group does show some reduction in depression but not statistically significant. Furthermore, there is only one statistically significant figure in the anxiety data, again in the cone group reporting a reduction. This is especially important given the association of depression and anxiety with heightened pain [471,472].

There were also well reported improvement in functionality and quality of life via both groups, with these results paralleling other replacement and arthroplasty studies, including previous cone studies [178, 467].

Although as stated the small sample size, large SD, and missing data make it difficult to discern differences between the two groups. It can be concluded that the cone group is not negatively impacting the questionnaire results, and is statistically improving both anxiety and depression scores, which the non-cone

group does not report, although as stated there is no statistical difference between groups.

In conclusion there is minimal difference between the groups, with both showing strong improvements in anxiety, depression, functionality and quality of life scores of those who undergo rTKR.

9.9 FUTURE WORK

Although the participants were randomised, and those who suffered with RA and OA were equally distributed within the two groups. For the full trial with a larger cohort, the BMD scores of the RA patients could be separated and analysed independently, severity could also be recorded. Additionally, the use of electronic questionnaires for those who are unable to complete or return them might help compliance, as might follow up phone calls, which were used in some instances. If possible, access to the medical records of the participants could also be introduced to address the issues of errors in the self-reported bone health questionnaire data, or at least checking the stated medications against NHS medicines databases and cross referencing the medication with the medical condition.

CHAPTER 10 SUMMARY OF RESULTS, CONCLUSIONS AND RECOMMENDATIONS

The aim of this study was to investigate and develop different imaging methods and analysis, and investigate the impact of cone implantation in rTKR patients, in order to quantify BMD change and alignment, and to monitor recovery over a 12 month period. This study involved recruiting participants and randomly assigning them to one of two groups; a cone group who received the implant, and the non-cone group (control), who received the standard revision.

Bone mineral density changes were assessed from baseline against subsequent visits over a 12 month period, this involved utilising and adapting DXA imaging of the total body, lumbar spine, bilateral hips and bilateral knees.

X-ray imaging was utilised and developed to investigate pixel density changes on long leg knee x-rays throughout the visits, additionally alignment angulation was also explored using x-ray imaging. Factors of depression, anxiety, function, quality of life, pain, treatments, health perceptions and mental wellbeing, that could potentially contribute to bone changes and recovery, were also investigated via questionnaire data.

The primary goal was to provide information relating to imaging for cone implantation, and its impact on BMD in and around the implant. This feasibility study helped develop and adapt different imaging methods, in order that recommendations could be brought forward into a full clinical trial. Furthermore, using these methods within this feasibility study, cone implantation could be investigated, with impacts regarding mitigating bone loss, and improving physical and functional recovery. In order to achieve these aims, a number of techniques were employed utilising questionnaires and imaging, with these results discussed and assessed chapters three, four, five, six, seven, eight, and nine.

10.1 RESULTS – CHAPTER 3 THE BOVINE MODEL

The results from this study are less important than the subsequent chapters, the primary reason for this chapter was to address and develop the imaging

methodology, in order to feed this information into the feasibility study. This raised and addressed several important issues such as region selection and pixel standardisation. Region selection in defining BMD and the importance of having lateral knee DXA images as well as PA to address BMD change due to anatomy being superimposed on the image. Pixel standardisation was also required moving forward, as the x-ray imaging required an object of known density for standardisation, in order to define pixel density change to determine in growth in and around the cone implant.

10.2 RESULTS – CHAPTER 4 3D SHAPE MODELLING

This chapter investigated an alternative method to standard imaging, including providing more depth analysis of the DXA imaging via 3D SHAPER modelling software.

10.2.1 CONTROL GROUP 3D-SHAPER RESULTS

For all control data there was minimal reported changes throughout for both the baseline and contralateral data, with some minimal changes reported as plausible natural bone changes. Although there was a statistically significant change at six months in the CSMI in the intertrochanteric ipsilateral hip region, this was matched in the contralateral hip, resulting in similar changes when compared. These control results reflected what we would expect to see in the control group supporting the idea that the software was accurate.

10.2.2 RTKR GROUP 3D-SHAPER RESULTS

In the rTKR group the cortical sBMD loss compared to baseline, got worse at six weeks and then started to recover at three months, but this loss continued at six and 12 months. In the trabecular vBMD recovery was seen immediately post-surgery within the rTKR group in the ipsilateral hip which continued throughout reaching an increase by 12 months. The integral vBMD showed a similar pattern in both baseline and comparison data and this was reflected in the combination of trabecular and cortical bone patterns.

For the rTKR there was a similar trend for CSA and CSMI in the neck, reported as an increase at six weeks (in comparison to the pre-op), and then a

continuing loss at 12 months, this trend was seen in both the baseline and comparison data. The rTKR group for the intertrochanteric data again showed a similar trend to the TKR group for the intertrochanteric CSA and CSMI data, reporting a loss throughout, although there was no increase at 12 months compared to six months.

The data demonstrated in the trabecular vBMD showed the impact of the higher turnover of trabecular bone, this was reflected within the subset rTKR group of the cone participants (of which these data are based), who reported increases in the wards triangle and femoral neck in the BMD cone data, both regions with a high concentration of trabecular bone. This was further supported by the cortical sBMD data that reported losses throughout all visits, this again was reflected in the BMD overall hip data, and the integral vBMD was a combination of these, unfortunately the CSMI and CSA were not recorded for this study so the changes cannot be compared.

10.2.3 TKR GROUP RESULTS

The TKR showed a similar trend to the rTKR group but without the recovery, and both groups end up on a similar sBMD cortical loss by 12 months in both the baseline and comparator data.

The trabecular vBMD in the TKR group reports post-surgery decline but showed some recovery between six and 12 months. As with the rTKR data the integral vBMD reports similar patterns in both baseline and comparison data. In the TKR group in the CSA and CSMI neck region it was reported as a loss at six weeks, and an increase at 12 months when compared to the six months score. In the intertrochanteric ipsilateral baseline data for CSA and CSMI, the TKR group showed a loss throughout, but by 12 months there is an increase when compared to the six month data, again this is shown in the baseline and comparison data.

Overall, both groups show cortical loss, adding weight to the cortical thinning issues and increase fracture risk reported [384, 386], and the loss of trabecular vBMD in the TKR group data also indicate increased fracture risk [387]. Moreover, the software's ability to be applied to hip DXA imaging showed

promise; this was reflected in the control participant's results showing minimal changes throughout. This was also supported by the trabecular vBMD data from the TKR group data agreeing with the reported BMD loss, as reported in the systematic review. The rTKR group data also supported this by reporting similar trends in hip BMD changes, and the CSA and CSMI data showing similar trends, due to their correlation in the femoral strength index.

10.3 RESULTS – CHAPTER 5 DXA IMAGING, ANALYSIS OF THE TOTAL BODY, LUMBAR SPINE AND BILATERAL HIPS

This chapter investigated the main DXA imaging methodology and reported on the BMD trends for the total body, lumbar spine, and bilateral hips.

10.3.1 TOTAL BODY DXA

The total body BMD was reported as higher in the cone group, with a statistical significance at 12 months between the two groups (the cone group reporting an increase of 1.187 %, and the non-cone group reporting -0.046 %).Therefore, the total body changes showed a possible association with the cone group, so there was the possibility of the cone impacting stabilisation and weight bearing, although it must be noted that the difference between the two groups was within the precision error range of LSC of 2.77 % (assuming a precision error of 1 % [258]). Unfortunately, there was also a lack of reported evidence in total body BMD changes in rTKR studies, so it is unknown if the reported decreases in the non-cone group are the standard change or if the increases in the cone group are the standard.

10.3.2 LUMBAR SPINE DXA

For the lumbar spine data the cone group changes are small compared to baseline, with a statistically significant change at three months in the L1-L4 region. In the non-cone group the lumbar spine changes were mainly increases, although none with statistically significance changes. The changes reported in the lumbar spine of both groups were most likely due to degenerative changes within individual participants elevating their BMD, with extensive literature reporting this link [409], especially given their mean age of the groups involved being 69.82 and 71.00 years old.

10.3.3 HIP DXA RESULTS

The BMD cone ipsilateral hip data reported early remodelling in rTKR patients at six weeks in the wards and neck (reporting a statistically significant change), and that by 12 months the participants had started to reach towards a plateau to that of the level of baseline. Although there are statistically significant losses reported in the trochanter, shaft, and overall hip at 12 months, which might be due to the impact of cortical to trabeculae bone ratios and their impact on BMD turnover.

This trend is less clear in the ipsilateral non-cone group, which showed remodelling in the wards at six weeks which throughout trends towards the baseline figure at 12 months. Although the neck BMD reported losses increasing at each visit, reaching just over -3.23 % at 12 months (which was statistically significant). The non-cone group did report losses in the shaft and overall total, which mimic the cone results at three, six and 12 months. When both groups were compared there were only two statistically significant results, both in the neck of femur at six weeks and 12 months. It is unknown if this is due to the impact of the cone on stabilisation or the small numbers in the non-cone group, based on the six week data also supporting the remodelling increase in the wards triangle area, I would conclude it is more likely the latter. Although, it must be noted that none of the hip data suggest a statistically significant negative association, when compared between the cone and non-cone data, with the cone data reporting the greater turnover in the neck of femur.

10.4 RESULTS – CHAPTER 6 DXA IMAGING, BMD ANALYSIS OF THE KNEE

10.4.1 RESULTS - BMD KNEE ANALYSIS

Along the tibial and femoral stems there were decreases in both the cone and non-cone groups when compared to baseline and beyond the femoral stem there are increases in both groups, this is seen in the PA and lateral DXA data. The medial tibial condyle were similar, with both groups reporting losses at every visit, the increases in the tibial lateral condyle in the cone group are

paralleled by the losses in the non-cone group. As well as the difference in the lateral tibial condyle between groups, there was also a difference in the medial femoral condyles, as the cone group reported increases across all three visits, with the non-cone group reporting losses in two of the three visits for the same region. This increase might have been due to the stabilisation of the cone, earlier WB exercising, and less about the alignment of the revision.

10.5 RESULTS – CHAPTER 7 X-RAY IMAGING OF THE KNEE, PIXEL DENSITY AND ALIGNMENT

10.5.1 RESULTS - PIXEL DENSITY KNEE ANALYSIS

The cone group reported an increase in pixel density mean in all regions (except one), and the non-cone group reported losses at each region, the greatest difference between the two groups was in the non-cone group in the tibial region, with large reported losses.

Many studies have reported osteointegration of cones demonstrated on radiographs [218, 437, 438, 439], with no radioluciencies identified [218, 222, 441, 442]. Unfortunately, the reported literature does not report pixel densities, only osteointegration. Moreover, it must be noted these pixel density changes may be for other reasons such as participant rotation during imaging or region placement, although the region placement had a reported COV precision range of 0.09 % to 0.35 %. There is the possibility of pixel density figures being used as a surrogate BMD results from DXA scans, although further research would be needed to create a robust association between the two. A feasibility study by Kinds et al [269] showed this was possible, and dentistry has researched something similar utilising an aluminium step wedge in determining BMD of the mandible.

10.5.2 RESULTS - ALIGNMENT ANALYSIS

Both the cone and non-cone HKA pre-op figures are similar, and close to the reported 5° variation from 180° [436]. Reported as 177.52° and 181.18° at pre-op, these figures trends towards the 180° figure (compared to their pre-op), with little difference between the groups after pre-op. For the LDFA data are

reported in the cone group as 90.44° at pre-op, and 89.30° in the non-cone group, this was within the same alignment as TKR patients [448]. With both groups showing a similar trend throughout the visits, as for the mPTA in reported similar pre-op scores to the reported TKR alignment data [448], with again both groups showing a similar pattern.

Both the LDFA and mPTA in the cone and non-cone data show both groups ending up in a negative position (over 90°) in the LDFA, and in the positive position in the mPTA (under 90°), the main difference being their starting alignment. When directly comparing the two groups as stated there was little difference between them across all three visits, and no statistical significance.

The pre-op scores HKA report no statistical significance between groups, but the more pre-op varus position in the cone group (compared to the non-cone) might be the reason for the slightly higher BMD loss (both groups reported losses) in the medial tibial condyle region. Therefore, post-surgery, and with realignment established, there would be reduced stress shielding, meaning the tibial medial condyle no longer underwent stresses due to alignment, and thus reported losses of BMD throughout the following visits.

10.6 RESULTS – CHAPTER 8 CT IMAGING OF THE KNEE

This imaging method did not provide any additional information, with in-growth undefined due to excessive artefact on the image. Therefore recommendation is to not use this methodology in the full study until greater optimised CT imaging has been developed.

10.7 RESULTS – CHAPTER 9 QUESTIONNAIRES

Questionnaire results showed promise as a methodological proxy to patient experience regarding pain and quality of life. Although statistical significance should be interpreted with caution due to repeated analysis between visits.

Bone health questionnaire – This questionnaire reported very similar traits for both groups, with no statistically significant differences between the two groups.

Although OA and RA were more prevalent in the cone group, neither had any statistical significance.

LEFS questionnaire – Reported statistically significant increases in mobility and functionality post-op in both groups at nearly every visit (six week cone is the only one with a p-value above 0.05), with no statistical difference between the two groups.

HADs questionnaire – Anxiety scores reported only one statistically significant result, reported in the cone group as a difference of -1.88 (p-value 0.02) at six months. All cone figures reported a reduction in anxiety post-op, in the non-cone group there was an increase at three months. Although there was no statistical difference between the two groups.

HADs questionnaire – Depression scores reported statistically significant results in the cone group at visits six weeks, three months and six months, as well as reporting decreases in depression across all visits. The non-cone also report decreases at six weeks and 12 months, not to a statistically significant level. There was no statistical difference between the two groups, although at six months the difference between the groups was a p-value of 0.06, with the cone group reporting a reduction in depression of -2.44 and the non-cone an increase of 0.10.

EQ-5D-3L QOL questionnaire – Reported a mean increase in QOL at all visits post-op, in both groups, with both groups reporting statistically significant findings at 6 months, reported as increase in QOL scores in the cone and non-cone group of 12.75 and 13.70 respectively. There was no statistical difference between the two groups.

OKS questionnaire – This questionnaire reported statistically significant increases compared to baseline at every visit (except six weeks in the cone group), with the highest increase in cone group reported of 14.63 at six months, and 16.67 at 12 months in the non-cone group. There were no statistically significant differences between the two groups.

The questionnaires used in this study were all well-known and validated, with the exception of the bone health questionnaire, although this questionnaire had been used in previous TKR research [23]. The questionnaires were all self-administered, and with the reported low cases of OA stated by both groups in the bone health questionnaire (as stated previously OA is the primary reason for original TKR), it can be concluded that not all data reported within the questionnaires is entirely accurate. Additionally, there is the possibility of participants interpreting the same question in different ways. That being noted, the questionnaire data used in this study showed that the cone group reported statistically significant changes in: lower depression, lower anxiety, and increased functionality and mobility. Although no corrections were made to the repeated measures of the questionnaire data therefore the significance of these results should be treated with caution. Additionally there was no statistical difference between the two groups. I would conclude based on the questionnaire data that the cones do not negatively impact the participants, and actually improve mental wellbeing and functionality at least to a similar level of a standard rTKR, with no statistical difference between groups.

10.8 LIMITATIONS

The study had several limitations, most notably the difficulties involved with recruitment and attrition.

The study showed some bias in the recruitment, as stated all participants were from the south west area, this was due to the participants having to attend multiple scans over multiple visits, so due to the intense nature of x-rays, DXA scans, CT images and physiotherapy, only those patients with appropriate support and within the area were able to take part. So longer distances were unlikely, although to reduce the impact of these visits, all scans/appointments were arranged of the same day were possible. The sample used in this study were all white Caucasian individuals, so these data are not representative of the country as a whole, therefore the results are limited in generalisability.

Moreover, the sample size was small, especially at 12 months were there was attrition of participants, this sample size impacted the results creating larger SD

and SE margins in the 12 month data, making the data less robust. Therefore, it is feasible that a larger sample size might have resulted in a stronger significant association between the groups across the different imaging modalities. As stated previously this was due to several factors, with the advent of COVID-19 affecting four participants' data across all imaging. Therefore, caution should be used when interpreting these results, as those subjects who did remain in the study might have had a natural bias to due to volunteering at the beginning. Furthermore, they might have been susceptible to the Hawthorne effect, modifying their behaviour to improve their recovery. Although it must be noted both groups were blinded to which group they were in.

Other limitations included the subjectivity of some of the questionnaires, particularly regarding quality of life, and mental health. Instructions in answering questions were as specific as possible, and these questionnaires have been validated, but some differences in participants' interpretation would be unavoidable. In the bone health questionnaire the cone group had a higher prevalence of OA and RA, with both diseases impacting BMD turnover in different ways, these diseases could have been separated and analysed separately. Although it must be stated there was no statistical significance between the two groups.

There was also the issue of a lack of data, not only from those who missed appointments or where the step wedge was not included, but there was also a lack of 24 month follow-up data, as stated this study included 12 month data, and although this study will continue to include 24 and 60 month data, this could not be included due to time commitments, this lack of data make conclusion regarding the 12-24 month plateau effect harder to ascertain, as well as long term changes. Although at a later date these additional data will be analysed and those questions answered.

Unfortunately, there is also a lack of comparison data for rTKR participants and DXA scans, with only two papers both by Jensen et al [178, 179] investigating such changes (one paper investigated tibial changes and the other femoral changes). So it is unknown if the trends reported in this research is consistent, as there is no direct data to correlate this to, with most of the data compared

directly to TKR or TKA instead of rTKR. As stated although there are cone studies, only the Jensen et al study [178] included BMD DXA data, with most just reporting osteointegration by a reporting radiographer, again making comparisons to known datasets difficult. This makes these data unique, as a randomised control trial of knee BMD in rTKR, but also limits this data, as there is a lack of evidence for comparison studies.

We are unsure of the impact of the physiotherapy instructions or exercise, although all patients received the same instructions it is unclear which participants were completely compliant in performing them, and if some participants went above and beyond with their rehabilitation.

10.9 CONCLUSION

The overall BMD results are incomplete after one year, and full recovery has not been established. The BMD data show an increase in the lateral tibial condyle in the cone group compared to a loss in the non-cone group; this is where the cone is situated. This difference is supported by the pixel density differences, and alignment data, which reports a lack of alignment difference between the cone and non-cone groups at all visits, although this alignment might be the reason for tibial medial condyle losses reported in both groups. Although it must be noted that there is no recorded alignment data for six weeks, so the impact during these weeks on alignment is unknown. Furthermore, the pixel density changes, although supporting the use of cones in osteointegration, used the three month long leg scan as a baseline (unlike the six week in DXA), and the lack of correlation data makes the comparisons between modalities more difficult. Additionally, the sample size is small, due to this the separation between the stem lengths was not established, so the influence of stem length is unaccounted for with the 26 who attended at six weeks, four had a cone and a long stem, 13 had a cone and a short stem, five non-cone and long, and four non-cone and short. Thus, this BMD change could be due to multiple complex reasons and could be impacted by early immobilisation and weight bearing.

It is in this researcher's opinion that the reported data across all three methods and questionnaires show no negative impact of cones in the DXA, pixel, or

alignment data. It is concluded that due to the already widely reported benefits of osteointegration and knee stabilisation of cones [218, 222, 381, 437, 438, 439, 440], the promising management of severe tibial bone loss [221], as well the reported good short-term results of cone implantation [219], it is concluded that cone implantation would be beneficial. Furthermore, this is supported by the positive results in the questionnaire data, showing a reduction in depression and anxiety, and increases in quality of life and functionality.

Additionally, cone implantation has been reported to reduce infection compared to other options [232], with the potential advent of increased fracture risk with low BMD, the use of implantation that can help increase or at least maintain BMD should be investigated further.

10.10 FUTURE WORK/RECOMMENDATIONS

Bringing this into a full trial several recommendations from the chapter should be implemented:

If possible, further development of the 3D-SHAPER software should be undertaken, with additional validation and testing. This software provided additional in-depth data as an alternative methodology, and although it is in its infancy its results mimicked the BMD changes reported and the control data. The data from this 3D SHAPER software also allows a greater knowledge in defining the trabecular and cortical bone within the hip, an issue especially important with the impact of osteophytes and degenerative disease influencing BMD. Paralleled with the addition that this modelling software can be retrospectively applied without the bias of known groups by the software, means this is a high quality tool that should be used in the full study. If licencing or purchase of the product can be arranged.

One of the main recommendations within this thesis from this feasibility study is regarding participation; although there were several issues (winter bed problems, delayed surgeries, and COVID-19). Moving forward attrition is an issue; the advent of using a focus group utilising public and patient involvement could be one plausible suggestion to address this issue. During the study,

reclassifying the appointment dates allows for a much larger range for scanning participants (e.g. the six month scan would still be a six month scan if it was closer to six months that 12 months, so eight months and 25 days would be classed as a six month scan). This increasing of the appointment window means COVID-19 cancellations and rearranged appointments would have less impact in losing that appointment data. The introduction of a follow up phone call prior to their appointment, to both check they had received their letter and to check they could still attend might help reduce the missed or cancelled appointments. Finally, the continued addition of paying for participants' petrol, bus ticket, and providing parking will help to reduce this attrition further.

Dual energy x-ray absorptiometry shows the greatest robustness out of the three main methodologies, having already established DXA knee positioning and being the gold standard for BMD investigations. In conjunction the systematic review data providing common ROI data that had been investigated within DXA knee imaging, albeit in TKR groups. This makes DXA the primary modality moving forward. Although x-ray imaging should still be utilised, the pixel density changes reported in the feasibility study show promise as both a method and parallel to the DXA BMD data. Although this data is limited, with two main issues, a lack of correlation data directly linking the pixel changes to BMD changes, and a lack of useable scan data as not all long leg images contained a step wedge. To address this, a phantom of known BMD could be utilised and imaged via DXA and x-ray, and a more direct correlation created between these two modalities. More importantly during the full study the research should be communicated to the radiography department, to show the importance of the step wedge being within the images. This might help reduce the loss of data from lack of step wedge. Regarding six month CT scan the recommendation would be to not include it due to a lack of defined in-growth.

Statistical analysis of the main BMD and questionnaire results should in part still use the continuation of paired t-tests which allows the understanding of the exact region or area that is significantly changing. Although due to repeated measures involved this should be used with caution, in which case the utilisation of the linear regression analysis model should be applied, as this was deemed more robust than ANOVA or Bonferroni's correction.

Moving forward, investigation beyond 12 months is also required, with 24 month appointment scans the changes in both cortical and trabecular bone would address issues that both the feasibility data and the systematic review have raised regarding plateau effects of BMD. Additionally, it must be noted that this full study will continue to 60 month visits and an extension to recruitment has been funded to ensure a sufficient sample size after accounting for participant attrition. Moreover, there should be investigations into the changes perceived between the rTKR and TKR groups, and the root cause for this possible difference and investigations into post-care influences. Although promising, additional research with a larger cohort of participant is required to truly reveal the impact of cone implantation in rTKR.

Currently there is no DXA reference data to compare these data to. So a reference database needs to be created to make more sense of the knee measurements reported within this study. This could be facilitated by companies such as GE who could refine their knee DXA offering to make it easier and quicker to undertake and analyse and standardisation of DXA knee scans, rather than them being scanned on a DXA “thin” spine setting.

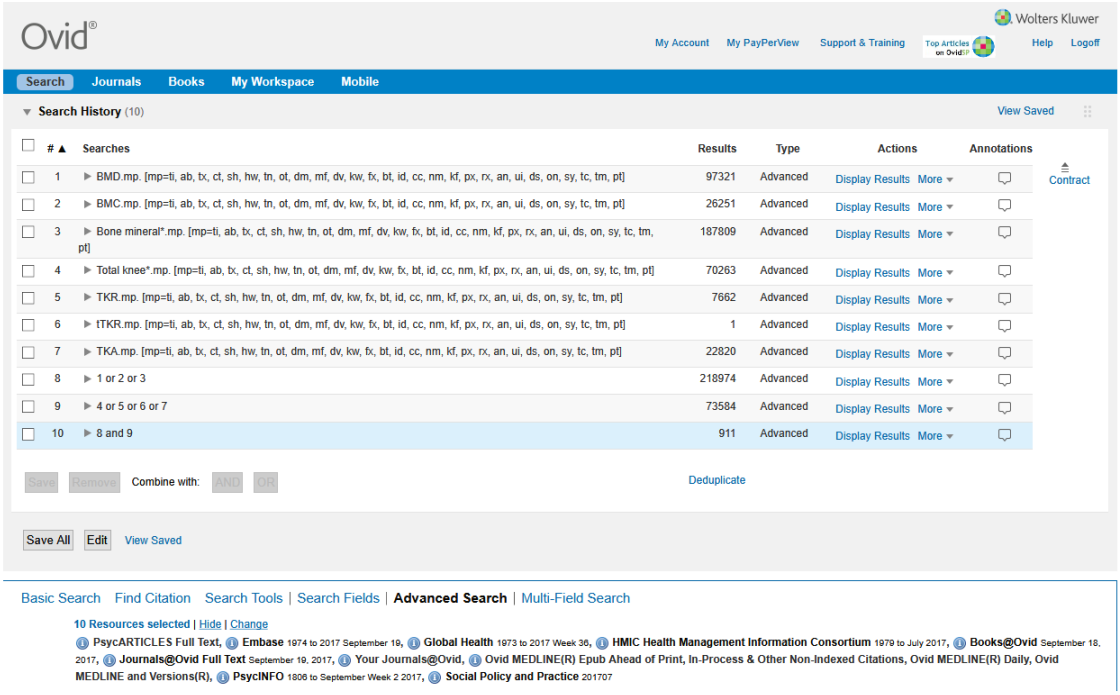
Regarding the questionnaire data, for the full trial with a larger cohort, the BMD scores of the RA and OA participants could be separated and analysed independently, with severity also recorded, this could address some of the possible BMD changes reported in feasibility study. Additionally, the use of electronic questionnaires for those who are unable to complete or return them might help compliance, as might follow up phone calls for those who have failed to return the posted originals. Gaining access to the medical records of the participants could also be introduced moving forward; this would address the issues of errors in the self-reported bone health questionnaire data. But this was not possible, then checking the stated medications against NHS medicines database and comparing the medication with the medical condition could help reduce the errors.

Overall, this feasibility study has allowed the development and trialling of useful imaging modalities and software, which can be employed in a wider context of a

full clinical trial, to help us better understand the impact of cone implantation in rTKR participants.

APPENDICES

Appendix 1. Search strategy



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Search History (10) — View Saved

# ▲	Searches	Results	Type	Actions	Annotations
1	BMD.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	97321	Advanced	Display Results More	
2	BMC.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	26251	Advanced	Display Results More	
3	Bone mineral*.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	187809	Advanced	Display Results More	
4	Total knee*.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	70263	Advanced	Display Results More	
5	TKR.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	7662	Advanced	Display Results More	
6	tTKR.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	1	Advanced	Display Results More	
7	TKA.mp. [mp=ti, ab, tx, ct, sh, hw, tn, ot, dm, mf, dv, kw, fx, bt, id, cc, nm, kf, px, rx, an, ui, ds, on, sy, tc, tm, pt]	22820	Advanced	Display Results More	
8	1 or 2 or 3	218974	Advanced	Display Results More	
9	4 or 5 or 6 or 7	73584	Advanced	Display Results More	
10	8 and 9	911	Advanced	Display Results More	

Contract

Save | Remove | Combine with: AND OR — Deduplicate

Save All | Edit | View Saved

Basic Search | Find Citation | Search Tools | Search Fields | **Advanced Search** | Multi-Field Search

10 Resources selected | Hide | Change

PsycARTICLES Full Text, **Embase** 1974 to 2017 September 19, **Global Health** 1973 to 2017 Week 36, **HMIC Health Management Information Consortium** 1979 to July 2017, **Books@Ovid** September 18, 2017, **Journals@Ovid Full Text** September 19, 2017, **Your Journals@Ovid**, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)**, **PsycINFO** 1806 to September Week 2 2017, **Social Policy and Practice** 201707

Appendix 2. Standardised extraction from

Source	Study/First author:	
	Title:	
	Year of Publication:	

Methods	Study design (if stated):	

Participants	Total number of participants (sample size):	
	How were participants/patients/ recruited/gathered (if stated)	
	Participants/patients demographics provided (e.g. age, gender):	
	Any medications the participants might be on (if stated e.g. calcitonin or bisphosphonates)	
	Setting (e.g. Chicago hospital, University of Exeter lab):	
	Country conducted in:	

Intervention/Index test	Specific intervention (e.g. TKR, TKA or rTKR):	
	Details of intervention (e.g. anything specific about it, cone implants, long or short stems):	
	Reference standard/comparator (e.g. matched control group, BMD baseline prior to surgery or contralateral leg to surgery):	

Outcomes	Main outcome from the study (e.g. BMD increases/ decreases after a	

	TKR):	
	BMD score compared to comparator at the hips, spine, knees, or whole body (include subset anatomy if recorded i.e. greater trochanter greater BMD difference). Also include the time the data were recorded (e.g. 6 weeks, 6 months, 2 years)	
	Stated point of BMD plateau (if any)	

Miscellaneous	Key conclusions of the study authors:	
	Miscellaneous comments from the study authors:	
	Miscellaneous comments from the review authors:	

Appendix 3. Newcastle-Ottawa Scale

NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE	Note: A study can be awarded a maximum of one star/dot for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability (see coding notes if unsure)
SELECTION **1) Representativemess of the exposed cohort**	a) The participants/patients are a true representative of the average TKR/TKA/rTKR in the community ●
	b) Somewhat representative of the average TKR/TKA/rTKR in the community ●
	c) A selected group of users
	d) No description of the derivation of the cohort
2) Selection of non-exposed cohort	a) Are they drawn from the same community as the exposed cohort ●
	b) Drawn from a difference source
	c) No description of the derivation of the non-exposed cohort
3) Ascertainment of exposure	a) Secure record (e.g. surgical records) ●
	b) Structed interview ●
	c) Written self report
	d) No description
4) Demonstration that outcome of interest was not present at start of study	a) Yes ●
	b) No

COMPARABILITY **1) Comparability of cohorts on the basis of the design or analysis**	a) Study controls for (select most important factor) (e.g. age, BMI, gender etc) ●
	b) Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)

OUTCOME **1) Assessment of outcome**	a) Independent or blind assessment (e.g. by reference to secure records such as x-rays or medical record) ●
	b) Record linkage (identified through ICD codes on database
	c) Self reported
	d) No description
2) Was follow-up long enough for outcome to occur	a) Yes (select an adequate follow-up period for outcome of interest) ●
	b) No
3) Adequacy of follow-up of cohorts	a) Complete follow-up - all subjects accounted for ●
	b) subjects lost to follow-up unlikely to introduce bias - small numbers lost ->_ % (select an adequate %) follow-up, or
	c) Follow up rate <_% (select an adequate %) and no description of
	d) No statement

Appendix 4. Controls and bisphosphonate groups

AP/PA Tibia			3 months	ROI 1 medial side	ROI 2 Lateral	6 months	ROI 1 medial	ROI 2 lateral	ROI 3 under replacement	Total of ROI (if reported)
Jaroma et al., (2015)	TKA (aldronate and calcuim 14 and calcuim only 12)	difference compared to control		4.22	6.87		4.18	5.95		
Wang et al (2003)	(48 in aldendronate, 48 control)	reported difference compared to control					13.3	13.6	16.6	15.9
		difference compared to control								15.40
Wang et al (2006)	TKA (29 oral alderstone, 25 without)	reported difference compared to control					15.8	25.7	17.7	16.4
		difference compared to control								16.47
AP/PA Tibia			**12 months**	**ROI 1 medial**	**ROI 2 lateral**	**ROI 3 under replacement**	**Total of ROI (if reported)**	**24**	**ROI 1 Medial**	**ROI 2 Lateral**
Jaroma et al., (2015)	TKA (aldronate and calcuim 14 and calcuim only 12)	difference compared to control		0.82	2.82				0.82	4.31
Wang et al (2003)	(48 in aldendronate, 48 control)	reported difference compared to control		12.4	14.9	11.3	9			
		difference compared to control					9.53			
Wang et al (2006)	TKA (29 oral alderstone, 25 without)	reported difference compared to control		12.8	16.2	16.6	12.3			
		difference compared to control					12.40			

Lateral Femur		3 Months	ROI 1 anterior aspect of femoral head	ROI 2 middle of femoral head	ROI 3 posterior aspect of femur	ROI 4 Above implant	TOTAL ROI 1-3	6 Months	ROI 1 anterior aspect of femoral head	ROI 2 middle of femoral head	ROI 3 posterior aspect of femur	ROI 4 Above implant	TOTAL ROI 1-3
Soininvaara et al., (2002)	All underwent TKA, 11 on calcuim and 8 on calcuim and alendronare acid	Relative BMD (%) difference compared to control	7.05	6.4	5.94	2.25	7.34		13.5	7.83	12.64	3.7	11.52
Jaroma et al., (2015)	TKA (aldronate and calcuim 14 and calcuim only 12)	Relative BMD (%) difference compared to control	3.75	6.78	4.72	1.53	5.27		12.17	7.58	8.76	6.01	8.84
		12 Months	ROI 1 anterior aspect of femoral head	ROI 2 middle of femoral head	ROI 3 posterior aspect of femur	ROI 4 Above implant	TOTAL ROI 1-3	**24 Months**	ROI 1 anterior aspect of femoral head	ROI 2 middle of femoral head	ROI 3 posterior aspect of femur	ROI 4 Above implant	TOTAL ROI 1-3
Soininvaara et al., (2002)	All underwent TKA, 11 on calcuim and 8 on calcuim and alendronare acid	Relative BMD (%) difference compared to control	14.95	12.71	16.48	11.2	15.31						
Jaroma et al., (2015)	TKA (aldronate and calcuim 14 and calcuim only 12)	Relative BMD (%) difference compared to control	9.02	11.32	14.56	7.52	12.44		4.23	6.91	13.42	7.52	7.59

Lateral Tibia		3 Months	ROI under implant	6 Months	ROI under implant	12 Months	ROI under implant	24 Months	ROI under implant
Jaroma et al., (2015)	TKA (aldronate and calcuim 14 and calcuim only 12)	difference compared to control	1.94		3.74		4.50		4.55

AP/PA Femur			6 Months	TOTAL	12 Months	TOTAL
Hagena F, W et al 2000 (Abstract)	TKA (76 on bisphophonates and 73 were controls)	reported difference compared to control		19.2		
Wang et al (2003)	(48 in aldendronate, 48 control)	reported difference compared to control		19		13.1
		difference compared to control		24.7		12.89
Wang et al (2006)	TKA (29 oral alderstone, 25 without)	reported difference compared to control		23.8		9.7
		difference compared to control		20.5		3.66

Appendix 5. PIS

Royal Devon and Exeter NHS
NHS Foundation Trust

A Prospective, Randomised Pilot Study Investigating the Use of Metaphyseal Cones versus a Cemented Stem Construct in Revision Total Knee Replacement in Patients with AORI Grade 2 Defects- a Comparison of Clinical, Functional and Radiological Outcome.

Information for Patients.

Introduction:

We would like to invite you to take part in a study comparing 3 different ways of undertaking revision total knee replacement surgery. It is important that you understand both why we are doing this research and what being involved in it means for you. Please take some time to read this information leaflet and to ask us any questions you may have about being involved. If you would like more time to think about this, or if you would like to discuss the research with your family, friends or GP, you do not have to make a decision now. We can contact you again at a later date if that is what you would prefer.

This research study is NOT a trial of an untested product nor a new type of surgical technique. All of the joint replacement parts and surgical techniques are currently in routine use both in this hospital and around the world. The research is being carried out at the Royal Devon and Exeter Hospital and is an independent piece of research.

Study details:

Knee replacement surgery has been successfully carried out for many years. However, in time, some knee replacements will fail-usually either because of wear or loosening of the replacement parts. This may mean the patient has to undergo further surgery-this is known as revision total knee replacement (rTKR). This revision surgery is often more complex than the original operation and presents the operating surgeon with several technical challenges. When the old knee replacement is removed, a large cavity can be left in the bone. The new knee replacement has to be placed into this, but it is essential that it is immediately stable and secure. The large cavity has to be somehow either filled in or bypassed to ensure the new knee replacement is secure enough for early weight-bearing and long term success.

Different techniques have been used for many years to overcome this problem. It may be possible to simply re-cement another knee replacement into the cavity. See Figure 1 below:

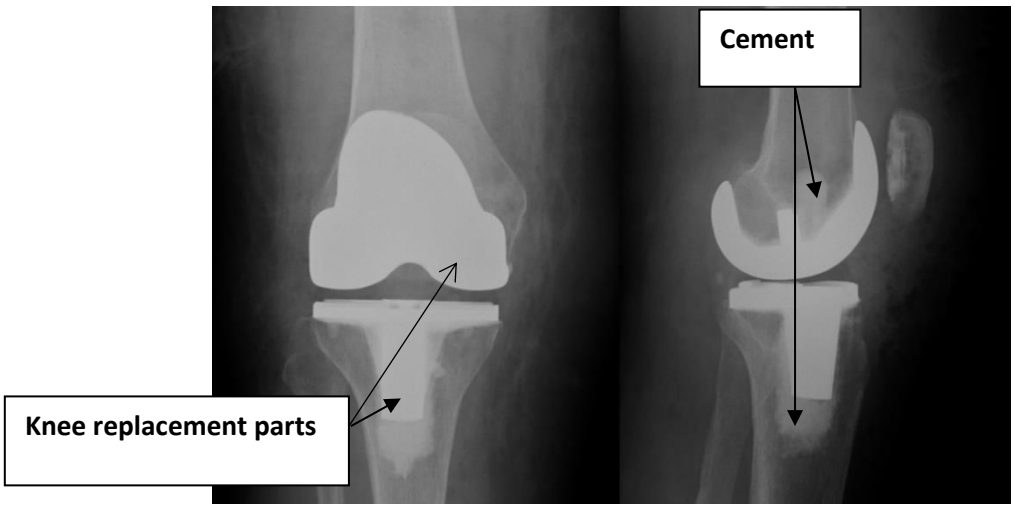


Figure 1: new knee replacement cemented in place.

An alternative to this is use a device called a "cone" which sits into the bony cavity and a new knee replacement can be cemented into the cone. See figure 2 below:

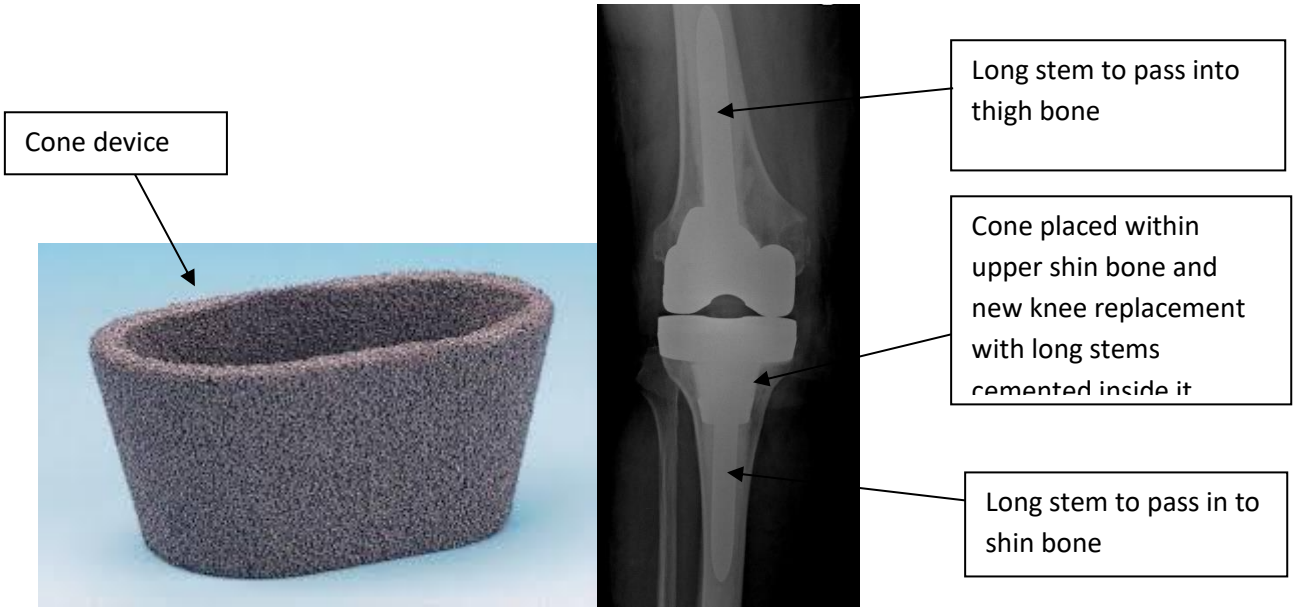


Figure 2.

Bone grows onto the cone to ensure its stability. The new knee replacement that is cemented into the cone can either be a standard replacement as seen in figure 1 above, or a long stem replacement can be used which bypasses the bony defects and allow the new joint to achieve stability by cementing the stem that sits further down the length of the bone as shown in figure 2 above.

All of these types of rTKR are presently in use throughout the UK. Currently, no-one knows which type is best. We are planning to run this study to see if we can identify which type of rTKR gives the best outcome for patients. We will measure the results using questionnaires to measure how well you feel your knee is performing, specific tests to measure knee function, and by using x-rays and scans.

We will identify patients suitable for inclusion in the study from their medical notes, x-rays and scans. If you consent to be in the study, you will randomly be allocated to 1 of the 3

types of surgery- to receive either a cemented rTKR (with a short or long stem depending on the findings at the time of surgery), or a cone device with a short stemmed knee replacement or a cone device with a long stemmed knee replacement. We will monitor your progress for 5 years after the operation. We will not tell you which type of operation you have had done until the end of the study.

What is the Purpose of the Study?

We are trying to establish which way of performing this type of surgery is any better than the other. Before we can do this we have to run a pilot study of the project. The pilot study is to make sure we are collecting the right information and to see if there are going to be any unexpected difficulties in running a full study.

If we can show that one method of doing this type of surgery is better than the others, it is likely that this would be the preferred surgical treatment in this hospital for patients having this operation in the future. We would inform our colleagues in the world of knee replacement surgery of the results so that they can improve the long term care for their patients also. At present, we do not know which type of operation is best and have no preference for one over another. All 3 methods of surgery are routinely used.

Why have I been asked to be involved?

You are being invited to participate in this study because your type of rTKR surgery meets the criteria for the question we are trying to answer.

What is involved? How will it affect me?

Every patient who is involved in this study has to sign a consent form which says that you are a willing participant and that you understand what it means to be involved.

You will attend for preparation for surgery appointment usually a few weeks before your surgery to ensure you are fit to proceed and will have had x-rays of your knees undertaken. Both of these are part of routine rTKR care whether you are involved in the study or not

In addition, you will be asked to attend the physiotherapy department here in Exeter for some tests that look at how well your knee is working before the operation. The tests include looking at the strength of your knee muscles, your balance, your speed and your walking ability. These tests are known as functional testing.

You will be asked to complete some questionnaires which measure how much trouble your knee is giving you on an everyday basis. For example, questions are asked about pain, sleep disturbance and limitation of activity. These questionnaires are widely used throughout the world so that different departments of knee surgery are accurately able to compare their surgical results with others.

Participants will be allocated to 1 of the 3 arms of the study- to receive either a cemented rTKR (with a short or long stem depending on the findings at the time of surgery), or a cone device with either a short or long stemmed knee replacement. This allocation is a random decision. A computer generated list has been drawn up and decides which treatment each patient will receive. Please remember that all 3 techniques are currently being routinely used so you are not being disadvantaged by having one treatment over another.

After your surgery, your immediate post-operative care will be the same as routine care in our hospital. You will be seen in the orthopaedic out-patient clinic at 6 weeks and then at 1, 2 and 5 years after the surgery. There will be an x-ray at the 1, 2 and 5 year appointment. We

will ask you to repeat the questionnaires that you did before your operation. Again, this is all routine care whether you are involved in the study or not.

In addition to routine care, we will ask you to attend the physiotherapy department here in Exeter at 3, 6 12, 24 and 60 months after the operation so that we can repeat the functional testing that you did before your operation. This allows us to see on a practical basis how your new knee is performing.

We will ask you to undergo 2 additional knee x-rays at 3 and 6 months after your operation and to complete 2 sets of additional patient questionnaires.

We will ask you to attend the Department of Medical Imaging at Exeter University on 7 occasions, once before your operation and then on 6 occasions afterwards-at 6 weeks, 3 months, 6 months and 1, 2 and 5 years, for a test known as a DEXA scan. This is a type of radiological test that looks at the density of the bone immediately around your new knee replacement. You will also be asked some questions about your level of activity and function as well as anxiety and depression. It is known that these can all affect bone density.

Some patients will be asked to attend the radiology department at the RD+E Hospital for a CT scan of the operated knee 6 months after your operation.

Being involved in the study will not affect the length of time you are in hospital. Any patient undergoing this type of surgery-whether involved in the study or not- will receive post-operative physiotherapy based on personal need.

<u>Do I Have to Take Part?</u>

No. Your participation in this study is entirely voluntary. If you choose not to take part, this will <u>NOT</u> affect your medical care in any way. Your rTKR surgery will go ahead as planned. If, at any time during the study, you change your mind and wish to withdraw from the study, you can do so. Again, this decision will have no impact on any of your future medical care.

As you can see, participating in this study involves a time commitment from you. Over a 5 year period, there will be 2 extra visits to the RD+E for knee x-rays, 6 extra visits to the physiotherapy department for functional testing, 1 visit for the CT scan for some patients and 7 visits to Exeter University for the DEXA scans. For these extra visits, we can contribute to travel expenses for you at public transport rates and also cover the cost of car parking.

Despite this time commitment from yourself, we hope you can become involved in our research. It is only by undertaking studies such as this that we can improve patient care.

We recognise that parking at the main RD+E Hospital Wonford site can be very difficult. The physiotherapy appointments are on the RD+E Heavitree site and the DEXA scans at St Lukes-part of the University of Exeter campus (on the other side of the road from RD+E Heavitree). Parking at the Heavitree site is easier and is also better served by nearby public car parks.

What Are the Possible Risks of Taking Part?

As the 3 surgical techniques being examined are already in routine use in this hospital, we do not anticipate any adverse events as a result of being involved in the study other than those that can occur with any patient having this type of surgery.

The 2 extra knee x-rays and DEXA scans add an additional dose of radiation exposure. This is calculated as being the equivalent to 33 days of background radiation (that which we are all exposed to in normal life) and is classed as minimal risk. For the patients also having a CT scan, their total increased radiation exposure is equivalent to 55 days of natural background radiation exposure to background radiation exposure and is classed as being very low risk. This has been calculated by our Medical Physics Expert, using the appropriate guidelines.

Are there any possible benefits?

As a result of being in this study, you will be more closely monitored by the physiotherapy department than is usual. This will give you an opportunity to ask any extra questions if you have them. As all 3 types of operation being studied are performed anyway, you may not get any extra benefit to being involved in the study, but the results will influence how we do this type of surgery in the future and therefore of long-term benefit of others.

Ethical Approval of the Study:

Before we were allowed to proceed with this study, we had to seek ethical approval to do so. This was provided by the Health Research Authority. The North West - Greater Manchester West Research Ethics Committee reviewed the study on their behalf and approved it. An ethics committee is made up of doctors, scientist and lay people who examine the study to ensure it has been carefully thought through, has minimised the possibility of risks to participants and ensures the highest standards of research safety.

Data Collection:

Using your hospital number (not your name) for identification, we will collect information regarding your progress. This information will be kept on encrypted and password protected RD+E Hospital computers. This information will be used only by hospital staff to allow us to analyse the results and also the regulatory authorities who ensure we meet all the requirements of the Health Research Authority in the conduct of our research. It will not be given to any one else for any other purpose. At the end of the study, all of the information kept on the computer database will be archived and stored in a secure environment.

If at any time during the study, you lose the capacity to provide on-going consent to continue in the study, we will withdraw you from the research at that time but will use any data about your knee replacement that we have collected up until that time.

Results:

When the study is completed, we hope to present our findings at national and international meetings, and to publish them in an orthopaedic journal. We will also write to you with a summary of the findings.

Complaints:

Should you have cause for complaint about this research, please discuss this with Patrick Hourigan (details below), or with your Orthopaedic Consultant. If you are unhappy to speak to either of them, you can contact the Patients Advisory Liaison Service (PALS) at the hospital who will act on your behalf. In the unlikely event of you coming to serious harm as a result of negligence, such harm will be covered by the NHS indemnity.

What Do I Do Now?

One of the research team will contact you to ask if you have any questions about the study, to ask if you would like to be involved and to make arrangements for you to sign a consent form if you are happy to participate.

If you would like to discuss the study further you can contact Patrick Hourigan via e-mail or in office hours on his number given below. Please note however, that Mr Hourigan is only able to answer your queries in relation to this piece of research. Any general queries about your operation should be made to your consultant knee surgeon's secretary.

Thank you very much for considering taking part in our research. Please discuss this information with your family, friends or GP if you wish.

Contact for Matters Relating to this Research Project:

Patrick Hourigan

Clinical Research Co-ordinator

Exeter Knee Reconstruction Unit

Princess Elizabeth orthopaedic Centre

Barrack Road

Exeter

EX2 5DW

E-mail: p.hourigan@nhs.net

Telephone 01392-408562

Appendix 6. Consent form

Royal Devon and Exeter NHS Foundation Trust

Consent Form

Name of patient/volunteer……Hospital Number:……..

Name of investigators: Mr A D Toms, Mr J R Phillips, Mr K S Eyres and Mr P Hourigan

Title: A Prospective, Randomised Pilot Study Investigating the Use of Metaphyseal Cones versus a Cemented Stem Construct in Revision Total Knee Replacement in Patients with AORI Grade 2 Defects- a Comparison of Clinical, Functional and Radiological Outcome.

This section to be completed by the patient. Please initial each statement below:

1. **I have read the version 1 (24/05/17) information sheet about this study** --------
2. **I have had an opportunity to ask questions about this study** --------
3. **I have received satisfactory answers to my questions** --------
4. **I am satisfied with the information I have been given** ---------
5. **I understand my GP will be informed of my participation in this study** ---------
6. **I understand that relevant sections of my medical notes and data collected during the study will only be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records** ---------

This study has been explained to you by: ……

I understand that am free to withdraw from the study:

1. **At any time** ----------
2. **Without having to give a reason** ----------
3. **Without affecting my future medical care** ----------

I agree to take part in this study

Patient's signature…… Patient Name……

Date……..

I confirm that I have fully explained the nature of this trial to the above named patient

Investigator's signature…….. Investigator Name……

Date……..

CC Medial notes, patient

Room 1.26, South Cloisters,
St Lukes
Exeter
EX1 2 LU
Telephone : 07973442892
Email: mg361@exeter.ac.uk

Appendix 7. DXA Appointment letter

22nd May 2017

Mr/s xxx
xxxxxxx
xxxxxx
xxxxxxx

Dear Mr/s

Re: Investigation of metaphyseal cones versus a cemented stem construct in revision total knee replacement patients

Thank you for your interest in the above study. An appointment has been made for you on

Date: -
Time: -

The appointment will be held in the Children's Health and Exercise Research Centre (CHERC) at the School of Sport and Health Sciences (SSHS), Baring Court at St Luke's campus.
Directions to St Luke's campus and to the CHERC are overleaf.

The appointment should take no longer than 2 hours.

Please wear (or bring) clothing that does not contain any metal or zips as these can obstruct the image during scanning.

We are aware that you may be experiencing difficulty with walking following your treatment and, if required, we can arrange a reserved parking space for you and a wheel chair escort from your car to the scanner. Please could you contact the researcher Michael Gundry on 07973442892 or E-mail mg361@exeter.ac.uk around one week in advance of your appointment so that we can arrange this. Please note that this phone line is not manned full time and we would be grateful if you could leave a message with your name, telephone number and some convenient times to return your call.

In addition to the appointment I have enclosed a questionnaire to be completed prior to your first appointment. If you have any difficulties filling in this form you can discuss it with the researcher at your appointment.

If you require any further information, please do not hesitate to contact me.

If you are unable to make this appointment, please let us know as soon as possible so that we can reschedule it at a more convenient time.

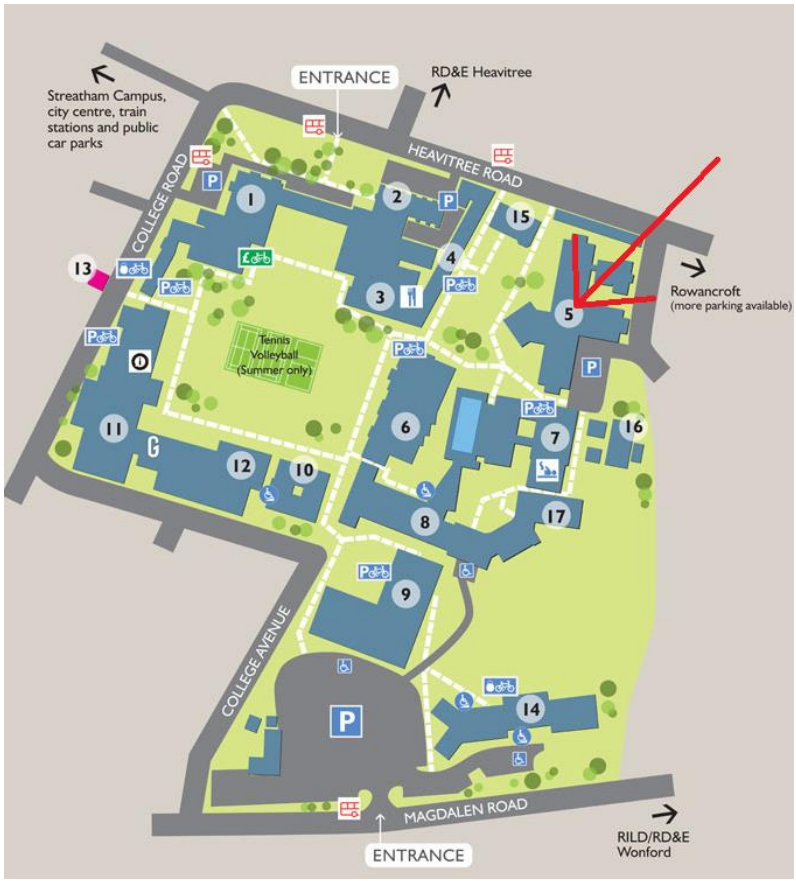
Yours sincerely

Michael Gundry
PhD Researcher

Directions to St Luke's campus:
University of Exeter
St Luke's Campus
Heavitree Road
Exeter EX1 2LU

If you are travelling by car using satellite navigation please use post code EX2 4TE, additional information on directions to the campus can be found on: www.exeter.ac.uk/visit/directions/stlukes/

St Luke's campus is shown below, number 5 (arrow) is Baring court where I will meet you outside the CHERC, once you arrive outside the building please ring me. If reserved parking is required please make sure you park in the area adjacent to the Magdalen entrance and ring me as soon as you arrive, and I will then meet you in the car park where I will issue you with a permit.



If you have any difficulty finding either the building or the campus please don't hesitate to contact me on: 07973442892 or E-mail mg361@exeter.ac.uk

Appendix 8. Checklist

ID number of study participant _____

Name:_____

Address:_____

_____

_____

Date of birth (these 3 are needed to perform an identity check): _____

Height: _____

Weight:_____

Stem length and side the knee revision is on (e.g. left or right): _____

Any previous hip replacement (including side) or metal work in spine:_____

Date of revision surgery_____

Has the participant had a DXA scan in the last 6 months_____

Copy of consent form

Appendix 9. DXA Report example

MEDICAL IMAGING
UNIVERSITY OF EXETER
MEDICAL SCHOOL

South Cloister's, St Luke's Campus,
Heavitree Road, Exeter, EX1 2LU

t +44 (0) 1392 724133
e K.M.Knapp@exeter.ac.uk

10th October 2020

Mr A Toms
Princess Elizabeth Orthopaedic Centre
Royal Devon and Exeter Hospital
Barrack Road
Exeter
EX2 5DW

Dear Andy

Re: Joe Bloggs, DoB 01/01/01
3 BBBBB, Exx, Devon, EX1 111

Your patient is enrolled in the Cones research study.

Your patient's bone mineral density results are outlined below:

Site	BMD (g/cm^2)	T-score
Lumbar Spine		
Left Total Hip		
Right Total Hip		
Total body		

These results fall within the normal/osteopenic/osteoporotic range as defined by the WHO criteria (1994) for the diagnosis of osteoporosis. Details of any clinical risk factors /secondary causes should be ruled out.

Treatment recommendations

You may wish to consider treatment with 1st line Bisphosphonate or 2nd line treatment if appropriate Lifestyle advice is recommended to encourage your patient to take regular weight bearing exercise, follow a diet rich in calcium, and have sufficient safe sun exposure to promote Vitamin D.

I would recommend a repeat scan in 2 years (osteoporosis)/3-5 years (osteopenia) to re-check their bone density/ A clinical follow-up scan is not required unless there is a change in your patient's clinical presentation, which includes a clinical risk factor for osteoporosis.

Please do not hesitate to contact me if you require any further information.
Kind regards

Karen Knapp BSc (Hons), PgCAP, PgC, PhD, SFHEA
Associate Professor in Musculoskeletal Imaging
HCPC RA35166

Appendix 10. Bone health questionnaire

Bone Questionnaire

Please complete **all** the appropriate sections, using the tick boxes where provided.

Date questionnaire completed ……

Surname ……..…….Forename(s)……Title..……

Address ….……

……Postcode…...……..
.

Telephone Number (including area code) ……..……

Date of Birth …… (day/month/year)

Gender Female / Male

Ethnic Background	White	[ ]	Oriental	[ ]
	Black	[ ]	Mixed	[ ]
	Asian	[ ]	Other	[ ]

Height …….. Weight
……..……...

Height at age 21…… Weight at age
21…….

GP Name ……

GP Address ……

……

GP Telephone Number ……

Are you willing to participate in research in the future? Yes [ ] No [ ]

Medical History

1. Have you ever suffered from any of these conditions?

	No	Yes	Please state when diagnosed and duration of disease
Rheumatoid arthritis			
Osteoarthritis			
Ankylosing spondylitis			
Diabetes -type 1 – insulin dependent			
Diabetes – type 2			
Overactive thyroid			
Underactive thyroid			
Breast cancer			
Other cancer			
Pagets disease of bone			
Liver disease			
Kidney disease			
Gastric surgery			
Lactose intolerance (milk allergy)			
Crohn's disease			
Coeliac disease			
Irritable bowel syndrome			
Malabsorption syndrome			
Osteomalacia (rickets)			
Osteogenesis Imperfecta			

Hypogonadism			
Chronic malnutrition / malabsorption			
Eating disorder eg anorexia nervosa			

2. Do you suffer from any other on-going disease? Yes [ ] No [ ]

If yes, please state disease and duration……..……

……..

3. Did your mother or father ever fracture (break) their hip?

Yes [ ] No [ ]

4. Do any other diseases run in your family? Yes [ ] No [ ]

If yes, please state the disease, and the relatives affected

…….....

5. Have you been immobilised for more than 6 wks (complete bed rest/.

hospitalisation)? Yes [ ] No [ ]

If yes, was this before the age of 25 [ ], or after the age of 25 [ ]

6. Have you ever taken any of the following drugs?

Drug	No	Yes	For how long did you take them?
Corticosteroids (Please state dose)			
Anticonvulsants			

Diuretics			
Chemotherapy			
Immunosuppresive agents			
Heparin			
Thyroxine			
Fosamax (Alendtronate)			
Actonel (Risidronate)			
Teriparatide (PTH)			
Protelos (Strontium Ranalate)			
Pamidronate (infusions)			
Zolendronate (injection)			
Ibandronate			
Arimidex (anastrozole)			
Androgen deprivation therapy			

7. Have you taken any other drugs for greater than 3 months in the past 5 years?

Yes [ ] No [ ]

What drug?	For how Long?

8. Do you take any of the following dietary supplements?

Supplement	No	Yes	For how long
Multivitamins			
Calcium			
Vitamin D			
Other (please state)			

9. Have you ever fractured (broken) any bones? Yes [ ] No [ ]

If yes, please state how old you were, which bone(s) you broke, and how it happened, (please be as accurate and specific as possible):

Age	Bone	What Happened and how was it treated?

10. Do you, or have you in the past suffered from back pain? Yes [ ] No [ ]

If yes, how many episodes and how severe was the pain?.....

……

……

……

……

11. Have you had any falls in the last year? Yes [ ] No [ ]

If yes, now many and how did they happen?

Fall No	How did it happen	Did you sustain any injuries?

12. Have you had any orthopaedic surgery?

Operation (ie knee replacement)	Date

Lifestyle

12. Please tick which best applies to you

Never Smoked [ ]

Current smoker [ ]

Ex-smoker [ ]

Use a vaporizer [ ]

13. How much alcohol do you drink on average per week?

(1 unit = ½ pint beer, a measure of spirits or a glass of wine)

Never [ ]
Less than weekly [ ]
1-5 units per week [ ]
6-10 units per week [ ]
11-15 units per week [ ]
16-20 units per week [ ]
More than 20 units per week [ ]

14. Are you vegetarian? Yes [ ] No [ ] If yes, for how long?.....…years

Are you vegan? Yes [ ] No [ ] If yes, for how long?.....…years

15. How many cups or cans of caffeine-containing beverages (coffee, tea and soft drinks such as cola) do you drink per day?

None [ ]
1 – 5 cups/cans per day [ ]
6-10 cups/cans per day [ ]
11 – 15 cups/cans per day [ ]
More than 15 cups/cans per day [ ]

16. How much time do you typically spend taking exercise (for example walking or cycling out of doors) each day?

None [ ]

Some, but less than half an hour [ ]

Half to one hour [ ]

More than one hour [ ]

17. Please outline any sporting or other activities you do partake in, and for how much time each week you spend doing these.

……

……

……
……

The rest of the questionnaire is for completion by women only

18. How old were you when your periods started?……..

Has there been any time when your periods have stopped for a time of more than 6 months except during pregnancy? Yes [ ] No [ ]

If Yes, for how long did they stop?……

If Yes, did they stop due to contraceptive injections, implants, coils or tablets?

Yes [ ] No [ ]

19. Have you had a hysterectomy? Yes [ ] No [ ]

If yes, at what age and for what reason? Age ……..

Reason……..

Have you had your ovaries removed? Yes [ ] No [ ] Don't know [ ]

If yes, was 1 ovary removed [ ] or both removed [ ] How old were you?

20. Are you having regular periods? Yes [ ] No [ ]

21. If no, please state how often you have a period and any reason they may be irregular (ie contraceptive device)

22. Are you on, or have you ever taken the oral contraceptive pill, contraceptive implants, injections of coils?

Yes [ ] No [ ]

If yes, for how long have you taken it?…….

Please state type (ie pill, injection etc.) and name if you know……..

……..

Are you still taking it? Yes [ ] No [ ]

23. How many children have you had?……

Did you breast feed your children? Yes [ ] No [ ]

If yes, for how many months did you breast feed each baby?

Baby	1	2	3	4	5
Months breast fed					

Appendix 11. CT positioning protocol

EXAMINATION	**CONES STUDY CT DUAL ENERGY (CT1)**	
PATIENT POSITION	Feet first Supine, foot supported on affected knee so patella pointing vertically. No knee support so in full extension	
AREA SCANNED	Scan 2cm above and 2cm below the TKR	
CLINICAL INDICATION	Dual Energy CT Knee- As per Cones study protocol. Dr Anaspure to report.'	
SCANNER	**Siemens Definition Edge CT1**	**Siemens AS plus CT2** **GE Lightspeed CT3**
SCANNER PROTOCOL	RH8 DE Extremity Metal	
DOSE REDUCTION **CARE dose 4D** **kV** **Auto mA** **SAFIRE**	 On 80/140kV 3	
SLICE THICKNESS	1mm	
INTERVAL	0.7mm	
RECONS	□□□□□□□□□Algorithm I70/ Shoulder □□□□□□□□□Algorithm Q30/Spine	

ADDITIONAL REFORMATS
Once scan data has been acquired, identify the patient to CT super user for dual energy reformats.

N PROCEDURE
can will be performed in accordance with **RACT0065.**

E QUALITY
The images will be assessed by a radiographer prior to completing the scan to ensure adequate coverage and diagnostic quality.

Appendix 12. HADS Questionnaire

Hospital Anxiety and Depression Scale (HADS) Date_____ PID_____

Tick the box beside the reply that is closest to how you have been feeling in the past week.

Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions Scoring:

Total score: Depression (D) _____ Anxiety (A)_____

0-7 = Normal

8-10 = Borderline abnormal (borderline case)

11-21 = Abnormal (case)

The Lower Extremity Functional Scale

Date_____ PID_____

We are interested in knowing whether you are having any difficulty at all with the activities listed below **because of your lower limb problem** for which you are currently seeking attention. Please provide an answer for **each** activity.

Today, *do you* or *would you* have any difficulty at all with:

	Activities	Extreme Difficulty or Unable to Perform Activity	Quite a Bit of Difficulty	Moderate Difficulty	A Little Bit of Difficulty	No Difficulty
1	Any of your usual work, housework, or school activities.	0	1	2	3	4
2	Your usual hobbies, re creational or sporting activities.	0	1	2	3	4
3	Getting into or out of the bath.	0	1	2	3	4
4	Walking between rooms.	0	1	2	3	4
5	Putting on your shoes or socks.	0	1	2	3	4
6	Squatting.	0	1	2	3	4
7	Lifting an object, like a bag of groceries from the floor.	0	1	2	3	4
8	Performing light activities around your home.	0	1	2	3	4
9	Performing heavy activities around your home.	0	1	2	3	4
10	Getting into or out of a car.	0	1	2	3	4
11	Walking 2 blocks.	0	1	2	3	4
12	Walking a mile.	0	1	2	3	4
13	Going up or down 10 stairs (about 1 flight of stairs).	0	1	2	3	4
14	Standing for 1 hour.	0	1	2	3	4
15	Sitting for 1 hour.	0	1	2	3	4
16	Running on even ground.	0	1	2	3	4
17	Running on uneven ground.	0	1	2	3	4
18	Making sharp turns while running fast.	0	1	2	3	4
19	Hopping.	0	1	2	3	4
20	Rolling over in bed.	0	1	2	3	4
	Column Totals:					

Minimum Level of Detectable Change (90% Confidence): 9 points SCORE: _____/ 80 (fill in the blank with the sum of your responses)

Source: Binkley et al (1999): The Lower Extremity Functional Scale (LEFS): Scale development, measurement properties, and clinical application. Physical Therapy. 79:371-383.

Appendix 14. EQ-5D-3L Questionnaire

Quality of Life Questionnaire EQ-5D

Participant ID ..... Participant initials.....

Date.....

EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ☐

I have some problems in walking about ☐

I am confined to bed ☐

Self-Care

I have no problems with self-care ☐

I have some problems washing or dressing myself ☐

I am unable to wash or dress myself ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities ☐

I have some problems with performing my usual activities ☐

I am unable to perform my usual activities ☐

Pain/Discomfort

I have no pain or discomfort ☐

I have moderate pain or discomfort ☐

I have extreme pain or discomfort ☐

Anxiety/Depression

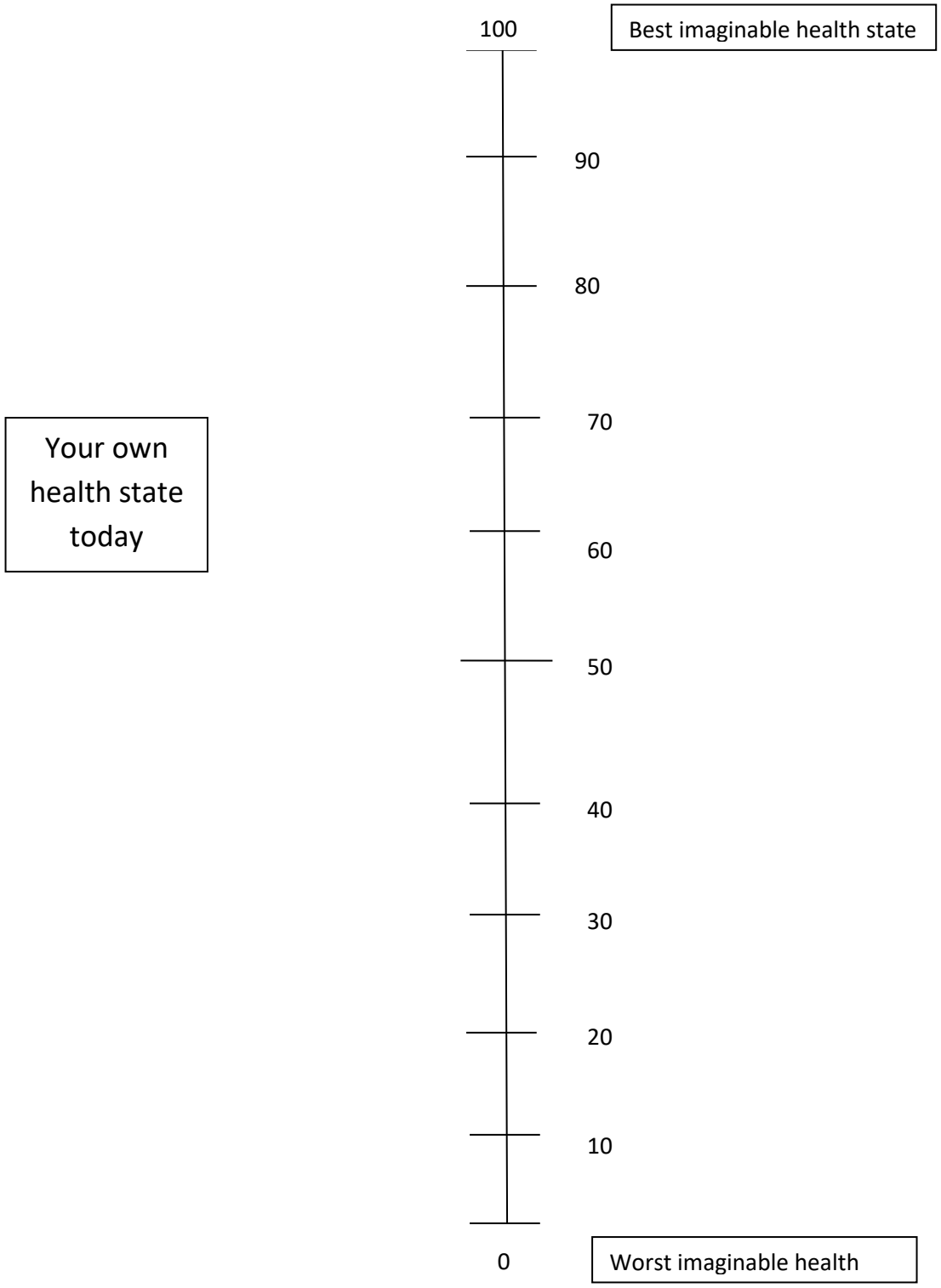
I am not anxious or depressed ☐

I am moderately anxious or depressed ☐

I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.


100
Best imaginable health state
90
80
70
60
50
40
30
20
10
0
Worst imaginable health
Your own health state today

Appendix 15. The OKS

WHAT TO DO NOW: If you have received this form by post before your appointment, please complete your questionnaire at home when received and bring it with	Study number: Patient initials:_____

Please enter your name and date of birth:	**And on what date did you complete this form?**

1: Which knee are you being reviewed for today?

☐ Left ☐ Right (go to #3) ☐ Both: Please fill in a form for **each knee** (go to #2)

2: Only if you are being reviewed for both knees: This form is for my…

☐ …Left knee ☐ …Right knee (now please go to #3)

3: If you have already had your knee replacement, please select one of the sentences below that best describes how you feel about the treatment or operation you have had:

☐ I am satisfied with the results of my surgery and I made the right choice in having the treatment

☐ I am satisfied with the results of my surgery but I would not have it again or recommend it

☐ I am not satisfied with the results of my surgery and / or I regret having the treatment

OXFORD KNEE SCORE

Please answer the following 12 multiple choice questions:

K1: During the past four weeks, how would you describe the pain you usually have from your knee?

☐ None ☐ Very Mild ☐ Mild ☐ Moderate ☐ Severe

K2: During the past four weeks, have you had any trouble with washing and drying yourself (all over) because of your knee?

☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble

☐ Extreme trouble ☐ Impossible to do

K3: During the past four weeks, have you had any trouble getting in and out of a car or using public transport (whichever you would tend to use) because of your knee?

☐ No trouble at all ☐ Very little trouble ☐ Moderate trouble

☐ Extreme difficulty ☐ Impossible to do

K4: During the past four weeks, for how long have you been able to walk before pain from your knee becomes severe? (with or without a stick)

☐ No pain for 30 minutes or more ☐ 16 to 30 minutes ☐ 5 to 15 minutes

☐ Around the house only ☐ Not at all (unable to walk)

K5: During the past four weeks, after a meal (sat at a table), how painful has

it been for you to stand up from a chair <u>because of your knee</u>?

☐ Not at all painful ☐ Slightly painful ☐ Moderately painful ☐ Very painful ☐ Unbearable

K6: During the past four weeks, have you been limping when walking, <u>because of your knee</u>?

☐ Rarely/never ☐ Sometimes, or just at first ☐ Often, not just at first

☐ Most of the time ☐ All of the time

K7: During the past four weeks, could you kneel down and get up again afterwards?

☐ Yes, easily ☐ With little or no difficulty ☐ With moderate difficulty

☐ With extreme difficulty ☐ No. Impossible

K8: During the past four weeks, have you been troubled by <u>pain from your knee</u> in bed at night?

☐ No nights ☐ Only 1 or 2 nights ☐ Some nights ☐ Most nights ☐ Every night

K9: During the past four weeks, how much has <u>pain from your knee</u> interfered with your usual work (including housework)?

☐ Not at all ☐ A little bit ☐ Moderately ☐ Greatly ☐ Totally

K10: During the past four weeks, have you felt that your knee might

suddenly "give way" or let you down?

☐ Rarely/never ☐ Sometimes, or just at first ☐ Often, not just at first

☐ Most of the time ☐ All of the time

K11: During the past four weeks, could you do the household shopping <u>on your own</u>?

☐ Yes, easily ☐ With little difficulty ☐ With moderate difficulty

☐ With extreme difficulty ☐ No, impossible

K12: During the past four weeks, could you walk down one flight of stairs?

☐ Yes, easily ☐ With little difficulty ☐ With moderate difficulty

☐ With extreme difficulty ☐ No. Impossible

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