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CHANGES IN BONE MINERAL CONTENT IN THE LUMBAR SPINE AND FEMORAL NECK IN RHEUMATOID ARTHRITIS AND JUVENILE IDIOPATHIC ARTHRITIS

– FOCUSING ON LONG-TERM DISEASE DURATION, PREMENOPAUSAL WOMEN, YOUNG ADULTS, DISEASE ACTIVITY, AND USE OF OSTEOPOROSIS DRUGS

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ACADEMIC DISSERTATION

To be publicly discussed with the permission of the Medical Faculty of
the University of Helsinki, in the auditorium of the Invalid Foundation, Tenholantie 10,
Helsinki, on 27.2.2015 at 12 noon.

Helsinki 2015

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To my family

CONTENTS

Contents

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by the Roman numerals I–IV.

I   Hämäläinen H, Kautiainen H, Kaarela K, Kotaniemi A (2005) The development of bone mineral density and the occurrence of osteoporosis from 15 to 20 years of disease onset in patients with rheumatoid arthritis. Clinical and Experimental Rheumatology 23:193–198

II   Hämäläinen H, Kaarela K, Kröger H, Kauppi M, Järvenpää S, Hakala M, Kotaniemi A (2007) Changes in bone mineral density in premenopausal women with rheumatoid arthritis during a two-year follow-up. Joint Bone Spine 74:482–487

III   Hämäläinen H, Arkela-Kautiainen M, Kautiainen H, Haapasaari J, Leirisalo-Repo M (2010) Bone mineral content in young adults with active or inactive juvenile idiopathic arthritis and in controls. Scandinavian Journal of Rheumatology 39:291–222

IV   Hämäläinen H, Kautiainen H, Pohjolainen T, Virta L, Järvenpää S, Puolakka K (2011) Use of osteoporosis drugs in patients with recent-onset rheumatoid arthritis in Finland. Clinical and Experimental Rheumatology 29:835–838

ABSTRACT

The purpose of this study was to explore bone mineral content (BMC) and bone mineral density (BMD) development and related factors in patients with rheumatoid arthritis (RA) between 15 and 20 years from disease onset (I), in premenopausal women with RA (II), and in young adults with juvenile idiopathic arthritis (JIA) (III), and to ascertain osteoporosis (OP) drug use in patients with early RA (IV). BMD of the lumbar spine and the femoral neck were measured by dual-energy X-ray absorptiometry in patients with RA in two longitudinal studies and in young adults with JIA in a cross-sectional study.

In assessing BMD at 15 years from disease onset in an inception cohort of RF-positive RA patients, it was found that eighteen out of 59 (31%) patients had OP. However, the decreases in central bone mineral in this patient group were of low degree and after the subsequent five years no essential change in central BMD was found. None of the explanatory variables: sex, age, ESR, HAQ, Larsen score, and cumulative prednisolone dose between 15–20 years from disease onset, proved to be a significant predictor of BMD change at the lumbar spine and femoral neck from 15- to 20-year check-ups (I).

In assessment of BMC and BMD development in premenopausal, regularly cycling RA patients with and without GCs and in controls, it was found that RA patients with GCs had lower BMD values than those without GCs at commencement of follow-up. Furthermore, the mean BMD decreased significantly in both lumbar spine (P=0.002) and femoral neck (P<0.001) only in the RA patients with GCs during the 2-year follow-up. However, there was no statistically significant difference between the three groups in change in BMC or projectional area in the lumbar spine or femoral neck. Comparing results on bone mineral density change between the three groups it is relevant to report changes both in bone mineral content and in projectional area to clarify the basics of the bone mineral density change. BMD is expressed as BMC per projectional area. Only weight was found to be a significant predictor of BMD change (II).

Assessment of BMC and BMD development in young adults with JIA and controls assumed to have reached their peak bone mass, showed that three (2.6%) out of 116 patients with JIA had OP. The male and female JIA patients had lower weight- and height-adjusted BMD values in the femoral neck than the controls. Dividing the patients into two groups, those with active and those with inactive JIA, both groups had lower BMC values in the femoral neck than the controls (P<0.001). Comparing BMC values in the femoral neck in both men and women with JIA a difference was found only among men (P= 0.006). Among men, use of

GCs and weight were significantly associated with BMC in the femoral neck. Among women, use of GCs, weight and also height were associated statistically significantly with BMC in the femoral neck, and among women GC use and height were also associated with BMC in the lumbar spine (III).

A total of 14 878 incident cases of RA were studied when evaluating the implementation of pharmaceutical OP drug use. Out of this total, 1351 (9%) patients with RA had purchased OP drugs, mainly bisphosphonates, during the first year after commencement of antirheumatic treatment. Of GC users, 14% of women and 6% of men were prescribed OP drugs. In addition, 8% of females and 3% of males not taking GCs received OP medication. Women were more prone to use OP medication. Of the RA patients who took GCs, 38% of women and 24% of men received concomitant calcium and vitamin D preparations by prescription during the same year, whereas the corresponding percentages for patients without GCs were 21% and 13%. (IV).

Study results suggest that bone loss takes place in earlier disease course in RA and JIA and bone loss is in the long-term disease course in RA of low degree. Further studies are needed to elucidate bone loss and OP development in early rheumatoid arthritis and to better focus the timing and means of OP prevention.

TIIVISTELMÄ

Lannerangan ja reisiluun kaulan luunmäärän muutokset nivelreumaa pitkään sairastaneilla aikuisilla ja premenopausaalisilla naisilla, sekä aktiivista että remisiossa olevaa lastenreumaa sairastavilla nuorilla aikuisilla huomioiden nivelreumaa sairastavien osteoporoosilääkkeiden käyttö.

Luun määrää ja luuntiheyttä sekä niihin vaikuttavia tekijöitä tutkittiin kahdessa nivelreumapotilaiden seurantatutkimuksessa ja lastenreumaa sairastavien nuorten aikuisten poikittaistutkimuksessa. Nivelreumapotilaiden osteoporoosilääkkeiden käyttöä vuosina 2000–2007 tutkittiin Kansaneläkelaitoksen rekistereistä huomioiden kortisonia käyttävien nivelreumapotilaiden luuston suojaaminen.

Ensimmäisessä osatyössä varhaiseen seropositiiviseen nivelreumaan sairastuneita aikuisia oli seurattu vuodesta 1973–1975 Reumasäätiön sairaalassa, Heinolassa. 74 potilasta osallistui 15-vuotisseurantaan ja uudelleen 59 potilasta 20-vuotisseurantaan, jolloin heiltä mitattiin lannerangan ja reisiluun kaulan luuntiheydet. Tutkittavien taudin aktiivisuutta, toimintakykyä, reumalääkkeiden ja kortisonin käyttöä arvioitiin. Osteoporoosia löytyi 15 vuotta nivelreumaan sairastumisesta noin kolmannekselta potilaista. Noin puolella nivelreumapotilaista olivat lievästi alentuneet luuntiheysarvot. Verrattaessa luuntiheyksiä saman ikäiseen väestöön nivelreumapotilaiden luuntiheydet olivat vain lievästi alentuneet. Tutkittavien luuntiheyksissä lannerangassa ja reisiluun kaulassa ei tapahtunut juurikaan muutosta viiden vuoden seurannan aikana. Mikään tutkituista kliinisistä tekijöistä ei selittänyt luuntiheyksien muutosta.

Toisessa osatyössä 74 nivelreumaa sairastavan naisen sekä 43 terveen verrokin lannerangan ja reisiluun kaulan luuntiheydet mitattiin tuplamittauksin kahden vuoden välein. Tutkittavilla oli säännöllinen kuukautiskierto eivätkä he olleet vaihdevuosissaan. Nivelreumaa sairastavat aikuiset jaettiin kahteen ryhmään: kortisonia käyttäviin (48) sekä kortisonia käyttämättömiin (26). Tutkittavien taudin aktiivisuutta, toimintakykyä, reumalääkkeiden ja kortisonin käyttöä arvioitiin. Seurannan alussa kortisonia käyttävillä oli alhaisemmat luuntiheysarvot lannerangassa ja reisiluun kaulassa kuin kortisonia käyttämättömillä reumaa sairastavilla. Kahden vuoden seurannassa lannerangan ja reisiluun kaulan keskimääräisen luuntiheyden lasku oli merkitsevä vain kortisonia käyttävien nivelreumaa sairastavien ryhmässä. Kuitenkin, kun tarkasteltiin luun määrän ja sen mitta-alueen pinta-alan muutosta seurannan aikana, ryhmien välillä lannerangassa ja reisiluun kaulassa ei havaittu merkitsevää muutosta. R.P. Heaney (2005) on pääkirjoituksessaan vaatinutkin, että seurantatutkimuksissa tulisi ryhmien välistä luuntiheyden muutosta aina tarkastella luunmäärän ja sen mitta-alueen pinta-alan

muutoksena. Tutkituista kliinisistä tekijöistä vain paino oli yhteydessä luuntiheyden muutokseen.

Kolmannessa osatyössä 116 lastenreumaa sairastavan nuoren aikuisen ja 68 saman ikäisen verrokin lannerangan ja reisiluun kaulan luuntiheydet mitattiin. Lastenreumaa sairastavat aikuiset oli jaettu kahteen ryhmään: aktiivista tautia sairastaviin sekä niihin, joilla ei voitu enää havaita taudin aktiivisuutta viimeiseen kahteen vuoteen. Lastenreumaa sairastavien aikuisten reisiluun kaulan luuntiheydet olivat alentuneet verrattuna verrokkeihin, erityisesti miehillä. Paino ja kortisonin käyttö olivat yhteydessä alentuneeseen luuntiheyteen. Osteoporoosia oli vain 2,6%:lla nuorista aikuisista lastenreumapotilaista.

Neljännessä osatyössä tutkittiin Kansaneläkelaitoksen rekistereistä vuosina 2000–2007 nivelreumalääkkeiden erityiskorvattavuuden juuri saaneiden nivelreumapotilaiden reseptillä ostamien osteoporoosilääkkeiden ja kortisonin käyttöä. Rekisteritietoa analysoitiin neljänä kahden vuoden jaksona, alkaen vuodesta 2000. Naisia 14 878 nivelreumapotilaasta oli 68% ja heistä iältään yli 55vuotiaita oli 55%. Ensimmäisen vuoden aikana lääkekorvattavuuden myöntämisestä osteoporoosilääkkeitä oli ostanut 9% nivelreumapotilasta, pääosin bisfosfonaatteja. Kalsium- ja D-vitamiinivalmisteita oli reseptillä ostanut 26% nivelreumapotilaista. Kortisonia käytti noin puolet nivelreumapotilaista vuosina 2000 – 2005. Heistä 24% miehistä ja 38% naisista oli ostanut reseptillä kalsium- ja D-vitamiinivalmistetta. Vastaavasti kortisonia käyttämättömistä nivelreumapotilaista 13% miehistä ja 21% naisista oli ostanut kalsium- ja D-vitamiinivalmisteita. Nivelreumapotilaista, jotka käyttivät kortisonia, osteoporoosilääkkeitä oli ostanut 6% miehistä ja 14% naisista, kun vastaavat luvut kortisonia käyttämättömillä nivelreumapotilailla olivat miehillä 3% ja naisilla 8%. Varhaista nivelreumaa sairastavilla osteoporoosilääkkeiden käyttö oli vähäistä ja tavallisinta iäkkäillä naisilla.

Havaittiin, että pitkään nivelreumaa sairastaneiden potilaiden lannerangan ja reisiluun kaulan luuntiheyden muutokset seurannan aikana olivat vähäisiä. Premenopausaalisilla nivelreumapotilailla havaittiin samantyyppinen muutos. Seurattaessa luuntiheyden muutosta ryhmien välillä on aina syytä tarkastella luuntiheyden muutoksen lisäksi myös luunmäärän ja sen mitta-alueen pinta-alan muutosta. Lastenreumaa sairastavilla nuorilla aikuisilla osteoporoosi oli vähäistä. Varhaista nivelreumaa sairastavien ja kortisonia käyttävien osteoporoosilääkkeiden reseptiostot oli vaatimattomat ensimmäisen vuoden aikana nivelreuman hoidon lääkekorvattavuuden myöntämisestä.

Lisätutkimuksia tarvitaan nivelreumaa sairastavien luuntiheyden muutoksen ja vaikuttavien tekijöiden selvittämiseksi.

LIST OF ABBREVIATIONS

ACPA   anti-citrullinated protein antibody
ACR   The American College of Rheumatology
ANA   antinuclear antibody
ANCOVA   analysis of covariance
ARA   The American Rheumatism Association
ATC   anatomical therapeutic chemical classification code of the drug
BMC   bone mineral content
BMD   bone mineral density
BMDvol   volumetric (apparent) bone mineral density
BUA   attenuation of transmitted ultrasonic waves
CI   confidence interval
CRP   C-reactive protein
CT   computer tomography
DAS28   modified disease activity score
DMARD   disease-modifying antirheumatic drug
DPA   dual-photon absorptiometry
DXA   dual X-ray absorptiometry
DXR   digital X-ray radiogammetry
ESR   erythrocyte sedimentation rate
EULAR   The European League against Rheumatism
GC   glucocorticosteroid
GIO   glucocorticosteroid-induced osteoporosis
HAQ   health assessment questionnaire
HRT   hormone replacement therapy
HSDS   height standard deviation score
HU   Hounsfield unit
ICD-10   international classification of diseases 10th version
ILAR   The Paediatric Standing Committee of the International League of Associations for Rheumatology
IQR   interquartile range
JA   juvenile arthritis
JAS   juvenile ankylosing spondylitis
JCA   juvenile chronic arthritis
JIA   juvenile idiopathic arthritis
JPA   juvenile psoriatic arthropathy
JRA   juvenile rheumatoid arthritis

LSC	least significant change
MDHAQ	multidimensional health assessment questionnaire
MTX	methotrexate
NSAID	non-steroid anti-inflammatory agent
OP	osteoporosis
PA	posterior-anterior
PBM	peak bone mass
pDXA	device designed to measure peripheral BMD in arm or leg
PRED	prednisolone
PTH	parathyroid hormone
PTHan	parathyroid hormone analogue
QCT	quantitative computed tomography
pQCT	quantitative computed tomography designed to measure peripheral
BMD	in arm or leg
QUS	quantitative ultrasound method
RA	rheumatoid arthritis
RF	rheumatoid factor
RFH	Rheumatism Foundation Hospital
RR	risk ratio
SD	standard deviation
SERM	selective estrogen-receptor modulators
SII	The Social Insurance Institute
SOS	velocity of ultrasonic waves
SPA	single-photon absorbtiometry
SXA	single-beam X-ray absorptiometry
TNF	tumor necrosis factor
VAS	visual analogue scale
WHO	World Health Organization

1   INTRODUCTION

'Osteoporosis is a disease characterised by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk' according to a study group appointed by the World Health Organization (WHO) 1994. The major fall in bone mineral density (BMD) at all sites is related to menopause (Kröger et al. 1992a, 1994, Ravn et al. 1994, Sirola et al. 2003a). Thus, postmenopausal bone loss is a strong confounding element in efforts to explain factors underlying axial bone loss among women.

Glucocorticosteroid-induced osteoporosis (GIO) is a form of secondary osteoporosis (OP) and is associated with prolonged use of glucocorticosteroids (GCs) in various inflammatory chronic illnesses such as rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) (ACR 2001). Furthermore, the role of GCs in bone loss among patients with RA is controversial and their benefit-risk ratio varies among individual patients (Strand and Simon 2003).

The most serious outcome of OP in patients with RA is fractures (Hooyman et al. 1984). The hip fracture risk is approximately doubled in RA patients and among those taking GCs (Cooper et al. 1995). GC use predicts a vertebral fracture risk even in patients with early RA (Michel et al. 1991, Peel et al. 1995). Van Staa and associates (2000) observed a GC dose dependence of fracture risk in their large retrospective cohort study conducted in a general medical practice setting. All fracture risks declined rapidly toward baseline after cessation of GC treatment.

Both ACR and EULAR have published recommendations for the prevention of OP in patients with rheumatic diseases and those who receive GC treatment. When an RA patient is started on prednisolone > 7.5mg daily for over three months, calcium and vitamin D supplementation should also be prescribed. Antiresorptive therapy should be considered when fracture risk factors are present (ACR 2001, Hoes et al. 2007).

Patients with JIA may not achieve optimal peak bone mass (PBM) during their growth and sexual maturation (Bianchi et al.1999). Disease activity itself and prolonged therapy with GC during childhood may affect patients' growth through various mechanisms (Woo 1994, Wang et al. 2002). Discontinuation of GC therapy has led to catch-up growth in 70% of children and the possibility to achieve greater final height (Simon et al. 2002). Stagi and colleagues (2010) revealed that children with JIA had delayed age at puberty onset in both boys and girls compared to the healthy Italian population.

BMD measurement forms the basis for the diagnosis of OP. BMD is measured as bone mineral content (BMC) per projectional area by dual X-ray (DXA)-

absorptiometry and expressed as g/cm² (WHO 1994). When measuring BMD in a subject over time, it is essential to distinguish between a true change in BMD and a random fluctuation related to variability in measurement procedure such as technician variability, patients' movements or other unpredictable sources (Nguyen et al. 2000, Phillipov et al. 2001, Lodder et al. 2004b). Heaney (2005) has stated in his editorial that 'all densitometric comparisons between groups should be based on BMC and area measurements, and that any use of BMD must be explicitly justified'. When comparing BMD changes over time, differences may be due to change in either BMC or projectional area or both (Hui et al. 2002).

RA is a chronic disorder with joint involvements and a variety of systemic manifestations causing functional impairment (Aletaha et al. 2010). Longitudinal studies have rarely been conducted on BMC and BMD measurements by DXA in patients with RA with disease duration exceeding over 10 years and follow-up times reaching two years or more (Hall et al. 1994, Buckley et al. 1997, Miyamoto et al. 1999, Haugeberg et al. 2002, Shibuya et al. 2002, Krieckaert et al. 2013).

2   REVIEWS OF THE CONCEPTS

2.1   EVALUATION OF BONE MINERAL DENSITY

Devices for every-day clinical use to assess noninvasively BMD in the human skeleton are decribed below. Portable, low-cost X-ray absoptiometry (pDXA) and quantitative ultrasound (QUS) devices for measurements of the peripheral skeleton, (heel, forearm and hand) have been developed for ready patient access to bone densitometry scanning. They are recommended for screening purposes, but not for diagnosis of OP (Kröger et al. 1995, Hans et al. 1996, Glüer 1997, Blake et al. 2005, Hans et al. 2008). Quantitative computed tomography (QCT) and peripheral pQCT allows 2D- and 3D-volumetric analyses of trabecular and cortical bone (Adams 2009). Digital X-ray radiogrammetry (DXR) is seeing a new renascence with automatic X-ray film reading software (Ward et al. 2003). In all, dual X-ray absorptiometry (DXA) has emerged as the "golden standard of BMD measurement" device and is the most widely used technique in clinical trials and epidemiologic studies (Genant et al. 1994, Blake and Fogelman 2009).

In both the photon absorptiometric (SPA) and the single X-ray (SXA) absorptiometric method, an analyzer measures both the transmitted radiation and the radiation attenuation at the measurement site. The analysis relies on the determination of differences in absorption values of iodine, hydroxyapatite in bone and soft tissues (water, proteins and fat) (Cameron and Sorenson 1963, Jacobson 1964). The absorptiometry is applied to the peripheral skeleton - like radius in distal parts of the forearm and calcaneus in the lower leg. The measurement requires a constant soft tissue path length, usually achieved by immersion in a water bath. The precision of measurement is 1–2%, the accuracy 4–6% (Cameron et al. 1968, Mazess and Cameron 1972, Kelly et al. 1994).

In dual-photon absorptiometry (DPA) two photoelectric peaks are applied, allowing density to be measured independently of soft-tissue thickness and composition. DPA is applied to the BMD measurement of the axial skeleton, the lumbar spine, proximal femur and total body (Christiansen et al. 1975, Christiansen and Rödbro 1977). Precision varies according to the measurement site: 1.4–3.7% at the lumbar spine, 3–5% at the hip. Accordingly, the accuracy is 5–10% at the lumbar spine and the hip (Christiansen and Rödbro 1977, Mazess and Barden 1988).

QCT utilizes X-rays and gathers information on a slice through the body using a rotate-translate scan mode and multiple rings of detectors. The tissues have different linear X-ray absorption coefficients and all clinical body computer tomography (CT) scanners are similarly calibrated to the X-ray attenuation of water, which is measured

in Hounsfield units (HU). Bone absorbs more X-rays and has a higher HU figure than water. HU can be transformed into bone mineral equivalents (g/cm^3) using the bone equivalent phantom in the scan field. 2D- and 3D-volumetric analyses give more information on cortical and trabecular bone qualities. In central QCT lumbar vertebrae L1–L3 are measured and expressed as trabecular BMD in mg/cm^3 of individual vertebrae scanned and as a mean BMD (Rüegsegger et al. 1976, Elsasser and Reeve 1980). The precision of QCT at the lumbar spine is 1.0–1.5% and the accuracy lies variably between 5% and 15% (Adams 2009). Peripheral QCT is applied to certain regions of the non-dominant forearm or tibia. Depending on the measurement site the parameters measured are expressed as total and trabecular BMC and BMD, shaft cortical BMC and BMD with many geometric parameters (Genant et al. 1982). Precision is 1–2% and accuracy lies between 2% and 8% at the radius (Genant 1997, Adams 2009, Engelke et al. 2009).

In DXR, an X-ray of the non-dominant hand is taken. The method was previously applied to the mid-point of the second metacarpal bone, but today it covers the second to fourth metacarpals, distal radius and ulna. Measurements of the total width and medullar width of a bone can be used to calculate several indices of bone status, for example the ratio of total bone width to cortical thickness, percentage cortical thickness, cortical area, the so-called Exton-Smith index, which is related to cortical area and surface area (Exton-Smith et al. 1969). Today the analysis is automated and errors are reduced considerably, to 1%, by using a digitiser inter- and intra-operator. The average BMD of the radius, ulna and second to fourth metacarpals is calculated. The precision of DXR lies between 0.68–0.61% (Jørgensen et al. 2000, Ward et al. 2003, Elliot et al. 2005). This method is recommended for screening purposes only (Reed et al. 2004).

In QUS, ultrasound is passed through bone. Bone has a mechanically anisotropic structure, which ultrasound parameters are thought to reflect. The velocity (SOS) and attenuation of transmitted ultrasonic waves (BUA) can be measured (Antich et al. 1991, Poet et al. 1994). Precision varies between 4–6% (Glüer et al. 1992, Poet et al. 1994). QUS measurements are applied to peripheral bone, mostly the heel (Kröger et al. 1995, Hans et al. 1996, Glüer 1997).

2.1.1 MEASUREMENT OF BONE MINERAL BY DUAL X-RAY ABSORPTIOMETRY

The X-ray tube produces a higher and more stable radiation flux in DXA than the gadolinium-153 radioisotope source in DPA, which allows increased precision and reduced scan times. DXA is applied to measure the BMD in grams $/cm^2$ of the lumbar spine (L1 to L4), hip (femoral neck, trochanter, Ward´s area), forearm, and total body. BMD is expressed as BMC per projectional area, g/cm^2 (Mazess and

Barden 1988). The precision of the posteroanterior DXA examination of the lumbar spine and the total hip is 1–2%, the femoral neck and trochanter 2.5%, Ward´s area 2.5–5%, peripherally in the distal forearm 1%, and in the calcaneus 1.4%. The accuracy of DXA lies between 5% and 10% (Ho et al. 1990, Kanis and Glüer 2000, Tothill and Hannan 2007, Blake and Fogelman 2008). DXA measurement is regarded as a golden standard for BMD measurement and is the most widely used technique in clinical trials and epidemiological studies (Genant et al. 1994, Blake and Fogelman 2009).

2.1.2 DEFINITION OF OSTEOPOROSIS

Some standard, T-score or Z-score, is required when measured BMD values are compared. The T-score is a patient's result interpreted in terms of the SD from the mean of sex-matched peak bone mass (PBM). The Z-score is accordingly interpreted in terms of age-matched BMD. In children and young adults up to about 18 years of age, interpretation can be made only using the Z-score. The scanner manufacturer supplies age-, sex-, and ethnically matched normal reference data (WHO 1994, Kanis et al. 2000).

The WHO has defined OP as a T-score at or below -2.5 in the lumbar spine, in the femoral neck, and total femur (WHO 1994) Table 1.

Table 1. World Health Organization study group osteoporosis classification according to T-score.

Diagnosis	T-score
Normal	> –1.0
Osteopenia	< –1.0 , > –2.5
Osteoporosis	< –2.5
Severe osteoporosis	< –2.5 plus fragility fractures

2.2 FACTORS AFFECTING BONE MINERAL DENSITY DEVELOPMENT

2.2.1 GENETIC DETERMINANTS

Genes affecting estrogen receptors and vitamin D receptors are involved in calcium homeostasis (Morrison et al. 1992, Sano et al. 1995). Genes determining neuroendocrine and inflammatory systems also appear to have an effect on bone (Stewart and Ralston 2000, Kung and Huang 2007). The condition seems to be determined by the effects of several genes on bone mass and structure, bone

turnover, bone loss and fracture risk (Gennari and Brandi 2001, Baldock and Eisman 2004, Brown et al. 2005, Ralston and Uitterlinden 2010). Family-based and twin studies have revealed that the heritability of gaining bone mass lies between 50–85% (Dequeker et al. 1987, Pocock et al. 1987, Zhai et al. 2009). There may be a familial predisposition to low BMD (Eisman 1999). In twin studies, heritability explains over all 56% of bone loss variance (Eisman 1999). A family history of fracture is a significant risk factor for fracture (Keen et al. 1999). In osteogenesis imperfecta, OP is inherited in a simple Mendelian manner (Rowe 1991).

2.2.2   PUBERTY, NUTRITIONAL FACTORS AND PHYSICAL ACTIVITY

The pre-pubertal growth spurt attaining height occurs about two years earlier in girls than boys. Girls are closer than boys to their predicted adult height peak at the same age and at the same pubertal stage (Clastre et al. 1990, Bonjour et al. 1991, Kröger et al.1992b).

PBM is defined as the amount of bone present in the skeleton at the end of the maturation process. It is mainly achieved between Tanner stages 2 and 4 of pubertal maturation and is completed by the end of the second decade of life (Bonjour et al. 1994, Bailey et al. 1999, Harel et al. 2007). Later menarcheal age in women is a risk factor for OP, though here genetic determinants of low bone mass and later puberty could be involved (Grainge et al. 2001, Chevalley et al. 2009).

Nutritional factors such as a balanced diet with adequate calory and calcium intake, are essential for normal growth and suitable PBM (Lloyd et al. 1996, Mølgaard et al. 2001, Nordin 2009, Greene and Naughton 2011). There seems to be a threshold of calcium intake, about 400mg per day, under which increasing intake of calcium is beneficial for children (Matkovic and Heaney 1992). The recommended daily allowance of calcium varies according to age, pregnancy and lactation. The daily intake recommended in Finland is shown in Table 2.

Table 2. Recommended daily calcium intake according to the National Nutrition Council of Finland

Group	Age, years	Recommended daily calcium intake, mg
Newborns	>0.5 0.5.1	360 540
Children	1—6 7—10	600 700
Youngsters	11—20	900
Adults	21—60	800
Pregnant or Weaning		900
Elderly	>60	800

Vitamin D has an important role in calcium homeostasis, increasing intestinal absorption of calcium and inhibiting parathyroid hormone synthesis and secretion (Lips 2001). Severe vitamin D deficiency leads to rickets in children and osteomalacia in adults, which in turn leads to bone deformities and increasing fracture risk (Lips et al. 1996, Heaney et al. 2000). Systematic vitamin D supplementation is recommended in infancy and in subjects not exposed to adequate solar UV radiation or vitamin D intake (Lehtonen-Veromaa et al. 1999, Outila et al. 2001, Viljakainen et al. 2006) Table 3.

Table 3. Recommended daily intake of vitamin D3 according to the National Nutrition Council of Finland

Under 2 years of age	10 µg	10 µg vitamin D3 preparation throughout the yearly recommended
2–74 years of age	10 µg	From 2 to 18 years of age 7.5 µg vitamin D3 preparation recommended for the whole year. From 60 years of age 20 µg vitamin D3 preparation throughout the yearly recommended
75 years of age and over	20 µg	20 µg vitamin D3 preparation throughout the yearly recommended
Pregnant or weaning women	10 µg	10 µg vitamin D3 preparation throughout the yearly recommended

There seems to be a window of opportunity to increase PBM by active physical exertion during pubertal development, especially combined with adequate calcium intake (Welten et al. 1994, Bonjour et al. 2001, Sundberg et al. 2001). Physical activity and particularly load-bearing exercise contributes to maintaining bone mass (Slemenda et al. 1991). Muscle mass and strength predict bone strength (Daly et al. 2008).

2.2.3   PREMENOPAUSAL BONE LOSS, PARITY, LACTATION AND MENOPAUSE

Young women may lose bone mass during amenorrhea (Miller and Klibanski 1999, Davies et al. 1990, Grainge et al. 2001, Ducher et al. 2009). Human lactation, weaning and postpartum amenorrhea, and resumption of menses induce reversible bone loss. It is suggested that during pregnancy and lactation, calcium needed for fetal and infant skeletal growth is drawn from the maternal skeleton (More et al. 2001). A systematic bone loss occurs during lactation and postpartum amenorrhea. BMD recovers after resumption of menstruation despite continued lactation (Holmberg-Marttila et al. 2000). Multiple pregnancies and extended lactation are not to be considered risk factors for future OP (Laskey and Prentice 1999, Karlsson et al. 2001).

Reduction in body weight induces bone loss in premenopausal women (Salamone et al. 1999, Fogelholm et al. 2001), whereas gain in body weight even protects from

premenopausal bone loss (Uusi-Rasi et al. 2002, Bainbridge et al. 2004). Physical activity and adequate calcium intake help to maintain bone mass (Fehily et al. 1992, Uusi-Rasi et al. 2002, Mein et al. 2004). Sex steroids and possibly early menarche are important for the maintenance of bone mass before menopause (Slemenda et al. 1996, Hui et al. 2002, Bainbridge et al. 2004).

Bone loss in the axial bone varies from a yearly bone gain of +0.3% in the lumbar spine, in the hip to a minor yearly bone loss of -0.3–1.0% in the lumbar spine, and -0.25%–0.6% in the hip according to study design, absorptiometry used, population measured and follow-up time (Ravn et al. 1994, Slemenda et al. 1996, Sowers et al. 1998, Salamone et al. 1999, Chapurlat et al. 2000).

The menopause in women is the result of physiological ovarian failure (Brambilla and McKinlay 1989). BMD loss is related to menopause. It would appear that bone loss in BMD at all sites is accelerated during the early years of menopause and then decreases (Kröger et al. 1994, Ravn et al. 1994, Sirola et al. 2003a). Periosteal apposition occurs and causes expansion of the medullar cavity of bone, increasing bone size. Periosteal apposition is inversely associated with postmenopausal estradiol levels (Ahlborg et al. 2003). Changes in body weight and especially weight loss are associated with postmenopausal bone loss. Bone markers, life style, smoking, alcohol use, physical activity, and nutritional factors do not seem to be associated (Sirola et al. 2003b). In longitudinal studies the mean annual postmenopausal bone loss in BMD lies between 0.2 to 2.1% according to the bone site measured and the method used (Riggs et al. 1986, Dennison et al. 1999, Melton et al. 2000, Uusi-Rasi et al. 2001, Warming et al. 2002, Sirola et al. 2003a).

2.3   OSTEOPOROSIS

2.3.1   CLASSIFICATION OF OSTEOPOROSIS

Primary OP is unassociated with any other disease function. It is related only to age (senile) and decreased hormonal production (postmenopausal). Secondary OP is related to certain medical conditions and medications, for example endocrine or metabolic causes, collagen and genetic disorders or nutritional factors, and medicines such as GCs (WHO 1994).

2.3.2   PROPHYLAXIS AND DIAGNOSIS OF OSTEOPOROSIS

Primary prevention of OP entails preventing the development of OP. The objective is peak bone acquisition in youngsters and preservation of bone mass. Educational resources are utilized. Nutritional factors such as adequate intake of calcium and vitamin D are advocated (WHO 1994).

Secondary prevention of OP comprises early detection of the disease or its precursors. It may thus have two major perspectives (WHO 1994, Kanis et al. 1994). Firstly, BMD can be measured in detecting those with low BMD values. Secondly, the individual fracture risk can be assessed according to known risk factors such as female gender, age, previous fragility fracture, family history of hip fracture, GC therapy, low body weight, prolonged immobilization, vitamin D deficiency, low calcium intake, excessive alcohol consumption, and cigarette smoking (Espallargues et al. 2001, Kanis 2002). The challenge is to find those individuals who run an increased risk of OP and for fracture.

Unfortunately, fractures occur over a range of bone densities (Siris et al. 2001). There is no exact cut-off point for a fracture to occur. This makes classification problematic. The WHO study group in 1994 selected a diagnostic guide for BMD measurements. OP is based on comparison of BMD values against a standard of healthy young women. It states ´a measured value of bone mineral density more than 2.5 standard deviations below the mean for young healthy adult women at any site (spine, hip or mid radius) identifies 30% of all post-menopausal women having osteoporosis, more than half of whom will have sustained a prior fracture of the proximal femur, spine, distal forearm, proximal humerus or pelvis´ (Kanis et al. 1994, Kanis and Glüer 2000). It would thus appear that BMD values will predict future fracture risk and resources of BMD measurements should be aimed at those with a high risk of fracture (Kanis 2002).

When the future facture risk of an individual is estimated three groups of individuals come into question. Two of these groups comprise such individuals who either have so high risk factors for fracture and OP that they do not need a BMD measurement to start treatment, or they have so low risk factors for fracture or OP that in any ease they do not need any treatment. In between lies a group of individuals who do need a BMD measurement to identify the need for OP treatment (Kanis 2002).

2.3.3   TREATMENT OF OSTEOPOROSIS

Calcium and vitamin D supplementation is the basis for OP treatment, aiming also at preventing fractures (Bischoff-Ferrari et al. 2005, Bischoff-Ferrari and Dawson-Hughes 2007).

Major pharmacological interventions comprise selective estrogen-receptor modulators (SERMs), bisphosphonates, calcitonin, strontium ranelate, agents derived from parathyroid hormone (PTH) and denosumabi (Delmas 2002). Hormone replacement therapy among peri- and postmenopausal women holds up bone loss and may reduce the fracture risk (Kiel et al. 1987, Torgerson and Bell-Syer 2001a, 2001b, Delmas 1997).

SERMs are non-steroidal agents which bind to estrogen receptor and act as estrogen agonists or antagonists depending on the target tissue. Raloxifene is a benzothiopene and an estrogen agonist on bone (Fontana and Delmas 2001). The effect of raloxifene in reducing the risk of vertebral fractures in postmenopausal women with OP has been studied in a 3-year Multiple Outcomes of Raloxifene Evaluation (MORE) study (Ettinger et al. 1999). The antiestrogen tamoxifen is used mainly in women with breast cancer, but it also protects bone (Love et al. 1992, Grey et al. 1995).

Bisphosphonates are pyrophosphate analogues having two PO_3 phosphonate groups covalently linked to carbon. They can be divided into nitrogen-containing and non-nitrogen-containing. Bisphosphonates have a very high affinity for bone and inhibit the resorption of bone by osteoclasts, thus turning homeostasis of bone towards bone formation. The potency of bisphophonates in inhibiting bone resorption varies, but their half-life in bone is prolonged (Russell et al. 2008). The ability of alendronate to reduce the risk of vertebral and non-vertebral fractures among postmenopausal women has been studied in the Fracture Intervention Trial (FIT) and in its vertebral fracture and clinical fracture arms (Black et al. 1996, 2000). The Health Outcomes and Reduced Incidence with Zolendronic Acid Once Yearly (HORIZON) Pivotal Fracture Trial assessed the effects of annual infusions of zolendronic acid on fracture risk during a three-year period (Black 2007). The effect of risedronate on vertebral fractures in women during a three-year period has been studied in the Vertebral Efficacy with RisendronateTherapy (VERT) Study Group (Reginster et al. 2000). Cranney and associates (2001) reviewed the effect of etidronate on fractures in postmenoausal women in a meta-analysis. The Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) evaluated the effect of ibandronate on the fracture risk in postmenoausal women after three years of use (Chesnut et al. 2004).

Calcitonin is an endogenous polypeptide hormone produced in the thyroid gland and exerts its action on osteoclasts, inhibiting bone resorption (Chesnut et al. 2000). A 5-year Prevent Recurrence Of Osteoporotic Fractures (PROOF) study revealed that nasal calcitonin may reduce the risk of vertebral fractures, while its effect on non-vertebral fractures is controversial (Chesnut et al. 2000). The European Medicines Agency has recommended (20.07.2012) that the nasal formula of calcitonin should not be used for OP treatment due to an increased cancer risk (European Medicines Agency 2012).

Strontium ranelate contains strontium between ranelatic acid molecules. It has a dual mode of action in increasing bone formation and reducing bone resorption (Meunier et al. 2004). It was shown to lower the risk of vertebral fractures among postmenopausal women during a three-year period in the Spinal Osteoporosis Therapeutic Intervention (SOTI) study (Meunier et al. 2004). The effect of strontium

ranelate on non-vertebral factures has been evaluated in the Treatment of Peripheral Osteoporosis (TROPOS) study (Reginster et al. 2005). The European Medicines Agency has recommended (21.02.2014) due to an increased risk of serious cardiac events and venous thrombosis that strontium ranelate be indicated only in those postmenopausal women and those men who have a high fracture risk and cannot be treated with other medicines approved for OP (European Medicines Agency 2014).

Agents derived from parathyroid hormone comprise the intact molecule with 1–84 amino acids and the 1–34 N-terminal fragment (teriparatide). They are given daily subcutaneously, mimicking intermittent administration of PTH, leading to an increase in bone mass and in an improvement in skeletal architecture (Jiang et al. 2003, Chen et al. 2007). They have been shown to reduce the risk of vertebral fractures (Neer et al. 2001, Greenspan et al. 2007). Teriparatide has proved to have a similar effect on non-vertebral fractures (Neer et al. 2001, Krege and Wan 2012). Their use has been limited to 24 months, as studies on rats with more long-term administration of high doses of teriparatide revealed an increased incidence of osteosarcoma (Neer et al. 2001).

Denosumabi is a long-acting human monoclonal antibody affecting osteoclasts and inhibiting bone resorption (Miller et al. 2008, 2011). It has been shown to reduce the incidence of vertebral and non-vertebral fractures in postmenopausal women (Cummings et al. 2009).

Robust long-term studies lasting longer than three years are relatively rare in the context of the OP treatments. Studies for some agents extending over five years seem to confirm maintenance of BMD levels with indirect evidence for an additional reduction in fracture incidence (Cooper et al. 2012). The antifracture efficacy up to three years of agents used in the treatment of postmenopausal osteoporosis is shown in Table 4.

Table 4. Antifracture efficacy up to three years of agents used in treatment of postmenopausal osteoporosis

Agents	Vertebral fractures	Nonvertebral fractures
Bisphosphonates [a]	Strong evidence	Good evidence
Calcitonin (nasal) [c]	Some evidence	No convincing effect
Raloxifene [d]	Strong evidence	No convincing effect
Hormone replacement therapy [e]	Good evidence	Good evidence
Strontium ranelate [r]	Strong evidence	Good evidence
Parathyroid hormone analogues*	Strong evidence	Good evidence
Denosumabi [h]	Some evidence	Some evidence

*Antifracture efficacy shown up to 18 months, Neer et al. 2001, Krege and Wan 2012
[a]Black et al. 1996, 2000, 2007, Reginster et al. 2000, Cranney et al. 2001, Chesnut et al. 2004
[c]Chesnut et al. 2000
[d]Ettinger et al. 1999
[e]Torgerson and Bell-Syer 2001a, 2001b
[r]Meunier et al. 2004, Reginster et al. 2005
[h]Cummings et al. 2009

2.4   RHEUMATOID ARTHRITIS

RA is a chronic disorder of unknown cause with a variety of systemic autoimmune and extra-articular manifestations. Its course can vary from mild to severe polyarticular illness with erosive synovial inflammation involving peripheral joints, this being characteristic of RA and manifested in particular as stiffness, pain, swelling of the joints of the hands, wrists and foreseeds (Aletaha et al. 2010).

The estimated prevalence of RA is 0.8% in seropositive RA among the Finnish population (Aho et al. 1989 and 1998). RA is more prevalent in women than in men, with a ratio 2:1. The annual incidence of RA in Finland has varied between 44.5–32 per 100 000 adults according to studies conducted in 1980, 1985, 1990 and 1995 (Kaipiainen-Seppänen et al. 1996, Kaipiainen-Seppänen and Aho 2000, Kaipiainen-Seppänen and Kautiainen 2006, Puolakka et al. 2010).

2.4.1   CLASSIFICATION OF RHEUMATOID ARTHRITIS

RA is classified according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria based on joint involvement, serology, acute phase reactants and duration of symptoms. The goal in this field is to identify patients with a relatively short duration of symptoms who may benefit from early institution of disease-modifying anti-rheumatic drug (DMARD) therapy or entry into clinical trials of promising new agents which may halt the development of the disease (Aletaha et al. 2010).

The chosen criteria are factors which best discriminate in the target population between those who are and those who are not at high risk of an erosive disease. The target population comprises patients having at least one joint with definitive clinical synovitis (swelling) and with the synovitis not better explained by another disease, i.e. early RA (Kaarela et al. 2012).

'Definite RA' is based on the confirmed presence of synovitis in at least one joint, absence of an alternative diagnosis better explaining the synovitis, and achievement of a total score of 6 or greater (out of a possible of 10) from the individual scores in four domains: number and site of involved joints (range 0–5), serological abnormality (range 0–3), elevated acute-phase response (range 0–1) and symptom duration (two levels; range 0–1) (Aletaha et al. 2010) Table 5.

Table 5. The American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for rheumatoid arthritis

Domains (A-D)	Score
Joint involvement 1 large joint[a] 2–10 large joints 1–3 small joints (with or without involvement of large joints)[J] 4–10 small joints joints (with or without involvement of large joints >10 joints (at least one small joint)	0 1 2 3 5
Serology (at least one test result is needed) Negative RF and negative ACPA Low-positive RF or low-positive ACPA High-positive RF or high-positive ACPA	0 2 3
Acute-phase reactants (at least one is needed) Normal CRP and normal ESR Abnormal CRP or normal ESR	0 1
Duration of symptoms <6 weeks ≥6 weeks	0 1

[a]Large joints refers to shoulders, elbows, hips, knees and ankles
[d] Small joints refers to the metcarpophalangeal joints, proximal interphalangeal joints, second to fifth metatrsophalangeal joints, thumb interphalangeal joints and wrists.
ACPA anti-citrullinated protein antibody
CRP C-reactive protein
ESR erythrocyte sedimentation rate

2.4.2   CLINICAL CHARACTERISTICS AND TREATMENT OF RHEUMATOID ARTHRITIS

Polyarticular joint involvement with tenderness and swelling of the small joints of the hands and foreseeds may be a common classic presentation (Ollier et al. 2001, Aletaha et al. 2010). Patients may report general symptoms such as morning stiffness, fever, fatigue, sweats and weight loss. Early peripheral joint destruction indicates a more severe disease and would appear to be associated with large joint involvement and increased functional disability (Scott et al. 2000, Jäntti et al. 2002). Disease activity seems to be associated more with functional capacity in early RA, while joint damage is associated with functional capacity in later stages (Welsing et al. 2001, Sokka et al. 2003).

Today both ACR and EULAR treatment recommendations include retarding disease activity as soon as possible and preventing and halting progression of joint damage. Remission of disease, which means absence of inflammation as determined by patient laboratory acute phase reactant and joint assessment, is the goal of treatment in RA. However, it is difficult to define remission in clinical practice (Jäntti et al. 2001, Pincus et al. 2004, 2006, Mäkinen et al. 2005).

Methotrexate (MTX) is nowadays the anchor drug in treating RA. Combination of DMARDs in early RA provides a better clinical response than is the case in treatment with a single DMARD (Möttönen et al. 2002, Moreland et al. 2012, de Jong et al. 2013). GCs have been used as a long-term low-dose strategy or as a bridge therapy when awaiting the effect of a newly started DMARD (van Riel et al. 1999, Knevel et al. 2010). Biological agents, which target cytokines and cells of the immune system, should be introduced if no response is seen with traditional DMARDs (Nam et al. 2010).

2.5   JUVENILE IDIOPATHIC ARTHRITIS

JIA is a heterogeneous condition emerging in childhood with variable clinical manifestations such as morning stiffness, pain, fatigue, and loss of function. Weight loss and failure to grow occur in children with severe disease and may lead to delayed puberty (Petty et al. 1998).

The diversity of classification criteria and selection bias are major problems in interpreting and comparing epidemiologic studies on chronic arthritis in children. According to the ILAR criteria the incidence rate was 15 per 100 000 children per year in the whole group of 315 children with JIA in Scandinavia and 21 per 100 000 per year in the Helsinki area in Finland (Berntson et al. 2003).

Similar figures for the incidence of JIA have been obtained in different regions of Europe (Moe and Rygg 1998, Hanova et al. 2006, Pruunsild et al. 2007, Modesto et al. 2010, Solau-Gervais et al. 2010).

2.5.1   NOMENCLATURE AND CLASSIFICATION OF JUVENILE IDIOPATHIC ARTHRITIS

The criteria for juvenile rheumatoid arthritis (JRA) were published by the American Rheumatism Association (ARA) in 1973 and were further revised by Brewer and colleagues in 1977. The age of patients at disease onset lay from 0 to 15 years and the disease duration was at least 6 weeks. The subgroups were systemic arthritis, pauciarticular with one to four joints affected and polyarticular arthritis with five or more joints affected.

EULAR published criteria for juvenile chronic arthritis (JCA) in 1978. Subgroups such as systemic arthritis, pauciarticular and polyarticular onset arthritis remained, but newer subgroups were introduced: juvenile ankylosing spondylitis (JAS), psoriatic arthropathy (JPA) and arthropaties associated with inflammatory bowel disease. The age of patients at disease onset lay from 0 to 15 years, but the disease duration was prolonged to 12 weeks (Wood 1978).

The Paediatric Standing Committee of the International League of Associations for Rheumatology (ILAR) introduced new criteria and the term juvenile idiopathic arthritis in 1995 (Fink 1995). These criteria were revised by Petty and associates in 1998. JIA can be divided into seven subgroups according to the clinical picture during the first six months: systemic arthritis, oligoarthritis (1–4 joints), rheumatoid factor (RF)-negative polyarthritis, RF-positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and other arthritis. The oligoarthritis form may progress to a polyarticular disease called extended oligoarthritis after 6 months. The age of patients at disease onset lies from 0 to 15 years. The disease duration is 6 weeks at minimum (Petty et al. 1998).

2.5.2 CLINICAL CHARACTERISTICS AND TREATMENT OF JUVENILE IDIOPATHIC ARTHRITIS

Articular manifestations and joint destruction can lead to limitations of movement, bony overgrowth and chronic disability (Guillaume et al. 2000, Minden et al 2002, Flatø et al. 2003, Foster et al. 2003, Packham and Hall 2002, Selvaag et al. 2005). The long-term outcome of JIA varies according to the disease sub-type (Zak and Pedersen 2000, Oen et al. 2003, Packham and Hall 2002, Ravelli 2004, Adib et al. 2005). Persistent oligoarthritis is considered the mildest form and systemic arthritis the most severe, with further susceptibility to amyloidosis (Packham and Hall 2002, Immonen et al. 2008).

Uveitis occurs in 5–20% of oligoarthritis patients (Kotaniemi et al. 2001, 2005). Other extra-articular manifestations comprise serositis or carditis and are linked to systemic onset JIA (Athreya et al. 1980, Svantesson et al. 1983, Goldenberg et al. 1992).

Treatment aims to control the inflammatory process, to preserve function and to prevent deformities of the joints. It should be started early and vigorously, the objective being to bring about remission (Beukelman et al. 2011). The treatment plan needs to be individualized according to JIA subtype (Tynjälä et al. 2011). In general, patients are considered to be in remission if they have had no active arthritis or extra-articular manifestations and no disease activity as assessed by a doctor for the past six months. Unfortunately, there is no agreement on common remission criteria (Adib et al. 2005).

It is estimated that 40 to 60% of JIA patients still continue to suffer from active disease during adulthood (Zak and Pedersen 2000, Minden et al. 2002, Flatø et al. 2003, Foster et al. 2003, Arkela-Kautiainen et al. 2005). Treatment is initiated by GCs in systemic onset JIA. A milder form such as oligoarthritis without uveitis is treated with NSAIDs. Early GCs, preferably intra-articularly, may be introduced until the diagnosis is confirmed. The second-line agents are DMARDs. MTX is generally

considered the first choice (Beukelman et al. 2011, Huppertz 2011). Biologic agents such as anti-TNF agents (etanercept, infliximab and adalimumab) are currently available and reserved for refractory JIA (Haapasaari et al. 2002, Pohjankoski et al. 2011, Tynjälä et al. 2011).

Multidisciplinary teamwork involving paediatric rheumatologists, rheumatology nurses, physio- and occupational therapeutists, social workers, psychologists, orthopedists, ophtalmologists and vocational counsellors provides coordinated care and rehabilitation besides the drug therapy line (Kuchta and Davidson 2011).

3   REVIEW OF THE LITERATURE

3.1   BONE MINERAL DENSITY IN RHEUMATOID ARTHRITIS

Disease duration and disease activity are factors threatening to lower bone mass, and it has been speculated that bone loss in patients with RA occurs early in the disease course (Laan et al. 1993a, Keller et al. 2001, Forslind et al. 2003, Lodder et al. 2004a, Tourinho et al. 2005).

In cross-sectional studies the focus has been on differences in bone mass between RA patients constantly using, ever-using and never-using GCs. Overall, patients with RA, both men and women, have seemed to have lower BMD values in the lumbar spine and in the hip than controls (Garton and Reid 1993, Peel et al. 1995, Mateo et al. 1995, Cortet et al. 1997, Sinigaglia et al. 2000, Stafford et al. 2000, Haugeberg et al. 2000a, 2000b, Nolla et al. 2006).

Laan and associates (1993b) in a double-blind placebo-controlled longitudinal study followed patients (N=40) with RA randomized to receive GC treatment or placebo for 44 weeks. The total GC dose was 1050 mg prednisone and on average 7.5 mg per day, which was tapered and stopped between 12–20 weeks. All patients were treated with aurothioglucose 50 mg weekly. Patients treated with GC lost mean lumbar trabecular BMD by 8.2% and controls gained 1.3% by 20 weeks of follow-up. They gained in mean lumbar BMD by 5.3% after cessation of GC treatment, but the placebo group lost mean lumbar BMD by 1.5% between weeks 20–44. BMD was measured by dual-energy quantitative computed tomography. For duplicate measurements, the in-vivo coefficient of variation was 6.1% for trabecular and 5.2% for cortical bone.

Hall and associates (1994) randomized postmenopausal women with RA to receive transdermal estradiol daily or calcium supplementation 400 mg daily for 2 years. Twenty-one per cent of the patients were taking corticosteroids. A total of 147 patients (84 in the calcium treatment group and 63 in the hormone replacement therapy (HRT) group) completed the study. The mean lumbar BMD increased after 2 years by 2.2% and the mean proximal femur BMD decreaseded by 0.41% in the HRT group. Correspondingly, the mean lumbar BMD decreased by 1.19% and the mean proximal femur by 0.56% in the calcium group. Differences between treatment groups were significant for the spine. BMD was measured by DXA Hologic QDR 1000/W absorptiometry. The coefficient of variation in replicate in vivo measurements was 0.9% for the lumbar spine and 1.5% for the proximal femur.

In a three-year prospective randomized, placebo controlled study of the effects of calcium 1000 mg and vitamin D 500 IU daily supplementation on bone density

Buckley and colleagues (1997) followed up 95 out of 133 patients with RA either using MTX (N=68) or non using MTX (N=27). Sixty-four out of 74 women were postmenopausal and 16% were on HRT. There were 71 users of GC. Their prednisolone daily dose was between 3.7–6.2 mg during the follow-up. The change in BMD was similar in MTX and non-MTX treated patients. BMD decreased by 2% in the lumbar spine and increased by 0.85% in the femoral neck. However, among those patients (N=28) receiving daily prednisone 5 mg or more, MTX users lost significantly more BMD in the lumbar spine (-8.08%) over 3 years than non-MTX users. BMD were measured by Lunar DPX absorptiometry. The coefficient of variation in BMD measurements was 1.2% for the antero-posterior lumbar spine and 2.2% for the femoral neck. Lateral measurement of the lumbar spine in 48 patients with RA was transformed to antero-posterior by adding the differences between the year 1 antero-posterior and lateral BMD value to the baseline lateral value.

A group under Everdingen (2003) randomly allocated patients with early active RA (N=81) to receive prednisone 10 mg or placebo and followed them for 2 years. No significant changes from baseline in BMD of the lumbar spine or the hips were seen in either group during the study.

Tengstrand and associates (2007) randomized 58 patients with RA treated with 5–7.5 mg prednisolone daily for at least 2 years either to withdraw or continue GC treatment. Eleven patients out of 26 randomized to stop GC treatment succeeded within 1 year. Their mean Z-score increased significantly by 0.50 in the lumbar spine and by 0.40 in the femoral neck from baseline to two years. Those not succeeding to taper GC treatment gained 0.08 in the lumbar spine and lost 0.08 in the femoral neck. Among the patients randomized to continue GC treatment there was a statistically significant increase by 0.35 in Z-score in the lumbar spine, as against a non-significant increase by 0.02 in the femoral neck. BMD measurements were made by Lunar DEXA and the reference population was the manufacturer's combined European/USA population.

Haugeberg and colleagues (2009) in a randomized double-blind, placebo-controlled study followed up patients with active early RA (N=20) for 12 months. Patients received infliximab + methotrexate or placebo + methotrexate. GC treatment was allowed after 14 weeks at the start of the study. The mean BMD loss was 1.26% in the lumbar spine and 1.83% in the femoral neck from baseline to 54 weeks. It was significant in the femoral neck and in the infliximab-treated group. BMD measurements were made by Lunar Expert. The percentage coefficient variation in vivo was 2.33% for the lumbar spine and 2.75% for the femoral neck.

There are only few longitudinal studies on patients with RA having both disease duration over 10 years, follow-up for at least two years and using DXA measurement for axial BMD (Hall et al. 1994, Buckley et al. 1997, Miyamoto et al. 1999, Haugeberg et al. 2002, Krieckaert et al. 2013) Table 6. (Appendix).

3.1.1 BONE MINERAL DENSITY, DISEASE ACTIVITY AND INFLAMMATION IN RHEUMATOID ARTHRITIS

In seeking to elucidate the role of disease activity and inflammation in bone loss in patients with RA, joint erosions, ESR, CRP, DAS28 and bone turnover markers have been evaluated in longitudinal studies. The lumbar spine, hip, femoral neck and hands seemed to be more sensitive to bone loss due to high disease activity, inflammation and erosions in patients with early RA (Dolan et al. 2002, Forslind et al. 2003, Book et al. 2008, Haugeberg et al. 2009). Bone loss in longer-term RA in the lumbar spine, hip, femoral neck and hands seemed to be associated with disease duration, and erosions in the hands, DAS28 (Miyamoto et al. 1999, Tengstrand et al. 2007, Güler-Yüksel et al. 2009, Wijbrandts et al. 2009, Krieckaert et al. 2013). On the other hand, active and early combination treatment with GCs seemed to arrest bone loss (Vis et al. 2006, Haugeberg et al. 2009, Wijbrandts et al. 2009).

3.1.2 BONE MINERAL DENSITY AND GLUCOCORTICOIDS IN RHEUMATOID ARTHRITIS

There was a high prevalence of vertebral deformities and clinical manifestations of vertebral fractures in RA patients on GCs when compared to those without GCs in the multicentre, cross-sectional and population-based studies conducted by groups under Hooyman (1984) and de Nijs (2001).

Reduced BMD values seem to be met in patients with long-term RA receiving GCs compared to RA patients not receiving GCs or controls. It is difficult to distinguish the effects of disease duration and severity of RA from the effect of GC treatment on BMD (Cortet et al. 1997, Buckley et al. 1997, Haugeberg et al. 2002, Engvall et al. 2011). Gough and associates (1994a) found that those who lost bone most continued to evince active disease and were on GC. It is challenging to achieve a favorable benefit to risk ratio in GC use and dosage in RA patients, as discussed by Strand and Simon 2003.

3.1.3 BONE MINERAL DENSITY, DISABILITY AND IMPAIRED PHYSICAL ACTIVITY IN RHEUMATOID ARTHRITIS

The Health Assessment Questionnaire (HAQ)-index has been found to correlate inversely with BMD development in the lumbar spine and the femoral neck in patients with RA (Tengstrand et al. 2007, Book et al. 2008, Haugeberg et al. 2009). Sinigaglia and colleagues (2000) considered HAQ score to be significantly associated with the risk of OP.

3.1.4 EXERCISE AND BONE LOSS IN RHEUMATOID ARTHRITIS

Regular dynamic strength training combined with endurance-type physical activities improved muscle strength and physical function, but not BMD, in patients with early RA in a randomized two-year study (Häkkinen et al. 2001). A long-term high-intensity weight-bearing exercise program for RA patients was effective in slowing down bone loss in the hip (de Jong et al. 2004). Physical activity reduced bone loss in premenopausal women in a two-year study (Tourinho et al. 2008).

3.1.5 OTHER RISK FACTORS FOR BONE MINERAL DENSITY IN RHEUMATOID ARTHRITIS

There is scant knowledge as to how life-style factors affect BMD in patients with RA. Tengstrand and Hafström 2002 showed that tobacco use had no effect on BMD.

3.2 BONE MINERAL DENSITY IN JUVENILE IDIOPATHIC ARTHRITIS

A group under Polito (1995) found a significant relationship between height standard deviation (HSDS) score, which describes growth and pubertal Tanner stage, and BMC in the distal radius in a cross-sectional study of children with JRA. There was no significant relationship between calcium and phosphorous intake and BMC.

Pepmueller and associates (1996) revealed depressed levels of bone formation markers and a significantly lowered BMD in the lumbar spine and total body than was the state in healthy controls.

Kotaniemi and colleagues (1997, 1999) found 13 explanatory variables for BMD, volumetric BMD (BMDvol) and bone width in cross-sectional studies of children with JCA. Significant positive variables were body size (comprising age, height, weight, Tanner stage), physical activity and calcium intake. Significant negative variables were disease activity and GCs. BMD and BMDvol were significantly decreased in the polyarticular subgroup at both the lumbar spine and the femoral neck, whereas in the oligoarthritis subgroup only BMDvol was a significant variable at the femur. Both Pereira (1998) and Cetin and their associates (1998) revealed in cross-sectional studies that there was bone loss in both the lumbar spine and the femoral neck in all three subtypes of JCA compared to healthy controls. GCs, disease activity and disease duration were important factors in the development of OP.

In a cross-sectional study of 62 children with JIA Valta and group (2007) found a low prevalence of OP, and that six out of 62 children had an asymptomatic vertebral fracture. No correlation was found between areal BMD or disease characteristics or

cumulative GC dose. Burnham and colleagues (2008) revealed that children with JIA are at risk of deleterious alternations in cortical bone strength and trabecular bone density and are prone to fracture. Markula-Patjas and associates (2012) found in a cross-sectional study of 50 patients with polyarticular or a systemic subtype of JIA 22% to have vertebral fractures, mostly thoracic. Furthermore, 30% of 50 patients had sustained at least one peripheral low-energy fracture. Compression fractures were associated with high disease activity, high body mass index and high recent cumulative doses of GC.

Hopp and associates (1991) in a longitudinal study of children with JRA found that the lumbar spine BMD in postpubertal girls was significantly lower than that in healthy controls. However, Bianchi and colleagues (1999) stated that the pubertal growth spurt and abatement of disease activity helps to maintain bone mass. In a randomized controlled trial Lovell and group (2006) found calcium and vitamin D supplementation to promote increase in BMD in the total body, but not in the lumbar spine in children with JRA.

In a longitudinal study of children with JCA Elsasser and colleauges (1982) found risk factors for vertebral fractures to be a longer duration of bed rest, GCs, reduced BMD values, and lowered serum levels of vitamin D. Furthermore, a group under Varonos (1987) in a retrospective study revealed that a cumulative GC dose of 5 g seems to be a threshold for vertebral fracture.

Lien and associates (2005) in a two-year follow-up study of children with JIA found that at baseline there was no significant difference in bone measurements between patients and healthy controls. There was a trend toward higher gains in femoral neck BMC and total femoral BMC in the controls. Changes in BMC in the lumbar spine and the distal radius were comparable in patients and controls during the follow-up. The cumulative GC dose and previous GC use were not significant predictors of reductions in bone mass gains.

Stagi and associates (2010)in a partly longitudinal study followed up 89 out of 219 children with JIA over their pubertal development, and compared bone mass and pubertal development to 80 age- and sex-matched controls. The patients showed a reduced bone mass in the lumbar spine at baseline. There was no significant improvement in bone mass in any subsets with JIA except systemic onset in comparison to controls during the follow-up. The onset age for puberty was significantly delayed in both boys and girls compared to the healthy Italian population. GC exposure in longitudinal evaluation correlated significantly with BMDvol in the lumbar spine in patients with systemic JIA onset compared to other JIA subsets.

A group under Havelka (1993) measured BMD in 26 adult women with JCA with a disease duration of between 8 to 33 years. BMD in the lumbar spine was significantly lowered in 6 out of 26 patients, all of whom were in the GC-treated

subgroup, compared to the healthy controls Table 7. Zak and group (1999) measured BMD in the lumbar spine and the femoral neck in 65 adult patients with JCA and revealed that BMD in the lumbar spine and in the hip were significantly lower than in the matched control group. Observed percentages of osteopenia and osteoporosis in both the hip and the lumbar spine were higher than expected in patients with JCA. Patients with polyarticular subtype JCA had significantly lower BMD in the hip compared to patients with pauciarticular subtype.

Haugen and associates (2000) measured BMD in the whole body, the femoral neck, lumbar spine and distal radius in 145 young adult patients with either persistent juvenile arthritis (JA) or a history of JA. Patients with persistent JA had significantly lower BMD at all measured sites compared with healthy subjects. Men with a history of JA had BMD values comparable with healthy subjects, but women with a history of JA had significantly lower BMD values in the total body and the femoral neck. Patients with a history of JA reached normal peak bone mass at the lumbar spine and forearm, despite the fact that most had had active disease during puberty.

French and group (2002) conducted a population-based study of BMD in 32 adults with JRA living in Rochester, Minnesota. Fourteen out of 32 subjects had osteopenia in at least one measured site, mainly either in the lumbar spine or the femoral neck.

Aggarwal and colleaugues (2006) assessed BMD in the lumbar spine, the left hip and the distal forearm in 30 men with active JIA and in 23 healthy men. BMD was significantly lower in the JIA group compared to controls at all measured sites. Osteopenia was detected in 73.3% of the patients and 26.7% had OP at the lumbar spine. Correspondingly, 73% out of 30 patients were osteopenic and 23.3% were osteoporotic at the hip. Osteopenia was seen 90% out of 30 patients and 12% had OP at the distal radius. The WHO criteria in Caucasian normative data were applied. A group under Thornton (2011) measured BMD in the lumbar spine and hip of 71 women and 16 men with JIA in their young adulthood attending a rheumatology clinic. Lowered BMD values were found in lumbar spine and hip in both men and women. Those with extended oligoarticular and polyarticular RF-negative subtype of JIA had lower BMD values in the hip.

Table 7. Percentages of osteoporosis in studies of young adults with juvenile chronic arthritis, juvenile rheumatic arthritis, juvenile arthritis, and juvenile idiopathic arthritis

Variable	Havelka 1993	Zak 1999	Haugen 2000	French 2002	Aggarwal 2006	Thornton 2011
Study type	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional	Cross-sectional
N (Female/Male)	26 (26/0	65 (52/13)	229 (145/84)	32 (27/5)	30 (0/30)	87 (71/16)
Mean age (SD), years	24	32 (5.7)	Women 24.9 (2.9) Men 25.2 (3.1)	27.1 (9.1)	22.09 (5.12)	Women 28.7 Men 31.4
Disease type	JCA	JCA	JA	JRA	JIA	JIA
Mean disease duration (SD), years	18	26.4 (5.6)	Women 15.6 (2.4) Men 14.9 (2.1)	NA	11.27 (5.39)	Women 20.6 Men 24.0
Number of glucocorticosteroid users	11	28	Women 34 Men 26	4	17	
Percentage of patients in remission	NA	20#	Women 60 Men 61	NA	NA	
Densitometry	DPA	DXA	DXA	DXA	DXA*	DXA
BMD measurement site	Lumbar spine Hip	Lumbar spine Hip	Lumbar spine Hip Radius	Lumbar spine Hip	Lumbar spine Hip Radius	Lumbar spine Hip
Percentage of osteoporosis	NA	Lumbar spine 7.7 Hip 7	9	0	Lumbar spine 8 Hip 7 Radius 12	
Remarks	T-score <-2.0 6/26	Control group N= 65	Control group N=96	Population-based cohort	Control group N=23	

*Caucasian normative data
#Criteria for remission different from those in Haugen et al. 2000
NA= not available
N= number, SD= standard deviation, JA= juvenile arthritis, JCA= juvenile chronic arthritis, JIA=juvenile idiopathic arthritis, DPA= dual-photon absorptiometry, DXA= dual X-ray absorptiometry

3.2.1 BONE MINERAL DENSITY, DISEASE ACTIVITY AND INFLAMMATION IN JUVENILE IDIOPATHIC ARTHRITIS

Disease activity, which is measured by ESR and bone turnover markers, appears to correlate negatively with bone mineral development in the lumbar spine and hip (Zak et al. 1999, Haugen et al. 2000, Aggarwall et al. 2006).

3.2.2 BONE MINERAL DENSITY AND GLUCOCORTICOIDS IN JUVENILE IDIOPATHIC ARTHRITIS

Groups under Bardare (1991) and Reed (1991) in longitudinal studies measured BMD in the midshaft of radius and ulna by SPA in patients with JRA, and found use of GC to have a negative association with BMD. Kotaniemi and associates (1993) in a cross-sectional study measured BMD in the lumbar spine and in the femoral neck by DXA in patients with JCA, and found GC use to have no correlation with BMD. In contrast, groups under Cetin (1998) and Pereira (1998) in cross-sectional studies of patients with JCA found especially the negative correlation of GC use to prevail in BMD of the lumbar spine. Haugen and colleagues (2000) in a cross-sectional study of BMD in the lumbar spine and femoral neck in young adults with JA found GC use partly to explain variations in BMD.

3.2.3 BONE MINERAL DENSITY, DISABILITY AND IMPAIRED PHYSICAL ACTIVITY IN JUVENILE IDIOPATHIC ARTHRITIS

When HAQ, Steinbrocker's functional classes and various inquiries into physical activity have been used to evaluate disability and physical activity, it seems obvious that patients who are more disabled and have lower levels of physical activity, will have a negative correlation with bone mass development (Zak et al. 1999, French et al. 2002, Aggarwall et al.2006, Thornton et al. 2011). Kotaniemi and associates (1999) found that calcium intake and physical activity helped to maintain BMD in patients with JCA.

3.2.4 BONE MINERAL DENSITY AND DELAYED PUBERTAL DEVELOPMENT IN JUVENILE ARTHRITIS

Disturbed growth patterns and delayed onset of pubertal development may affect bone mass development in children with JRA, JCA and JIA. Laaksonen (1966) found disturbances in growth in Finnish children with JRA. Further, Berstein and

group (1977) and later Liem and Rosenberg (2003) revealed diminished growth patterns especially in children with the systemic subset of JRA compared to poly- and pauciarticular subsets. Wang and colleagues (2002) estimated that prolonged GC treatment for more than one year can lead to irreversible growth impairment in children with JRA.

Woo (1994) reported that persistent disease activity disturbs growth in children with JCA through various mechanisms. Administration of growth hormone improved BMD parameters in patients with JCA. Kotaniemi (1997) estimated that the bone loss seems to develop with concurrent growth retardation at the spine, but without detectable growth retardation at the femoral neck in children with JCA.

Simon and associates (2002) assessed final heights in patients with JIA on long-term GCs, and revealed that chronic inflammation and prednisone therapy may adversely affect growth. Discontinuation of prednisone therapy led to catch-up growth in 70% of children and to the possibility to achieve greater final height. Valta and colleagues (2007) found normal growth in children with JIA over two years of disease duration and on systemic GC treatment for at least three months. Stagi and group (2010) revealed that children with JIA had delayed age at puberty onset in both boys and girls compared to the healthy Italian population.

3.3   PREVENTIVE OSTEOPOROSIS DRUG USE IN RHEUMATOID ARTHRITIS

A group under Soucy (2000) surveyed the practice pattern in GIO among Canadian rheumatologists via questionnaire. The initial strategy for prevention of OP was calcium and vitamin D3 (53%) in premenopausal women and HRT and calcium (29%) in postmenopausal women with RA. The pattern in the treatment of established OP was bisphosphonates (53%) in premenopausal women and bisphosphonates +/- HRT (53%) in postmenopausal women with RA.

Thiele and colleagues (2005) found that 63 per cent of patients with RA on GCs received OP treatment compared to 26% of those who were not on GC therapy. Solomon and group (2006) found that 48% received either a BMD test or a medication for OP. Patients with a prior fracture or diagnosis of OP and those receiving long-term GC treatment were much more likely to receive management.

Wall and Walker-Bone (2008) found 51 out of 58 patients with RA to fulfil criteria for bisphosphonates to receive OP treatment. Barrett-Connor and group (2009) in a longitudinal, multicenter cohort study of osteoporosis therapy in postmenopausal women in primary care including one rheumatology practice found that 63% of 4994 patients used a single osteoporosis agent, mainly bishosphonate, and 934 women (19%) were prescribed only calcium or vitamin D.

Ledwich and Clarke (2009) evaluated patients with RA with long-term GC use in an urban setting practice, but only 38.9% of them received the recommended OP treatment according to the ACR guidelines. A group under Heberlein (2011) surveyed prophylaxis and treatment of OP in 101 out of 532 patients with RA who had had both a daily dose of GC 7.5 mg or less and in DXA measurements T-scores below -2.0 at any site. Among women, 41% of 83 menopausal and 17% of 6 premenopausal women received medication with both calcium/vitamin D and bisphosphonate. Correspondingly, 42% of 12 men received medication with both calcium/vitamin D and bisphosphonate. Gamez-Nava and associates (2013) explored OP drug use in 520 patients with RA attending an outpatient rheumatology clinic during a period of three months. A total of 409 (79%) out of these 520 patients with RA had GCs, and in 21% of these patients the daily dose of GC was at least 7.5mg. All in all, 13% of the 520 RA patients and 14% of the 409 GC users received OP drugs, and 20% of the 520 RA patients received calcium and vitamin D supplements.

4   AIMS OF THE STUDY

1. To obtain information on the development of OP, BMC and BMD in the lumbar spine and femoral neck and related factors in an inception cohort of patients with RA between 15 and 20 years from disease onset (I).

2. To obtain information on BMC, projectional area and BMD development and related factors in premenopausal women with RA with or without GC treatment and in healthy controls followed up for two years (II).

3. To obtain information on the development of OP, BMC and BMD and related factors in young adults with active or inactive JIA (III).

4. To obtain information on DMARD and GC use in patients with RA and JIA and possible predictive factors for OP, BMC and BMD development

5. To evaluate the implementation of pharmaceutical OP drug use in early rheumatoid arthritis in Finland during the years 2000-2007 (IV).

5 MATERIALS AND METHODS

5.1 DEVELOPMENT OF BONE MINERAL DENSITY AND THE OCCURRENCE OF OSTEOPOROSIS 15 TO 20 YEARS FROM DISEASE ONSET IN PATIENTS WITH RHEUMATOID ARTHRITIS (I)

Table 8 shows the flow of studies I, II and III.

A cohort of 108 patients with recent onset (<6 months) and RF-positive RA were followed up from 1973–75 at the Rheumatism Foundation Hospital (RFH) in Heinola, Finland (Kaarela 1985). The follow-up examinations took place at one, three, eight and 15 years from entry. A total of 74 patients with RF-positive and erosive RA attended the 15-year follow-up in 1989, when for the first time BMD measurements were available. Viewed in retrospect they all met the 2010 ACR/EULAR classification criteria for RA (Kaarela et al. 2012).

Central BMDs were measured by DXA, Lunar DPX, Lunar Radiation Corporation, Madison, WI. The device had a wide angle fan beam technology, which meant a longer scanning time and a wider range of accuracy. The left hip could be scanned without further positioning the patient. Measurement sites were lumbar vertebrae L2–L4 in the spine and the left femoral neck. The precision of BMD measurements in adults was 1.0% in the lumbar spine and 1.8% in the femoral neck. To check for scanner-induced variability in longitudinal measurements, daily quality assurance measurements were made by a phantom provided by the manufacturer. Two women did not have BMD measured at the left hip due to endoprothesis in it. Two men and four women did not have BMD measured at the lumbar spine due to severe osteoarthrotic changes in the spine.

The use of DMARDs was registered. The cumulative dose of prednisolone from entry to 15 years of follow-up and between the 15- and 20-year check-ups was evaluated from patient registers simultaneously with determination of the erythrocyte sedimentation rate (ESR, mm/h) and C-reactive protein (CRP, mg/L).

The Larsen method was used to evaluate radiographs of hands and feet and to demonstrate the severity of RA at both 15- and 20-year follow-up visits. The joints to be interpreted were compared with standard series on a scale of 0 to 5. Joints with only soft tissue swelling or OP were assigned a Larsen grade of 0, joints with pre-erosive changes or marked space narrowing grade 1, and joints after reconstructive surgery grade 5. Grades for the 1st to 5th metacarpophalangeal joints and wrists and the 2nd to 5th metatarsophalangeal joints (20) were summed to form a Larsen score of 0–100 (Larsen et al. 1977, Larsen 1995, Kaarela and Kautiainen 1997).

Table 8. Chart of studies I, II, III

Variable	Study I	Study II	Study III
Study type	longitudinal	longitudinal	cross-sectional
Lunar DPX Lumbar vertebrae L2-L4	at 15 and 20 years from disease onset	at the start and at two years of follow-up*	
Lunar DPX Left femoral neck	at 15 and 20 years from disease onset	at the start and at two years of follow-up*	
LUNAR Prodigy Lumbar vertebrae L2-L4			x
LUNAR Prodigy Femoral neck			x
Height	at 15 and 20 years from disease onset	at the start and at two years of follow-up	x
Weight	at 15 and 20 years from disease onset	at the start and at two years of follow-up	x
The use of disease-modifying anti-rheumatic drugs	at 15 and 20 years from disease onset	at the start and at two years of follow-up	x
Larsen score of 0-100	at 15 and 20 years from disease onset	at the start and at two years of follow-up	
Health Assessment Questionnairre	at 15 and 20 years from disease onset	at the start and at two years of follow-up	
MDHAQ			x
The number and location of large joint replacements	at 15 and 20 years from disease onset		
The Ritchie articular index		at the start and at two years of follow-up	
Erythrocyte sedimentation rate	at 15 and 20 years from disease onset	at the start and at two years of follow-up	x
C-Reactive protein	at 15 and 20 years from disease onset	at the start and at two years of follow-up	x
S-Calcium		at the start of follow-up	
S-Albumin		at the start of follow-up	
S-Phosphate		at the start and at two years of follow-up	
S-Parathormone		at the start of follow-up	
S-D-25 hydroxyvitamin D		at the start of follow-up	
Modified Disease Activity Score DAS28		at the start and at two years of follow-up	
HLAB27 factor and Antinuclear antibody			x
Pain Visual Analogue Scale			x

*Double measurements, MDHAQ= multidimensional health assessment questionnaire

Accordingly HAQ was registered. The HAQ includes questions on activities of daily living, 20 activities grouped into 8 categories. The highest score for each of these eight categories is summed (range 0–24) and divided by eight to yield a continuous scale (0–3). In HAQ scoring, 0 represents good functional ability and 3 the poorest (Fries et al.1980). The number and location of large joint replacements were registered at the 20-year follow-up. Height and weight were measured at both visits.

5.2 CHANGES IN BONE MINERAL DENSITY IN PREMENOPAUSAL WOMEN WITH RHEUMATOID ARTHRITIS DURING A TWO-YEAR FOLLOW-UP (II)

Women attending wards in the RFH, Heinola, Finland, during the years 1991–95 were consecutively recruited for a two-year study of bone mass and RA. Premenopausal women (N=74) were eligible if they had RA and were menstruating regularly. Women who were pregnant, planning pregnancy, or taking oral contraceptives or other medications possibly affecting bone metabolism were ineligible. The use of DMARD and cumulative prednisolone (PRED) dose and calcium supplementation was evaluated.

Subjects were divided into two groups: 48 women with RA and with prednisolone, the RA with PRED group (mean age 37, SD 5 years), and 26 women with RA and without prednisolone, the RA without PRED group (mean age 37, SD 6 years). The control group (N=43) comprised age-matched, premenopausal, regularly menstruating healthy subjects recruited from the local population and hospital staff. Their mean age was 37 (SD 5) years.

Central BMDs were measured by DXA, Lunar DPX, Lunar Radiation Corporation, Madison, WI, the measurement sites being the three lumbar vertebrae L2–L4 in the spine and the left femoral neck as in study I. Furthermore, in comparing BMD changes over time, differences may be due to change in either BMC or projectional area or both. Thus, double measurements were made at all skeletal sites for all subjects at the start and at 24 months of follow-up.

The Larsen score of 0–100 was used to evaluate radiographs of hands and foreseed, and to demonstrate the severity of RA at both start and 2-year follow-up visits (Larsen et al. 1977, Larsen 1995, Kaarela and Kautiainen 1997) and correspondingly HAQ was registered (Fries et al. 1980).

Height and weight were measured, and women with RA were examined for swollen and tender joints. The Ritchie articular index scores 53 joints as 26 joint groups, and each joint group was scored on a scale of 0–3. The Ritchie articular index ranges from 0 to 78, (26 times 3) (Ritchie et al. 1968).

Blood samples were drawn for measurements for ESR, (mm/h), CRP, (mg/L), serum calcium (Ca, mmol/L), albumin (Prot, g/L), phosphate (Pi, mmol/L), parathormone (PTH, ng/L), and 25-hydroxyvitamin D (S-D-25, nmol/L) at the start of follow-up. We had no data on estrogen levels in our study subjects.

The Modified Disease Activity Score (DAS28) is calculated by a complex mathematical formula, which includes the number of tender and swollen joints: shoulder, elbow, wrist, upper metacarpophalangeal and proximal interphalangeal and knee (a total of 28), ESR, and the patient's 'global assessment of global health' (indicated by marking a 10 cm line between very good and very bad). A DAS28 score greater than 5.1 implies active disease, less than 3.2 well controlled disease, and less than 2.6 remission (Prevoo et al. 1995).

5.3 BONE MINERAL CONTENT IN YOUNG ADULTS WITH ACTIVE OR INACTIVE JUVENILE IDIOPATHIC ARTHRITIS AND IN CONTROLS (III)

From the files of juvenile patients (aged <16 years) treated at the RFH, Heinola, Finland, children born between 1976 and 1980 were identified, altogether 587. Data on patients who had been diagnosed as suffering from JA were collected; 189 patients were thus excluded as having some other diagnosis than JA. From among the remaining 398 patients those in whom JA was diagnosed at the RFH were collected. This led to the exclusion of a further 211 patients as their treatment had been initiated elsewhere.

The comparability of the study group and the withdrawal group was analyzed and no difference was found in the distribution of diagnoses and clinical characteristics. The only difference between the groups was in the proposition of men, 28% in the study group, and 43% in the remainder.

There were thus 187 patients with early untreated JIA whose diagnosis was made at the RFH and treatment initiated there. Four had Down's syndrome and could not attend due to social and educational problems. Two patients had died due to accidental causes. All these patients were reclassified using JIA (Petty et al. 1998) criteria. Thus 181 patients were invited by mail to take part in the study. There were 20 refusals, 12 could not be reached, 26 could not make time for the visit and three did not fulfil the JIA criteria.

Altogether, 120 patients (68%) participated, but 116 (33 men and 83 women) comprised the final study group, as four patients were pregnant. The mean age was 23 (SD 1.8) years for men and 23 (SD 1.5) for women. Seventy-four out of the 116 (26 men and 48 women) had oligoarthritis and 42 (seven men and 35 women) polyarthritis subset of JIA. Fifteen out of 74 patients with oligoarthritis at onset were classified as having the extended form.

The JIA patients were further divided into two groups: those having active disease (the JIA-active group, N=73) and those in remission (the JIA-inactive group, N=43). A patient was considered to be in remission at check-up if ESR was < 20 mm/h, morning stiffness lasted < 15 minutes, there were no tender or swollen joints, and the patient had been off DMARDs, or GCs for at least the past two years. The control group comprised 21 men and 47 women between 21 and 26 years of age gathered from the local population. The mean age was 23 (SD 1.7) years for men and 23 (SD 1.4) years for women.

BMC measurement was carried out at the lumbar spine and the proximal femur, using LUNAR Prodigy, Lunar Radiation Corporation, Madison WI. This is a DXA-absorptiometry-using digital beam device providing shorter scanning time and better accuracy than Lunar DPX. Both hips could be scanned simultaneously without further positioning of the patient. The software of the absorptiometry guides the operator during the examination to follow the examination protocol. The precision of BMD measurements in adults was 0.10% [95%CI: 0.02 to 0.04] in the lumbar spine and 1.21% [95%CI: 0.02 to 0.04] in the femoral neck.

Height, weight, diagnosis, time from diagnosis to check-up, and disease duration, ESR (mm/h), CRP (mg/L), HLAB27-factor, antinuclear antibody (ANA), and DMARD and prednisolone use were evaluated.

Pain was evaluated by a 10 cm Visual Analogue Scale (VAS). The scoring was 0, representing no pain, to 100, representing pain as severe as could be endured (Huskisson 1974).

The multidimensional health assessment questionnaire (MDHAQ) includes 10 activities, one from each eight category of the HAQ plus two items concerning advanced function, and three items on psychological stress; pain, global and fatigue VAS. Scoring in MDHAQ was from 0 to 3, 0 representing good functional ability and 3 the poorest (Pincus et al.1999).

5.4 USE OF OSTEOPOROSIS DRUGS IN PATIENTS WITH RECENT-ONSET RHEUMATOID ARTHRITIS IN FINLAND (IV)

Finland provides general health insurance covering the entire population. The Social Insurance Institution (SII) reimburses 42% of the costs of medication prescribed by a doctor. Patients with certain chronic and severe diseases such as RA are entitled to a special reimbursement rate (72% or 100%) to defray drug costs. To establish entitlement, a patient must file a doctor's certificate based on clinical examination by a rheumatologist describing the appropriate diagnostic procedure, giving the ICD-10 code, and providing a treatment plan according to good clinical practice. The International Classification of Diseases (ICD) and its 10th version have been

designed to promote international comparability in the collection, processing and classification and presentation of mortality statistics and medical files. The ICD-10 codes M05, seropositive RA and M06 seronegative RA were used to identify patients. Codes M05 and M06 are used by rheumatologists in early RA and these codes are required for entitlement to the higher reimbursement granted by the SII.

Reimbursement decisions were recorded in a nation-wide register in 2000-2007. From this register those RA patients were obtained who during the period from 1.1.2000 to 31.12.2007 were for the first time granted special reimbursement for medication for RA (DMARDs and GCs).

The SII also keeps a prescription register which collects and stores data on purchases of all reimbursed drugs, including the date of purchase, the amount of medication and the Anatomical Therapeutic Chemical classification (ATC) code of the drug. The ATC codes of the drugs used were: M05BA04, M05BB03, M05BB04, M05BA06, M05BA01, M05BA03, M05BA03, M05BA08, H05BA01, G03XC01, H05AA02, H05AA03, M05BX03, A11CC05, A11CC01, A12AA04, A12AA02, A12AA12, A12AX, H02AB06, H02AB07, H02AB01, H02AB08, H02AB09, H02BX01.

By means of these registers, data on the OP medication which index patients with RA had purchased was obtained. The focus was exclusively on medication during the first treatment year. Information for 30 days before and up to 365 days after the index day was included to take into account medications bought after the first doctor visit but before the reimbursement decision. Data on four two-year periods: 2000–1, 2002–3, 2004–5, and 2006–7 were analysed.

In Finland, preparations containing calcium and vitamin D, which are also used in OP preventions, were available over the counter; data on their overall use could thus not be obtained. Many preparations, however, were included in the reimbursement system and reimbursed (42%) to the patient, if purchased upon doctor's prescription. Data on these purchases were gathered. Some GC preparations were temporarily excluded from the reimbursement system during the years of 2006 and 2007, which caused some bias. Consequently, GC use only from 2000 to 2005 inclusive was analysed. HRT was not included, as it is indicated mainly for reasons other than OP per se. The prescription register does not collect data on medications used in hospitals and institutions.

5.5 STATISTICAL ANALYSIS

Results are expressed as mean or median, SD or interquartile range (IQR), and 95 per cent confidence intervals (95%CI). Statistical comparison between groups was made using either t-test or permutation (Monte Carlo P-value) test or Chi-square test.

Analysis of covariance (ANCOVA) was used to analyse BMC between groups, followed by a Sidak test. The normality of variables was evaluated by Shapiro-Wilk statistics. Correlation coefficients were calculated by the Spearman method.

Regression analyses with biased corrected bootstrapping (10,000 replications) confidence intervals were used to model the relationship between BMD change and predictor variables. A generalized linear model with the binomial family, log link, was used to produce the adjusted relative risk (RR).

Repeated measures were analyzed using generalized linear mixed models. Fixed effects were group, time, and time-group interaction, and the covariate was weight. Subject effects were assumed to be random. This is the most suitable technique for estimating rates of change, allowing for the correlation structure (unstructured) of repeated measures data.

Associations of BMC with explanatory variables were analyzed using robust regression. The α level was set at 0.05 for all tests.

6 RESULTS

6.1 BONE MINERAL DENSITY IN PATIENTS WITH RA (STUDIES I, II)

In study I at the 15-year check-up 18 (31%) out of 59 patients had OP and 32 (54%) patients were osteopenic. After the subsequent five years the mean Z-score increased 0.45 at the lumbar spine and the mean T-score decreased 0.20 at the femoral neck. Correspondingly, the mean change in BMD was 0.01 g/cm² in the lumabr spine and 0.02 g/cm² in the femoral neck during the five years of follow-up.bv

In study II, assessing BMD change in 74 patients with RA, the patients in the RA with PRED group had lower BMD values than those in the RA without PRED group at commencement of follow-up. The mean weight-adjusted BMD percentage change in the lumbar spine up to two years was -1.5% in the RA with PRED group, +0.6% in the RA without PRED group and -0.6% among the controls; a significant difference (P=0.030) was found between the RA groups. Correspondingly, the mean weight-adjusted BMD percentage change in the femoral neck to two years was -2.6% in the RA with PRED group, +0.4% in the RA without PRED group and -0.9% among the controls, the difference between the RA groups being again significant (P=0.049).

However, when BMD is expressed as BMC and projectional area there was no statistically significant difference between the three groups in change in BMC or projectional area in the lumbar spine or femoral neck.

The mean BMC percentage change in the lumbar spine was -2.2% in the RA with PRED group (P =0.003), +0.0 in the RA without PRED group and -0.6% in the control group. Correspondingly, the mean BMC percentage change in the femoral neck was -1.9% (P=0.006), -0.4% and -0.8%, respectively, Table 9.

Table 9. Bone characteristics at baseline and change up to two years in controls and patients with RA in study II.

Bone characteristic	Baseline			Change to 2 years			P-value Between groups (multiple comparison)‡
	Controls Mean (SE)†	RA Mean (SE)	RA with PRED Mean (SE)	Controls Mean (95%CI)	RA Mean (95%CI)	RA with PRED Mean (95% CI)	
Lumbar spine							
BMD, g/cm²	1.22 (0.02)	1.19 (0.03)	1.11 (0.02)	-0.01 (-0.02 to 0.00)	0.01 (-0.01 to 0.02)	-0.02 (-0.03 to -0.01)	0.030 (RA/GC)
BMC, g	52.7 (1.2)	51.4 (1.6)	48.9 (1.2)	-0.30 (-1.05 to 0.45)	0.01 (-0.93 to 0.95)	-1.07 (-1.78 to -0.37)	0.14
Area, cm²	42.9 (0.5)	42.9 (0.7)	43.6 (0.5)	-0.03 (-0.40 to 0.34)	-0.20 (-0.65 to 0.25)	-0.25 (-0.59 to 0.09)	0.67
Femoral neck							
BMD, g/cm²	0.96 (0.02)	0.91 (0.02)	0.88 (0.02)	-0.01 (-0.02 to 0.00)	0.00 (-0.01 to 0.02)	-0.02 (-0.04 to -0.01)	0.049 (RA/GC)
BMC, g	4.60 (0.09)	4.43 (0.12)	4.20 (0.09)	-0.03 (-0.10 to 0.03)	-0.02 (-0.09 to 0.06)	-0.08 (-0.13 to -0.02)	0.37
Area, cm²	4.78 (0.05)	4.81 (0.06)	4.77 (0.04)	0.01 (-0.07 to 0.10)	0.00 (-0.08 to 0.13)	-0.02 (-0.10 to 0.05)	0.70

† Mixed model with REML estimation, weight at baseline as covariate.
‡ Statistically significant difference (p<0.05) between groups detected by Sidak's test.
RA= rheumatoid arthritis, PRED= prednisolone, BMD= bone mineral density, BMC= bone mineral content, GC= glucocorticosteroid

6.2 BONE MINERAL CONTENT IN YOUNG ADULTS WITH JIA (STUDY III)

The mean BMC in the femoral neck was 5.76 (SD 0.21) g for men and 4.74 (SD 0.10) g for women in the JIA-active group; 5.84 (SD 0.23) g for men and 4.59 (SD 0.06) g for women in the JIA-inactive group; and 6.65 (SD 0.20) g for men and 4.78 (SD 0.07) g for women in controls.

Both JIA groups had lower BMC values in the femoral neck than the controls (P <0.001). In comparing BMC values in the femoral neck in men and women with JIA, a significant difference was found among men (P=0.006). There was no significant difference in weight-, height- and sex-adjusted BMC values in the lumbar spine between JIA groups and controls (P=0.33), nor was there any significant difference between men and women (P=0.43 and 0.59, respectively).

The male and female JIA patients had significantly lower weight- and height-adjusted BMD values in the femoral neck than the controls, but according to T-score < -2.5, only three [2.6%(95%CI: 0.5 to 7.4)] out of 116 patients with JIA had OP.

6.3 USE OF DMARDS AND GLUCOCORTICOIDS (STUDY I, II, III)

In study I, at the first visit during the years 1973–1975, 90% of patients had received treatment initially with gold sodium thiomalate, hydroxychloroquine, penicillamine and/ or prednisolone or their combinations. Sulfasalazine was introduced in the treatment regimen after 1982. Only six patients used methotrexate periodically during the years 1991–96 (Jäntti et al. 2002). GC use among patients with RA from entry to the 15-year-, and between the 15- and 20-year follow-ups is set out in Table 10.

Table 10. Glucocorticosteroid use from entry to the 15-year- and between the15- and 20-year follow-ups in 59 patients with RA in study I.

Variable	men	women
Median (IQR) cumulative dose of prednisolone from entry to 15-year follow-up, g	8.0 (0.00 , 15)	1.0 (1 , 9)
Median (IQR) cumulative dose of prednisolone from 15-year to 20-year follow-up, g	0.5 (0.00 , 6.12)	1.0 (0.00 , 6.75)

RA= rheumatoid arthritis, IQR= interquartile range

In study II, treatment of RA patients consisted mainly of single DMARDs: 73% in both the RA without PRED group and the RA with PRED group. None of the patients in the RA without PRED group had previous corticosteroid treatment. The median (IQR) cumulative dose of prednisolone before the outset was 4.0 (0.5 , 9.0) g and the median duration of previous GC use was two years in the RA with PRED group. The median (IQR) cumulative dose of prednisolone during the two-year follow-up was 3.6 (1.5 , 4.5) g in the RA with PRED group. There was no difference in serum Ca, Pi and PTH values between the two RA groups.

In study III, patients in both JIA groups used DMARDs mainly as single therapy. Table 11 shows DMARD and glucocorticoid use among JIA patients during their disease course.

Table 11. Number of glucocorticosteroid users and median time on both disease-modifying anti-rheumatic drug and glucocorticosteroid in 116 patients with JIA in study III.

Variable	JIA active group N=73	JIA inactive group N=43
Number and percentage of GC users	35* (48)	7 (16)
Median (IQR) time on GC use, years	4.8 (0.7 , 8.8)	1.1 (0.7 , 3.5)
Median (IQR) time on on DMARDs, years	13.3 (6.6 , 19.9)	3.4 (2.1 , 8.8)

*P<0.001
GC= glucocorticosteroid, DMARD= disease-modifying anti-rheumatic drug, IQR= interquartile range, JIA= juvenile idiopathic arthritis

6.4 DISEASE SEVERITY AND REMISSION (STUDIES I, II, III)

In study I at the 15-year follow-up, the median (IQR) ESR was 32 (18 , 48) in men and 20 (11 , 41) in women. Between the 15- and 20-year follow-up visits the median difference in ESR was 2 [95%CI: -6 to 2], (P=0.32). Correspondingly, the median (IQR) CRP was 14 (3 , 63) in men and 2 (2 , 24) in women. Between the two follow-ups the median difference in CRP was 2 [95%CI: -2 to 4], (P=0.53). Furthermore, at the 15-year follow-up the median (IQR) Larsen score of 0-100 was 44 (32 , 62) in men and 33 (17 , 61) in women. Between the 15- and 20-year follow-up visits the median difference in median Larsen score of 0-100 was 6 [95%CI: 4 to 6] points, (P<0.001).

In study II at the start of follow-up the mean DAS28 score was 3.8 in the RA without PRED group and 4.4 in the RA with PRED group. During the two-year follow-up the mean DAS28 score decreased by 0.22 (95%CI: -0.67 to -0.22) in the RA with PRED group and by 0.30 [95%CI: -0.91 to 0.32] in the RA without PRED group, but the decrease was not significant. Correspondingly, the median (IQR) Larsen score of 0–100 at the start of follow-up was 16 (7 , 34) in RA without PRED and 31 (7 , 64) in the RA with PRED group. Furthermore, during the two-year study period the median Larsen score of 0–100 increased by 8 points, [95%CI: 5–9] in the RA with PRED group and by 3 points, [95%CI: 2–8] in the RA without PRED group (P=0.074).

In study III 18 out of 33 (55%) men and 25 out of 83 (30%) women were in remission (P= 0.014). The median (IQR) ESR was 3 (2 , 5) in men and 9 (5 , 13) in women and the median (IQR) CRP was 2 (2 , 3) and 2 (2 , 3), respectively. The mean MDHAQ FN-score was 0.13 (SD 0.30) in men and 0.15 (SD 0.30) in women.

6.5 PREDICTIVE FACTORS FOR BONE MINERAL DENSITY (STUDIES I, II, III)

Concerning the clinical data in study I none of the explanatory variables: sex, age, ESR, HAQ, Larsen score, and cumulative prednisolone dose between 15–20 years from disease onset, was found to be a significant predictor of BMD change at the lumbar spine and femoral neck in the 15- to 20-year check-ups.

Furthermore, concerning the clinical data in study II none of the explanatory variables: age, ESR, CRP, number of tender or swollen joints, HAQ, Larsen score, and cumulative prednisolone dose was found to be a significant predictor of BMD change at the lumbar spine or femoral neck. Only weight emerged as a significant predictor of BMD change, Table 12.

Table 12. Main results of multivariate analyses modeling the relationship between bone mineral density changes and clinical variables in 74 patients with RA in study II

Explanatory variables	Regression model			
	Lumbar spine		Femoral neck	
	β † (95% CI ‡)	P-value	β † (95% CI ‡)	P-value
Age, years	0.06 (-0.43 to 0.63)	0.81	-0.04 (-0.51 to 0.55)	0.87
Weight, Kg	0.74 (0.29 to 1.25)	0.003	0.65 (0.23 to 1.14)	0.004
Duration of disease, years	0.11 (-0.38 to 0.66)	0.63	-0.40 (-0.87 to 0.12)	0.10
ESR, mm / h	0.08 (-0.25 to 0.06)	0.27	-0.09 (-0.23 to 0.03)	0.34
CRP, mg/L	-0.08 (-0.25 to 0.09)	0.32	-0.09 (-0.23 to 0.03)	0.10
Number of swollen joints	-0.15 (-0.82 to 0.54)	0.66	-0.16 (-0.69 to 0.38)	0.54
Number of tender joints	0.03 (-0.62 to 0.66)	0.91	-0.16 (-0.66 to 0.40)	0.50
Health Assessment Questionnaire	-4.1 (-13.0 to 3.5)	0.34	-2.0 (-9.19 to 3.81)	0.54
Cumulative prednisolone dose, g	-0.03 (-0.28 to 0.27)	0.81	-0.04 (-0.51 to 0.55)	0.48
Constant	74.9		64.5	

† Coefficients multiplied by 100.
‡ 95% confidence interval obtained by bias corrected bootstrapping (10 000 replication).
RA = rheumatoid arthritis
ESR = erythrocyte sedimentation rate
CRP = C-reactive protein

Study III showed in regression analysis that among men, use of GCs and weight were significantly associated with BMC in the femoral neck. Among women, use of GCs, weight and also height were associated statistically significantly with BMC in the femoral neck, and among women GC use and height were also associated with BMC in the lumbar spine.

6.6 USE OF OSTEOPOROSIS DRUGS IN PATIENTS WITH RECENT-ONSET RA

All officially known 14 878 incident cases of RA in Finland from 1.1.2000 to 31.12.2007 were identified. Of these, 10 119 (68%) were female and 4739 (32%) male. The male-female ratio was 1:2.1. Mean age, percentage of MTX, GC, calcium and vitamin D users are shown in Table 13.

Table 13. Mean age, and percentages of methotrexate, glucocorticosteroid, and calcium and vitamin D users during the first drug treatment year in 14 878 cases of early RA in study IV.

Variable	Men N=4739	Women N=10 119
Mean age (SD), years	56 (15)	57* (14)
Percentage of MTX users	56	58
Percentage of GC users[a]	52	49
Percentage of calcium and vitamin D users by a doctor´s prescription[a]	19	29

*55% of the women were 55 years of age or older
[a]During the period 2000 to 2005 inclusive
MTX= methotrexate, GC=glucocorticosteroid, RA= rheumatoid arthritis, SD= standard deviation

A total of 1351 (9%) patients with RA (11% of females and 5% of males) had purchased OP drugs during the first year after commencement of antirheumatic treatment. Women were more likely to use OP medication. Consequently, the age-adjusted relative risk of purchase was 2.60 (95% CI 2.26 to 2.99) for women compared to men.

Bisphosphonates constituted the bulk of purchases. Calcitonin was used by 7%. Purchases of SERMs and PTHan were almost negligible. During the first year, 26% of patients (29% of females and 19% of males) received calcium and vitamin D supplementation on doctor's prescription.

The use of OP drugs during the years 2006 – 2007 increased over time compared to 2000–2001. RR (95% CI) for purchase was 1.62 (1.38 to 1.92) in women and 2.10 (1.34 to 3.30) in men. During the year 2006, 12% of women and 5% of men bought OP medication within 365 days of the index day. The highest proportion was found for the age groups 75 to 79 years.

Patients on OP medication received MTX marginally more often (in women 61% and in men 57%) than other DMARDs. Of RA patients who took GCs, 38% of women and 24% of men received concomitant calcium and vitamin D preparations by prescription during the same year, whereas the corresponding percentages for patients without GCs were 21% and 13%.

Of GC users, OP drugs were prescribed to 14% of women and 6% of men. In contrast, 8% of females and 3% of males not taking GCs received OP medication.

In multiple regression analysis, GC use was determined as a "risk factor" for OP medication: its risk ratio (RR) was 1.45 (95% CI 1.31 – 1.61), whereas female gender had an RR of 2.54 (95% CI 2.21 – 2.91) and higher age had an RR of 1.060 (95% CI 1.057 – 1.065).

6.7   SUMMARY OF THE RESULTS

In assessing BMD at 15 years from disease onset in an inception cohort of RF-positive RA patients, it was found that eighteen out of 59 (31%) patients had OP. However, the decreases in central bone mineral in this patient group were of low degree and after the subsequent five years no essential change in central BMD was found. None of the explanatory variables: sex, age, ESR, HAQ, Larsen score, and cumulative prednisolone dose between 15–20 years from disease onset, proved to be a significant predictor of BMD change at the lumbar spine and femoral neck from 15- to 20-year check-ups (I).

In assessment of BMC and BMD development in premenopausal, regularly cycling RA patients with and without GCs and in controls, it was found that RA patients with GCs had lower BMD values than those without GCs at commencement of follow-up. Furthermore, the mean BMD decreased significantly in both lumbar spine (P=0.002) and femoral neck (P<0.001) only in the RA patients with GCs during the 2-year follow-up. However, there was no statistically significant difference between the three groups in change in BMC or projectional area in the lumbar spine or femoral neck. BMD is expressed as BMC per projectional area. Only weight was found to be a significant predictor of BMD change (II).

Assessment of BMC and BMD development in young adults with JIA and controls assumed to have reached their peak bone mass, showed that three (2.6%) out of 116 patients with JIA had OP. The male and female JIA patients had lower weight- and height-adjusted BMD values in the femoral neck than the controls. Dividing the patients into two groups, those with active and those with inactive JIA, both groups had lower BMC values in the femoral neck than the controls (P<0.001). Comparing BMC values in the femoral neck in both men and women with JIA a difference was found only among men (P= 0.006). Among men, use of GCs and weight were significantly associated with BMC in the femoral neck. Among women, use of GCs, weight and also height were associated statistically significantly with BMC in the femoral neck, and among women GC use and height were also associated with BMC in the lumbar spine (III).

A total of 14 878 incident cases of RA were studied. Out of this total, 1351 (9%) patients with RA had purchased OP drugs, mainly bisphosphonates, during the first year after commencement of antirheumatic treatment. Of GC users, 14% of

women and 6% of men were prescribed OP drugs. In addition, 8% of females and 3% of males not taking GCs received OP medication. Women were more prone to use OP medication. Of the RA patients who took GCs, 38% of women and 24% of men received concomitant calcium and vitamin D preparations by prescription during the same year, whereas the corresponding percentages for patients without GCs were 21% and 13%. (IV).

7 DISCUSSION

7.1 THE STUDY POPULATIONS

Study I comprised RF-positive and erosive RA patients from the Heinola community-based inception cohort. Follow-up initiated at the RFH in 1973-75 involved 108 patients with age 16 years or more, swelling in at least one joint, and duration of complaint not more than six months (Kaarela 1985). These community-based patients have been evaluated thereafter at 1, 3, 8, 15, and 20 years from entry (Nissilä et al. 1983, Kaarela 1985, Kaarela et al. 1993, Jäntti et al. 1999, 2001, 2002, Jäntti 2004, Palm et al. 2002). Treatment with parenteral gold and/or hydroxychloroquine did not essentially change the natural course of RA, and the outcomes of these patients were mainly severe diseases (Jäntti et al. 2002). According to 20-year follow-up of the subjects the limitation is the low number of subjects and men in study I.

In study II the patients represented inhabitants of the Päijät-Häme district, as the RFH during the years 1991–95 served as the principal site for treatment of patients with RA covering the responsibility area of Päijät-Häme Central Hospital. Postmenopausal bone loss is a strong confounding element in efforts to identify other factors underlying axial bone loss among women, and therefore premenopausal women with regular cycles were chosen to participate.

Patients with JIA in study III represented children whose diagnosis was made and treatment started at the RFH. Their disease course and treatment was sought in their files until young adulthood. Furthermore, being in young adulthood they were presumed to have reached their peak bone mass.

7.2 DISEASE SEVERITY AND REMISSION

In the control of disease severity in RA, bone destruction (erosion) seems to be the most important long term variable (Larsen 1995, Kaarela and Kautiainen 1997, Scott et al. 2000, Jäntti et al. 2002). Indeed, the Larsen score of 0–100 in patients with RA increased over time in studies I and II, emphasizing the inevitable course of RA.

The median HAQ scores in patients with RA were rather low in both studies I and II. Sokka and associates (2003) compared HAQ scores between patients with RA and a community population in Finland, and found RA to be associated with a >7-fold risk of disability compared with that in the general population of adults. Further, the HAQ scores increased with age in patients with RA and in controls.

Hakala and colleagues (1994) found that patients´self-reported functional ability in RA reflected their physical impairment due to their arthritic joint disease. Wolfe (2000) held that HAQ scores at group level seemed to have a stable course, but there was also major individual variation over time, scores tended to be high at disease onset rather than gradually increasing, and the increase over time was 0.03 units/year.

The variables of disease activity ESR and CRP were stable in study I. The DAS28 score decreased in both RA groups in study II, but not significantly. There were more men in remission than women in study III. In all, these outcomes give an overview of disease course and disease activity as elegantly discussed by Buchbinder and colleagues (1995). The chosen remission criteria seemed to be clinically comprehensive in study III, while there is no general agreement on remission criteria in JIA (Adib et al. 2005).

7.3   MEASUREMENT OF BONE MINERAL CONTENT AND BONE MINERAL DENSITY

The software implementations of absorptiometry devices assume an average fat-to-lean body mass ratio and different machines therefore give different results in BMC at the same measurement site (Pocock et al. 1992). These results are however in close correlation with each other (Genant et al. 1994). Furthermore, at different measurement sites of bone there are variable proportions of cancellous and cortical bone. Thus, measurements of BMD at several sites give a better overview of BMD (El Maghraoui et al. 2006). Variation in accuracy in DXA measurements is partly explained by variation in soft tissue, shape and size of bone at the measurement site (Svendsen et al. 1993). With this in mind a group under Engvall (2011) determined whether low-dose prednisolone affects body composition and BMD measurement in patients with RA. Those with prednisolone treatment had significantly higher fat mass than those without, but there was no association between prednisolone treatment and muscle mass or BMD. It is thus important to use appropriate reference ranges provided by the manufacturer to avoid technical discordance when the average BMD of the normative group used to calculate the T score is significantly different from the average value found for the whole population. In studies I, II (Lunar DPX) and III (Lunar Prodigy) 'the Finland AP spine and Femur reference population 20–45 years' was applied and provided by the manufacturerer.

The presence of osteophytes and disc space narrowing in degenerative disc disease in the lumbar spine and aortic calcification may increase BMD artificially in PA measurement of the lumbar spine (Drinka et al. 1992, Frye et al. 1992, Watts 2004, El Maghraoui et al. 2006). The collapse of lumbar vertebrae may substantially

increase BMC and BMD values (Ryan et al. 1992). Thus, four out of 49 women and two out of 10 men did not have BMD reliably measured at the lumbar spine due to severe osteoarthrotic changes in study I.

The reproducibility (precision error) is expressed by the coefficient of variation (CV). This depends on quality assurance of the BMD measurement process. To ensure at least 95% confidence that a measured BMD change is a real effect, the change must exceed the precision error 2.8 times (Bonnick et al. 2001). This is also termed the least significant change (LSC, Glüer 1999, Ravaud et al. 1999).

The protocol of BMD measurement was monitored and obeyed as well as possible in studies I, II and III. Reproducibility was 1.0% for the lumbar spine and 1.8% for the femoral neck in studies I, II (Lunar DPX), and 0.10%, and 1.21% (Lunar Prodigy) in study III, respectively. Correspondingly, the LSC was 2.8% for the lumbar spine and 5.0% for the femoral neck in studies I and II and 0.28% and 3.4% in study III, respectively. Furthermore, double measurements were made in study II.

In measuring BMD in a subject over time there is a need to distinguish between a true change in BMD and a random fluctuation in BMD related to variability in the measurement procedure, scanner-induced variability or other unpredictable sources such as weight change in the object (Sievänen et al. 1994, Ngyen et al. 2000, Phillipov et al. 2001, El Maghraoui et al. 2007, Rajamanohara et al. 2011). Scanner-induced variability occurs in daily performance and in silently degrading scanner performance in the longterm. It is due to inhomogeneity of the scanners' X-ray beam intensity over the tabletop, and changes in internal filtration (Sievänen et al. 1994). Phillipov and associates (2001) revealed that the measurement of BMD will present greater variation as the number of operators is increased. A group under Rajamanohara (2011) examined the effect of weight and weight change on the long-term precision of spine and hip BMD in 64 postmenopausal women over a 10-year period. Long-term precision errors were 50% larger than short-term errors. Weight changes up to 5 kg had little effect on precision. Furthermore, El Maghraoui and colleauges (2005) stated that at group level the reproducibility of BMD measurements by DXA in patients with chronic rheumatic diseases expressed by different means is good. This reproducibility seems to be independent of age and clinical status and the measurement of both hips improves the reproducibility. Both hips were measured in study III and the same operators performed the BMD measurements in studies I, II and III.

In comparison of BMD changes between study groups over time it is necessary to distinguish between a true change in BMC and projectional area. This was explored in study II when changes in BMD, BMC and projectional area were assessed between three groups. In fact there was no statistically significant difference between the three groups in the change in BMC or projectional area in the lumbar spine or femoral neck. Comparing changes in BMD alone between the three groups a statistically

significant difference was found. This is in line with Heaney´s editorial statement in 2005, 'all densitometric comparisons between groups should be based on BMC and area measurements'.

Due to the LSC the time interval between two measurements in the same patient must be long enough, about two years, to allow changes in BMD to take place (Philippov et al. 2001). In study I the time lapse was five years and in study II two years.

7.4   DMARD AND GLUCOCORTICOIDS

It is difficult to evaluate the impact of DMARDs on BMD changes in patients with RA and JIA. Bias by treatment indication should be considered when RA patients with a severer disease course could have been treated aggressively. MTX was used in various combinations in studies II, III. Buckley and associates (1997) in a 3-year follow-up study observed that low-dose MTX was not associated with change in BMD in the lumbar spine or femoral neck treated without prednisone at least 5 mg per day. Combined treatment with MTX and prednisone was associated with greater bone loss in the lumbar spine. Di Munno and group (2004) found no negative effect of low-dose MTX on BMD in women with RA. A group under Tascioglu (2003) found that low-dose MTX had no negative effect on BMD in premenopausal RA patients. Goes and group (2013) revealed that the addition of 10 mg prednisone daily to a MTX-based tight control strategy did not lead to bone loss in early RA patients on bisphosphonates. Biologics seem to stop systemic bone loss in patients with rheumatic diseases (Confavreux and Chapurlat 2011, Krieckaert et al. 2013). Use of biologics was scant according to mean person years of DMARD use in study III.

HRT was not allowed in study II. No reliable information was available on HRT use in study I. Forsblad and group (2003) showed that HRT has a beneficial effect on BMD in the lumbar spine and total hip in women with long-lasting RA. No reliable data on calcium and vitamin D substitution was available in study I.

Vitamin D, 25-hydroxyvitamin D levels were measured only in study II and there was no difference in serum Ca, Pi, and PTH values between the two RA groups. Vitamin D deficiency seems to be prevalent among youngsters and adults (Chapuy et al. 1997, Lehtonen-Veromaa et al. 2002). Vitamin D deficiency also affects bone mass, inducing secondary hyperparathyroidism (Outila et al. 2001, Lips 2001). The international problem in standardization of 25-hydroxyvitamin D assays may bias personal analysis results (Sempos et al. 2012).

7.5   SENSITIVITY OF THE SICKNESS INSURANCE REGISTERS

The advantage in study IV was the availability of nationwide official register data. The case definition was based on eligibility for special reimbursement for DMARDs used in the treatment of RA, that is, a clinical diagnosis of RA by a rheumatologist and the need to initiate antirheumatic medication. No data were available on the fulfilment of the ACR classification criteria for RA, but the use of antirheumatic medication can be regarded as highly indicative for an actual diagnosis of RA. A register study can assess effectiveness such as the performance of a treatment plan in everyday practice. It was thus possible more reliably to catch those with RA who had purchased OP drugs in Finland, although the registers were not designed for such a study. The male-female ratio was 1:2.1, resembling the RA prevalence in Finland (Aho et al. 1989 and 1998). Those patients with RA who did not apply for special reimbursement for DMARD were naturally not caught.

GCs were gathered in 2000–05 because in 2006–07 some GC preparations did not qualify for reimbursement. Calcium and vitamin D preparations were also available over the counter, but many preparations were included in the reimbursement system and reimbursed (42%) to the patient if purchased in compliance with a doctor's prescription. Data were gathered on these purchases. HRT was not included, being indicated mainly for reasons other than OP per se. The prescription register does not collect data on medications used in hospitals and institutions.

7.6   RESULTS IN RELATION TO OTHER STUDIES

Study I

There are earlier longitudinal studies of patients with RA exceeding a disease duration over 10 years and the follow-up time exteding to at least two years and using DXA for BMD measurements. Study populations have comprised only postmenopausal women in studies by groups under Hall (1994), Miyamoto (1999), Shibuya (2002). Comparing the study populations of Buckley (1997), Haugeberg (2002), Krieckaert (2013) to the population in study I there were also about the same proportion of men among postmenopausal women.

The cumulative dose of GC varied from 0.1 g to 78.3 g and the estimated mean daily dose of GC seldom exceeded 12 mg in these earlier studies. GC users in study I had a similar type of daily low dosage of prednisolon. Furthermore, the proportion of GC users in the population in study I resembles those in the studies by Hall (1994), Buckley (1997), Shibuya (2002), and Krieckaert (2013).

GC users with RA in these earlier studies tended to have reduced BMD in the lumbar spine and the femoral neck compared to controls or the BMD reference population. Furthermore, the mean percentage change in BMD in the lumbar spine and femoral neck in patients with RA was negative in these studies (Hall et al. 1994, Buckley et al. 1997, Miyamoto et al. 1999, Haugeberg et al. 2002, Shibuya et al. 2002). Krieckaert´s group (2013) found the percentage of BMD in the lumbar spine to become positive towards the end of their four-year follow-up. Likewise, the change in Z-score in the lumbar spine in patients in study I became positive during the five-year follow-up.

Furthermore, Buckley and group (1997) found RA patients on both MTX and on prednisone at a daily dose of at least 5 mg to have lost their BMD in the lumbar spine significantly more over three years than those without MTX. Miyamoto and colleagues (1999) found that BMD in the femoral neck decreased significantly during the four years of follow-up in the GC group compared to a control group comprising RA patients only with NSAIDs. Six patients only used methotrexate periodically during the years 1991–96 in study I (Jäntti et al. 2002).

Haugeberg and colleagues (2002) found in RA patients who used antiresorptive drugs concurrently that their BMD loss was arrested at the hip. Use of vitamin D and calcium alone did not protect patients from the bone loss. Krieckaert and associates (2013) followed up 184 patients with RA and 41 (22%) of them used bishosphonates at entry to follow-up. They found that BMD in the hip decreased significantly in those patients who were not on bisphosphonates during their four-year follow-up. The limit of study I was that there were not data on OP drug use.

Stratifying annual BMD changes according to disease duration in patients with RA, Shibuya and colleaugues (2002) found that the annual reduction in BMD was least in patients with disease duration over 10 years. This is also in line with study I.

Study II

It would appear that premenopausal patients with RA had lost bone in the lumbar spine and femoral neck quite early in their disease course and those with GC even more so. Kalla and associates (2002) in a cross-sectional study of premenopausal women with RA on GC at a mean daily dose of 5mg/day found significantly reduced BMD at the femoral neck compared to those without GC, but this was not the case in the lumbar spine. Tourinho and group (2005) in a cross-sectional study of patients with RA of relatively short duration found significantly lower BMD in the lumbar spine compared to controls. The daily dose of GC ranged from 1 to 30 mg.

BMD in study II decreased significantly in both lumbar spine and femoral neck only in those RA patients with GC during the two-year follow-up, even when stratifying it in BMC values. Their median daily dose of prednisolone was only 5 mg.

Use of HRT and OP drugs, especially together, seems to protect from bone loss (Hall et al. 1994). There were only regularly cycling premenopausal women in study II to avoid the confounding effect of postmenopausal bone loss. Use of HRT was not allowed in study II.

Study III

There are only a few earlier studies available on the subject of BMD in young adults with JIA (Havelka et al. 1993, Zak et al. 1999, Haugen et al. 2000, French et al. 2002, Aggarwal et al. 2006, Thornton et al. 2011). Subsets of JCA, JRA and JIA varied and oligo- and polyarticular subsets prevailed in these studies. The mean age of the subjects varied from 22.6 to 35.7 years and the mean disease duration was between 12.4 to 27.1 years. The percentage of past or current GC users varied from 12.5 to 57%.The oligoarthritis subtype of JIA prevailed in the JIA-inactive group, while the extended oligoarthritis and polyarthritis subtypes prevailed in the JIA-active group in study III. The percentage of GC users was higher in the JIA-active group.

BMD in the lumbar spine and in the hip in adult patients with JCA, JRA, and JIA appeared to be reduced compared to healthy controls in all these studies. Furthermore, osteopenia tended to prevail and its percentage varied from 23 to 50% when measured at the lumbar spine or at the hip. Accordingly, the percentage of OP varied from 0 to 26.7%. In study III both JIA groups, active and inactive, had lower BMC values in the femoral neck than the controls, this especially among men. There was no significant difference in weight-, height- and sex-adjusted BMC values in the lumbar spine between the JIA groups and the controls, nor was there any significant difference between men and women. Accordingly, the percentage of OP was low 2.6 % in study III.

The remission criteria in patients with JIA still varied in earlier studies. Zak and associates (1999) found that the disease subtype of polyarticular course of JCA seemed to be associated with significantly reduced BMD in the hip while 20% patients with JCA were in remission. Haugen and colleaugues (2000) considered JA to be in remission when there was no disease activity and the patient had not taken medication for the past six months. Thus, 60% of the patients with JA were in remission in their study. Both men and women with active JA had significantly lower BMD at all measured sites than healthy controls. JA patients in remission had a frequency of osteopenia similar to healthy controls and ten out of 229 patients had OP.

The remission criteria in study III were the same as those implemented by Zak´s group (1999). Further, in the JIA active group the extended oligoarthritis and

polyarticular subtypes of JIA prevailed and the percentage of patients in remission (37%) was higher than that reported by Zak.

Predictive factors

Possible predictive factors for BMD, for example life-style factors in adolescence such as lack of participation in organized sports during adolescence, tobacco use during adolescence, and lower calcium intake during adolescence were significantly associated with low BMD in earlier studies of JIA. Furthermore, revised Steinbrocker functional class >2 during adolescence, HAQ score, and joint deformities and limitation of joint movements correlated negatively with BMD (Zak et al.1999, French et al. 2002). Weight, height, GC use, ESR, disease activity and bone turnover were associated with BMD both in the lumbar spine and in the femoral neck, but age was associated with BMD in the femoral neck. BMI correlated positively with BMD (Haugen et al. 2000, Aggarwal et al. 2006, Thornton et al. 2011).

GC use, weight and height, but not disease activity, showed same association with lower BMC in study III. Predictive factors for bone mass development depend on study population and study design (Kröger et al. 1992a, 1992b, Jones et al. 1994, Greenspan et al. 1994, Blum et al. 2001, Pesonen et al. 2005). The limitation of studies I, II, and III is that no reliable data were available on life style factors and exercise.

Study IV

Studies of implementation of OP prevention in patients with RA rely on patient chart reviews, on questionnaires or multicenter studies (Soucy et al. 2000, Thiele et al. 2005, Solomon et al. 2006, Wall and Walker-Bone 2008, Ledwich and Clarke 2009, Barrett-Connor et al. 2009, Heberlein et al. 2011, Gamez-Nava et al. 2013). Numbers of participants in these studies are low compared to those in study IV, which benefited from access to nation-wide register data over a number of years. It was possible to verify actual purchases of OP drugs in study IV.

Predictors for OP management in these earlier studies were older age, female gender, GC dosage, prior fracture, and diagnosis of OP. This is in line with study IV, but the percentage of OP treatment users was lower than in previous works. Furthermore, in study IV it was estimated that the use of OP drugs increased over time and the use was more frequent among patients with known risk factors for OP and fracture.

8 CONCLUSIONS

1. In a long-term disease course at the 15-year check-up about third of the patients with rheumatoid arthritis had osteoporosis and about half osteopenia according to the T-score. At the 20-year check-up the mean Z-score had increased 0.45 at the lumbar spine and decreased only 0.20 at the femoral neck. Correspondingly, the mean change in BMD was 0.01 g/cm² in the lumabr spine and 0.02 g/cm² in the femoral neck during the five years of follow-up. None of the studied parameters explained patients' bone loss.

2. Premenopausal rheumatoid arthritis women with and without glucocorticosteroid treatment and the controls lost bone according to bone mineral content statistically similarly during the two years of follow-up. Comparing results on bone mineral density change between the three groups it is relevant to report changes both in bone mineral content and in projectional area to clarify the basics of the bone mineral density change. The amount of bone loss due to treatment with low-grade prednisolone remains controversial.

3. The male and female young adults with juvenile idiopathic arthritis had lower weight- and height-adjusted bone mineral density values in the femoral neck than the healthy controls, but only 2.6% had osteoporosis. Comparing bone mineral content values in the femoral neck in both men and women with active or inactive juvenile idiopathic arthritis a difference was found among men. Glucocorticosteroid use and weight were associated with bone mineral content in the femoral neck in both men and women with juvenile idiopathic arthritis. Among women GC use and height were also associated with BMC both in the lumbar spine and femoral neck.

4. A total of nine per cent of patients with rheumatoid arthritis had purchased osteoporosis drugs, mainly bisphosphonates, during the first year after commencement of antirheumatic treatment. Of glucocorticosteroid users, 14% of women and 6% of men were prescribed osteoporosis drugs, whereas in those who did not have glucocorticosteroids the percentage was 8% for women and 3% for men. Patients with early rheumatoid arthritis were increasingly receiving osteoporosis drugs, and use was more frequent among patients with known risk factors and among women. OP drug use according both ACR and EULAR recommendations for the prevention of OP in patients with rheumatic diseases and those who receive GC treatment was of low degree, but improving.

Study results suggest that bone loss takes place in earlier disease course in RA and JIA and bone loss is in the long-term disease course in RA of low degree. Further studies are needed to elucidate bone loss and osteoporosis development in early rheumatoid arthritis and to better focus the timing and means of osteoporosis prevention.

9 ACKNOWLEDGMENTS

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Table 6. Longitudinal studies of BMD change in patients with RA measured by DXA in lumbar spine and femoral neck

First author	Fem/Male (postmenopausal)	Follow-up time	GC users N	Densitometry, (precision)	Δ mean* BMD lumbar spine (SD) CI	Δ mean* BMD femoral neck (SD) CI	Δ mean Z score lumbar spine [T score]	Δ mean Z score femoral neck [T score] (SD)	Controls Δ mean BMD lumbar spine (SD) CI	Controls Δ mean BMD femoral neck (SD) CI	Comments
Sambrook 1992	38 (38)	3.6 SD 0.2 years	22	Lunar DPX (1.2%) Lunar DP-3 (1.8%)	GC+ -0.5 (SD 3.4)/y HRT+ +2.0 (SD6.1) GC- HRT- +0.2 (SD 3.6)/y	GC+ -2.5 (6.0)/y HRT+ -1.2 (SD 5.4)/y GC- HRT- -1.1 (SD 3.2)/y			GC- HRT- +0.2 (SD 3.6	GC- HRT- -1.1 (SD 3.2)	Controls (N=17) had also RA. GC users had lower levels of BMD at the start and longer disease duration
Hall 1994	147 (147)	2 years	42	Hologic QDR 1000 (lumbar 0.9%, femoral neck 1.5%)	GC- HRT+ +2.22 CI: +0.72 to 3.72 GC- Ca+ -1.19 CI: -2.29 to -0.09 GC+ HRT+ +3.75 CI: +0.72 to +6.78 GC+ Ca+ -0.85 CI: -4.89 to +3.19	GC- HRT+ -0.41 CI: -1.89 to +1.07 GC- Ca+ -0.56 CI: -2.60 to +1.48 GC+ HRT+ +1.62 CI: -1.27 to +4.51 GC+ Ca+ +1.12 CI: -3.36 to +5.60			HRT- Ca+ -1.46 CI: -3.16 to +0.26	HRT- Ca+ -1.88 CI: -3.97 to +0.21	Randomized either HRT or Calcium group. Controls N=18

First author	Fem/Male (post-menopaus-al)	Follow-up time	GC users N	Densitometry, (precision)	Δ mean* BMD lumbar spine (SD) CI	Δ mean* BMD femoral neck (SD) CI	Δ mean Z score lumbar spine [T score]	Δ mean Z score femoral neck [T score] (SD)	Controls Δ mean BMD lumbar spine (SD) CI	Controls Δ mean BMD femoral neck (SD) CI	Comments
Gough 1994a	42/20 (28)	mean 12.8 months	8	Lunar DPX (lumbar 0.8 (SD 0.25)%, femoral neck 1.6 (SD 0.8)%	CRP<20 +1.3 (SD3.9)/y CRP>20 -2.1 (SD 3.7)/y	CRP<20 +0.6 (SD5.1)/y CRP>20 -3.5 (SD 4.8)/y					50 female healthy controls measured. Patients were DMARD-and GC-naïve at the start
Gough 1994b	99/49 (71)	mean 12.8 months	102	Lunar DPX (lumbar 0.8 (SD 0.25)%, femoral neck 1.6 (SD 0.8)%	-1.0 (SD 0.3) male -0.2 (SD 0.5) female -1.3 (SD 0.4)	-2.0 (SD 0.4) male -1.2 (SD0.7) female -2.3 (SD 0.6)			-0.6 (SD 0.4)	-0.9 (SD 0.5)	50 female healthy controls measured. Patients were DMARD-and GC-naïve at the start
Shenstone 1994	40/27 (24)	1 year	0	Hologic QDR 1000 (NA)	NA	RA< 6 months -3.9 (SD 1.5) RA> 6 months -0.2 (SD 0.7)			NA	-0.8 (SD 0.6)	Controls N=72
Buckley 1997	74/21 (64)	3 years	71	Lunar DPX (lumbar 1.2% femoral neck 2.2%)	-2	0.85					Densitometry's database as control N=48 lateral lumbar BMD measurements converted to antero-posterior BMD by calculation
Miyamoto 1999	78 (78)	3 years and 8 months	44	Lunar DP-X (NA)	-3.32	-3.6			-3.28	-1.9	Remaining 34 RA patients out 78 served as controls

First author	Fem/Male (post-menopausal)	Follow-up time	GC users N	Densitometry, (precision)	Δ mean* BMD lumbar spine (SD) CI	Δ mean* BMD femoral neck (SD) CI	Δ mean Z score lumbar spine [T score]	Δ mean Z score femoral neck [T score] (SD)	Controls Δ mean BMD lumbar spine (SD) CI	Controls Δ mean BMD femoral neck (SD) CI	Comments
Kroot 2001	46/30 (39)	6.6 years	21	Hologic QDR 1000 (1.7%)		-0.28 (SD 0.11)/y CI: -0.07 to -0.49		+0.13 (SD 0.05) CI: +0.02 to 0.23			Densitometry's database as control Only hips measured
Dolan 2002	26/14 (26)	2 years	0	Hologic QDR 4500 (lumbar 1.12%, femoral neck 2.21%)	No significant change	No significant change					Densitometry's database as control
Haugeberg 2002	298/68 (298)	mean 2.2 (SD 0.2) years	250	Lunar Expert (lumbar 2.5%, femoral neck 1.6%)	-0.29 (SD 0.38)/2y male -1.01 (SD 0.72)/2y female -0.11 (SD 0.44)/2y	-0.64 (SD 0.29)/2y male -0.94 (SD 0.70)/2y female -0.57 (SD 0.32)/2y					BMD improved in patients without GC OP drugs alleviated bone loss in those with GC
van Everdingen 2003	52/29	3 years	40	Hologic QDR 4500A (NA)	NA	NA	GC+ [-1.1(SD 0.3)] GC- [-0.6 (SD 0.3)]	GC+ [-1.8 (SD 0.2)] GC- [-1.9 (SD 0.2)]			Randomly allocated either 10mg GC or placebo No significant changes from baseline to 3 years in BMD or between the groups
Marotte 2007	152/37	1 year	118	Hologic QDR 4500 (lumbar 0.9%, femoral neck 1%)	-0.2	+0.2			-3.9	-2.5	Control group comprised 99 consecutive RA patients on MTX

First author	Fem/Male (post-menopausal)	Follow-up time	GC users N	Densitometry, (precision)	Δ mean* BMD lumbar spine (SD) CI	Δ mean* BMD femoral neck (SD) CI	Δ mean Z score lumbar spine [T score]	Δ mean Z score femoral neck [T score] (SD)	Controls Δ mean BMD lumbar spine (SD) CI	Controls Δ mean BMD femoral neck (SD) CI	Comments
Tengstrand 2007	42/16 (35)	2 years	30	Lunar DXA (NA)			GC withdrawn +0.50 GC failure +0.08 GC continued +0.35	GC withdrawn +0.40 GC failure -0.08 GC continued +0.02			Reference Lunar's combined European/US population Randomized to withdraw or continue GC
Book 2008	97 (74)	2 years	30	Lunar DPX-L (NA)	No significant change	No significant change	No significant change	No significant change	No significant change	No significant change	Age- and gender matched healthy controls
Güler-Yüksel 2009	218 (153)	2 years	65	Hologic QDR 4500A Lunar DPX (NA)	-1.0 CI: -3.9 to 1.6	-0.5 CI: -2.8 to 2.1					Multicenter study, randomization to one of 4 treatment groups
Wijbrandts 2009	37/9 (19)	1 year	13	Hologic QDR 4500A (NA)	+0.3	+0.3					Reference manufacturer's database
Haugeberg 2009	13/7	1 year	0	Lunar Expert (lumbar 2.33%, femoral neck 2.75%)	-1.26 placebo -1.77 infliximab -0.75	-1.83 placebo -3.43 infliximab -0.35					Randomized either placebo + mtx or infliximab+mtx BMD loss significantly lower in femoral neck in the infliximab+mtx subgroup
Krieckaert 2013	144/40 (76)	mean 4.0 (SD 1.0) years	60	Lunar (NA)	+0.28	-2.45					Reference Lunar database N=89/184 followed-up to five years and N=41 on bisphosphonates

*percentage of change
NA= not available
BMD = bone mineral density
RA = rheumatoid arthritis
DXA = dual X-ray absorptiometry
Fem = female

GC = glucocorticosteroid
HRT= hormone replacement therapy
Ca = calcium
MTX = methotrexate
OP = osteoporosis
US = United States