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# THE IMPACT OF INTRA-ARTICULAR HYALURONIC ACID ON THE GAIT OF KNEE OSTEOARTHRITIS PATIENTS

Joseph E. DeCaria
*Western University*

# THE IMPACT OF INTRA-ARTICULAR HYALURONIC ACID ON THE GAIT OF KNEE OSTEOARTHRITIS PATIENTS

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by

Joseph E. DeCaria

School of Kinesiology
Faculty of Health Sciences

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The School of Graduate and Postdoctoral Studies
The University of Western Ontario
London, Ontario, Canada

## ABSTRACT

The present study investigated the impact of intra-articular hyaluronic acid (HA) on the gait velocity of knee OA patients, along with patient pain, stiffness, and function. Thirty mild-moderate knee OA patients were randomized to receive three weekly injections of HA (2 ml of 20 mg/ml HA), or placebo (P) (1.2 ml of .001 mg/ml HA). Self-selected (SSGV) and fast (FGV) gait velocity were determined with the GAITRite system; self-reported pain, stiffness, and function were measured with the WOMAC OA Index; and overall patient function was determined with the six minute walk test. Data from one week, three months, and six months post-treatment was analyzed. At six months follow-up, SSGV was significantly improved in both the HA and P groups while only the HA group had significantly improved FGV. The effect of HA injections on knee OA patient gait velocity was not significantly different than P injections.



**KEYWORDS:** knee osteoarthritis, hyaluronic acid, gait, pain, function

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# CHAPTER ONE – LITERATURE REVIEW

## 1.1 Introduction

### 1.1.1 Osteoarthritis

Arthritis affects the synovial joints of the body, causing pain and dysfunction, severely impairing the quality of life of patients with persisting disease[1]. In 2005, arthritis and rheumatism affected an estimated 51.2% of Ontario's population aged 75 years and older; the majority of this burden was attributable to osteoarthritis (OA)[1]. Indeed, OA is the most prevalent form of arthritis and is among the most frequent and symptomatic health problems for middle aged and older adults[2, 3]. For example, estimates of the prevalence of OA in the United States indicate that approximately 1 out of 4 people in their 60's have had a radiographic confirmation of OA[4]. While estimates of OA prevalence in developing countries are less than those in developed countries, OA does afflict a significant portion of Asian and South American populations[5].

OA is a chronic degenerative disorder, characterised by the gradual loss of articular cartilage[6], and is most common in the hands, knees, and hips[3]. Moreover, OA has traditionally been considered a non-inflammatory arthropathy that does not result from a single insult, but rather is multi-factorial in origin[3, 5]. For instance, risk factors contributing to the development of OA include old age, genetic predisposition, obesity, female gender, greater bone density, joint laxity, and damaging repetitive and/or excessive mechanical loading[2]. This musculoskeletal disease results in one or more of the following clinical features: pain, stiffness, limitation of movement, crepitus, and occasionally inflammation/effusion[2, 3, 6, 7]. The societal burden of OA (both in terms of personal suffering and use of health resources) is expected to increase with the increasing prevalence of obesity and the ageing population[1, 6]. With the number of OA patients

anticipated to double by the year 2020[8, 9], there is growing concern about the increasing economic encumbrance of OA with the ageing "baby boomer" generation[10]. Already it has been reported that OA costs more than 60 billion dollars per year in the United States, and that it is second only to ischemic heart disease as a cause of work disability in men over 50 years old[2].

## 1.2 The Normal Synovial Joint

Synovial joints are highly evolved articulations which permit free movement, and make up most of the joints of the extremities[11]. Normal function of any joint requires that all of its many structures act in unison to allow smooth steady motion while maintaining stability[12]. Since synovial joints are directly affected by OA, this section will discuss the normal structure and function of the synovial joint; thus establishing an understanding of how erosion of joint structures, through physiological disequilibrium, can lead to joint pain and patient disability.

### 1.2.1 Synovial Joint Structure

#### *1.2.1.1 Articular Cartilage*

Articular cartilage is a specialized, avascular, aneural connective tissue that provides covering for the osseous components of diarthroidal joints[11, 13]. The cartilage matrix is composed of water (70%), and a collagen framework which supports an arrangement of proteoglycans and glycosaminoglycans[6]. Articular cartilage is divided into four zones (Figure 1.1): the superficial zone, which is in direct contact with the synovial fluid, and is responsible for

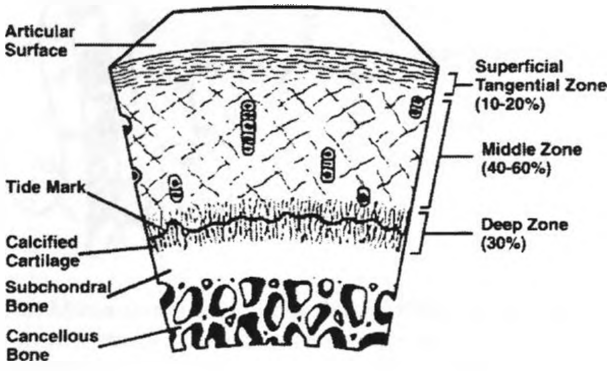


**Figure 1.1: Schematic of articular cartilage.** ***Adapted from The American Journal of Sports Medicine at*** **ajs.sagepub.com/content/26/6/853/F3.large.jpg**

most of the tensile properties of cartilage; the middle zone; the deep zone; and the zone of calcified cartilage, which anchors articular cartilage to the subchondral bone, and is divided from the other zones by the tidemark [13, 14].

Although water is most abundant in articular cartilage, chondrocytes, glycoproteins, collagen, and aggrecan (proteoglycans) all play important structural and functional roles. Chondrocytes synthesize aggrecan and type II collagen, as well as enzymes capable of breaking them down such as collagenase and proteinases[15], which interact with glycoproteins such as proteases and their inhibitors[14], to control cartilage matrix turnover. Type II collagen fibrils, the most abundant collagen in hyaline cartilage, impart tensile strength to articular cartilage, and provide a framework in which proteoglycans and chondrocytes are embedded[14, 16]. Aggrecan exists in association with proteoglycans, composed of the glycosaminoglycans chondroitin sulphate and keratin sulphate, attached to a hyaluronic acid (HA) chain via link protein[13, 14, 16]. Proteoglycans have an affinity for water, and their ability to release and attract water within the cartilage matrix when pressure is applied or removed allows the articular cartilage to act elastically, resisting compressive loads[12, 13]. All of these components must act in unison in order to maintain a healthy functional environment for articular cartilage (Figure 1.2).

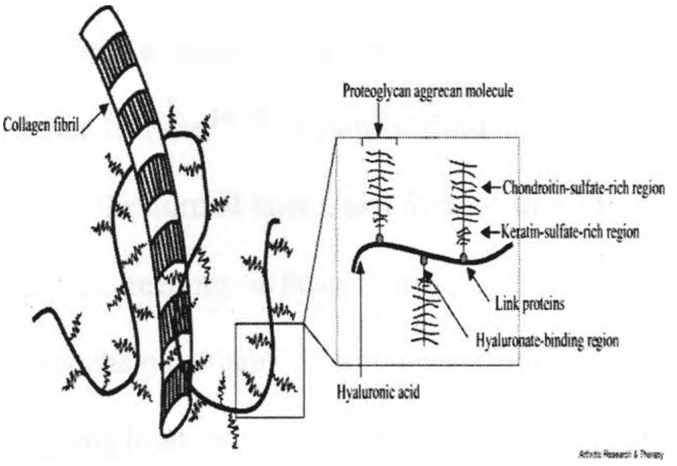


**Figure 1.2: Micro-structure of articular cartilage components.** ***Adapted from Arthritis Research and Therapy at http://arthritisresearch.com/content/5/2/54/figure/F2?highres=y***

*1.2.1.2 Capsule, Synovium, and Synovial fluid*

The joint capsule is of vital importance to the function of a synovial joint. It forms part of the seal that keeps lubricating synovial fluid in position, provides passive stability by limiting joint movements, contributes to active stability via its proprioceptive nerve endings, and may also form articular surfaces[17]. The articular capsule forms a complete envelope for a freely moveable joint, and is composed of two layers. The external layer is composed of fibrous connective tissue and completely surrounds the bony components of the joint. This layer is richly innervated and is reinforced by ligaments[11, 18]. The internal layer, or synovium, is composed of a bed of hyaluronan interspersed with collagen fibrils[14]. The synovium covers the inner surface of the fibrous capsule forming an enclosed sac (synovial cavity) around the articular cartilage, and is highly vascularised[14]. This layer also contains specialized cells called synoviocytes that synthesize HA, the main component of the viscous synovial fluid secreted into the joint cavity[11, 14, 18]. Normal synovial fluid is clear with a composition similar to blood plasma, but also contains HA and a glycoprotein called lubricin[14, 18]. Synovial fluid is present in small amounts within the joints (2.5 ml within the normal knee), and forms a thin film that covers the synovium and articular cartilage, keeping surfaces lubricated and reducing friction between bony compartments[18]. Thus, the outer capsule and inner synovium afford protection to the articular cartilage during joint movement, enhancing joint stability and lubrication.

*1.2.1.3 Accessory structures*

The synovial joint is also composed of a number of accessory structures that help provide stability and participate in joint movement. Ligaments are passive stabilizers, whereas muscles are active stabilizers. The ligaments and muscles limit the extent of

motion, while muscle force transmitted to bone through tendons controls the degree of speed with which motions occur[12, 17]. Also, synovial tendon sheaths, and bursae facilitate gliding of muscles or tendons over bony or ligamentous processes[11], aiding in the frictionless movement of synovial joints.

### 1.2.2 Synovial Joint Function

#### *1.2.2.1 Biomechanics*

Motion at a joint occurs as the result of movement of one joint surface in relation to another, and combinations of rolling, sliding, and spinning may occur between articular surfaces[18]. Combination motions, wherein a moving component alternates rolling in one direction with sliding in the opposite direction, help to increase the range of motion available to the joints and keep opposing joint surfaces in contact with each other[18]. Muscle-tendon systems span the periphery of rotational joints to control their actions and stabilize them in all directions. The peripheral tendon insertion also gives the muscle a mechanical advantage – leverage – which creates the greatest torque with the least effort[12]. Muscle contraction imposes substantial compressive forces across the articulating surfaces of the joint, ranging between three to four times body weight in most weight-bearing joints[12]. However, the synovial joints of the body have protective properties intrinsic to their structure that can help prevent mechanical damage.

#### *1.2.2.2 Synovial fortification and viscoelasticity*

Damage to articular cartilage is a consequence of the synovial joint sustaining high and repetitive loads during movement[2]. Primary protection comes from the dissipation of forces by the soft tissues of the joint, including muscles and ligaments, along with the subchondral bone[12]. Simultaneously, the elasticity of articular cartilage itself, along with the viscous synovial fluid, augments synovial joint protection during

activity. For instance, the elasticity of the articular cartilage relies on the concentration of collagen and proteoglycans within the matrix. The tensile property of collagen initially resists deformation during loading[14]. However, as loading continues, water flow through the porous matrix takes place causing extra strain or stress relaxation[16]. When pressure is released, water is osmotically attracted back to the charged proteoglycans, and the cartilage regains its pre-compressed thickness[16]. Cartilage matrix permeability is controlled by the electrical properties of proteoglycans and their interactions with surrounding substances[12]. Under most circumstances, this fluid flow under pressure allows articular cartilage to compress under load without permanent damage to its matrix[12]. Moreover, the viscosity of the synovial fluid provides lubrication to the synovial joint, shielding the articular cartilage from damaging friction between articular surfaces during movement. The HA component of synovial fluid is responsible for fluid viscosity and is essential for lubrication of the synovium, while the glycoprotein lubricin is responsible for cartilage-on-cartilage lubrication[14, 18]. Therefore, numerous external and internal factors contribute to preserve synovial joint health, and equilibrium amongst components must be maintained to sustain joint function.

*1.2.2.3 Cartilage Nutrition*

Normal physiological loading does not harm articular cartilage. In fact, the functional and structural properties of articular cartilage appear to be conditioned to stresses to which it is most regularly subjected[16]. There is a direct exchange between the synovium and the intracapsular space where nutrients can be supplied and waste products removed from the joint by diffusion[18]. Nutrients may enter the cartilage from synovial fluid either by diffusion or by mass transport of fluid during compression-relaxation

cycles[14]. Consequently, the composition of synovial fluid is extremely important for articular cartilage health, not only for mechanical protection, but also for nourishment.

## 1.3 Osteoarthritis: Disease Processes

### 1.3.1 Etiology

The capacity of the chondrocyte to remodel and repair cartilage may diminish with age, evidenced by the alterations in content, composition and structural organization of the extra cellular matrix[20, 22]. Although age is the primary risk factor for OA, the development of OA with old age is not universal. Therefore, an external stimulus must be present in order to initiate the degenerative cycle of OA. For example, the levels of catabolic cytokines and degradative enzymes are elevated immediately after injury and stay increased for several subsequent years[20]. Consequently, an imbalance in cartilage metabolism occurs which weakens the articular cartilage matrix, thereby reducing its ability to effectively dissipate intra-articular force, facilitating cartilage damage with recurrent joint use. Therefore, the onset of OA ultimately involves a mechanical insult to a joint with a reduced physiological capacity to deal with such an event, predisposing older adults to this musculoskeletal disease.

OA has been separated into two classes: primary OA, which arises without acute trauma, and secondary OA, initiated by joint injury. However, Brandt, et al 2009[19] argue that OA is always secondary to something, and usually to a combination of factors. For example, excessive intra-articular mechanical stress via malalignment, obesity, trauma, joint laxity, muscle weakness, impaired proprioception, and occupation have all been shown to play a role in OA initiation[19, 20, 21]. The effect of abnormal mechanical loading likely contributes to deregulation of chondrocyte function[20, 22]. For instance, in normal circumstances chondrocytes respond to mechanical stress by up-regulating both anabolic

and catabolic activity, producing the components for the extracellular matrix (type II collagen and proteoglycans)[15, 23, 24], as well as increasing the expression of catabolic mediators, such as cytokines, and matrix metalloproteinases[19, 22], which all act synergistically to create new cartilage. However, in OA the metabolic activity of the chondrocytes is shifted toward a state where new matrix synthesis is outweighed by breakdown of matrix constituents[25]. For example, up-regulation of proteases, particularly matrix-metalloproteinases (MMP), and aggrecanases, have been established in OA as the major cause of increased matrix catabolism[20, 25, 26]. Moreover, OA has been associated with elevated levels of cytokines, such as interleukin-1β (IL-1β) and tissue necrosis factor-α (TNF-α), which decrease collagen synthesis and increase degradative proteases[15, 25]. Thus, if chondrocyte function is altered sufficiently from mechanical perturbation, OA can begin to degenerate the synovial joint.

### 1.3.2 Pathology

Although the articular cartilage is the most recognized tissue structure that is affected in OA, all structures of the synovial joint are involved, including the subchondral bone, capsule/synovium, as well as surrounding ligaments and musculature. The development of marginal outgrowths, osteophytes, and increased thickness of subchondral bone are commonly associated with OA[25], following dissipation of abnormal mechanical loads. Stiffness resulting from subchondral bone sclerosis reduces the ability of the subchondral bone to dissipate forces across the joint surfaces, contributing to the advancement of cartilage deterioration[21]. Additionally, vascular invasion from the subchondral bone into the zone of calcified cartilage may advance the tidemark region, further reducing articular cartilage thickness[22]. The majority of cartilage loss in OA seems to be attributable to breaking off of enzymatically weakened segments of the joint

surface, which can become embedded into the synovial membrane, inciting inflammation[19]. Inflammation causes joint pain and stiffness, but may also contribute to the acceleration of articular cartilage destruction. Catabolic enzymes and inflammatory mediators, such as cytokines, are released from the inflamed synovium in response to irritation from fragmented cartilage. Consequently, these substances contribute to cyclical articular cartilage degradation, while simultaneously increasing their own concentration[15, 22, 25].

OA progresses slowly but consistently[27], as insufficient cartilage repair reduces tissue viscoelasticity, diminishing its natural protective mechanism, facilitating disease progression. As articular cartilage degrades, and the smooth articular surfaces become rough, movement of the synovial joint becomes difficult and painful, limiting movement[27]. As a result, to avoid uncomfortable movement of the joint, the OA patient may refrain from physical activity. With limited use, the ligaments of the synovial joint can become lax and the muscles weakened[25]. Consequently, the OA patient will fall into a degenerative cycle of cartilage deterioration and limited mobility, which propagates itself through reduced protection from the peri-articular shock absorbers and viscoelastic joint tissues.

## 1.4 Knee Osteoarthritis

Knee OA is the leading cause of chronic disability in North America[28]. For example, painful knee OA causes mild to moderate disability in up to 10% of adults aged over 55[29]. Furthermore, knee OA in the active individual compromises activities of daily living and participation in sports[30, 31]. Due to the repetitive loading of knee joints during locomotion, and the resultant stress placed on knee cartilage, the incidence of knee OA may be even more strongly associated with mechanical insults. Knee OA increases in

prevalence with age and is more common in women than in men. Risk factors include obesity, knee injury, previous knee surgery, familial history, and occupational bending and lifting[31, 32]. The following section will discuss how the knee structures are affected during knee OA, as well as the resulting symptoms, disability, and altered gait patterns patients are afflicted with.

### 1.4.1 Knee structure and OA

Knee OA is a condition primarily characterized by degenerative articular cartilage on the medial or lateral tibio-femoral or patello-femoral compartments, or a combination of the three[31]. Knee OA is a progressive disorder, and the early to late stages of cartilaginous degeneration are described by the Outerbridge classification system[30, 33] (Table 1.1). However, the entire knee joint can become compromised by OA, and this

**Table 1.1: The Outerbridge classification system of cartilaginous degeneration.**

| Stage | Description |
|---|---|
| 0 | Normal articular cartilage. |
| I | Softening and swelling of articular cartilage. |
| II | Early fissuring that does not reach subchondral bone, and is < 1.3cm in maximal diameter. |
| III | Fissuring that reaches the subchondral bone but is not exposed and has a diameter > 1.3cm. |
| IV | Exposed subchondral bone of any diameter. |

**Legend: Progression from early to late stage OA represented by stages I-IV, respectively.** ***Based on description by Cole, B., et al. Journal of the American Academy of Orthopeadic Surgeons. 1999; 7: 389-402.***

condition may be associated with meniscal disruption, ligamentous instability, and malalignment, as the disease progresses towards its later stages[31, 33]. Quadriceps weakness is also often seen in knee OA, either due to atrophy or neuropathy[19, 32]. Knee OA patients may present with sclerosis of the subchondral bone, osteophyte formation, and joint space narrowing, all detectable on radiographs[19, 30, 32, 33]. Finally, local inflammation of the synovium often presents in knee OA intermittently, leading to pain

and stiffness[19, 30, 31]. Figure 1.3 depicts the comparison of a healthy knee to an OA knee in the later stages of the disease process.

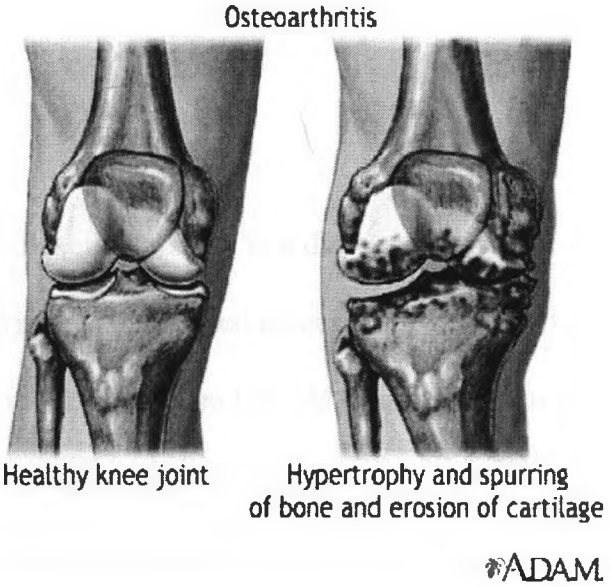


**Figure 1.3: Comparison of healthy knee to OA knee.** ***Photo © ; A.D.A.M. Adapted from About.com: Osteoarthritis at http://osteoarthritis.about.com/od/osteoarthritis101/ss/explained_2.htm***

### 1.4.2 Symptoms and disability

Knee OA patients suffer from a symptomatic spectrum, stemming from structural deterioration of the knee joint, which causes mobility impairment and disability. Pain and disability are the main presenting features and the targets of primary management in knee OA patients[29]. Knee OA patients typically experience pain of varying severity and duration that is activity related, while knee pain at rest occurs in the later stages of the disease[30, 31]. Knee pain could result from local inflammation in the synovium and cartilage, instability, impingement, crepitus, stiffness, or malalignment[31, 33]. Although the tissue of origin of pain in knee OA may vary from patient to patient, a variety of evidence points to the synovium and subchondral bone as the two major sources[19]. Beyond knee pain, mechanical symptoms of intermittent catching or locking may suggest gross articular surface irregularity, a loose osteochondral fragment, or a meniscal abnormality[30]. Moreover, the experience of the knee giving way may indicate the presence of an internal derangement, such as a meniscal tear, a tear of the anterior cruciate ligament, or may reflect quadriceps weakness[31]. Knee OA is the leading cause of impaired mobility in the elderly[31], and pain combined with mechanical irregularities can result in an antalgic gait. The breakdown of normal locomotion can

severely limit a knee OA patient in their daily activities, and may increase the risk of activity related adverse events, such as falling.

### 1.4.3 Knee OA and Gait

Knee OA patients are subject to daily disability, which is a direct consequence of pain and altered gait mechanics. Knee OA is an age associated disease and an altered gait pattern is related with old age, but there is evidence that knee OA plays an additional role in altering gait[34]. Table 1.2 presents four relatively recent studies that demonstrate knee OA patients walk more slowly than healthy age matched counterparts, signifying the added impact of knee OA on reducing gait velocity in older adults. Also, previous research on the spatio-temporal gait characteristics in knee OA has indicated these patients walk with a reduced stride length, and a longer duration stance phase of the gait cycle than healthy control subjects[35, 36, 37, 38]. Although the gait velocity of knee OA

**Table 1.2: Gait velocity of knee OA patients compared to healthy controls.**

| Study | Knee OA patients [Age; Gait velocity] | Healthy controls [Age; Gait velocity] | *P* value |
|---|---|---|---|
| **Al-Zahrani et al (2002)[38]*** | 71 (8.4) yrs;<br>55 (37-72) cm/s | 69 (7.3) yrs;<br>117 (104-129) cm/s | <0.00 |
| **Chen et al (2003)[43]** | 65.5 (9.3) yrs;<br>71.82 (10.44) cm/s | 63.5 (11.3) yrs;<br>91.66 (17.06) cm/s | <0.01 |
| **Rudolph et al (2007)[41]**** | 49.2 (39-57) yrs;<br>138 (12) cm/s | 49.2 (40-57) yrs;<br>151 (15) cm/s | 0.023 |
| **Tang et al (2004)[84]** | 61.3 (10.2) yrs;<br>78.11 (18.52) cm/s | 63.5 (11.3) yrs;<br>94.84 (17.06) cm/s | <0.01 |

**Legend: Values reported in Mean(SD) unless stated otherwise; *Values for gait velocity reported as Mean(Range); **Values for age reported as Mean(Range); yrs=years; *P* value=significant difference between knee OA patients and matched controls.**

patients varies from study to study, this may be the result of heterogeneity of study protocol, the activity levels of subjects, as well as the severity of subject knee OA. Importantly, however, the common recurring theme between knee OA gait studies is

altered spatio-temporal gait characteristics that lead to a slower gait velocity than healthy older adults.

Kinematic and kinetic factors influence the spatio-temporal gait changes in knee OA patients. Although gait characteristics may vary by knee OA patient, some common principles have presented themselves. Many studies have reported a reduced knee range of motion in knee OA patients, [35, 36, 37, 38, 39], as well as reduced stance phase flexion and extension angle[36, 38, 39]. Furthermore, there is evidence of an offset of the internal/external rotation of the knee in knee OA patients[37, 40]. Knee laxity is also present in knee OA patients, and has been implicated in the occurrence of co-contraction of the surrounding muscles of the knee[39, 41]. Abnormal co-contraction of knee muscles, in addition to greater knee extension at heel strike during gait[39, 40, 42], concurrently contribute to increased forces across the knee joint and on the articular cartilage. Moreover, several studies observing the ground reaction forces (GRF's) at the OA knee have observed significant alterations of the distinctive two-peak force vector curve associated with normal gait, including a greater first peak knee adduction moment, greater force during time of mid-stance, and a smaller second peak force[42, 43, 44]. The peak knee adduction moment is considered an indirect measure of knee load, and the presence of an increased knee adduction moment during the gait of knee OA patients, has frequently been reported[39, 41, 42, 44, 45]. Furthermore, Mundermann, et al 2005[42] suggested that the increase in knee load is associated with greater knee OA severity and that the vertical loading rate was elevated by 50.1% in all knee OA patients compared to matched controls. Higher loading rates have been linked with more surface fissuring of cartilage than lower loading rates, and surface fissures in the cartilage can propagate mechanically if the joint surface is subjected to rigorous repetitive loading[42]. Alternatively, Messier, et al 1994[34] and Chen,

et al 2003[43] reported a slower loading rate at heel strike in knee OA patients, with a greater force during the time of minimal mid-stance, but did report reduced force during toe off phase of the two peak force vector diagram. Consequently, the articular cartilage in knee OA patients is subject to greater forces represented by increased knee load during the gait cycle. However, the changes in the two-peak force vector curve that contribute to increased knee load may differ depending on the severity of knee OA. Moreover, Andriacchi, et al 2006[40] and Maly 2008[39] report that not only is abnormal loading an important factor in knee OA initiation and progression, but also that excessive and repetitive loading on the knee, described as cumulative loading, contribute to knee cartilage deterioration in knee OA.

Altered knee mechanics play a large role in both the initiation and progression of knee OA. Abnormal mechanics are thought to facilitate degradation of tissues[46], and will deviate further from healthy gait as the disease progresses. A degenerative cycle ensues and is difficult to ameliorate. Generally, reduced knee range of motion, compiled with knee muscle co-contraction, interact to produce a stiffer knee, ultimately leading to poor dissipation of mechanical loads. Increased knee load will contribute to cartilage deterioration, whose breakdown products result in synovial inflammation, as well as subchondral bone sclerosis, all contributing to pain experienced by the knee OA patient. Pain and stiffness, combined with muscle weakness, act to inhibit knee function, resulting in an antalgic gait pattern that decreases patient mobility.

## 1.5 Diagnostic Procedures

The diagnosis of knee OA can be made based on clinical symptoms, radiographic criteria, or the combination of the two. When clinically evident, OA diseases are characterised by joint pain, tenderness, limitation of movement, crepitus, occasional

effusion, and variable degrees of inflammation without systemic effects[47]. To confirm diagnosis of knee OA, physicians will frequently use radiographic criteria, such as narrowing of the joint space, increased density of subchondral bone, and the presence of osteophytes on the ridges of the articulating bones[2, 7, 15, 19, 33, 47]. A weight-bearing antero-posterior radiograph, with the patients' body weight evenly distributed on both legs, is commonly used. Also, lateral, tangential patella-femoral, and tunnel radiographs allow objective evaluation of the three knee compartments[30, 33, 48]. The most widely used knee OA radiographic grading scale is the Kellgren/Lawrence system, which has been adopted by the World Health Organization as the standard measure for radiographically assessing OA[49]. Table 1.3 describes the radiographic criteria used by the Kellgren/Lawrence scale for the grading of knee OA at different stages of the disease.

**Table 1.3: Kellgren/Lawrence radiographic grading scale for knee OA.**

| OA grade | Description |
|---|---|
| 0 | No radiographic findings of OA. |
| 1 | Minute osteophytes of doubtful clinical significance. |
| 2 | Definite osteophytes with unimpaired joint space. |
| 3 | Definite osteophytes with moderate joint space narrowing. |
| 4 | Definite osteophytes with severe joint space narrowing and subchondral sclerosis. |

***Adapted from Kijowski, R. et al. American Journal of Roentgenology. 2006; 187: 794-799.***

Significant limitations of the radiograph include an indirect measure of articular cartilage and a two-dimensional assessment of bony features, inhibiting the detection of three-dimensional intra- and extra-articular changes[49]. Moreover, Bedson et al, 2008[48] recently conducted a systematic review of investigations examining the correlation of radiographs with pain, and concluded that there is a lack of existing relationship between these two measures. Magnetic Resonance Imaging (MRI), on the other hand, enables the

direct assessment of cartilage, rather than the indirect approach allowed by radiology[49] (Figure 1.4). MRI images are sensitive to cartilage defects, along with changes in thickness and volume, and to changes in surrounding soft tissue joint structures. However, MRI images are expensive, and the interpretation of cartilage findings on MRI is still evolving[49]. Until further advances in imaging present themselves,

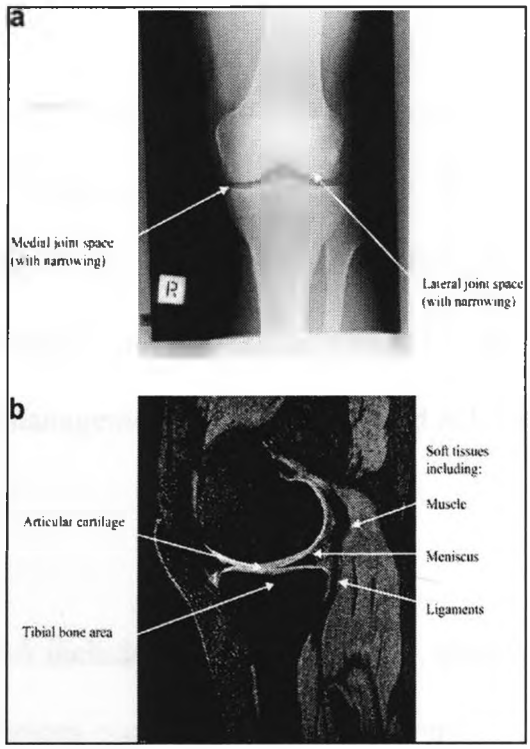


**Figure 1.4: Comparison of information obtained from (a) knee X-ray and (b) TI-weighted MRI (saggital).** ***Adapted from Teichtahl, A., et al. Best Practice & Clinical Research. 2008; 22(6): 1061-1074.***

particularly with the availability and standardization of MRI, clinical evaluation combined with radiographic confirmation will remain as the most appropriate diagnostic procedure for knee OA. This is in accordance with the criteria developed by the American College of Rheumatology for the diagnosis of knee OA, presented in Table 1.4.

**Table 1.4: American College of Rheumatology classification criteria for knee osteoarthritis.**

| |
|---|
| **Traditional format** |
| **Knee pain and radiographic osteophytes and at least 1 of the following 3 items:** |
| **Age >50 years** |
| **Morning stiffness <=30 minutes in duration** |
| **Crepitus on motion** |
| **Classification tree** |
| **Knee pain and radiographic osteophytes** |
| **or** |
| **Knee pain and age >=40 years and morning stiffness <=30 minutes in duration and crepitus on motion** |

***Adapted from The American College of Rheumatology at http://www.rheumatology.org/publications/guidelines/oa-knee/oa-knee.asp***

## 1.6 Osteoarthritis Prevention and Therapy

Several accepted strategies have been developed in the prevention and treatment of knee OA. These strategies range from lifestyle alteration to surgical replacement of the articular surfaces of the knee joint. Preventing knee OA would be ideal and therefore intervention begins early if risk factors are acknowledged and addressed. The following section discusses several common prevention and management approaches aimed at knee OA.

### 1.6.1 Prevention

The major risk factors described for knee OA include old age, female sex, obesity, occupational knee bending/heavy lifting, genetic factors, quadriceps weakness, joint trauma, immobilization, joint deformity, and sports that subject the knee joint to overuse due to repetitive high impact or torsional forces[15, 16, 32, 50]. Accounting for all knee OA risk factors in an individual may be impossible; however, targeting a few of them may help to alleviate stress the knee joint is subject to, reducing potential for knee OA to occur. Lifestyle modification and patient education, the principal factors in preventing knee OA, will differ according to the individual[30, 50]. Furthermore, weight reduction in obese people to a normal BMI remains the most important tool in decreasing the development of knee OA[5, 30]. In addition, avoiding high impact activities and altering employment responsibilities, such as avoiding heavy lifting and squatting, may prevent knee OA in people who are overweight[30, 32, 51]. Quadriceps strengthening may also help individuals at higher risk for knee OA to dissipate the force at the knee joint more effectively, protecting the articular cartilage from mechanical stress[50, 51]. Although a number of risk factors cannot be modified, such as old age, female sex, and genetic

factors, this should not preclude preventative strategies from being implemented early in the life of those people at risk for developing knee OA.

### 1.6.2 Management and Therapy

The goals of knee OA treatment include patient education about the disorder, pain reduction and functional improvement, increasing mobility, and altering disease progression where possible[3, 5, 6, 52, 53]. Both the European League Against Rheumatism (EULAR) and Osteoarthritis Research Society International (OARSI) have provided guidelines[53, 54, 55] for the treatment of knee OA patients, founded on evidence based research and expert opinion. These guidelines recommend that optimal management of knee OA requires a combination of non-pharmacological and pharmacological treatment modalities, with non-pharmacological intervention considered initially. Figure 1.5 depicts the recommended step-wise approach to OA management as the severity of the disease increases.

#### *1.6.2.1 Non-Pharmacological Intervention*

The EULAR and OARSI guidelines[53,54,55] recommend that non-pharmacological knee OA intervention incorporate education about treatment objectives and lifestyle modification, exercise, weight reduction, and knee load modifying devices, such as canes,

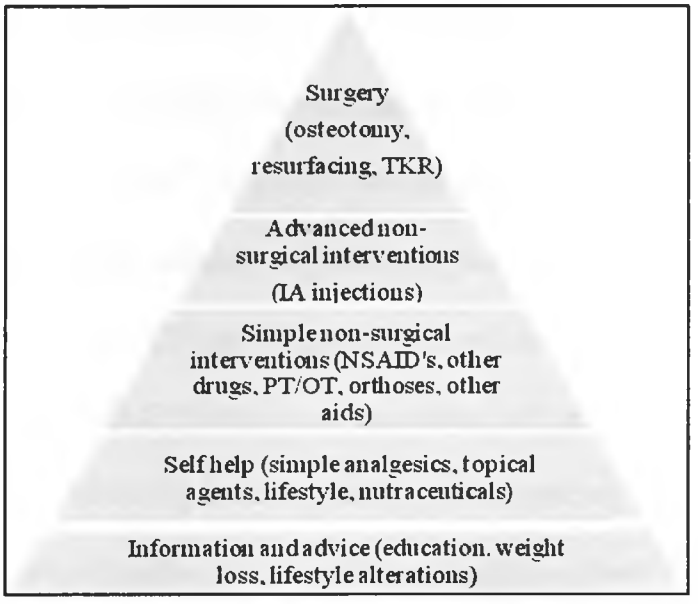


**Figure 1.5: Sequential, pyramidal approach to knee OA management: Management should progress from bottom to top of pyramid as patient condition increases in severity. Legend: TKR=total knee replacement; IA=intra-articular; NSAID's=non-steroidal anti-inflammatory drugs; PT=physical therapy; OT=occupational therapy.** ***Adapted from Dieppe, P. et al. Lancet. 2005; 365:965-973.***

braces, and wedged insoles. Particularly, rehabilitative exercise in the form of both aerobic and knee strengthening exercises, along with weight reduction, have demonstrated clear benefits to both pain reduction and improved function in knee OA patients[52]. Furthermore, bracing and wedged insoles/orthotics may also provide pain relief by correcting malalignment in those patients suffering with varus or valgus knee deformities, reducing excessive knee load[31, 33].

*1.6.2.2 Pharmacological Intervention*

When non-pharmacological intervention proves ineffective, pharmacological treatment of knee OA is indicated. The EULAR and OARSI guidelines[53, 54, 55] report that pharmacological intervention primarily consists of simple analgesics, such as acetaminophen, oral and topical NSAID's, intra-articular knee injections of corticosteroids or HA, and glucosamine and/or chondroitin sulphate. Acetaminophen has been recommended as the oral analgesic of choice, up to 4 g/day for mild to moderate pain in OA, and is generally well tolerated[5, 6, 52]. However, a recent meta-analysis of 15 randomized controlled trials suggested that oral NSAID's were superior to acetaminophen in reducing moderate to severe pain in OA patients[56]. NSAID's are the most commonly prescribed drugs for OA world-wide due to their efficacy as good analgesics and high rates of patient compliance[5]. Furthermore, NSAID's are the preferred medication for the swollen and painful OA knee[30]. However, NSAID's have been associated with a greater occurrence of gastro-intestinal disorders, renal complications, and peptic ulceration[6, 52]. As a result, selective COX-2 inhibitors are prescribed, however these drugs have been associated with increased cardiovascular complications[3]. Another pharmacological option might be intra-articular corticosteroids, which provide short-term pain relief in knee OA patients, but their effect generally does not last longer than 4 weeks after

treatment[57]. Moreover, potential side effects such as post injection flares of pain, articular cartilage atrophy, as well as systemic corticosteroid effects, limit the allowable number of injections to three to four times per year[33, 53].

Although the above pharmacological therapies for knee OA provide adequate symptomatic relief in most knee OA patients, they do nothing to slow the progression of the disease. Two common treatments that are thought to have disease modifying characteristics, and are recommended in the EULAR and OARSI guidelines[53, 54, 55], include viscosupplementation and glucosamine/chondroitin sulphate. Viscosupplementation involves intra-articular injection of HA into the synovial space, is believed to restore the viscoelastic properties of synovial fluid, and is used to relieve pain and improve function in knee OA patients[55]. Alternatively, glucosamine and chondroitin sulphate are components of articular cartilage proteoglycans. These nutritional supplements are theorized to provide the building blocks to enhance the articular cartilage within an osteoarthritic joint, thereby providing protection from further cartilage deterioration[31]. Although these nutritional supplements are not associated with serious adverse events, the clinical efficacy of glucosamine and chondroitin sulphate on knee OA symptoms remains controversial[53]. Other recommendations from the EULAR and OARSI guidelines[53, 54, 55] include thermal modalities, transcutaneous electrical nerve stimulation, acupuncture, weak opioids and narcotic analgesics. However, their level of recommendation was not as high as the previously mentioned modalities, and in the case of opioids and narcotic analgesics, should only be used for in exceptional circumstances.

*1.6.2.3 Surgical Intervention*

When non-pharmacological and pharmacological interventions have failed, surgical manipulation of the joint structure may be indicated. In the past, arthroscopic

lavage with debridement was thought to dilute inflammatory mediators, and correct mechanical problems leading to symptomatic relief in the knee OA patient[30, 33]. However, this procedure has been controversial since Moseley, et al 2002[58] demonstrated no significant difference in treatment effect between a group of knee OA patients receiving arthroscopic lavage, and another group receiving debridement, when compared to a group receiving a placebo procedure. More recently, Kirkley et al, 2008[59] have demonstrated that arthroscopic surgery in knee OA patients provides no additional benefit to optimized physical and medical therapy. Then again, arthroscopic removal of loose bodies or meniscal flaps that cause mechanical symptoms, especially locking or catching, may benefit patients in this sub-group[3].

Due to the inherent risk of surgical procedures, the benefit derived by the patient should be substantial, such as disease alteration. Repair of the injured articular surface, either through transplantation with osteochondral autographs or cultured autologous chondrocytes, seem to form hyaline cartilage-looking tissue and relieve pain[16]. However, these procedures are expensive and not currently recommended by the EULAR and OARSI treatment guidelines[53, 54, 55]. Another surgical procedure that may alter the disease progression in knee OA patients is osteotomy, which alters the mechanical load across the articular surfaces of the knee joint. General indications for osteotomy include relatively young and/or obese patients with either varus alignment and medial compartment arthrosis, or valgus alignment and lateral compartment arthrosis[30]. In high tibial osteotomy a wedge of bone is resected (closing-wedge osteotomy) or added (opening-wedge osteotomy) to realign the lower limb[21]. This procedure is specifically designed to reduce compartmental load in tibio-femoral OA patients[40], thereby decreasing pain and delaying cartilage degeneration[21]. The OARSI guidelines[53, 54] recommend high tibial

osteotomy in young, active knee OA patients, and suggest that this procedure can delay total knee replacement for up to ten years. When knee OA patients have not received benefit from non-pharmacological or pharmacological intervention, or present as poor candidates for the aforementioned surgical procedures, total knee arthroplasty is an option[5, 33]. This last resort procedure is recognised by the EULAR and OARSI guidelines[53, 54, 55] as a cost effective measure for improving the quality of life of knee OA patients.

Limiting the number of knee OA patients receiving total knee replacements is becoming extremely important due to the worlds aging demographic and the financial burden these surgeries will place on the health care system. Targeting treatments that alleviate symptoms and discourage disability, while simultaneously slowing the progression of cartilage deterioration, should be a primary goal when considering intervention strategies for a knee OA patient. Viscosupplementation appears to have the potential to simultaneously improve knee OA symptoms, reduce disability, and protect articular cartilage from further damage. Therefore, viscosupplementation will be examined in greater detail in the next section of this literature review.

## 1.7 Intra-articular Hyaluronic acid and OA

Hyaluronic acid (HA) is a glycosaminoglycan composed of glucuronic acid and N-acetyl-glucosamine[60, 61, 62, 63, 64] (Figure 1.6). HA is the main constituent of synovial fluid and coats the surface of articular cartilage. In the extra-cellular matrix of cartilage, HA provides the backbone to

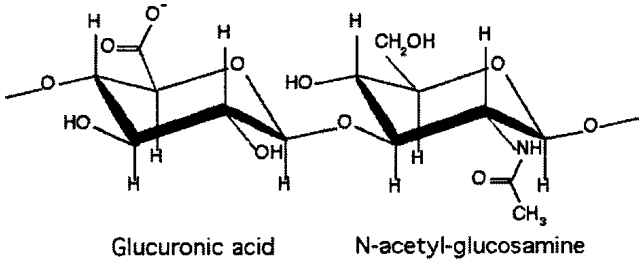


**Figure 1.6: HA chemical structure.** ***Adapted from*** **http://www.madsci.org/posts/archives/2001-04/986571103.Bc.1.gif**

which proteoglycans are attached, and is intertwined among collagen fibres[65, 66]. In theory, the viscoelastic properties of synovial fluid are provided by HA[60, 64], which contribute to joint lubrication and cartilage shock absorption. For instance, during low shear forces, such as walking, HA is thought to exhibit high viscosity, dissipating mechanical energy as heat, and during high shear forces, such as running, HA is thought to act more elastically, absorbing mechanical energy[60, 63]. In OA the molecular weight and concentration of HA in synovial fluid are decreased, reducing viscoelasticity and leaving articular cartilage susceptible to mechanical damage[63, 65, 67]. Therefore, the rationale for the use of viscosupplementation with HA in knee OA is to restore the normal synovial fluid milieu and improve the rheological environment, to enhance both cartilage protection and knee function.

Intervention with intra-articular HA in knee OA patients is purported to have several therapeutic actions. Intra-articular HA provides analgesic effects in knee OA patients by reducing mechano- and chemo-sensitive signals from nocioceptive afferent nerve fibres in the synovium[64, 65]. HA can also inhibit inflammatory mediators such as cytokines, proteases, and prostaglandins[63, 64], reducing synovial inflammation in knee OA patients. Furthermore, after exogenous HA has left the joint following intra-articular injection, HA is produced endogenously by the synoviocytes, and therefore is thought to have a long term physiological effect within the OA knee joint[64]. Consequently, HA intervention in knee OA has a slow onset, as it establishes itself within the joint, but lasts for several months up to a year after injection[65]. HA is also thought to inhibit cartilage deterioration, and proteoglycan resorption, as well as stimulate synthesis of collagen and proteoglycans by chondrocytes[60, 64, 65].

Intra-articular HA is typically administered with either an antero-medial or antero-lateral injection approach (Figure 1.7). More than a dozen HA preparations are available worldwide with treatment recommendations varying from 3 to 10 injections[65]. Although the five HA preparations approved for knee OA treatment in the United States specify a treatment course of 3 – 5 injections, there is no guidance as to how clinicians should determine the appropriate number of injections for the individual patient. Furthermore, the number of injections administered can be adjusted based on the patients' response to treatment[68]. The number of HA injections administered is related to the molecular weight and concentration of the preparation used, which determine the residence time of the exogenously injected HA within the joint, and influence the intensity and duration of HA's treatment effect[65]. Moreover, HA's treatment effect is shown to have a dose-response relationship with the physiological response dependent on HA molecular weight and concentration[65].

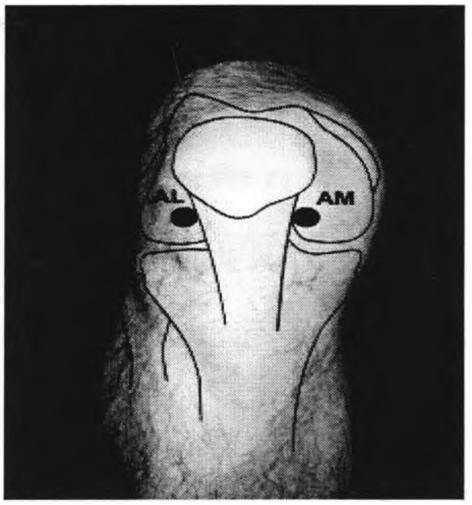


**Figure 1.7: Anatomical landmarks directing injection location. AM=Antero-medial; AL=Antero-lateral.** ***Adapted from Jackson, D., et al. The Journal of Bone & Joint Surgery. 2002; 84: 1522-1527.***

Arthrocentesis is considered by many to be an effective treatment, which could account for some improvement versus baseline in 'placebo' arms of HA studies [69]. However, several studies have demonstrated that HA's clinical effect is greater than that of placebo, suggesting that intra-articular HA does indeed have an active treatment mechanism in reducing pain and improving patient function. Brandt, et al 2001[70] found HA superior to placebo when improving WOMAC scores, while Huskisson, et al 1999[71] demonstrated HA superior to placebo injections on improving visual analog scale (VAS)

pain scores and Lequesne index functional scores six months following treatment. Furthermore, Karlsson, et al 2002[72] and Kotevoglu, et al 2006[69] reported that patients treated with HA had a significantly longer duration of symptomatic improvement, when compared to patients treated with placebo injections, six months after their respective injection series. In comparison with other accepted knee OA treatments HA appears to have similar effectiveness, with a reduced risk for systemic complications. Furthermore, a number of randomized studies have determined that HA is equally as effective as NSAIDs[73, 74, 75] and of equal short-term effectiveness, but greater long-term effectiveness, than corticosteroids[76, 77] (Table 1.5).

**Table 1.5: Randomized trials comparing HA preparations to other knee OA treatments.**

| Study | Population (Age; OA classification) | N | Intervention | Outcome Measure | Comments |
|---|---|---|---|---|---|
| **Adams et al (1995)[73]** | 61.3 yrs; KL I-III | 102 | NSAIDs+arthrocentisis v. Hyalgan GF 20 v. Hyalgan GF 20+NSAIDs | 100mm VAS (pain) | HA as effective as NSAIDs 3 months post-treatment. |
| **Altman et al (1998)[74]** | 63.3 yrs; KL II-III | 333 | Hyalgan v. P (Saline) v. Naproxen | 100mm VAS (pain); WOMAC | HA effect > P; HA as effective as Naproxen 3 months post-treatment. |
| **Petrella et al (2002)[75]** | 65.3 yrs; mild-moderate | 120 | Suplasyn v. P (Saline) v. Diclofenac+misoprostol v. oral P | WOMAC | HA as effective as NSAIDs at rest; HA effect > NSAIDs during activity. |
| **Frizziero et al (2002)[76]** | 49.5 yrs; KL I-III | 99 | Hyalgan (20mg/ml) v. Methylprednisolone acetate (MP) (1mg/ml) | VAS (pain) | HA effect similar to MP, but longer lasting. |
| **Caborn et al (2004)[77]** | 63.1 yrs; n/a | 216 | Hylan GF 20 v. Triamcinolone Hexacetamide (TH) (20mg/ml) | WOMAC (pain); 100mm VAS (pain) | HA effect > TH 3 and 6 months post-treatment. |

**Legend: n=sample size; yrs= years old; KL=Kellgren-Lawrence grading scale; NSAID=non-steroidal anti inflammatory drugs; VAS=visual analog scale; P=placebo; WOMAC=Western Ontario McMaster Universities Osteoarthritis index; HA=hyaluronic acid.**

The balance of studies mentioned above comparing HA to placebo, NSAIDs, or corticosteroids reported only a few minor adverse events with the intra-articular HA injection. The most common adverse events reported were transient mild-moderate pain, and local inflammation at the injection site.

Scepticism about the effectiveness of HA in the treatment of knee OA patients is reported in a systematic review conducted by Arrich, et al 2005[78]. These authors reported that the methodological quality of most clinical trials observing the effectiveness of HA was poor, and that HA did not prove effective in relieving pain at rest, nor in improving patient function. However, several other systematic reviews and meta-analyses report intra-articular HA has a small – modest effect size, comparable to other knee OA treatments, and that HA treatment is safe for use in knee OA patients[79, 80, 81, 82]. Furthermore, Bellamy, et al 2006[83] conducted the largest review of randomized controlled trials observing the effect of HA in knee OA to date, and reported that HA is superior to placebo, and comparable in efficacy to systemic knee OA treatments. However, they also reported that there is considerable between product and time dependent variability regarding clinical response, but detected no major safety issues with this treatment. Although the effectiveness of intra-articular HA on knee OA symptoms has been extensively studied, its impact on knee OA gait variables has yet to be determined. Given the link between knee OA and gait perturbations, it is important to assess how knee OA treatments may affect the gait characteristics of this patient population. The potential for HA to modify the rheological environment in the knee joint is intriguing when considering how these changes may manifest in modified gait function. Although limited research has been conducted on the impact of intra-articular HA injections on the gait characteristics of knee OA patients, the interest in this area seems to be accelerating with

a few recent studies. Therefore, the next section of this review outlines these preliminary studies observing the impact of intra-articular HA on the gait of knee OA patients.

**1.8 Intra-articular HA and knee OA gait function**

To our knowledge, the first study to be published analyzing the impact of HA injections on knee OA gait characteristics was conducted by Tang, et al 2004[84]. These authors conducted an open label study observing how mild-moderate knee OA patients responded to five consecutive weekly injection of ARTZ (2.5 ml, 0.1% NaHA, molecular weight – 860 kd), and compared the gait characteristics of this treatment group to aged and anthropometrically matched healthy controls. They found that the knee OA group walked with a reduced gait velocity, and with an altered GRF curve; the distinctive two-peak 'M-shaped' GRF curve was blunted and shifted to the right of the first peak force, when compared to healthy controls. However, one-week after treatment with HA, knee OA patients experienced significant improvements in gait function that were also observed three and six months post-treatment. These changes included a significant increase in self-selected gait velocity of [mean(SD)] 20.07 (22.33) cm/s, as well as significant improvements in cadence and step length. Furthermore, the GRF curve was restored to a normal shape, coming close to resembling that of the healthy controls; changes included reduction in delay in first peak rise time and the minimum force under mid-stance (Figure 1.8). Yavuzer, et al 2005[85] also conducted an open label study observing the use of three consecutive weekly injections of Hylan GF-20 (Synvisc) on the gait characteristics of knee OA patients. Conversely to Tang, et al 2004[84], these authors did not find significant improvements in spatio-temporal gait parameters one week post-HA injection, with gait velocity only improved by 0.02 cm/s. Interestingly, however, they did report a statistically significant reduction in peak knee adductor and extensor

moments, indicating intra-articular HA may impact the abnormal loading traits of knee OA patients in a favourable fashion. Finally, Briem, et al 2009[86] reported on the treatment of

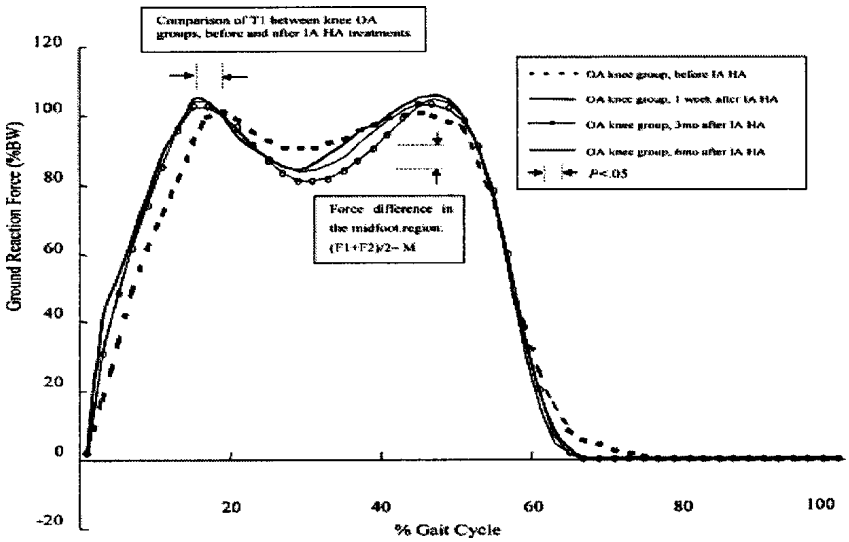


**Figure 1.8: HA's impact on ground reaction force curve in knee OA patients.** ***Adapted from Tang, S., et al. Archives of Physical Medicine and Rehabilitation. 2004; 85: 951-955.***

symptomatic knee OA patients with five consecutive weekly injections of Hyalgan, and compared the gait characteristics before and after treatment, as well as between responders and non-responders to treatment. This study found that mean gait velocity did not significantly change three weeks after the last HA injection, nor at five months follow-up, for the group as a whole. They also found no significant interaction effect between responders and non-responders to HA and impact on gait velocity. However, in contrast to Yavuzer, et al 2005[85], Briem, et al 2009[86] found that responders to HA treatment experienced a significant increase in first peak knee adduction moment at both the knee afflicted with OA and with their uninvolved knee, while non-responders to HA treatment did not experience change in knee adduction moment in either knee. Furthermore, although sagittal plane gait adaptations were largely unaffected in this study, a significant increase in co-contraction of the peri-articular knee muscles was found to be associated with pain relief with HA treatment.

By all accounts more research should be undertaken to elucidate the effect of HA on gait characteristics including the spectrum of spatio-temporal, kinematic, and kinetic

gait variables. Particularly, it would be important to establish firstly whether or not HA treatment can indeed enable knee OA patients to walk faster, and if in turn this will lead to increased loads on the knee joint. If knee load increases as a result of increasing gait velocity in knee OA patients treated with intra-articular HA, then it would be important to determine if the increase in load is additively damaging to the already diseased knee cartilage. Given the ability of exogenously introduced HA to coat and protect articular cartilage, as well as become incorporated into the cartilage itself[87], there may be the potential for viscosupplementation to enable the knee OA patient to function at a higher level and withstand otherwise potentially damaging knee loads because of increased cartilage health and protection. There remains the challenge of preserving the integrity of the knee cartilage in knee OA patients while allowing for the beneficial increases in walking-related activities[88]. Thus, establishing the relationship between HA's impact on gait characteristics and disease progression would be valuable in addressing this challenge.

## 1.9 Osteoarthritis therapy study methodology

### 1.9.1 Symptomatic Outcome Measures

The Outcome Measures in Rheumatology committee (OMERACT) 3 conference, has established, by international consensus, that the core set domains of pain, physical function, and patient global assessment are important for determining health status in knee OA patients[89]. This establishment was further ratified by the Osteoarthritis Research Society International (OARSI) task force on clinical trials[90]. Several self-report outcome measures that determine clinical symptoms in knee OA patients have been developed. For example, various VAS's have been used to determine knee pain during rest, weight bearing, and physical activities. Furthermore, questionnaires have been

developed specifically to measure patient function and overall well being, such as the Lequesne functional index and the SF-36, respectively. However, the Western Ontario McMaster Universities OA index (WOMAC) has been distinctively designed for standardized assessment of knee and/or hip OA symptoms[91]. The WOMAC is a self-report functional status measure which professes to assess three health concepts: pain, stiffness, and physical function[92]. The WOMAC is a valid, reliable, and responsive measure of clinical outcomes that has been used in diverse clinical and interventional environments[93]. Both VAS and Likert scale versions have been created, both of which have been extensively validated in over 60 languages, and are commonly used to assess efficacy in pharmaceutical and biotechnology environments[94]. The Likert scaling provides simple and easy scoring, while the more demanding VAS may be slightly more sensitive[94]. Additionally, in daily clinical practice the WOMAC questionnaire is a suitable tool for optimizing patient monitoring as the data are directly provided by the patient and are very reproducible[95]. The WOMAC is broken into the three sections of pain, stiffness, and physical function, each with its own specific set of questions (5 for pain, 2 for stiffness, and 17 for physical function). Each question in each section of the VAS is scored from 0 – 100 on a 100mm line, while each question on the Likert scale is scored from 0-4, ranking symptoms as either none, mild, moderate, severe, or extreme[96, 97]. The WOMAC is an important tool for determining clinical outcomes in knee/hip OA patients because of its ability to tap into the commonalities that exist in the symptomatic dimensions of OA, and because the WOMAC OA index has frequently outperformed other disease-specific and generic health status measures[98, 99, 100].

### 1.9.2 Mobility Outcome Measures

Although different functional outcomes are assessed from a variety of widely used self-reported scores, patient responses are often subjective, and disparities between patients' and doctors' evaluations can be significant. Therefore, objective and quantified data from gait analysis can be useful[101]. Gait analysis is an important modality for estimating joint mechanics in activity. The advantage of gait analysis is that movement is relatively unconstrained by the measurement system, and therefore a large range of activities can be analyzed[21]. Three-dimensional (3D) motion analysis is the most inclusive gait analysis system, and it measures both kinetic and kinematic gait parameters. In 3D motion analysis, movement of the joint segments is tracked with an optical, magnetic, or optoelectronic system[21]. A series of cameras, along with tracking markers, and electromyographic measurement systems, are used to determine not only the spatio-temporal characteristics of gait, but also the muscular activity and GRF's about the lower limb segments. Several studies have used 3D motion analysis to determine altered gait characteristics in knee OA patients[42, 43, 44, 45, 46].

Although 3D motion analysis is highly sophisticated, it is not clinically practical. The process of data collection is time consuming, and the equipment is not only expensive, but also requires considerable space to set-up and operate. On the other hand, simple measurements of spatio-temporal gait characteristics prove useful in gauging immediate patient goals, which would have an impact on their daily community mobility. For instance, rehabilitation professionals frequently observe spatio-temporal gait deviations to screen elderly people for risk of falling, to monitor patient progress, and to determine the effectiveness of therapy interventions[102, 103, 104]. Three spatio-temporal gait characteristics including walking speed, cadence, and stride length provide a rudimentary

assessment of walking performance[104]. Furthermore, gait velocity alone has been demonstrated as an operative tool to detect elderly patients with balance and mobility impairment[104, 105], and to predict adverse events in well functioning elderly persons[106]. Methods to clinically determine gait velocity include timed measures of gait using a stopwatch, measurement of footstep patterns using a paper and pencil method or an ink pad method, as well as electronic footswitches and video based analysis. All of the aforementioned strategies can be labour intensive, time consuming, cumbersome, and otherwise inefficient for collecting valid and reliable data[103, 107]. Conversely, portable (flexible) walkways with embedded, pressure-sensitive switches reduce the labour intensive and time-consuming aspects of measuring temporal and linear gait parameters[107]. The GAITRite walkway system is one such instrument. GAITRite has been demonstrated as a valid and reliable tool to determine spatio-temporal gait parameters, from the foot-fall patterns of healthy individuals, at self-selected and fast walking speeds[102, 103, 107]. However, the system's ability to measure temporal and spatial gait parameters in subjects without disabilities approximates its performance in persons with gait disturbance[107]. For instance, the GAITRite software calculates elapsed time after sensor activation; it does not rely on derived formulas to document temporal events. Consequently, the time span between sensor activations is the same whether the source of the activation is mechanical force from a normal subject, or from an individual with a disability[107]. The GAITRite system is easy to use and does not require extensive training. Its digital walkway and software are compatible with PC computers, data is calculated instantaneously, and data collected is readily converted into a Microsoft Excel spreadsheet format. Consequently, the GAITRite is a practical tool that can be used in a clinical setting to provide clinicians with immediate results on patient gait characteristics,

which could be used to diagnose mobility impairment, or to objectively monitor the functional gait response of a patient to intervention.

The issue surrounding functional impairment and disability are particularly critical with chronic diseases such knee OA[108]. Although gait velocity can objectively demonstrate functional decline in elderly individuals, the nature of its measurement may not paint the entire picture of functional limitation in knee OA patients. For instance, when recording gait velocity, a subject must only walk a short distance of only a few meters or more, limiting functional analysis to identifying limitations in mobility activities of short duration. An important adjunct to gait velocity for the determination of mobility impairment would be a walking test of longer duration, potentially indicating the functional capacity of knee OA patients that is closer to real time community activity. The six minute walk (SMW) test is easier to administer, better tolerated and more reflective of activities of daily living than other walk tests[109]. Although typically used to determine the functional capacity and intervention outcomes in cardiopulmonary patients, the SMW test has been demonstrated to have excellent test-retest reliability when utilized within a battery of tests to assess performance-related disability in knee OA patients[108]. The SMW test does not provide specific information on the function of each of the different organs and systems involved during mobility[110]. However, this test may be able to demonstrate improvement in knee OA patients who are primarily limited by knee dysfunction, when treated with intervention. The SMW test is simple, requiring no exercise equipment or technician training[110]. Therefore, the SMW test could be used as a practical clinical tool to evaluate the functional capacity of knee OA patients, who are limited primarily by knee dysfunction.

## 1.10 Summary

Knee OA patients have altered gait characteristics resulting from knee pain and the dysfunction of intra-articular structures. Particularly, knee OA patients experience a reduced gait velocity, which has been associated with an increased risk for adverse health outcomes, such as mobility impairment and falling[104, 105, 106]. Mobility impairment may further facilitate the declining health status of knee OA patients commonly associated with old age. For instance, reduced gait velocity may limit the capacity for physical activity in knee OA patients, discouraging participation in worthwhile exercise programs that prevent overall health deterioration. Therefore, improving the gait function of knee OA patients should be considered an important treatment goal to not only prevent adverse health outcomes, but also to improve overall patient health. Viscosupplementation with HA is commonly indicated for symptomatic relief in knee OA, however, this medical device has the unique potential to restore the joints rheological properties, which may improve gait function in knee OA patients.

## 1.11 Purpose

The purpose of this study was to determine the impact of viscosupplementation with HA on the gait function of knee OA patients, particularly its effect on both patients' self-selected and fast gait velocity. Furthermore, this study was designed to determine the impact of HA on reducing knee pain and stiffness, and improving function in knee OA patients. The impact of intra-articular HA on the aforementioned variables was compared to the effect of placebo injections administered to age and diseased matched control patients.

## 1.12 Hypotheses

We hypothesize that knee OA patients treated with HA will experience improved self-selected and fast gait velocity to a greater extent than knee OA patients receiving placebo injections. Additionally, we hypothesize that knee OA patients receiving intra-articular HA injections will experience reductions in knee pain and stiffness, as well as improvements in function, to a greater extent than knee OA patients receiving placebo injections.

# CHAPTER TWO – METHODOLOGY

## 2.1 Study design

We conducted a randomized, double-blind, placebo controlled trial to evaluate the effect of intra-articular HA on gait function, and the clinical outcomes of pain, stiffness, and physical function, in radiographically diagnosed knee OA patients. Participants received three consecutive weekly knee injections of either 2.0 ml of 20 mg/ml HA (molecular weight – 730kD), or 1.2 ml .001 mg/ml HA, which was considered as the placebo injection (P). We randomized 30 participants into two groups of 15, one group to receive HA and one group to receive P. A sample size of 30 participants was determined based on evidence provided Tang et al, 2004[84], and Yavuzer et al, 2005[85], who used treatment groups of 15 and 12 participants respectively to observe the impact of HA on the gait of knee OA patients. Also, a sample size of 30 participants was acceptable for practical reasons, given the logistical constraints considered during this Masters thesis project. We constructed a pre-determined randomized study list. A graduate student with no stake in this study was entrusted with the randomization process using Microsoft Excel, and held the randomization code key until the final follow-up visit. Before the randomized number list was created, study numbers were assigned to HA or P injections, with odd study numbers assigned to HA and even study numbers assigned to P. The randomization function (RANDBETWEEN) in Microsoft Excel returns a random number between specified numbers. We specified a range of numbers between 1 and 60, and the numbers were randomly assigned to study numbers 1 through 30. The random list of numbers returned were then ordered from lowest to highest, and the corresponding HA or P designation associated with that random number was arranged in the resultant order. Duplicate numbers were assigned with letters a, b, c, etc., and were ordered accordingly.

Study numbers were then assigned, along with their pre-determined randomization number coding for their specific injection, to participants sequentially as they were enrolled.

Gait function was analyzed using the GAITRite system[102, 103, 107]; clinical outcomes of pain, stiffness, and physical function were determined by administering the self-report Western Ontario and McMaster Universities (WOMAC) OA index for knee and hip OA[92, 93] (see Appendix II); and the Six Minute Walk (SMW) test was also used to determine patient physical function[108, 109]. Gait analysis, WOMAC administration, and SMW tests were performed prior to each study injection, one week post-treatment, and at three and six months post-treatment.

## 2.2 Study population

### *2.2.1 Inclusion and exclusion criteria*

Participants included were between sixty and eighty years old, all providing informed consent after reading the study letter of information at the pre-treatment visit, one week before the first injection. All participants had diagnosed knee OA based on the criteria set forth by the American College of Rheumatology. Specifically, participants had radiographically diagnosed knee OA and presented clinically with knee pain. Radiographic evidence of knee OA was based on a routine lateral view and a standing anterior-posterior weight bearing radiograph, taken at the pre-treatment visit and at the final study visit. Participants were included if they had a knee OA grade of I-III based on the Kellgren-Lawrence scale. If participants had bi-lateral knee OA, the knee regarded as the worst symptomatically by the participant was considered as the study knee. At the time of consent, participants were asked to discontinue any pharmacological knee OA medication they were taking for the duration of the study, and at the first treatment visit a

medical history for each participant was taken, including number and type of co-morbidities/co-medications, history of knee OA medication, height, weight, leg length, and primary knee symptoms.

Participants were excluded from the study if they were afflicted with a joint disease other than OA, if they had OA in any other of the lower limb joints besides the knee, or if they had end stage knee OA. Furthermore, participants were excluded if they had lower back pathology that limited their walking capacity, had a leg length differential > 2 cm (as reported by Shradder, et al 2004[85]), were diagnosed with a neurological or cardiovascular condition that could impair gait function, were cognitively impaired, underwent knee surgery on the study knee (barring arthroscopy $\geq$ 18 months prior to study commencement), or received an intra-articular injection within six months prior to study commencement.

*2.2.2 Recruitment*

Participants were recruited from referrals to the Joint Pain and Relief Clinic (JPaRC) in the Aging Rehabilitation Geriatric Care Research Center (ARGC) at Parkwood Hospital, as well as a large primary care referral center (The Canadian Center for Activity and Ageing), both in London, Ontario, Canada.

**2.3 Study intervention**

Study intervention was provided by the study physician out of the JPaRC in the ARGC at Parkwood Hospital, London, Ontario. Each syringe was pre-filled, masked with tape, supplied in sealed packages, and were similar in appearance and design. The HA syringe contained 2.0 ml of a 20 mg/ml preparation of HA, while the placebo syringe contained 1.2 ml of a .001 mg/ml HA. The HA preparation was selected because it represents a current standard of therapy in Canada and Europe[111]. An active placebo

injection was selected in order to prevent complete restriction of therapy to study participants, however the dose of HA in the placebo injection was so low we did not expect long-term effects to be greater than typical arthrocentesis. All participants received three consecutive weekly (±2 days) administrations of their respected injections by the blinded study physician. Each injection was given through a 23 gauge 1.5 inch needle using an antero-medial approach, after outcome assessments were conducted; no anaesthetic was used. The schedule of study procedures and assessments is shown in Table 2.1.

**Table 2.1: Visit Schema.**

| | Pre-Tx (Week 1) | 1st Visit (Week 2) | 2nd Visit (Week 3) | 3rd Visit (Week 4) | Follow-Up (3 Months) | Follow- Up (6 months) |
|---|---|---|---|---|---|---|
| **Informed Consent** | X | | | | | |
| **Inclusion/Exclusion** | X | | | | | |
| **Medical History** | X | | | | | |
| **Clinical Examination** | X | | | | | |
| **Radiographic Examination** | X | | | | | X |
| **Randomization** | X | | | | | |
| **Injection** | | X | X | X | | |
| **Synovial Fluid Extraction** | | X | | | X | X |
| **WOMAC OA Index** | | X | X | X | X | X |
| **GAITRite Assessment** | | X | X | X | X | X |
| **Six Minute Walk** | | X | X | X | X | X |
| **Adverse Events** | | X | X | X | X | X |
| **Concurrent Medication/ Rescue Medication** | X | X | X | X | X | X |

**Legend: Pre-Tx=Pre-Treatment; WOMAC=Western Ontario McMaster osteoarthritis index.**

Additionally, all study participants were given rescue medication in the form of 500 mg acetaminophen, and were allowed an upper limit of 4g/day to deal with any intolerable knee pain. Participants were not permitted to take the rescue medication eight

hours before their next study visit, and they were given a diary to record their use of rescue medication throughout the study, which was assessed and documented by the study coordinator at each study visit. Finally, participants in each group were given a home exercise program specifically designed for knee OA patients[112], in accordance with standard appropriate clinical care. The program consisted of joint unloading, as well as range of motion, and strength training activities. The frequency and level of difficulty increased as outlined by the program progression chart (see Appendix III).

## 2.4 Outcome measures

### *2.4.1 Gait function*

Spatio-temporal gait deviations are frequently used by rehabilitation professionals to screen elderly people for risk of falling, to monitor patient progress, and to determine the effectiveness of therapy interventions[102, 103, 104]. Particularly, gait velocity alone has been demonstrated as an operative tool to detect elderly patients with balance and mobility impairment[104, 105], and to predict adverse events in well functioning elderly persons[106]. GAITRite has been demonstrated as a valid and reliable tool used to determine a myriad of spatio-temporal gait parameters[103, 107], including gait velocity. The GAITRite system is a portable (flexible) electronic walkway compatible with computer software specifically designed to calculate spatio-temporal gait characteristics. Encapsulated within the electronic walkway are multiple sensor pads connected across its length. As the subject ambulates, the pressure exerted by the feet onto the walkway activates these sensors. The walkway does not only sense the geometry of the activating objects but also the relative arrangement between them in a two dimensional space. In addition, the walkway senses the vertical component of the relative pressure exerted by the objects, while the algorithms built into the system isolate the objects and identify

them as footprints[113]. Furthermore, the GAITRite systems digital walkway and software are compatible with PC computers, data is calculated instantaneously, and data collected is readily converted into a Microsoft Excel spreadsheet format. Consequently, the GAITRite is a practical tool that can be used in a clinical setting to provide clinicians with immediate results on patient gait characteristics, which could be used to diagnose mobility impairment, or to objectively monitor the functional gait response of a patient to intervention. The specifications of the GAITRite (Gold version) used in this study are presented in Table 2.2.

**Table 2.2: GAITRite (Gold version) specifications.**

| | |
|---|---|
| **Overall Dimensions** | 914.40 x 90.17 x 0.635 cm (L x W x H) |
| **Active area** | 878.40 x 60.96 cm (L x W) |
| **Weight** | 36.36 kg |
| **Sampling rate** | 80 Hz |
| **Communications** | RS-232, 57.6 Kbps or 19.2 Kbps |
| **Power requirements** | 12 Vde |
| **Number of sensors** | 27, 648 sensors are placed on 1.27 cm centers arranged in a 48 x 576 grid |
| **Sensor** | 1.02 $cm^2$, dual control |
| **Top cover** | Vinyl with square thread reinforcement, waterproof and chemical resistant |
| **Bottom cover** | Open cell foam rubber |
| **Computer requirements** | IBM® compatible personal computer with: Windows 95/98/ME/NT/2000, Pentium processor, 64 MB RAM |

The GAITRite walkway was set up in a low-traffic corridor of approximately 20 m in length in the Geriatrics Division of the participating hospital. Participants were asked to wear shoes that they considered comfortable to go for a walk with, and were asked to wear those same shoes at each study visit. Participants were given instruction to walk at their self-selected (usual) speed, and at their fastest speed. Furthermore, they were asked to start 1 m before the walkway, to account for the acceleration phase of gait, and to walk clear of 1 m beyond the walkway, in order to account for the deceleration phase of gait. In this way we could be sure we were collecting the 'core' of a participant's gait. Participants were allowed a practice walk at both speeds at each visit,

and were asked to walk for three trials, allowing for a 20 second rest between each trial. The participants first walked at their self-selected gait speed for three trials, and then at their fast gait speed for three trials, all after the prompt 'ready, go'. Participants were not given verbal encouragement of any kind during the protocol, and were not permitted to talk as they walked. An average of the three trials was calculated and recorded for analysis.

*2.4.2 Clinical outcomes*

Joint pain, stiffness, and reduced physical function are common and important clinical symptoms targeted by intervention in knee OA patients. The WOMAC OA index is a self-report functional status measure which professes to assess these three clinical outcomes specifically in knee/hip OA[92]. The WOMAC is valid, reliable, and is a responsive measure of clinical outcomes, and has been used in diverse clinical and interventional environments[93]. The WOMAC LK3.1 version was used in this study. It consists of 24 questions grouped into 3 domains; pain (5 questions), stiffness (2 questions), and physical function (17 questions). Each item was scored on a 5 point Likert scale, with participants rating the severity of their symptoms as either none, mild, moderate, severe, or extreme. Each response was scored 0, 1, 2, 3, or 4 respectively. A higher score on any of the WOMAC sections of pain, stiffness, and physical function represents greater severity of the respective symptom/limitation. Participants completed the WOMAC questionnaire prior to gait analysis at each study visit, and were to rate the severity of their symptoms over the past 48 hours.

*2.4.3 Functional capacity*

The Six Minute Walk (SMW) test was utilized to evaluate the overall functional capacity of study participants in each group as the study progressed. A 304.80 m course

was set up in a low-traffic wing of the participating hospital, with 30.48 m intervals marked along the course. The test was administered under the conditions specified by Rajeski, et al 1995[108], who reported on data collected from the Fitness and Arthritis in Seniors Trial (FAST). SMW test variations, approved by the American Thoracic Society[110], were included; such as using a linear instead of a circular course, and informing participants of how much time had elapsed between laps. Participants were asked to walk at a comfortable speed for six minutes, and were instructed to walk as many laps as they could in that time. One lap was considered walking a distance of 609.60 m, and every time the participant walked one lap they were informed of the amount of time elapsed, determined with a stopwatch. Participants were allowed to stop and rest for any reason, and were allowed to rest as long as they wanted, all of which was documented. At the end of six minutes the distance covered was calculated, and any knee symptoms the participants were experiencing during or after the test were recorded.

*2.4.4 Synovial fluid analysis*

Synovial fluid samples were taken from each participant in each group by the study physician prior to the first injection, and at the three and six month follow-up visits. Analysis of the impact of intra-articular injection of HA on the biomolecular composition of synovial fluid in knee OA patients is pending, and results will be reported in the near future.

**2.5 Data Management and Statistical analysis**

*2.5.1 Data management*

All recorded data on patient gait characteristics were initially stored within a laptop designated for GAITRite data collection in the Division of Geriatrics in Parkwood Hospital, London, Ontario. Data was exported from the GAITRite program and saved on

the laptop within a Microsoft Excel spreadsheet, as well as to a backup disc stored in a secure office. WOMAC scores were recorded on a paper version of the WOMAC questionnaire. Scores were totalled at the end of each patients study visits and were recorded on the case report form, which also contained patient information collected at the pre-treatment visit. SMW distances were also recorded on the case report form, which was stored in a secure office in the ARGC in Parkwood Hospital, London, Ontario. At the end of each participants study visit, data from gait velocity recordings, WOMAC scores, and SMW distances were all documented within a Microsoft Excel spreadsheet, which also contained participant baseline characteristics, amount of rescue medication consumption reported at each visit, as well as participant reported number of falls since each study visit.

*2.5.2 Statistical analysis*

Paired-samples and independent-samples t-tests were used to determine if there were any within and between group differences, respectively, at baseline and at each subsequent follow-up visit, in the means of the following outcome measures: both self-selected and fast gait velocity; the WOMAC scores of pain, stiffness, and function; and the SMW distances. Also, repeated measures multivariate analysis of variance (MANOVA) was performed to determine between and within group differences over the collective time of one week, three months and six months post-treatment. A MANOVA was conducted to determine the overall effect of HA when compared to P regarding improvement in gait function, modelled with both self-selected and fast gait velocity, as well as for improvement in clinical outcomes, modelled with WOMAC pain, stiffness, and function scores. Furthermore, repeated measures analysis of covariance (ANCOVA) was performed to detect the impact of the amount of rescue medication used, age, body

mass index (BMI), and baseline WOMAC pain and function scores on gait function, as well as the impact of rescue medication used on clinical outcomes. Level of significance was set at $p = 0.05$ for all tests. SPSS version 17.0 was used for each statistical analysis.

**2.6 Ethics Approval**

The study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario, and by the Clinical Research Impact Committee at Parkwood Hospital, London, Ontario.

# CHAPTER THREE – RESULTS

## 3.1 Study population and demographics

A total of 38 potential participants were screened for inclusion, and 30 participants were deemed acceptable. Eight potential participants were excluded; two who did not think they would be able to abide by the study visit schedule, as outlined in the protocol; two who did not have significant signs of knee OA, based on radiographic criteria; two who did not agree to discontinue NSAID treatment; one who opted for surgical knee repair; and one who presented with a torn anterior cruciate ligament. There were no dropouts or significant protocol deviations during the study. All participants completed each outcome measure at the one week, three months, and six months post-treatment follow-up visits.

There were no statistically significant differences between the HA and P groups with respect to demographic characteristics at baseline (Table 3.1). The distribution of males and females was equal between groups (53% male, 47% female). The mean age was [Mean (SD)] 71.93 (6.83) years old in the HA group, and 72.93 (5.48) years old in the P group. Participant BMI was also comparable across groups. The mean BMI was 30.48 (6.16) $kg/m^2$ for participants in the HA group, and 29.40 (4.11) $kg/m^2$ for participants in the P group. The HA and P groups had similar histories of falling, reporting on average one fall prior to study commencement. However, fewer participants in the HA group reported a fear of falling at baseline than in the P group. At baseline, 3 participants in the HA group reported a fear of falling, while 9 participants in the P group reported a fear of falling. The mean number of co-morbidities in the HA group was 2.07 (1.98), while the participants in the P group had 1.94 (1.03) co-morbidities. Finally, the HA and P groups were similar regarding the number of uni-lateral and bi-lateral knee OA

patients; the HA group contained 5 patients with uni-lateral knee OA and 10 patients with bi-lateral knee OA, while the P group had 6 uni-lateral knee OA patients, and 9 bilateral knee OA patients.

**Table 3.1: Baseline participant demographics.**

| | HA | P |
|---|---|---|
| **N** | 15 | 15 |
| **Gender (%)** | | |
| **Male** | 53 | 53 |
| **Female** | 47 | 47 |
| **Age (yrs) [Mean(SD)]** | 71.93 (6.83) | 72.93 (5.48) |
| **Height (cm) [Mean(SD)]** | 164.34 (8.21) | 168.60 (8.32) |
| **Weight (kg) [Mean(SD)]** | 81.79 (14.32) | 83.58 (13.10) |
| **BMI (kg/m$^2$) [Mean(SD)]** | 30.48 (6.16) | 29.40 (4.11) |
| **Number of Falls [Mean(SD)]** | 1 (1.81) | 1 (0.76) |
| **Fear of Falling [# Reported]** | 3 | 9 |
| **Number of Co-morbidities [Mean(SD)]** | 2.07 (1.98) | 1.94 (1.03) |
| **Knee OA [# Uni-/Bi-lateral]** | 5 Uni. /10 Bi. | 6 Uni. /9 Bi. |

**Legend: HA=group receiving hyaluronic acid; P=group receiving placebo; n=group size; yrs=years old; SD=standard deviation; BMI=body mass index; OA=osteoarthritis.**

## 3.2 Gait velocity

At baseline, the mean values for both self-selected and fast gait velocities of the participants in the HA and P groups were not significantly different from each other ($p > 0.05$). The HA group had a [Mean(SD)] self-selected gait velocity of 113.72 (23.80) cm/s, while the P group had a self-selected gait velocity of 108.55 (25.63) cm/s. Furthermore, the HA group had a fast gait velocity of 151.92 (33.49) cm/s, while the P group had a fast gait velocity of 140.02 (32.02) cm/s. Table 3.2 displays both self-

selected and fast gait velocities for both groups at baseline, one week post injection series, and at three and six months follow-up, along with their respective changes and 95% confidence intervals (CI's) at these time points. Both HA and P groups experienced significant improvement from baseline in their self-selected gait velocities at one week, three months, and six months post injection series ($p < 0.05$). However, only the HA group experienced significant improvement from baseline in their fast gait velocity, which was realized at three months follow-up and sustained at six months follow-up ($p < 0.05$). The HA and P groups were not significantly different from each other at any of the follow-up visits regarding both self-selected and fast gait velocity ($p > 0.05$).

**Table 3.2: Changes in gait velocity throughout study.**

| | HA [Mean (SD)] | Mean Δ (95% CI) | P [Mean (SD)] | Mean Δ (95% CI) | Mean Difference† (95% CI) |
|---|---|---|---|---|---|
| **Self-selected velocity (cm/s)** | | | | | |
| Baseline | 113.72 (23.80) | - | 108.55 (25.63) | - | 5.17 (-13.33; 23.67) |
| Week 4 | 126.04 (24.79)* | 12.32 (5.95; 18.69) | 116.78 (23.63)* | 8.23 (2.44; 14.02) | 9.26 (-8.85; 27.37) |
| 3 month Follow-up | 124.82 (23.77)* | 11.10 (4.78; 17.42) | 118.41 (26.42)* | 9.86 (4.20; 15.52) | 6.41 (-12.39; 25.21) |
| 6 month Follow-up | 123.25 (25.61)* | 9.53 (1.59; 17.47) | 121.38 (25.35)* | 12.83 (6.26; 19.41) | 1.86 (-17.19; 20.92) |
| **Fast velocity (cm/s)** | | | | | |
| Baseline | 151.92 (33.49) | - | 140.02 (32.01) | - | 11.90 (-12.60; 36.41) |
| Week 4 | 156.70 (32.95) | 5.84 (-0.45; 12.14) | 141.91 (31.58) | 1.88 (-4.55; 8.32) | 15.86 (-8.33; 40.05) |
| 3 month Follow-up | 159.38 (34.21)* | 7.45 (2.85; 12.05) | 145.14 (35.07) | 5.12 (-1.43; 11.67) | 14.24 (-11.68; 40.15) |
| 6 month Follow-up | 163.11 (37.82)* | 11.19 (2.00; 20.38) | 144.20 (36.51) | 4.17 (-4.64; 12.99) | 18.92 (-8.89; 46.72) |

**Legend: Δ = increase from baseline; † = between group differences; Week 4=one week post-treatment; *$p < 0.05$ within groups comparison v. baseline.**

Table 3.3 displays multivariate output for the repeated measures MANOVA model of gait function, combining self-selected and fast gait velocity. The multivariate

output revealed a non-significant between groups effect of patient group assignment (HA v. P) ($p = 0.196$) on gait function. The overall within groups effect of time was significant ($p = 0.003$), while the time-patient group interaction effect on gait function within groups was not statistically significant ($p = 0.075$). However, Maulchly's test of sphericity was significant for the fast gait velocity component of the gait function model ($p = 0.009$). Therefore, distributions of variance for the repeated measures of fast gait velocity were not equal, an assumption necessary for MANOVA. To correct for the degrees of freedom of the averaged tests of significance, the Greenhouse-Geisser univariate test was used to determine the significant within group effect of group assignment on fast gait velocity, while Sphericity was assumed when determining the within groups effect of group assignment on self-selected gait velocity (Table 3.3).

**Table 3.3: Repeated measures MANOVA multivariate tests output.**

| Effect | F | *P* | Observed Power |
|---|---|---|---|
| **Between Subjects** | | | |
| Intercept (Gait function) | 357.12 | 0.000 | 1.00 |
| Patient group (Gait function) | 1.73 | 0.196 | 0.331 |
| Intercept (Clinical outcomes) | 159.32 | 0.000 | 1.00 |
| Patient group (Clinical outcomes) | 1.43 | 0.256 | 0.334 |
| **Within Subjects** | | | |
| Time (Gait function) | 4.75 | 0.003 | 0.959 |
| Self-selected gait velocity† | 15.29 | 0.000 | 1.00 |
| Fast gait velocity†† | 4.76 | 0.010 | 0.795 |
| Time*Patient group (Gait function) | 2.24 | 0.075 | 0.663 |
| Self-selected gait velocity† | 1.26 | 0.293 | 0.326 |
| Fast gait velocity†† | 0.912 | 0.414 | 0.207 |
| Time (Clinical outcomes) | 2.76 | 0.028 | 0.835 |
| Pain† | 5.61 | 0.001 | 0.935 |
| Stiffness† | 8.42 | 0.000 | 0.991 |
| Function† | 11.25 | 0.000 | 0.999 |
| Time*Patient group (Clinical outcomes) | 0.79 | 0.628 | 0.278 |
| Pain† | 0.757 | 0.522 | 0.206 |
| Stiffness† | 1.22 | 0.307 | 0.316 |
| Function† | 1.14 | 0.338 | 0.297 |

**Legend: All figures presented based on Pillai's trace unless otherwise indicated; †=Sphericity Assumed; ††=Greenhouse-Geisser; Patient group=HA v P; Gait function = MANOVA model including both self-selected and fast gait velocity; Clinical outcomes = MANOVA model including all WOMAC scores of pain, stiffness, and function.**

The consequent analysis revealed that the within group effect of time was significant for both self-selected ($p < 0.0001$) and fast gait velocity ($p = 0.01$), while the time-patient group interaction was not significant for self-selected ($p = 0.293$) or fast gait velocity ($p = 0.414$).

Table 3.4 displays the MANOVA output for the differences between assignment to HA or P groups derived from pairwise comparisons. The differences between HA and P groups regarding self-selected and fast gait velocities were not significantly different. However, although the 95% CI is wide, [Mean difference (CI)] 15.23 (-9.82; 40.28), an observed trend suggests the increased fast gait velocity after intervention in the HA group is greater than that of the P group, as the positive upper bound of the CI is quite large relative to a value of no difference and to the negative lower bound.

**Table 3.4: Repeated measures MANOVA between group pairwise comparison**

| Measure | Mean Difference (HA-P) | SE | *p* | 95% Confidence Interval | |
|---|---|---|---|---|---|
| | | | | Lower Bound | Upper Bound |
| **Self-selected gait velocity** | 5.68 | 8.78 | 0.523 | -12.30 | 23.65 |
| **Fast gait velocity** | 15.23 | 12.23 | 0.223 | -9.82 | 40.28 |
| **Pain** | -2.47 | 1.17 | 0.043 | -4.86 | -0.79 |
| **Stiffness** | -0.87 | 0.441 | 0.059 | -1.77 | 0.037 |
| **Function** | -7.23 | 3.61 | 0.055 | -14.63 | 0.16 |

**Legend: SE = standard error; HA = intervention group; P = placebo group; positive score = increase; negative score = decrease; confidence intervals calculated using Bonferroni adjustment for multiple comparisons.**

### 3.3 Clinical outcomes

Mean WOMAC scores for both the HA and P groups at baseline and each follow-up visit, along with change scores and 95% CI's, are presented in Table 3.5. At baseline the HA and P groups were not significantly different for any of the WOMAC pain, stiffness, and function scores ($p > 0.05$). At one week post-injection series, the HA group experienced significant decreases in their WOMAC pain, stiffness, and function scores (*p*

< 0.05), and these changes in WOMAC scores were sustained at six months follow-up. The P group experienced significant improvement in the physical function score on the WOMAC one-week post-injection series and was sustained at three months ($p < 0.05$), but not six months follow-up ($p > 0.05$). Meanwhile, the P group experienced significant reduction stiffness scores at three months follow-up ($p < 0.05$), but not at one-week post-injection series or at six months follow-up ($p > 0.05$).

**Table 3.5: Changes in WOMAC scores throughout study.**

| | HA [Mean (SD)] | Mean Δ (95% CI) | P [Mean (SD)] | Mean Δ (95% CI) | Mean Difference† (95% CI) |
|---|---|---|---|---|---|
| **WOMAC - Pain (/20)** | | | | | |
| Baseline | 5.20 (3.43) | - | 7.27 (3.75) | - | 2.07 (-4.75; 0.62) |
| **Week 4** | **3.80 (2.91)*** | **- 1.40 (-2.42; -0.38)** | 6.47 (3.72) | **- 0.80 (-2.28; 0.68)** | **2.67 (-5.16; -0.17)**** |
| 3 month Follow-up | 3.80 (3.43) | - 1.40 (-2.94; 1.35) | 5.53 (3.80) | - 1.73 (-3.50; 0.04) | 1.74 (-4.44; 0.97) |
| **6 month Follow-up** | **3.67 (3.29)*** | **- 1.54 (-2.64; -0.43)** | 6.67 (4.40) | **- 0.60 (-2.49; 1.29)** | **3.00 (-5.91; -0.09)**** |
| **WOMAC - Stiffness (/8)** | | | | | |
| Baseline | 3.27 (1.44) | - | 3.73 (1.34) | - | 0.47 (-1.50; 0.57) |
| **Week 4** | **2.20 (0.94)*** | **- 1.07 (-1.81; -0.33)** | 3.20 (1.52) | **- 0.53 (-1.22; 0.16)** | **1.00 (-1.96; -0.05)**** |
| 3 month Follow-up | 2.13 (1.41)* | - 1.13 (-1.68; -0.59) | 2.93 (1.39)* | - 0.80 (-1.32; -0.28) | 0.80 (-1.85; 0.25) |
| 6 month Follow-up | 2.27 (1.67)* | - 1.00 (-1.66; -0.34) | 3.40 (1.64) | - 0.33 (-1.19; 0.52) | 1.13 (-2.37; 0.10) |
| **WOMAC - Physical function (/68)** | | | | | |
| Baseline | 23.40 (11.54) | - | 28.73 (7.28) | - | 5.34 (-12.61; 1.94) |
| **Week 4** | **16.00 (10.99)*** | **- 7.40 (-11.80; -3.01)** | 22.93 (10.21)* | **- 5.80 (-10.11; -1.49)** | **6.93 (-14.87; 1.00)** |
| 3 month Follow-up | 16.80 (12.03)* | - 6.60 (-11.58; -1.62) | 21.27 (11.58)* | - 7.47 (-13.04; -1.90) | 4.47 (-13.30; 4.37) |
| **6 month Follow-up** | **15.13 (12.83)*** | **- 8.27 (-12.51; -4.02)** | 25.20 (12.79) | **- 3.53 (-9.16; 2.09)** | **10.07 (-19.65; -0.49)**** |

**Legend: Δ = decrease from baseline; † = between group differences; Week 4=one week post-treatment; *$p < 0.05$ within groups comparison v. baseline; **$p < 0.05$ between groups comparison.**

Table 3.3 displays multivariate output for the repeated measures MANOVA model of clinical outcomes, combining the WOMAC scores of pain, stiffness, and physical function. The multivariate output revealed a non-significant between groups effect of patient group assignment (HA v. P) ($p = 0.256$) on clinical outcomes. The overall within groups effect of time was significant ($p = 0.028$), while the time-patient group interaction effect on clinical outcomes within groups was not statistically significant ($p = 0.628$). Maulchly's test of sphericity was not significant for any of the WOMAC subsections of pain, stiffness, or physical function of the clinical outcomes model ($p > 0.05$). Therefore, the assumption of sphericity was met for the MANOVA, and the Sphericity assumed univariate test was used for all within group comparisons regarding clinical outcomes. Table 3.4 displays the MANOVA output for the differences between assignment to HA or P groups derived from pairwise comparisons. The differences between HA and P groups regarding the clinical outcome of pain was statistically significant ($p = 0.043$), while the clinical outcomes of stiffness ($p = 0.059$), and physical function ($p = 0.055$) approached statistical significance. Furthermore, the 95% CI's for stiffness -0.87 (-1.77; 0.037) and function -7.23 (-14.63; 0.160) demonstrate that the negative lower bounds of the CI's are larger relative to the positive upper bounds, indicating that a distinction between the HA and P groups after intervention was close to being met. This suggests that the effect size in score reduction for the stiffness and function sections of the WOMAC may have been greater in the HA group when compared to the P group.

**3.4 Six minute walk test**

Table 3.6 displays the mean SMW distances for each group throughout the study, along with the amount of change at each follow-up visit. Mean SMW test distances were

not significantly different between the HA and P groups at baseline ($p > 0.05$). The HA group experienced significantly improved SMW distances at three months follow-up ($p < 0.05$), while the P group experienced significantly improved SMW distances at one week post-treatment and at three months follow-up ($p < 0.05$). Neither the HA or P group experienced a significant improvement from baseline regarding SMW distances at the six month follow-up ($p > 0.05$). Also, the HA and P groups' SMW distances were not significantly different from each other at any of the follow-up visits throughout the study ($p > 0.05$).

**Table 3.6: Changes in SMW distance throughout study.**

| | HA [Mean (SD)] | Mean Δ (95% CI) | P [Mean (SD)] | Mean Δ (95% CI) | Mean Difference† (95% CI) |
|---|---|---|---|---|---|
| Baseline | 437.70 (117.13) | - | 409.00 (114.87) | - | 28.70 (-58.07; 115.46) |
| Week 4 | 461.25 (135.67) | 23.55 (0.54; 47.64) | 443.75 (112.40)* | 34.75 (18.24; 51.26) | 17.50 (-75.69; 110.68) |
| 3 month Follow-up | 459.34 (123.41)* | 21.64 (1.06; 42.21) | 438.00 (134.88)* | 29.00 (6.14; 51.86) | 21.34 (-75.36; 118.03) |
| 6 month Follow-up | 456.19 (126.47) | 18.49 (-9.62; 46.59) | 432.39 (131.52) | 23.39 (0.83; 47.61) | 23.79 (-72.71; 120.30) |

**Legend: All SMW distances reported in m; Δ = increase from baseline; † = between group differences; Week 4=one week post-treatment; *$p < 0.05$ within groups comparison v. baseline.**

## 3.5 Covariates

The repeated measures ANCOVA determined that none of the amount of rescue medication used, BMI, or baseline WOMAC pain scores had a significant between groups effect on gait function ($p > 0.05$), although baseline WOMAC pain scores approached significance ($p = 0.053$). Furthermore, the aforementioned covariates were not found to have a significant within group effect on gait function when interacting with time. However, the covariates of age ($p = 0.03$) and baseline WOMAC physical function score ($p = 0.008$) were found to have a significant between groups effect on gait function, but

not a significant within groups effect when interacting with time. Finally, the amount of rescue medication consumed did not have a significant between or within group effect on the clinical outcomes based on the WOMAC pain, stiffness, and physical function scores.

### 3.6 Adverse events

No significant adverse events were reported in this study. A limited number of patients reported minor discomfort during the injection process, but were not in discomfort immediately after the injection.

# CHAPTER FOUR – DISCUSSION

This study did not detect a statistically significant improvement in gait velocity, symptom severity, or SMW distances in mild-moderate knee OA patients treated with intra-articular HA, when compared to age and disease matched patients receiving placebo. As a result, the treatment effect of intra-articular HA on gait function and clinical outcomes was not superior to placebo injections in this trial. However, a number of notable trends were observed which may support the contention that HA treatment may affect some measures of gait function and clinical outcomes. Our findings demonstrate that participants in both HA and P groups experienced statistically significant increases in self-selected gait velocity, while only the HA group experienced an increase in fast gait velocity, which was both statistically and clinically significant. Furthermore, both HA and P groups experienced statistically significant improvement in self-reported symptom severity, while only the HA group remained improved at six month follow up.

## 4.1 Gait function

When performance measures are used in clinical research, results may be impacted by co-variables such as motivation, motor-learning, and psychosocial factors, which contribute to measurement error[114, 115, 116, 117, 118]. Therefore, improvements in performance observed in trials with repeated measures designs may not necessarily indicate the treatment effect of the study intervention, nor may improvements represent the true performance of controls. Curiously, both HA and P groups experienced very similar improvements in self selected gait velocity throughout the study, while only the HA group experienced improvement in fast gait velocity. The impact of the aforementioned co-variables on our results may have been exacerbated by the fact that it may be more difficult to replicate the same pace during self-selected gait velocity than

during fast gait velocity, adding to measurement error. For instance, Fransen, et al 1997[119] reported greater intra-session and inter-session reliability of quantitative gait analysis at fast gait velocity than with self-selected gait velocity. These authors suggested that greater variability with sub-maximal effort could be attributed to more complex recruitment coding and feedback requirements. Moreover, it has been reported that greater variability is present with sub-maximal effort during muscle testing[120], and with slower functional movements[121]. Fransen, et al 1997[119] further demonstrated a significant learning affect on self-selected gait velocity in knee OA patients that reduced measurement reliability. However, they found that at subsequent sessions the reliability of this measurement began to increase, suggesting a deceasing influence of learning and adaptability effect at this walking speed. Our results demonstrate a similar trend as the self-selected gait velocity of both groups improved significantly one-week post-treatment, but were not much different at this time point or at the three and six month follow up visits. In contrast, maximal effort or fast movements involve a simple all-out effort, and may be the reason for the greater intra-subject reliability at fast gait velocity[119]. Consequently, patients in both groups in this study may have learned to improve their self-selected gait velocity over time, until the leaning effect reached a plateau, while the results from the fast gait velocity may be more indicative of HA's treatment effect.

When knee OA patients walk with a greater velocity they are increasing the stress on their diseased knee joint, evidenced by several studies reporting increased knee load with increased gait velocity[44, 88, 122, 123]. Fast gait velocity may aggravate the knee OA condition to a greater extent than self-selected gait velocity, intensifying functional limitation in knee OA patients. Consequently, fast gait velocity may be of greater utility for detecting interventional treatment effects in knee OA patients, which are distinguished

from learning effects, because increased gait speed increases detection of gait limitation[124]. This further implies that fast gait velocity would be a more responsive tool than self-selected gait velocity for detecting the effect of intervention in knee OA patients. Since self-selected gait velocity may not be able to stress the OA knee sufficiently to identify intervention treatment effects, this outcome measure may not have been sensitive enough to distinguish between learning and treatment effect in the knee OA patient population in this study. The greater ability of fast gait velocity to elicit gait limitation in knee OA patients provides further support for fast gait velocity as being the more relevant indicator of patient gait response to intra-articular HA in this study.

A significant distinction between intra-articular HA and placebo injection was not established in this study regarding improved gait velocity in knee OA patients. However, an interesting trend was observed when looking into the 95% CI of the fast gait velocity component of the MANOVA model for gait function. Non-significance does not mean 'no effect', as small studies will often report non-significance even when there are clinically important, real effects[125]. It is the size of the effect that determines the importance, not the presence of statistical significance; therefore, CI's are preferable to *p*-values because they tell us the range of possible effect sizes[125]. Accordingly, looking at CI's may provide more insight into actual treatment effect compared to just observing statistical significance at a certain set *p*-value. When observing the between group pairwise comparison for the fast gait velocity component of the MANOVA model we find a mean difference of 15.23 cm/s between HA and P groups with a 95% CI (-9.82; 40.28). Although the CI contains the null hypothesis (i.e. a mean difference of zero) within it, the greater positive portion of the CI signifies a difference greater than zero, demonstrating a trend that may suggest that there might be an actual difference between

the effect of HA and P on the fast gait velocity of knee OA patients in this study, favouring a greater fast gait velocity for the HA group. However, this CI is wide, decreasing the precision of our measurement, and precluding an accurate determination of an actual effect size. As precision of CI's depends upon sample size[126], this may indicate that this study was underpowered due to a small study population. On the other hand, HA's impact on fast gait velocity is evident when observing the improvement within the HA and P groups. At six months follow-up the HA group experienced a clinically significant improvement in their fast gait velocity of > 0.1 m/s[127], while the P group only achieved an improvement in fast gait velocity that could be considered a small effect size, which ranges from 0.04-0.06 m/s[127].

Improving the speed with which an elderly person can walk is important because gait velocity is considered an indicator of physiological reserve[128]. Particularly, generating greater fast gait velocity may assist an elderly person in coping with external stressors requiring a rapid mobility response, such as crossing the street or avoiding oncoming traffic[117]. The maximum walking velocity that is necessary to cross a signalled crosswalk has been reported as 1.22 m/s in the United States[129]. Although the fast gait velocity of both the HA and P groups were above this value, after the seventh decade of life fast gait speed may decrease at a rate of 20% per decade[130]. Compounded with the negative impact knee OA has on gait velocity, an improvement of fast gait speed > 0.1 m/s[127] may significantly support the maintenance of physical function in older knee OA patients. Consequently, increasing the ability of an elderly knee OA patient to walk more quickly may allow them to respond to environmental stimuli more effectively, allowing greater community function without the occurrence of activity related adverse events, such as falls. In addition, increasing the ability to walk at a greater fast speed without

limitation would facilitate greater improvement in overall fitness and quality of life in knee OA patients. Efforts to maximize disability free living include promotion of physical activity[131], which should emphasize walking and leg strengthening, two key components that are associated with better physical function[132]. When attempting to limit disability, the intensity of physical treatment possible in older people with marked chronic joint disease is often limited[133]. However, the literature suggests that greater improvements in strength are due to more intense training regimens[134, 135]. Furthermore, gait speed has known relationships with overall aerobic capacity and functional status, so it can be linked to cardiovascular health and capacity to perform daily activities[128]. Consequently, we can infer that increasing the fast gait speed of knee OA patients may enable them to maintain or improve their overall health status through more vigorous participation in physical activity, simultaneously discouraging adverse health outcomes (such as cardiovascular disease, or further musculoskeletal degenerative disease) and preventing the downward spiral of co-morbid health conditions frequently associated with older age.

**4.2 Clinical outcomes**

The MANOVA output revealed that although there was a significant improvement over time regarding the clinical outcomes of pain, stiffness, and physical function collectively, no significant effect of HA over P was found when observing the improvement in patient symptoms. However, when broken down into individual subsections of the WOMAC, the repeated measures analysis revealed that pain scores in the HA group were significantly different from P scores, [mean difference (95% CI)] 2.47 (4.86; 0.79) ($p = 0.043$), while the difference between groups regarding stiffness, 0.87 (1.77; 0.037) ($p = 0.059$), and function, 7.23 (14.63; 0.16) ($p = 0.055$) approached

significance. Again, a trend is observed in the CI regarding differences between HA and P groups, and although the CI's may be relatively wide, this may indicate once more that our study was underpowered to detect this difference due to a small sample size. When comparing our results to others who observed the effect of HA in knee OA patients using a randomized controlled trial with the WOMAC LK3.1, we found that the reduction in pain of our participants at six months follow-up was less than found previously in the literature[70, 136, 137, 138]. However, our results were comparable to studies that found a reduction in stiffness[70, 136] and improvement in self-reported function[70, 77, 136] at six months follow-up.

Alternatively, when comparing our results to the OMERACT-OARSI set of intervention responder criteria[139], we find that the HA group in our study was very close to achieving responder status, while the P group was not. To be considered as having a response to treatment, these criteria dictate that a group of patients must have an improvement in pain or function (based on WOMAC scores) with $\geq$ 50% and an absolute change of $\geq$ 20 (on a 0-100 interval scale). If these criteria are not met, a response could be indicated by improvement in at least two of the following: pain $\geq$ 20% and absolute change $\geq$ 10; function $\geq$ 20% and absolute change $\geq$ 10; and/or patient's global assessment $\geq$ 20% and absolute change $\geq$ 10. The HA group approached meeting responder criteria for pain at one week post-treatment [Relative improvement; Absolute improvement] (26.92%; 7.00), and at six months follow-up (29.42%; 7.65), while they did achieve responder criteria for function at one week post-treatment (31.62%; 10.88) and at six month follow-up (35.34%; 12.16). The P group on the other hand was not close to meeting OMERACT-OARSI responder criteria for pain at one week post-treatment (11.00%; 4.00) or six months follow-up (8.25%; 3.00). However, the P group

was close to meeting responder criteria for function at one week post-treatment (20.19%; 8.53), but not close at six months follow-up (12.29%; 5.19). Furthermore, the HA group enjoyed relative and absolute improvements in their WOMAC function scores that achieved the level of minimal clinically important improvement (MCII), both at one-week post-treatment and six months follow-up, while the P group did not. Tubach, et al 2005[140] reported MCII as being an absolute change (on a 0-100 interval scale) of 9.1, and a relative change of 26.0% on the WOMAC Likert function scale. Moreover, Tubach, et al 2005[96] describe the patients acceptable symptom state (PASS) as the value beyond which patients consider themselves well, and define this state as being a score less than 31.0 on the WOMAC Likert function score (on a 0-100 interval scale). Both the HA and P groups WOMAC function scores were above the PASS level at baseline, while only the HA group experienced improvement in their WOMAC function score beyond a level of PASS, at one week post-treatment and six months follow-up.

Thus, although this study did not detect a statistically significant difference between HA and P groups regarding WOMAC scores after intervention, improvements in clinically relevant concepts such as the MCII and PASS in WOMAC function scores were observed in the HA group, but not in the P group. Furthermore, the HA group met three quarters of OMERACT-OARSI responder criteria at both one week post-treatment and at six months follow-up, while the P group only met one of the criteria at one week post-treatment. These findings may be indicative of the clinically relevant treatment effect of intra-articular HA therapy that is distinctive from placebo effect, demonstrating its usefulness in improving knee OA patient pain and function, also reported in previous studies[79, 80, 81, 82, 83].

### 4.3 Functional capacity

Functional performance on short-distance walking speed may not be representative of independence within the community[141], and self-report measures of physical function do not provide objective evaluation of patient community function. Therefore, participants completed the SMW test at each study visit to determine the overall physical function of participants before and after HA or P injection. After their respective injection series, participants in both the HA and P groups experienced improvements in the distance they could walk within six minutes. However, similar to what was observed for improvement in self-selected gait velocity, the improvements in the HA and P groups resembled each other. Once again, this could have been a consequence of the effect of learning and motivation. For instance, during the SMW test participants walked at a pace which was similar to their self-selected gait velocity. We have already established that self-selected gait velocity is not as reliable as fast gait velocity[119], and that self-selected gait velocity may not be strenuous enough to elicit gait limitation[124]. Furthermore, reliability is population specific and any measure will have certain reliability when applied to a specific population, and under specific conditions[116]. Consequently, the SMW test, like self-selected gait velocity, may not have been sensitive enough to demonstrate improvement derived from intra-articular injection of HA or P on the mild-moderate knee OA patients in this study. Instead, learning and training effects may have accounted for improvement in SMW distances during the repeated follow-up visits. These factors may have masked the performance of participants that was, or was not, affected by intervention or control injections. For instance, the effect of encouragement on distance walked in the SMW test has been reported to account for 30.5 m of improvement[114], similar to the improvements found within both groups in this study.

Furthermore, the participants in either group did not obtain a clinically significant improvement in SMW test distances. Redelmeier, et al 1997[142] found that differences in SMW distances need to be at least 54 m to be associated with subjective improvement in walking velocity, improvement participants in both groups did not achieve. Therefore, the improvement in SMW distances in this particular study population cannot be attributed to intra-articular HA, and these improvements may be the result of participant learning and motivation.

**4.4 Limitations**

The primary limitation to the current study stems from the lack of statistical power, due to a small sample size. Since sample size heavily influences the statistical significance of an improvement in performance in a clinical trial[127], the small sample size may have inhibited the detection of a significant difference between HA and P groups for improvement in both gait velocity and WOMAC scores. In accordance, it has been previously reported that a sample size of 37-42 per group for 80% power in a between-group comparison trial would be ideal to detect a substantial meaningful change (0.1 m/s) in gait speed measured for 10 m[127]. Furthermore, the lowest sample size required for the OMERACT-OARSI set of responder criteria to be sensitive enough to detect the observed treatment effect in an intra-articular specific OA drug trial in knee OA has been reported as 52 patients per arm[139]. Another limitation to this study is the fact that the differences at baseline regarding gait velocity and WOMAC physical function scores may have negatively impacted our findings. For instance, the ANCOVA demonstrated a significant between groups effect of WOMAC physical function scores on gait function. This interaction may indicate that those patients in the P group who started the study reporting more severely limited physical function, and with slower gait velocities, may either not

have had the physical capacity to improve to as great an extent as those in the HA group, or conversely, they had more room to improve than the participants in the HA group. Additionally, our patient population was not acutely symptomatic, meaning that their symptoms of pain, knee stiffness, and decreased function were not very severe at baseline, compared with previous studies[70, 77, 137, 138]. For instance, the total score for the pain section of the WOMAC is out of 20, and the baseline pain scores for the HA and P groups were 5.20 (3.43) and 7.27 (3.75), respectively. Therefore, a ceiling effect may have taken place regarding reduction in WOMAC scores. Since participants already started off with relatively mild symptoms, they would therefore not have much room for improvement, restricting the difference to be found. Furthermore, the WOMAC LK3.1 may not have been as sensitive as the WOMAC VAS3.1 to detecting a difference of this kind between two such mildly symptomatic groups of knee OA patients[94]. Finally, the decision to use an active placebo may have exacerbated the placebo response, providing a longer than expected physiological benefit within the knee joint. For instance, after intra-articular injection, HA is produced endogenously by the synoviocytes, and therefore is thought to have a long term physiological effect within the OA knee joint[64]. Moreover, the inclusion of a home exercise program that was not strictly controlled may have conditioned the knee structures of those participants who used it regularly to a greater degree compared to those who did not. For instance, a home exercise program prescribed as usual care has recently been shown to provide a small but significant benefit in improving self-selected gait velocity, but not in fast gait velocity[117]. Thus, participants in the P group may have experienced mild symptomatic relief and functional improvement afforded by the low dose HA and exercise program, blunting differences between the HA group regarding gait velocity and symptomatic severity.

# CHAPTER FIVE – CONCLUSIONS

To our knowledge, this is the first study to determine the impact of intra-articular HA on both self-selected and fast gait velocity in knee OA patients using a randomized controlled trial. Furthermore, we are aware of only three published studies reporting on HA's impact on the gait velocity of knee OA patients[84, 85, 86], all observing gait characteristics at a self-selected gait velocity. Consequently, it is difficult to compare our findings to other attempts of observing the impact of HA on the gait of knee OA patients. Of the aforementioned studies only Tang, et al 2004[84] found a significant increase in self-selected gait velocity of [mean(SD)] 20.07 (22.33) cm/s three months post-treatment in knee OA patients treated with five consecutive knee injections of Hyalgan. Although these authors found a greater improvement in self-selected gait velocity than in our study, their patient population was younger, and had slower baseline gait velocities than our population. Therefore, this population may have had more capacity and room for improvement than ours. Furthermore, they did not compare their knee OA subjects to the repeated measures of diseased matched controls, excluding the potential to compare the effect of learning on gait speed.

The effect of intra-articular HA injections was not significantly different than that of placebo injections on improving gait velocity or the clinical outcomes of pain, stiffness, and impaired physical function in knee OA patients. However, a lack of statistical difference between groups could have been due to lack of statistical power. On the other hand, the results from this study demonstrate that the knee OA patients treated with intra-articular HA indeed experienced improvements in fast gait velocity and self-reported function, both of which improved to a clinically significant level. Thus, viscosupplementation with HA may be a useful therapeutic tool for increasing the

functional reserve in this patient population, thereby promoting safe and meaningful physical activity in their community. Given the postulated protective effects that intra-articular HA affords knee cartilage, viscosupplementation remains an intriguing intervention to consider when prescribing a pain relieving treatment to facilitate intensified physical therapy programs. Our results provide rationale for a larger long-term trial observing the impact of HA on knee OA patients enrolled in physical activity programs, and how this combined intervention may not only enhance improved knee health, but also overall patient health and community safety.

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# APPENDIX I

# ETHICS APPROVAL

Western

**Office of Research Ethics**

The University of Western Ontario
Room 00045 Dental Sciences Building, London, ON, Canada N6A 5C1
Telephone: (519) 661-3036 Fax: (519) 850-2466 Email: ethics@uwo.ca
Website: www.uwo.ca/research/ethics

## Use of Human Subjects - Ethics Approval Notice

**Principal Investigator:** Dr. R.J. Petrella

**Review Number:** 14017 **Review Level:** Full Board

**Review Date:** May 20, 2008

**Protocol Title:** The Impact of Intra-articular Hyaluronic Acid on loading at the Osteoarthritic Knee joint: A randomized, double blind, placebo controlled study

**Department and Institution:** Geriatric Medicine, Parkwood Hospital

**Sponsor:** CIHR-CANADIAN INSTITUTE OF HEALTH RESEARCH

**Ethics Approval Date:** June 25, 2008 **Expiry Date:** November 30, 2008

**Documents Reviewed and Approved:** UWO Protocol, Letter of information & consent form dated January 30, 2008

***Documents Received for Information:***

This is to notify you that The University of Western Ontario Research Ethics Board for Health Sciences Research Involving Human Subjects (HSREB) which is organized and operates according to the Tri-Council Policy Statement: Ethical Conduct of Research Involving Humans and the Health Canada/ICH Good Clinical Practice Practices: Consolidated Guidelines; and the applicable laws and regulations of Ontario has reviewed and granted approval to the above referenced study on the approval date noted above. The membership of this REB also complies with the membership requirements for REB's as defined in Division 5 of the Food and Drug Regulations.

The ethics approval for this study shall remain valid until the expiry date noted above assuming timely and acceptable responses to the HSREB's periodic requests for surveillance and monitoring information. If you require an updated approval notice prior to that time you must request it using the UWO Updated Approval Request Form.

During the course of the research, no deviations from, or changes to, the protocol or consent form may be initiated without prior written approval from the HSREB except when necessary to eliminate immediate hazards to the subject or when the change(s) involve only logistical or administrative aspects of the study (e.g. change of monitor, telephone number). Expedited review of minor change(s) in ongoing studies will be considered. Subjects must receive a copy of the signed information/consent documentation.

Investigators must promptly also report to the HSREB:

a) changes increasing the risk to the participant(s) and/or affecting significantly the conduct of the study;
b) all adverse and unexpected experiences or events that are both serious and unexpected;
c) new information that may adversely affect the safety of the subjects or the conduct of the study.

If these changes/adverse events require a change to the information/consent documentation, and/or recruitment advertisement, the newly revised information/consent documentation, and/or advertisement, must be submitted to this office for approval.

Members of the HSREB who are named as investigators in research studies, or declare a conflict of interest, do not participate in discussion related to, nor vote on, such studies when they are presented to the HSREB.

Chair of HSREB: Dr. John W. McDonald

| Ethics Officer to Contact for Further Information | | | |
|---|---|---|---|
| ☑ Janice Sutherland | ☐ Elizabeth Wambolt | ☐ Grace Kelly | ☐ Denise Grafton |

*This is an official document. Please retain the original in your files.*

cc: ORE File
LHRI

# APPENDIX II

# WESTERN ONTARIO McMASTER

# OSTEOARTHRITIS INDEX

## WOMAC OSTEOARTHRITIS INDEX LK3.1

### Instructions to Patients

In Sections A, B, and C, questions will be asked in the following format. You should give your answers by putting an "x" in one of the boxes.

Examples:

1. If you put your "x" in the left hand box, i.e.

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| [x] | [ ] | [ ] | [ ] | [ ] |

Then you are indicating that you have **NO** pain.

2. If you put your "x" in the right hand box, i.e.

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| [ ] | [ ] | [ ] | [ ] | [x] |

Then you are indicating that your pain is **EXTREME**.

3. Please note:

   a) That the further to the right you place your "x" the **MORE** pain you are experiencing.

   b) That the further to the left you place your "x" the **LESS** pain you are experiencing.

   c) Please do not place your "x" outside the box.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Think about your knee when answering the questionnaire. Indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your knee.

Your study joint has been identified for you by your health care professional. If you are unsure which joint is your study joint, please ask before completing the questionnaire.

WOMAC OA Index

Dr. N. Bellamy

A User's Guide, London, Victoria Hospital, 1996

London, Ontario Canada

---

Date of Visit: _____ _____ _____ Patient study #: _____
Day Month Year

Patient initials: _____

| | | | | | | |
|---|---|---|---|---|---|---|
| Day | | 1 | 7 | 14 | 101-107 | 185-191 |
| Please circle: | | | | | | |
| Visit | Pre-therapy | 1 | 2 | 3 | Follow up | Follow up |

**Section A : Pain**

Question: How much **pain** do you have?

1.When walking on a flat surface.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

2. Going up or down stairs.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

3. At night while in bed, i.e. Pain that disturbs your sleep.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

4. Sitting or lying.

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

5. Standing upright.

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Section B: Stiffness**

Think about the stiffness (not pain) you felt in your knee due to your arthritis during the last 48 hours. Stiffness is a sensation of **decreased ease in moving your joint.**

6. How severe is your stiffness after first awakening in the morning?

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

7. How severe is your stiffness after sitting, lying or resting later in the day?

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

**Section C: Difficulty Performing Daily Activities**

Think about the difficulty you had in doing the following daily physical activities due to arthritis in your knee during the last 48 hours. By this we mean **your ability to move around and to look after yourself.**

Question: What degree of difficulty do you have?

8. Descending stairs.

| None | Mild | Moderate | Severe | Extreme |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

9. Ascending stairs.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

10. Rising from sitting.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

11. Standing.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

12. Bending to the floor.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

13. Walking on a flat surface.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

14. Getting in or out of a car, or getting on or off a bus.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

15. Going shopping.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

16. Putting on your socks or stockings.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

17. Rising from bed.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

18. Taking off your socks or stockings.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

19. Lying in bed.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

20. Getting in or out of the bath.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

21. Sitting.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

22. Getting on or off of the toilet.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

23. Performing heavy domestic duties.

None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

24. Performing light domestic duties.

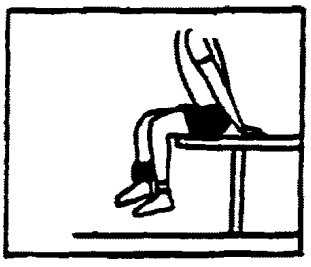
None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme ☐

# APPENDIX III

# EXERCISES FOR OSTEOARTHRITIS OF THE KNEE

# EXERCISES FOR OSTEOARTHRITIS OF THE KNEE

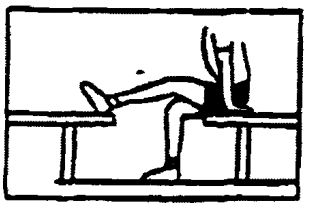
A: "UNLOADING THE KNEE"/ "JOINT CAPSULE STRETCH"



* In a position that allows leg to dangle freely (ie. a bench, tall stool, end of bed)
* Apply light weight (2.5-5 kg) at ankle
* Routine: Hold 5-15 minutes, 1-3 times, daily.

B: RANGE OF MOTION EXERCISES

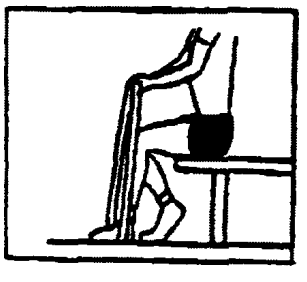
* KNEE EXTENSION



* Sit in chair and rest your foot on another chair
* GENTLY push raised knee (with leg muscles only) toward the floor

* Alternatively, sit down on floor or bed, put rolled towel behind heel (achilles tendon), GENTLY push raised knee as above toward floor

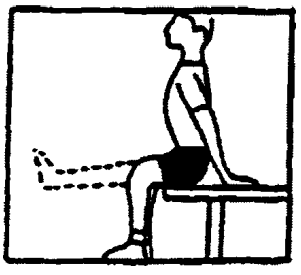
* KNEE FLEXION



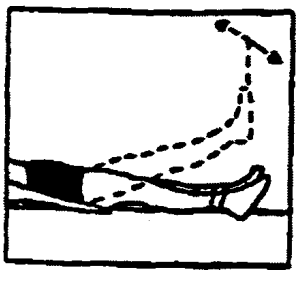
*Sitting down, with the use of a long towel folded in two, put loop of towel underneath foot.
* GENTLY pull on towel with hands to bend knee

* ROUTINE: Hold 5-10 seconds, rest a minute, repeat 10 times. Do every day, up to 3 times each day.

## C: STRENGTH EXERCISES: "OPEN-KINETIC" ISOTONIC RESISTANCE

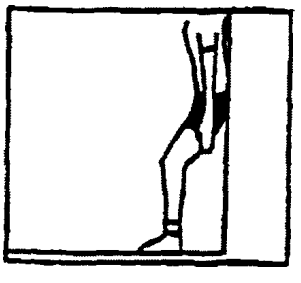


- Sitting in a chair, straighten each leg as shown; hold .



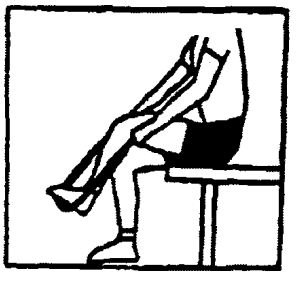
- Alternatively, lay on flat and firm surface with extended leg, elevate off ground one foot and make a "T" pattern in the air with each leg.
- To start: repeat 5-10 times, MWF with rest on weekends
- Do every day, up to 3 times each day.

## D1: STRENGTH EXERSISES: "CLOSED- KINETIC" ISOTONIC RESISTANCE



- This requires weight bearing
- Standing up against a wall, bend knees 30 degrees as shown and straighten up again. Proceed through the entire movement slowly and smoothly.
- Keep feet and legs parallel, try to keep centre of knee cap lined up over second toe.
- To start: Repeat 5-10 times MWF with rest on weekends
- See Progression of Strengthening Exercise (Part E)

## D2: STRENGTH EXERCISES: MODIFIED "CLOSED KINETIC"



- If weight bearing is to painful for D1, then use a Thera-Band as shown in diagram.
- Loop tubing around bottom of foot and hold onto ends in a sitting position, bend knee 30 degrees at most
- Then extend knee against the resistance of the tubing using whatever force can be tolerated.
- May progress to D1 if weight bearing tolerance improves

## E: PROGRESSION OF STRENGTHENING EXERCISES (PARTS C & D)

- ( Mark with date when commence new level)
- You may do C & D concurrently or D after progressing to a higher level with C or avoid C or D if too painful.

| STAGE | DATE | REPEATS | SETS | DAYS | SAT/SUN |
|---|---|---|---|---|---|
| Stage 1 | | 5-10 times | 1 | MWF | off |
| Stage 2 | | 10 times | 1 | daily | off |
| Stage 3 | | 10 times | 1 | daily | Sat or Sun |
| Move slowly between the remaining stages, specifically after a break or later in the day. Do an extra set of 2 more repetitions MWF. Increase this extra set by 2 on MWF at your pace. Use the same routine to attain an extra set daily. | | | | | |
| Stage 4 | | 10 times<br>10 times | 1 | daily<br>MWF | Sat or Sun<br>Sat or Sun |
| Stage 5 | | 10 times | 2 | daily | Sat or Sun |
| Stage 6 | | 10 times<br>10 times | 2<br>3 | daily<br>MWF | Sat or Sun<br>Sat or Sun |
| Stage 7 | | 10 times | 3 | daily | Sat or Sun |

## F: ADVICE FOR POST-EXERCISE SORENESS

- ICE knee for 10-20 minutes, with at least a towel between the ice(cold source) and the skin to protect from cold injury
- Use this time to rest your leg elevated on a chair

- Use tylenol before or after exercise if ice is not enough.