Physiopathology and Intervention in Osteoarthritis: A Systematic Review

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PHYSIOPATHOLOGY AND INTERVENTION IN OSTEOARTHRITIS: A SYSTEMATIC REVIEW

by

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A capstone project submitted to the Graduate Faculty in Physical Therapy in partial fulfillment of the requirements for the degree of Doctor of Physical Therapy (DPT), The City University of New York

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Abstract

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In the United States, osteoarthritis (OA) is the most common chronic illness in the adult population affecting an estimated 27 million individuals with a yearly health care cost of over $150 billion (CDC, 2014; Lawrence et al., 2008). The pathological osteoarthritic process results in the progressive degradation of articular cartilage due to chemical and biological imbalances within a joint (Weiland et al., 2005). These imbalances are not well understood and neither are the biomechanical joint changes that occur as a result. Due to these limitations, treating and monitoring this condition is a challenge to clinicians and the processes are currently inefficient.

The purpose of this targeted literature review is to identify the main factors contributing to OA, identify the state of the art in diagnosis and physical therapy treatment in OA and to identify the role of animal models in OA research. To accomplish this, 76 peer reviewed journal articles on the relationship between musculoskeletal biomechanics and osteoarthritis have been selected for analysis. Articles were generated from search criteria with key words osteoarthritis, diagnosis, physical therapy, and animal model from the following databases: PubMed, Cochrane Library, ISI Web of Knowledge, and Academic Search Complete.
In conclusion, it was found that OA is a multifactorial disease leading to joint failure from abnormal biomechanics, however the exact pathogenesis remains unknown. There is also no quintessential diagnostic tool for OA, however WOMAC score reporting is recommended to monitor patient progress. For conservative treatment, there is also no gold standard protocol but a multimodal approach is necessary to optimize the loading on the pathological joint. Non-invasive animal models will be essential for the future of intervention research regarding OA to assess disease onset and progression in an attempt to translate these findings into a human population.
THE CITY UNIVERSITY OF NEW YORK

ACKNOWLEDGEMENTS

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B. Pathological osteoarthritic knee
1.1 Objectives:
To identify the main factors contributing to the OA process
To identify the state of the art diagnosis and monitoring interventions for OA
To identify the state of the art in physical therapy treatment for OA
To identify the role of animal models in OA research

2.1 Introduction

Osteoarthritis (OA), the most common form of arthritis, is a degenerative joint disease that occurs either in one or a few diarthrodial joints at a time, primarily affecting the hips, knees, hands, feet, and spine. In the United States, osteoarthritis is the most common chronic illness in the adult population. There were an estimated 27 million people, 12% of the adult population, affected by the disease in 2005, a 6 million increase from 1995 (Lawrence et al., 2008). Knee OA in particular is a leading cause of disability among older adults where 25% of patients cannot perform major activities of daily living (WHO, 2003). As OA is becoming more prevalent in middle aged adults, early retirement may become necessary which can lead to social isolation and depression (Kean et al., 2004). It is also the most common reason for total hip and knee joint replacements as 905,000 knee and hip replacements were performed in 2009 at a cost of $42.3 billion (Murphy et al., 2012). As a huge portion of the United States healthcare spending is allocated to treating OA, it is important to understand the pathogenesis to be able to stop/slow the disease progression. Currently, the pathogenesis is not fully understood; however, it is believed to occur as a result of pathological, mechanical, and molecular events in the affected joint (Wieland et al., 2005).
2.2 Pathogenesis

OA results in a progressive degradation of articular cartilage, which is the dense connective tissue at the ends of articulating bones. In the non-pathological patient, articular cartilage acts as a cushion to help glide the bone during movement and thereby protects the joint from damage during severe loading. The cartilage can prevent biomechanical damage that is caused by severe loading, however, patients with OA hinder attempts at repair and result with a disrupted cartilage homeostasis (Wieland et al., 2005). As the articular cartilage degrades, there are also associated joint conformational changes that occur in an attempt to repair or compensate for the loss of the articular cartilage. This characterizes OA as an active repair process and not purely a degenerative disease only affecting the cartilage (Brandt et al., 2006). These changes include subchondral bone sclerosis, or thickening and hardening, and the formation of bone cysts and marginal osteophytes (bone remodeling). All of these changes cause the joint space to narrow (Wieland et al., 2005). Specifically, the changes that occur in the subchondral bone may predispose the cartilage for further damage. As the subchondral bone is less able to absorb forces/load that is place on the joint, this may cause further degradation as the cartilage loses its integrity (Neogi et al., 2012).

Ultimately osteoarthritis affects the whole joint due to synovial inflammation and fibrosis of the joint capsule (Poulet et al., 2011). The chondrocytes produce cytokines, chemokines, and proteolytic enzymes which are all mediators associated with inflammation that cause further damage to the cartilage (Wieland et al., 2005). These changes to the joint cause loss of range of motion/stiffness, tenderness, and pain. The development of OA, due to the chemical and biological imbalances, can be illustrated by means of a self-sustaining vicious cycle where each step in the process influences and amplifies each other (Wieland et al., 2005).
2.3 Pain

As hyaline cartilage is not innervated, the pain associated with OA most likely comes from the synovium, subchondral bone and periosteum which are innervated by small-diameter nociceptive neurons. The nociceptive stimuli is generated by tissue damage during joint degradation. The inflammatory mediators produced by the synovium and chondrocytes increases the excitation of the nociceptive neurons, producing an amplified painful response (Adatia et al., 2012; Weiland et al., 2005).

2.4 Risk factors

The development of this vicious cycle of OA is complex and is likely caused by an involvement of both modifiable and nonmodifiable risk factors. There is no one risk factor contributing to the disease process, rather an involvement of risk factors together. These include age, gender, ethnicity, genetic predisposition, hormonal factors, bone density, and biomechanical factors such as occupation, joint injuries caused by sports or other traumas, joint misalignment
and obesity (Adatia et al., 2012; Caine et al., 2011; Lawrence et al., 2008; Murphy et al., 2012; Weiland et al., 2005). Understanding the biomechanical factors that affect loading on joints is a critical component of understanding the disease process, as OA is now starting to be viewed as joint failure caused by abnormal joint loading as opposed to a disease of cartilage degradation (Dieppe et al., 2011).

2.4.1 Age

One of the predominant risk factors of OA is age. Although there is an exponential increase in occurrence of OA in adults over 50 years old, it cannot be simply a disease of joint wear and tear as not all older adults develop OA, not all joints are equally affected in the elderly, and OA changes can develop without the aging process (Adatia et al., 2012; Loeser et al., 2009). Aging and OA may be interrelated, but are not inter-dependent (Loeser et al., 2009). Aging may contribute to the disease process, but it is not a direct cause of OA. The natural aging process results in the chondrocytes inability to produce proteoglycans to maintain the cartilage matrix which gives the cartilage its compressive strength, and the inability to produce and repair the extracellular matrix due to a decline in growth factor activity (Adatia et al., 2012, Loeser et al., 2009). This results in a tissue that is less likely to maintain homeostasis when stressed, thereby causing degeneration of articular cartilage, leading to OA (Loeser et al., 2009). Therefore OA rarely occurs in adults below 30 years old, even with serious injuries, because the joint tissues in younger adults are able to withstand the severe loading put on it more than older adults. However those with sports injuries younger than 30 years old are found to be at increased risk of OA. Because of the increased risk, it may be beneficial to start the prevention of OA as early as childhood by providing appropriate balance, strength, and flexibility training to young athletes as
these interventions have been found to decrease the risk of injury. (Caine et al., 2012; Loeser et al., 2009).

2.4.2 Obesity

Obesity is another risk factor that has a strong correlation to OA due to biomechanical and systemic factors. Obese individuals have a 66% chance of developing symptomatic knee OA, while non-obese individuals have a 45% chance of developing OA (Murphy et al., 2012). In addition, the Framingham OA study shows that women who lost about 5 kg (2 units of body mass index) reduced their risk of knee OA by half (Murphy et al., 2012). The correlation of obesity and OA in the knee is largely due to the increased biomechanical loading on the joints. On the basis of the multiplier effect of lever arms outside the body’s central axis, a force of three to six times the body weight is exerted across the knee during single-leg stance in walking. In an obese individual, the increase in weight may be roughly multiplied by this factor to cause an increase in force across the knee during walking (Felson et al., 1996). The correlation between weight and OA in the hip is not as strong, which can be explained because the force across the hip is at a maximum of 3 times the body weight, thereby the multiplier effect is not as great (Felson et al., 1996). However, it is important to note that a study done by Felson et al., in 2004 suggested that the effect of weight on the progression of knee OA was limited to knees that were moderately misaligned (2-7°). The study also suggested that knees with severe misalignment would lead to an OA regardless of the increased weight. Additionally, the correlation between obese patients and OA is further strengthened by the understanding that adipose tissue secretes adipokines, biologically active substances, that contribute to inflammation found in obese patients. These substances directly affect cartilage homeostasis making affected individuals more susceptible to OA (Goldring et al., 2011). The high bone mass density found in obese individuals
may be a risk factor for OA as well. These systemic factors allow for a greater understanding of the association of hand OA and obesity, as there is no additional load on the hand of an obese versus non-obese individual (Felson et al., 1996).

2.4.3 Biomechanical Load

High shear stress loading is found to play a pivotal role in OA progression. It has been hypothesized that cartilage loss is a mechanically mediated process more likely to occur in areas of high stress (Neogi et al., 2012). There was found to be an increased expression of inflammatory mediators that contribute to the cartilage destruction in response to high fluid shear stress where low fluid shear was found to be chondroprotective (Wang et al., 2013). Biomechanically overloading a joint through activities requiring repetitive and excessive joint loading, such as knee bending, is associated with knee OA. In a systematic review performed by Ezzat and Li in 2014, occupational activities that included both high loading and kneeling were found to have moderate evidence as being a risk factor for knee OA (2014). Deep squatting has been shown to increase compressive and posterior shear forces on the knee, both 7 and 5 times body weight respectively. However, it is not yet proven deep squatting directly leads to OA. It is hypothesized that the increase in stress on the posterior horn of the meniscus during deep flexion loading may initiate the degenerative process in the joint (Nagura et al., 2006). High impact sports activities such as hockey, football, and soccer, put undue stress on joints and place an increased risk of hip and knee OA in adults (Caine et al., 2011). Young male soccer players as young as age 13 were found to have CAM-type deformity, which is a type of femoroacetabular impingement found to cause OA, more than non-athletic age matched peers (Bessems et al., 2012, Heijboer et al., 2014).
High stress loading may also be influenced by joint malalignment. Due to the changes in joint geometry, the joint’s ability to adapt to its biomechanical environment decreases which contributes to damage in pathological joints. Those with hip dysplasia, femoroacetabular impingement, legg cathe perthes and slipped capital epiphysis are predisposed to hip OA due to the joint malalignment in these conditions (Adatia et al., 2012; Caine et al., 2011). Varus knee malalignment and dynamic knee adduction moments have been found to cause medial compartment knee OA due to the increase in mechanical stress on the medial compartment of the knee; the reverse is true for a valgus knee alignment (Miyazaki et al., 2002; Sharma et al., 2001). In addition, leg length discrepancies lead to asymmetrical joint mechanics during weight bearing activities, contributing to the development of hip OA. To compensate for the discrepancies, an individual may increase knee flexion or hip adduction of the longer limb during stance, increasing the force at those joints (Caine et al., 2011; Golightly et al., 2010). It has also been found recently that individuals with only slight bone alterations are at increased risk of OA (Neogi et al., 2012). This can be seen when looking at the variations in the shape of the proximal femur. A larger femoral head and longer, slightly thinner femoral neck was found to be most correlated with hip OA (Lynch et al., 2009).

Joint injuries, specifically those that are sports related, have been found to be a risk factor for OA. ACL and meniscal injuries are found to increase the risk of knee OA. Among Swedish soccer players, the incidence of radiographic OA 14 years after injuring the ACL was 41% compared to 4% in uninjured knees regardless of the presence of surgical intervention. In long-term follow up studies of young athletes with meniscus surgery, more than 50% had OA and associated pain and functional impairment (Caine et al., 2011). The lack of a functionally normal ACL or meniscus changes the static and dynamic loading of the knee, generating increased
forces on the cartilage and other joint structures leading to OA (Lohmander et al., 2007). There also is an increase in the prevalence of ankle OA with sports related ankle sprains (Caine et al., 2011). Even minor injuries may contribute to OA. Minor injuries of the hip caused by repeated sports-related impacts, are often sudden without adequate proprioception and muscle absorption, resulting in groin pain and muscle fatigue and may eventually lead to joint stiffening and degradation (Tveit et al., 2012).

2.5 Pathogenesis Summary

Currently the pathogenesis of OA is not fully understood. The vicious cycle is used as a paradigm to explain the disease process, where the exact starting point is unknown. It is now being thought of as joint failure that is driven by abnormal joint loading, rather than a discrete disease entity. OA is primarily a mechanical problem, where the risk factors elaborated above are all found to affect the biomechanical loading of the joint contributing to the disease progression.

3.1 Diagnosis

There are many methods that clinicians use to diagnose a patient with osteoarthritis. These methods include the assessment of specific clinical criteria, imaging methods such as radiograph and MRI as well as determining the presence of biomarkers within the joint. Biomarkers are endogenous molecules that are indicative of a specific pathological process (Weiland et al., 2005). More precisely, a biomarker can help to show whether a pathology has a more rapid progression occurring or a slower progression. Therefore, the ability to use biomarkers that identify the patient’s predictability to progress can accelerate the pace of the therapeutic intervention (Hunter et al., 2007). If they are modifiable, they may help to reduce the progression of OA, and if they are not modifiable, they can be used to identify those patients
who are considered in a high-risk group, who may have implications for medical treatment (Cheung et al., 2010).

Biomarkers can also identify whether the certain tissue properties within the joint being investigated can be used for an early detection of osteoarthritis. Since early diagnosis is still an ongoing issue for patients with OA, newer studies are using animal models to explore the molecular mechanisms leading to OA. These animal studies have shown that there are subtle biochemical changes in the articular cartilage that can be detected before any clinical or radiologic evidence of joint destruction is shown (Sharif et al., 2004). Molecular biology provides powerful tools to detect the molecular/cellular processes that are involved with the disease progression and that can allow an early diagnosis before the disease is too far advanced (Fang et al., 2014).

3.2 Patient characteristics in OA

Aside from imaging and identifying biomarkers, there are certain patient characteristics that are predictive of OA progression. For example, one characteristic demonstrating a strong relationship is malalignment of the knee. The malalignment of the knee includes whether a knee is valgus or varus, however, there is a higher correlation with varus knees and the progression of OA (Cheung et al., 2010). A varus knee is when there is more than a 180 degrees from the line coming from the center of the femoral head to the middle of the distance between the tibial spines and a second line coming from the center of the ankle to the center of the tibial spines (Sattari et al., 2011). Biomechanical factors, such as the adduction moment of the knee being an influential factor in OA, are found in joints with a varus deformity. It was suggested that varus knees undergoing stress may be sufficient by itself to produce progression of OA without the
addition of an excess load such as obesity (Niu et al., 2009). Progression of the disease can be seen using imaging techniques such as X-ray, MRI, and CT scans.

3.3 X-ray

OA is primarily diagnosed via X-ray using both anteroposterior and lateral views that may demonstrate the presence of osteophyte formation, subchondral sclerosis and joint space. The Kellegren and Lawrence system and the Ahlback classification are two grading systems that are most commonly used to diagnose OA radiographically. The two systems vary in that the Kellegren and Lawrence scale primarily focus on osteophyte presence, joint space narrowing, or both, whereas the Ahlback classification system for osteoarthritis focus on joint space reduction as an indirect sign of the loss of cartilage (Petersson et al., 1997). Table 1 compares the two scales.

Table 1: Comparison of the Ahlback scale and the Kellegren & Lawrence scale

<table>
<thead>
<tr>
<th>Ahlback grade</th>
<th>Ahlback definition</th>
<th>Kellgren &amp; Lawrence grade</th>
<th>Kellgren &amp; Lawrence definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade I</td>
<td>Joint space narrowing (joint space &lt; 3 mm)</td>
<td>Grade 1 'Doubtful'</td>
<td>Minute osteophyte, doubtful significance</td>
</tr>
<tr>
<td>Grade II</td>
<td>Joint space obliteration</td>
<td>Grade 2 'Minimal'</td>
<td>Definite osteophyte, unimpaired joint space</td>
</tr>
<tr>
<td>Grade III</td>
<td>Minor bone attrition (0-5 mm)</td>
<td>Grade 3 'Moderate'</td>
<td>Moderate diminution of joint space</td>
</tr>
<tr>
<td>Grade IV</td>
<td>Moderate bone attrition (5-10 mm)</td>
<td>Grade 4 'Severe'</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone</td>
</tr>
<tr>
<td>Grade V</td>
<td>Severe bone attrition (&gt;10 mm)</td>
<td>Grade 4 'Severe'</td>
<td>Joint space greatly impaired with sclerosis of subchondral bone</td>
</tr>
</tbody>
</table>

The Ahlback classification system also analyzes bone attrition which can be defined by a subchondral bone change that represents the bone remodeling that typically occurs early in the osteoarthritis disease (Reichenbach et al., 2008). More specifically it is a flattening, or depression, of the articular surfaces.
3.4 MRI

The benefit of using MRI is that this technology images the whole joint in a single examination, visualizing the cartilage defects directly regardless of their location (Hunter et al., 2007). In addition to viewing the whole joint, MRI also gives a better visualization of non-ossified structures such as articular cartilage, menisci, ligaments, synovial fluid, and periarticular tendons and muscles (Peterfy et al., 2004). There are a number of scoring methods that may be used to determine whether a patient has OA using an MRI. One example of a scale that is both valid and reliable is the Whole-Organ Magnetic Resonance Imaging Score (WORMS). Using the WORMS, images are scored with respect to fourteen independent features that can be evaluated in the diagnosis of OA (Peterfy et al., 2004). Those fourteen features are cartilage signal and morphology, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis, loose bodies and periarticular cysts/bursae. The first five of the fourteen features are evaluated in fourteen different subdivisions within the knee, which are divided by its anatomical landmarks, as the knee is in full extension. The explanation of the scoring for each of the five features is explained in table 2.
Table 2: Scoring the Whole-Organ Magnetic Resonance Imaging Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Scale</th>
<th>How it is scored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cartilage signal &amp; morphology</td>
<td>0-6</td>
<td>0  normal thickness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  normal thickness but increased signal on T2 weighted images</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  partial thickness focal defect &lt;1 cm in greatest width</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 full-thickness focal defect &lt;1 cm in greatest width</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  Grade 2 defect wider than 1 cm but &lt;75% of the region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4  &gt;75% of the region partial thickness loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5  Grade 2.5 lesion wider than 1 cm but &lt;75% of the region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6  &gt;75% of the region full-thickness loss</td>
</tr>
<tr>
<td>Subarticular bone marrow abnormality</td>
<td>0-3</td>
<td>0  none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  &lt;25% of region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  25% to 50% of the region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  &gt;50% of the region</td>
</tr>
<tr>
<td>Subarticular bone cysts</td>
<td>0-3</td>
<td>0  none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  &lt;25% of region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  25% to 50% of the region</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  &gt;50% of the region</td>
</tr>
<tr>
<td>Flattening, or depression of the articular</td>
<td>0-3</td>
<td>0  normal/no deviation from the normal contour</td>
</tr>
<tr>
<td>surfaces, also known as bone attrition</td>
<td></td>
<td>1  mild</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  severe</td>
</tr>
<tr>
<td>Osteophytes</td>
<td>0-7</td>
<td>0  none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1  very small</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2  small</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3  small to moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4  moderate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5  moderate to large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6  large</td>
</tr>
<tr>
<td></td>
<td></td>
<td>7  very large</td>
</tr>
</tbody>
</table>
All ligaments were independently scored as either a 0 indicating it is intact, or a 1 indicating it is torn. Menisci were graded from 0-4, 0 indicating it is intact and 4 indicating complete maceration. Synovial thickening and joint effusion were graded collectively from 0-3 and the loose bodies in the synovial cavity were also graded from 0-3. In order to formulate a final WORMS score, each cumulative score for each feature throughout the knee were tabulated and a total was combined for the score of the entire knee (Peterfy et al., 2004). This semiquantitative method allows a multi-feature assessment of the knee using an MRI results however it is not the only available option for clinicians to diagnose the pathology.

Another semiquantitative method to evaluate the presence of OA using MRI imaging is the Boston Leeds Osteoarthritis Knee Score (BLOKS). A study was performed in 2010 comparing how these two systems differ in assessing cartilage loss, meniscal damage, and bone marrow lesions (BMLs) in order to determine which scale to use for each individual feature (Felson et al., 2010). Results are presented on table 3.

Table 3: Comparing the BLOKS and WORMS methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Cartilage Loss</th>
<th>Meniscal Damage</th>
<th>Bone Marrow Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLOKS</td>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>WORMS</td>
<td>X</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
After comparing the two scales, the results suggested that the BLOKS meniscal score was preferable to WORMS in predicting cartilage loss. This could be because BLOKS was more sensitive to meniscal damage such as differentiating between the specific types of meniscal tears. The same goes for using the BLOKS in predicting bone marrow lesions. On the other hand, WORMS was preferable in predicting later cartilage loss and better at agreeing with joint space loss found in radiographs. The results also suggested that the BLOKS was more time consuming than the WORMS, thus being another disadvantage. Including the BLOKS and the WORMS, there are a number of other methods that have been accepted, however, no single method has been the standard for clinical research thus far (Peterfy et al., 2004).

3.5 CT Scan

CT (computerized tomography) scans are advantageous compared to conventional radiographs because they can provide an assessment of soft-tissue structures in the joint along with osseous changes. CT allows visualization of structures such as ligaments and menisci as MRI does, in addition to the osseous changes that are viewed in conventional radiographs such as bone spurs and sclerosis formation. CT scans also provide an additional benefit in that the imaging process is faster and better at viewing subchondral bone cysts than MRI (Wenham et al., 2014). The use of CT scans had been further investigated and contrast enhanced computed tomography (CECT) has been proposed for the diagnosis of cartilage lesions. More recently, contrast enhanced cone beam computed tomography (CE-CBCT) has also been applied successfully for detection of osteochondral lesions (Turunen et al., 2015). CE-CBCT can also be used as a tool to diagnose OA because it can detect changes in the subchondral bone with a higher resolution and lower cost and radiation than conventional CT or MRI. This means that the
bone mineral density values found in CBCT can also be used to detect sclerosis of the subchondral bone which can be used to diagnose OA.

3.6 Biomarkers

Another way to detect the presence of OA is by identifying specific biomarkers in the target tissue. For example, due to inflammatory flare-ups that occur there is evidence that a way to diagnose OA is to identify the markers of inflammation such as C-terminal crosslinking telopeptide of type II collagen (CTX-II) in the patient’s urine. This was investigated because type II collagen is the most abundant protein of the cartilage matrix, therefore, when it is broken down it may have an involvement in the loss of articular cartilage leading to OA. The result of a study done in 2003 suggested that increased urinary CTX-II levels are associated with a rapidly progressing disease (Garnero et al., 2003).

Another biomarker that has been explored is cartilage oligomeric matrix protein (COMP), which is a cartilage matrix macromolecule and is the third largest matrix protein in articular cartilage, after collagen and proteoglycan (Sharif et al., 2004). Results of previous studies have shown that COMP levels can also be used to identify patients who are at risk of OA progression in the hips and knees (Hunter et al., 2007; Sharif et al., 2004). COMP was initially thought to only be present in a patient’s cartilage, however, studies have suggested that it has a presence in other joint tissues such as menisci, ligaments, tendons and the synovium (Dicesare et al., 1994; Neidhart et al., 1997; Recklies et al., 1998). Mutation of the COMP gene can lead to premature development of OA because degradation of this protein will lead to a reduced interaction with chondrocytes, collagens, and other matrix proteins, ultimately leading to a loss of cartilage (Sharif et al., 2004).
Investigators explored COMP as a biomarker through a 5 year longitudinal study. Subjects were broken into two categories, progressors and nonprogressors, using criteria that consisted of a distance of the width of the tibiofemoral joint space that was greater than 2 mm or the patient undergoing a total knee replacement. The COMP levels, obtained from the patient’s serum, were measured at baseline and over the 5 years of follow up by using a sample of the patient’s blood and an enzyme-linked immunosorbent assay (ELISA) kit. The results suggested that the patients with a higher baseline of COMP levels were found to be the progressors and those with abnormally high variations in COMP levels were the patients that had undergone the total knee replacement surgery. These same patients, the progressors, also had a higher level of COMP throughout the longitudinal study reflecting the activate degradation of articular cartilage, thus indicating that COMP can be used to identify whether a patient is at risk for a more rapidly progressing OA (Sharif et al., 2004).

3.7 Clinical Diagnosis

A popular clinical approach that physical therapists and other health care providers typically use to diagnose OA is with the use of the Western Ontario and McMaster Universities Arthritis Index (WOMAC). It was recommended to be used as the primary measure of efficiency in OA trials in a consensus meeting (Woolacott et al., 2012). The WOMAC is a self-administered test and assesses the levels of pain, stiffness and function in patients affected with OA of the hip or knee, and under each dimension there are a number of questions that answered to assess the severity of the disease.

The three subscales (pain, stiffness, and function) are scored based on the patient's response out from zero to four where a 0 indicates the patient has no difficulty and a 4 indicates
extreme difficulty. A total score, known as the WOMAC index, is produced to reflect the disability overall.

Table 4: The WOMAC index

<table>
<thead>
<tr>
<th>Instructions: Please rate the activities in each category according to the following scale of difficulty: 0 = None, 1 = Slight, 2 = Moderate, 3 = Very, 4 = Extremely</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
</tr>
<tr>
<td>1. Walking</td>
</tr>
<tr>
<td>2. Stair Climbing</td>
</tr>
<tr>
<td>3. Nocturnal</td>
</tr>
<tr>
<td>4. Rest</td>
</tr>
<tr>
<td>5. Weight bearing</td>
</tr>
</tbody>
</table>

| **Stiffness** |
| 1. Morning stiffness | 0 1 2 3 4 |
| 2. Stiffness occurring later in the day | 0 1 2 3 4 |

| **Physical Function** |
| 1. Descending stairs | 0 1 2 3 4 |
| 2. Ascending stairs | 0 1 2 3 4 |
| 3. Rising from sitting | 0 1 2 3 4 |
| 4. Standing | 0 1 2 3 4 |
| 5. Bending to floor | 0 1 2 3 4 |
| 6. Walking on flat surface | 0 1 2 3 4 |
| 7. Getting in / out of car | 0 1 2 3 4 |
| 8. Going shopping | 0 1 2 3 4 |
| 9. Putting on socks | 0 1 2 3 4 |
| 10. Lying in bed | 0 1 2 3 4 |
| 11. Taking off socks | 0 1 2 3 4 |
| 12. Rising from bed | 0 1 2 3 4 |
| 13. Getting in/out of bath | 0 1 2 3 4 |
| 14. Sitting | 0 1 2 3 4 |
| 15. Getting on/off toilet | 0 1 2 3 4 |
| 16. Heavy domestic duties | 0 1 2 3 4 |
| 17. Light domestic duties | 0 1 2 3 4 |

**Total Score: ______ / 96 = ______%**
A 2012 study analyzed the subscale of pain due to the ambiguities across the literature (Woolacott et al., 2012). They concluded that different variations of the WOMAC pain subscales were used such as a Likert scale, visual analog scale (VAS), and a numerical rating scale (NRS). In other words, the same subscale was not being used in all studies that used the WOMAC which can be a problem when investigating the influence of the subscale of pain (Woolacott et al., 2012).

3.8 Issues with current diagnosis strategies

Routine radiography is an insensitive measure of the molecular changes that presage cartilage and bone abnormalities (Attur et al., 2013). Traditional radiographs cannot be used to obtain an early diagnosis of OA and are therefore limited in their usefulness for clinicians (Hunter et al., 2009). The limitation regarding the effectiveness of MRI results is due to the difference between semiquantitative measures used determine cartilage loss. There is also a high potential for observer bias and possible measurement error. Studies have looked to find biologic associations with cartilage loss on MRI including alignment, bone marrow lesions and meniscal involvement, however, none of these factors serve as strong biomarkers for the early detection of OA. The other limitations regarding the use of MRI results is in the technique. MRIs are taken in a non-weight bearing position, thus giving different results in terms of loss over time (Felson et al., 2010). MRIs are also slower and more expensive to administer than CT scans. While MRI may give better visualization of soft tissue structures, the technique is limited as it does not detect osseous changes concurrently. While CT scans are able to visualize both soft tissue as well as bony changes in the joint, they emit harmful radiation to the patient so are not indicated for frequent use (Wenham et al., 2014). Another limitation with CT scans is that CBCT provides less
radiation and a lower cost than traditional CT scans. However, CBCT is still a new technique so efforts are still being made to increase image resolution (Turunen et al., 2015).

Using specific biomarkers as an indicator for detecting OA early in the disease process or determining whether a patient is at an increased risk for rapid progression is promising. However, the CTX-II and COMP biomarkers have limitations on their effectiveness as well. One limitation regarding CTX-II was that the investigators did not determine whether baseline levels may predict progression of joint damage (Garnero et al., 2003). Other limitations included a lack of radiographic results from healthy controls as well as the limited sample size. Finally, this was the first study done using a new highly specific urinary marker to detect type II collagen degradation, therefore, the research is very limited.

There have been inconsistencies within the literature regarding using COMP levels as a biomarker. Studies have shown that serum COMP levels are higher in patients with early OA and can be associated with OA severity, however, those same studies also show an overlap between the OA patients and the unaffected individuals thus being a limitation in using COMP as a biomarker (Sharif et al., 2004). There also needs to be further investigation of COMP as a biomarker because, surprisingly, levels dramatically increased in the period following a total knee replacement (Sharif et al., 2004). Table 3.5 shows a breakdown of the diagnostic tool technique and its limitations.
# Table 5: Comparison of all diagnostic tools

<table>
<thead>
<tr>
<th>Diagnostic Tool</th>
<th>How it diagnoses OA</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imaging X-ray</td>
<td>Can view joint space narrowing and presence of osteophytes and sclerosis to indicate presence of OA</td>
<td>Does not view entire joint and other joint tissues. Results can only be seen after joint destruction has occurred.</td>
</tr>
<tr>
<td>Imaging MRI</td>
<td>Can view the entire joint so cartilage defects can be viewed regardless of location within the joint. MRI can also view other joint tissue such as ligaments and menisci better than x-rays</td>
<td>Results can only be seen after joint destruction has occurred. Slower and more expensive than CT. No single semiquantitative method has been the standard for clinical research thus far. Inter-rater and intra-rater reliability and validity.</td>
</tr>
<tr>
<td>Imaging CT scan</td>
<td>Can view soft-tissue structures in addition to the osseous changes occurring in OA, better at viewing subchondral bone cysts than MRI</td>
<td>More radiation and higher cost than CBCT. More radiation than MRI. MRI better at viewing non-ossified structures</td>
</tr>
<tr>
<td>Imaging CE-CBCT</td>
<td>Can view the same structures in CT but with less radiation</td>
<td>New technique so efforts are still being made to increase image resolution.</td>
</tr>
<tr>
<td>Biochemistry analysis- Biomarker COMP</td>
<td>Found in patient’s serum and increased levels associated with “at risk” patients</td>
<td>Inconsistencies within the literature, patient compliance</td>
</tr>
<tr>
<td>Biochemistry analysis- Biomarker CTX-II</td>
<td>Found in patient’s urine and found in patient’s with a more “rapidly progressing” OA</td>
<td>Inconsistencies within the literature, patient compliance</td>
</tr>
</tbody>
</table>
In order to slow down the progression of the disease, it is necessary to detect OA early in the disease progression. Currently there is no single best diagnostic tool for OA, however imaging such as traditional radiographs, MRI and CT have proven to be useful for clinicians to diagnose and track the disease progression. CE-CBCT imaging technology also seems promising for future assessment of OA once image resolution improves and validity in the literature becomes more consistent. For physical therapists the WOMAC is recommended to periodically monitor patient progress.

4.1 Physical Therapy

Current conservative treatment of osteoarthritis focuses on relieving symptoms of pain and stiffness as well as improving function. There is currently no cure for OA and the progression of the disease cannot be prevented as of now. Patient education, physical therapy, weight control, use of medications and eventually total joint replacement are all ways to treat OA (Center for Disease Control, Teeple et al., 2013).

Physical therapy takes a patient-centered active approach using interventions aimed at decreasing the load of the joint to slow the progression of the pathological disease process. Many interventions have shown their efficacy through clinical trials providing physical therapists with the most appropriate evidence based treatment mechanisms. Some of these interventions have shown more promise than others to effecting knee OA and it is one of the purposes of this review to highlight those for the practicing therapist below.

4.2 Exercise

Exercise interventions have been a long appropriate intervention used by physical therapists in the treatment of knee OA. Up until recently however, there has been limited
literature on the effectiveness of specific exercises on the osteoarthritis disease process. Because of this, much of the exercise interventions prescribed in the physical therapy clinic was theoretical or expertise based. This demonstrated a significant void as the profession is moving towards a more autonomous and evidence-based intervention strategy.

In 2007, an overview of multiple systematic reviews was conducted and exercise was one of the main parameters the researchers investigated. Through analysis of 49 randomized control trials (RCTs) assessing the effectiveness of exercise interventions on knee OA, it was concluded that there is high quality evidence that exercise reduces pain and improves physical functioning in individuals with knee OA. This exercise analysis was unspecific to one type of intervention and including aerobic, walking, strengthening, and home exercise based interventions (Jamtvedt et al., 2007).

Table 6: Summary of included exercise study

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jamtvedt et al (2007)</td>
<td>Review</td>
<td>49 RCTs</td>
<td>Exercise effects on knee OA</td>
<td>Reduces pain Improves physical function</td>
</tr>
</tbody>
</table>

4.3 Strengthening Exercise

In assessing the effects of strengthening exercises on knee OA in isolation, nine randomized control trials (RCT) were analyzed through a review and it was concluded that strengthening exercises improved both pain and physical function (Wang et al., 2012). Outcome measures were assessed using VAS and WOMAC, respectively, and it was concluded to be of
low quality evidence due to medium risk of bias across the studies via criterion assessment in the Cochrane Risk of Bias tool. Although in this particular review there was no mention of the specific strengthening exercises used, it has been long reported that isometric exercises where a constant muscular contraction is sustained against a force without alteration in muscle length, is an appropriate intervention for knee OA.

A recent study assessing the effect of isometric quadriceps exercise was performed. Patients with knee OA executed various isometric exercises five times a week for five weeks compared to a non-treatment control group. At the end of the five weeks the isometric treatment group showed significant improvements in quadriceps strength, physical function, and pain. Assessments of these variables were performed with a strength gauge device, reduced WOMAC index, and the Numerical Rating Scale (NRS), respectively. It was further concluded that these improvements might be attributed to the increased strength of the quadriceps further increasing the stability of the knee joint. With an increase in muscular strength across the joint, there is a more proper alignment of structures to absorb shocks placed on the joint, which minimize the effects of the impact by spreading the forces out over a greater area (Anwer et al., 2014). An illustration of this proposed mechanism can be observed in Figure 2.
These findings coincide with the hypothesis derived from a study assessing patients with bilateral quadriceps weakness following a meniscal resection. The researchers attributed that this weakness may be an etiological factor underlying the pathological changes of osteoarthritis and that quadriceps weakness seems to precede degenerative changes at the knee joint (Becker et al., 2004).

Table 7: Summary of Included Strengthening Exercise Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improves physical function</td>
</tr>
<tr>
<td>Anwer et al (2014)</td>
<td>RCT</td>
<td>Treatment (n=21), control (n=21)</td>
<td>Isometric quadriceps exercise effects on knee OA</td>
<td>Increase in quadriceps strength</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Reduces pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improves physical function</td>
</tr>
</tbody>
</table>
4.4 Aerobic Exercise

Classification of aerobic exercises would include any physical activity that utilizes oxygen as the main energy source through metabolic processes. These exercises are typically of low intensity and long duration. In a review designed to observe the effects of aerobic exercise on knee OA it was concluded that aerobic interventions decrease long-term pain (>26 weeks), decreased disability, and improved physical function within 3 months. Variables were assessed using VAS, European Quality of Life-5 Dimensions (EQ-5D), and WOMAC and walking speed, respectively. The review further observed that there were greater improvements in physical function at 3 months in the RCTs that were not supervised by a physical therapist (Wang et al., 2012).

Mechanisms for these improvements may be attributed to the altered metabolic and chemical processes that occur during and after aerobic exercise in individuals with OA. In a control trial (CT) analyzing the effects of aerobic exercise on the blood concentrations of inflammatory mediators in elderly female (≥65 years of age) with knee OA, it was found that increased plasma levels of soluble tumor necrosis factor receptor 1 (sTNFR1) correlated with improved physical function (Gomes et al., 2012). These results suggest that this inflammatory mediator may increase in concentrations in order to control the inflammation and provide a protective mechanism against cartilage degradation.

In a follow-up study, these same researchers further analyzed another chemical mediator in the inflammatory response following aerobic activity in elderly females (≥65 years old) with knee OA. Analysis of brain-derived neurotrophic factor (BDNF) concentrations showed no correlation to the improvements in physical function or the reduction in pain seen in the participants (Gomes et al., 2014). Although these results showed statistically significant
improvements in pain and function, it was not well correlated to BDNF plasma concentrations demonstrating that this particular inflammatory mediator may not be related to the osteoarthritic disease process.

Table 8: Summary of included aerobic exercise studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wang et al (2012)</td>
<td>Review</td>
<td>11 RCTs</td>
<td>Aerobic exercises effects on knee OA</td>
<td>Reduces long term pain&lt;br&gt;Reduces disability&lt;br&gt;Improves physical function</td>
</tr>
<tr>
<td>Gomes et al (2012)</td>
<td>CT</td>
<td>Females (≥65) n=15</td>
<td>Assess correlations of inflammatory marker concentrations with clinical and functional responses to aerobic exercise in knee OA</td>
<td>Increased plasma sTNFR1 correlate with improved physical function</td>
</tr>
<tr>
<td>Gomes et al (2014)</td>
<td>CT</td>
<td>Females (≥65) n=15</td>
<td>Assess correlations of BDNF concentrations with functional or pain responses to aerobic exercise in knee OA</td>
<td>No correlation of BDNF concentrations and function or pain</td>
</tr>
</tbody>
</table>

4.5 Aquatic Exercise

Therapeutic aquatic exercise is a common approach to OA treatment due to the potential benefits of using the body’s buoyant properties to manipulate and decrease the load across the lower extremity in accordance with patient symptoms. A review analyzing the effects of aquatic exercise on lower limb OA (knee and hip), found that it is significantly appropriate in reducing
pain, increasing self reported function, increasing physical function, and increasing quality of life. These significant results all showed a small effect size and were analyzed from 11 RCTs (Waller et al., 2014). These beneficial effects have also been postulated to be a result from exercising in a warmer water environment. The thermal effects may encourage muscle relaxation and prevent muscle guarding across the joint further enhancing movement and the ability to exercise in a more functional range of motion (Hinman et al., 2007).

In an attempt to observe differences between two common exercise protocols in the treatment of knee OA, a study was performed to compare the efficacy of aquatic exercises and land-based exercises on pain. Analysis demonstrated similar results to previous literature with improvements in pain, range of motion, function, and quality of life across both intervention groups but no significant difference between groups for the effects on pain (Wang et al., 2011). Despite these findings, special considerations should be made for individuals with severe progressions of OA where land based exercises cause too much pain and the only exercise the individual can tolerate is in an aquatic setting.
Table 9: Summary of included aquatic exercise studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waller et al (2014)</td>
<td>Review</td>
<td>11 RCTs</td>
<td>Assess effects of therapeutic aquatic exercise on lower limb OA</td>
<td>Reduces pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increases self-reported function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increases physical function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increases quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No effect on strength</td>
</tr>
<tr>
<td>Hinman et al (2007)</td>
<td>RCT</td>
<td>Treatment (n=36), Control (n=35)</td>
<td>Aquatic exercise effects on hip and knee OA</td>
<td>Reduces pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improves physical function</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Improves quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Increases hip strength</td>
</tr>
<tr>
<td>Wang et al (2011)</td>
<td>RCT</td>
<td>Aquatic (n=26), Land-based (n=26), Control (n=26)</td>
<td>Compare aquatic and land-based exercise effects on pain in knee OA</td>
<td>No significant differences between groups</td>
</tr>
</tbody>
</table>

4.6 Ultrasound

The use of ultrasound (US) is a widely used modality in physical therapy to reduce pain and inflammation across various musculoskeletal pathologies including knee OA. A review designed to assess the benefits of using ultrasound on knee OA observed consistent significant reductions in pain and possible improvements in physical function. It was also proposed that the reductions in pain might be sustained for 10 months after US discontinuation, but further definitive trials are needed to assess these effects due to the low quality of evidence (Loyola-Sánchez et al., 2010). These observations were also detected by other reviews, concluding that
US is effective at reducing pain (Jamtvedt et al., 2007), and US is effective at reducing pain and improving physical function in participants with knee OA (Wang et al., 2012).

Regarding US application parameters, Loyola-Sánchez concluded that low intensity (< 1 W/cm$^2$), pulsed mode, at a therapeutic dose < 150 J/cm$^2$ could be more effective at reducing pain than high intensity (≥ 1 W/cm$^2$), continuous mode, at a therapeutic dose >150 J/cm$^2$ (Loyola-Sánchez et al., 2010). Due to the minimal support of these conclusions, further studies should aim to compare the effectiveness of different parameter settings to develop a standard of practice in the treatment of pain in knee OA.

Outside of treating impairments, US may also have the ability to repair or regenerate cartilage after injury and thus may be able to reverse the effects of the degeneration process seen in OA. A proposed mechanism for the cartilage repair pathway is explained through the ‘mechanotransduction theory’. The theory proposes that mechanical stimuli will increase the chondrocyte production of proteoglycans and anti-inflammatory proteins leading the regeneration and repair of cartilage within a joint (Choi et al., 2007). This theory provides the foundational framework for the possibility of stopping and reversing the degenerative disease process of OA and should be further explored as to its effectiveness.
Table 10: Summary of included ultrasound studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loyola-Sánchez et al (2010)</td>
<td>Review</td>
<td>6 RCTs</td>
<td>Ultrasound effects on knee OA</td>
<td>Reduces Pain</td>
</tr>
<tr>
<td>Jamtvedt et al (2007)</td>
<td>Review</td>
<td>3 RCTs</td>
<td>Ultrasound effects on knee OA</td>
<td>Reduces pain</td>
</tr>
<tr>
<td>Wang et al (2012)</td>
<td>Review</td>
<td>6 RCTs</td>
<td>Ultrasound effects of knee OA</td>
<td>Reduces Pain Improves physical function</td>
</tr>
</tbody>
</table>

4.7 Electrical Stimulation

Electrical stimulation (ES) is another physical therapy modality that is a common intervention for patients suffering from pain and muscle weakness or dysfunction. Patients with knee OA present with both of these impairments and therefore application of ES around the knee joint has been a standard of practice in profession. Despite the widespread use, there has been some conflicting literature onto its effectiveness on the osteoarthritic condition. In a review focused on the non-specific use of ES on knee OA, it was observed that there was a short-term reduction in pain but participants later reported an increase in pain 6 months after treatment cessation (Wang et al., 2012). Conversely, in a meta-analysis observing the effects of transcutaneous electrical nerve stimulation (TENS), it was concluded that all forms of TENS showed a significant benefit for pain relief in knee OA (Brosseau et al., 2004). TENS is the main form of ES indicated for a reduction in pain, and maybe this discrepancy between reviews can be attributed to the nonspecific ES provided in the first review leading to negative long-term results.
It was also concluded by Brosseau et al., that TENS that was designed to only produce a ‘tingling’ sensation but no muscle contraction was effective at reducing pain in knee OA, but exacerbated pain in hip OA, which leads to further questions on its overall efficacy (Brosseau et al., 2004).

Another primary use for ES is the to increase muscle strength and function, commonly referred to as neuromuscular electrical stimulation (NMES). In a review designed to observe the efficacy of NMES on knee OA, the researchers concluded that there was inconclusive evidence of its effects due to the inconsistency across the studies analyzed. Conversely, in the review assessing the nonspecific ES, it was concluded that ES does have a significant effect on increasing muscular strength, although the researchers did report that this was of low strength evidence. The review further concluded that ES had no significant improvements on gait function (Wang et al., 2012). Further, a CT study observed that an 8-week NMES training program leads to increases in isometric quadriceps torque, fascicle length, and muscle thickness as well as a reduction in pain and functional limitations in participants with knee OA (Vaz et al., 2014).

These conflicting results on the effectiveness of different forms of ES on knee OA has led to much controversy onto its application in clinical physical therapy treatment. The conflicting results may be a product of inadequately designed studies and future attempts to assess its usefulness on knee OA should address this. However, despite this lack of continuity, the use of ES in the clinical setting may still be an appropriate intervention in specific situations. This notion has lead to the recommendation that NMES might prove to be a useful alternative for individuals with knee OA who are unable to carry out conventional exercise due to the extent of the disease process (Giggins et al., 2012).
Table 11: Summary of included electrical stimulation studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
</table>
| Wang et al (2012)| Review    | 7 RCTs                        | Electrical stimulation effects on knee OA        | Short term reduction in pain  
                                                                |                                                                                       | Long term increase in pain  
                                                                |                                                                                       | Increase muscle strength  
                                                                |                                                                                       | No effect on gait function       |
| Giggins et al (2012) | Review | 9 RCTs & 1 CT                  | NMES effects on knee OA                          | Inconclusive evidence                                                  |
| Vaz et al (2014) | CT        | Healthy (n=10), Knee OA (n=20) | NMES effects on Quadriceps and knee OA           | Increases isometric strength  
                                                                |                                                                                       | Reduces pain  
                                                                |                                                                                       | Reduces functional limitation  
                                                                |                                                                                       | Increased muscle thickness and length |

4.8 Combined Interventions

Despite the fact that many of the previously investigated interventions have shown significant effects on knee OA, it was observed that there has been a discrepancy between most studies and The Guide to Physical Therapy Practice (Wang et al., 2012). The guide outlines the standards of practice for clinicians on the various diagnoses that may be presented to a physical therapist. These standards of practice include a variety of interventions that are appropriate for a given diagnosis and they should be used in conjunction with one another. This recommended
method of treating patients is dissimilar to the way the previously mentioned studies have been conducted, in that they only observe the effects of one single intervention in isolation. To observe the effectiveness of patient management as set forth by the guide, studies that included multiple interventions in the treatment of knee OA have been assessed.

In a study conducted to evaluate the effectiveness of using manual therapy and exercise to treat knee OA, it was observed that when compared to patients in a placebo group, the intervention group demonstrated significant effects in both objective and subjective measures. Manual therapy included joint mobilization to the lumbar spine, hip, knee, and ankle as deemed necessary by an experienced therapist and the placebo group received sub-therapeutic ultrasound. Objective findings showed an increase in the 6 minute walk test and significant subjective findings were observed through the WOMAC questionnaire (Deyle et al., 2000). This study was one of the first of its kind in assessing the effectiveness of multiple interventions in the treatment of knee OA. Due to the significant findings presented, further studies can be conducted to assess whether these findings are more significant than previously determined effective interventions performed in isolation.

In a follow-up study performed by the same researchers, a combined intervention group that included manual therapy and exercise was compared to an exercise only intervention group. Although both groups demonstrated significant improvements in physical function as evidence of the 6 minute walk test, greater significance was observed in the combined intervention group for subjective testing using the WOMAC questionnaire (Deyle et al., 2005). Despite the only significant difference between the groups was seen in subjective testing, it is the implications of these results that may end up being the most influential. The subjects in the combined intervention group reported to be more satisfied with their treatment and even less likely to be
taking medication to combat the effects of their knee OA. This increase in satisfaction may lead to better patient compliance and willingness to seek more conservative management for this particular condition reducing the need for total joint arthroplasty.

In a systematic review performed in 2011, similar results on pain and disability in knee OA were found when comparing strength training alone, exercise therapy alone, and exercise with passive manual mobilization. It was established by the review that exercise therapy included strength training, active range of motion exercises and aerobic activity. The review found that both strength training alone and exercise therapy alone showed only a small effect size for pain, where exercises with passive manual mobilization demonstrated a moderate effect size on pain. These results on pain also significantly correlated with the results of improvement in physical function but no significant differences between the groups were observed. The researchers concluded that an active exercise program involving strength training, aerobic activity, and active range of motion exercises with the addition of manual mobilization techniques should be used to achieve better pain relief in patients with knee OA (Jansen et al., 2011)

The published results of these studies have shown that treating patients with knee OA with a single intervention may provide benefits, but when combined with other interventions, specific manual mobilization techniques, the effects on pain are greater. There also seems to be an additional effect on improving physical function within these individuals but further studies should be performed to investigate within these parameters. It is thus the recommendation of this review that clinicians should utilize a combined intervention approach, including mobilization techniques, in the treatment of patients suffering from knee OA.
Table 12: Summary of included combined interventions studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Objectives</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deyle et al (2000)</td>
<td>RCT</td>
<td>Treatment (n=42), Placebo (n=41)</td>
<td>Manual therapy and exercise effects on knee OA</td>
<td>Improves physical function Reduces pain Reduces stiffness</td>
</tr>
<tr>
<td>Deyle et al (2005)</td>
<td>RCT</td>
<td>Clinical Treatment (n=66), HEP (n=68)</td>
<td>Manual therapy and exercise vs. exercise</td>
<td>Both groups had improved physical function Combined interventions had greater reduction in pain and stiffness</td>
</tr>
<tr>
<td>Jansen et al (2011)</td>
<td>Review</td>
<td>12 RCTs</td>
<td>Compare strength training alone, exercise alone, and exercise with passive mobilization effects on knee OA</td>
<td>Strength training has small effect size in reducing pain Exercise has small effect size in reducing pain Exercise and mobilization has moderate effect size in reducing pain</td>
</tr>
</tbody>
</table>

4.9 Conclusion Regarding Exercise and OA

Despite the numerous significant findings from analysis of the above published studies, it was observed that one major aspect of patient treatment has not been well documented and could potentially have the most influence on patient outcomes. The researchers of an extensive review on knee OA interventions explained that exercise was an effective treatment, but a focus should be placed on patient compliance to the treatment program rather than increasing the amount or intensity of the exercise. It was further reported that there may be a possible association between high adherence to exercise intervention and the improvement of pain and function within the
individual (Wang et al., 2012). Other than compliance to a continued exercise program, it has been observed that between a 10-15% reduction in body weight has shown to significantly decrease joint pain and improve physical function in patients with knee OA (Bliddal et al., 2011; Huang et al., 2000). The implications of patient compliance and weight reduction demonstrates the importance of proper patient education on the pathological process and the necessity of ongoing treatment in a clinical setting with a physical therapist and also at home by the patient themselves. This is why, despite the lack of documented quantitative evidence on the subject, it is the suggestion of this review that patient education should be included in all aspects of care for a patient with knee OA.

In conclusion, it is the recommendation of this review that in treating individuals suffering from knee OA, physical therapists should utilize a multimodal, combined interventions approached treatment including aerobic exercise, strength training, low intensity pulsed ultrasound, and manual mobilization techniques with a heavy emphasis on patient education for weight reduction and exercise compliance.

5.0 Animal Models of OA

Although many randomized control trials and systematic reviews have explored the best intervention to prevent the onset and progression of osteoarthritis, it remains difficult to evaluate their effectiveness. Objective outcome measures in these studies generally include patients self-reported pain and stiffness as well as functional abilities and, in rare cases, serial radiographic testing. While these studies are able to assess patient function, they remain an inadequate method to determine the conformational changes that occur within the joint (Fang et al., 2014). Animal models of osteoarthritis have proven to be useful in researching the causes and progression of the disease on with increased sensitivity.
Animal models of OA are used to replicate and investigate the progression of osteoarthritic changes that occur within a joint. Many animal models exhibit reproducible OA progression with outcomes significant enough to identify differences within a short time period with relatively low cost. The highly controlled nature of these models allow for greater opportunity to identify and regulate symptoms and disease progression to develop the best interventions possible for osteoarthritis (Teeple et al., 2013). A list of animal models of osteoarthritis used in the research setting can be seen in Table 13 below.

Table 13: Comparison of animal models [modified from Fang & Bier, 2014]

<table>
<thead>
<tr>
<th>Model</th>
<th>Advantages</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous/genetic</td>
<td>-Mimics primary human OA</td>
<td>-Variable onset/progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Slow disease progression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-High cost</td>
</tr>
<tr>
<td>High fat diet/obesity</td>
<td>-Major risk factor for OA</td>
<td>-Long research period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Variable etiology of OA</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-High cost</td>
</tr>
<tr>
<td>Surgical</td>
<td>-Reproducibility</td>
<td>-Surgery confounding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Mimics post-traumatic OA</td>
</tr>
<tr>
<td>Mechanical loading</td>
<td>-Non-invasive</td>
<td>-Induce cartilage lesions on lateral compartment</td>
</tr>
<tr>
<td></td>
<td>-Mimics injury in human knee</td>
<td></td>
</tr>
</tbody>
</table>
While spontaneous idiopathic osteoarthritis development has been defined in many laboratory animal species including lab mice, the progression of the disease generally occurs slowly over time. It has been shown that STR/ort strain mice have develop knee osteoarthritis at approximately 12 weeks of age, however it was determined via histological studies that male C57 black mice revealed a high incidence of osteoarthritic changes in the knee joint around the 17th month of life. In animals of the same strain aged 15.5 months the incidence was only 19% (Sokoloff et al., 1962; Wilhelmi et al., 1976). While these models may be advantageous as they epitomize the most common form of human OA, the variability of disease incidence and progression between genetically variable mice strains decrease their usefulness in the research setting, especially as it applies to physical therapy.

Obesity is a known risk factor for the development of osteoarthritis (Murphy et al., 2012). Models in which mice are fed a high fat diet, comprised of food with 60% of calories from fat, are effective and have a marked increase in severity of osteoarthritic lesions (Griffin et al., 2012). While obesity may be a major factor in the development and progression of the disease, it remains difficult to attribute osteoarthritic changes associated with the disease to one particular condition of obesity. Change may occur as a result of an altered biomechanical load from a muscular imbalance at the knee or hip causing increase shearing force across the articular cartilage. It is also possible that joint degeneration occurs as a result of altered systemic factors due to a high fat diet or decreased level of physical activity of the individual. Since the exact entrance and pathogenesis to the disease process cannot be pinpointed using this model, it is also not the most appropriate for physical therapy osteoarthritis research.

Surgically induced joint instability models have also been used to hasten the onset and progression of OA. Surgical methods of OA induction work multimodally using a combination
of joint destabilization, altered force distribution across the articular cartilage and inflammation inside of the joint. Three main surgical models of osteoarthritis exist and include meniscectomy, meniscal destabilization surgery (DMM) and anterior cruciate ligament (ACL) transection (Fang et al., 2014). Partial medial meniscectomy has been shown to induce cartilage damage initially at 4 weeks and then progressive OA lesions at 8 and 12 weeks post-surgery. While this method is effective at inducing OA, there is inconsistency of how much of the medial meniscus is removed which may make results inconsistent (Knights et al., 2012). DMM is also effective and has been found to induce mild articular cartilage lesions as early as 2 weeks post-surgery and progress over a 16 week period (Loeser et al., 2013). ACL transection induces change in chondrocytes as early as 4 weeks post-surgery and osteophytes at 8 weeks. Also, the combination of ACL transection with another surgical procedure lead to more severe damage in the joint than ACL transection alone (Kamekura et al., 2005).

Surgical models of osteoarthritis are advantageous as they create a fast and reproducible time course of disease progression as well as creating an evident relationship between the traumatic event and the onset of pathological joint changes. Although these models do accelerate the progression of osteoarthritis, they are more closely associated with inflammatory OA as opposed to spontaneous, naturally occurring human osteoarthritis that we are concerned with as physical therapists. These approaches may also have confounding results due to the invasive techniques employed. Understanding which animal models accurately correspond to human OA progression is critical to converting interventions from clinical trials to clinical practice guidelines (Teeple et al., 2013).

Non-invasive models of OA have been developed in recent years in an attempt to emulate the spontaneous osteoarthritis onset and progression that is induced biomechanically. These
methods do not break the skin or disrupt the joint surgically and therefore avoid complications and confounding variables present when using invasive techniques. A limited number of non-invasive models of OA have been developed including intra-articular fracture of tibial subchondral bone and the cyclic tibial compression loading of articular cartilage (Christiansen et al., 2015).

One non-invasive mouse model of post-traumatic osteoarthritis, first described in 2007 by Furman et al, initiates symptoms using intra-articular fracture (IAF) of the proximal tibia. Osteoarthritic changes are induced by positioning the lower limb of the mouse in 90 degrees of flexion, introducing a 10 Newton compressive pre-load, which was used to ensure proper alignment of the indenter, then progressing to a compressive force of 55 Newtons at a rate of 20 Newton-seconds. Mice were allowed immediate full weight bearing with unlimited range of motion for 2, 4 or 8 weeks until sacrifice. Fractures were evaluated by anterior-posterior and lateral radiographs yielding results that this protocol was successful in 87% (27 of 31) mice (Furman et al., 2007). The injuries sustained by mice were more commonly located on the lateral side of the tibial plateau and resemble those often seen clinically. While this model is advantageous over other models due to its non-invasive nature, it is illustrative of high force impact injuries that occur in the human population such as a motor vehicle accident. Therefore it may not be ideal for studying low-energy non-contact injuries that commonly lead to human osteoarthritis.

Another successful non-invasive model of osteoarthritis includes cyclic tibial compression of the articular cartilage in the knees of mice. For this loading method, a mouse is subjected to recurrent axial compressive loads through the ankle and knee joints with loads transferred through joint articulations. This technique, first described by Poulet et al., has proven
useful for the study of articular cartilage degeneration and allows investigators to explore both long and short-term joint degeneration in mice.

The original study, conducted by Poulet et al. in 2011, used a 9 Newton compressive load applied every 10 seconds with 40 cycles for each loading session which occurred 3 times per week. After 2 weeks of loading, articular cartilage lesions were observed on the lateral femur. After an added 3 weeks of either loading or non-loading, the mean grade of severity of lesions increased significantly in the group with extra loading however the maximum lesion severity remained the same. It was also found that a single episode of loading damaged the articular cartilage however was not sufficient enough to create a progressive lesion. Results found early osteophyte signs on the lateral femur in 57% of mice that received 2 weeks of loading and osteophyte formation occurred on both the medial and lateral femoral articular surfaces in 83% of mice loaded for 5 weeks (Poulet et al., 2011).

Non-invasive animal models of osteoarthritis are integral to future research of the pathology. These models are able to induce articular cartilage degeneration without an incision, which significantly decreases confounding variables and translate more easily to the type of osteoarthritis that occurs in the human population. These models may allow for innovative discoveries regarding the mechanisms behind the onset and progression of the destructive joint disease that may be translatable to the human population using computational modeling software.

6.1 Conclusion

This targeted literature review was created to help physical therapists understand the vicious cycle in which osteoarthritis operates, how OA is diagnosed both in the clinic as well as
through imaging, what interventions physical therapists currently use to treat it, as well as understanding the future of research using non-invasive animal models. Understanding the OA as a multifactorial process is the first step for clinicians and researchers alike to begin to devise specific interventions to decrease the onset and progression of osteoarthritis.
7.1 Appendix

1. OA: osteoarthritis
2. ACL: anterior cruciate ligament
3. MMPs: matrix metalloproteinases
4. PIC: proinflammatory cytokines
5. MRI: Magnetic Resonance Imaging
6. WORMS: Whole-Organ Magnetic Resonance Imaging Score
7. BLOKS: Boston Leeds Osteoarthritis Knee Score
8. BML: bone marrow lesions
9. CT scan: computerized tomography scan
10. CECT: contrast enhanced computed tomography
11. CBCT: cone beam computed tomography
12. CE-CBCT: contrast enhanced cone beam computed tomography
13. CTX-II: C-terminal crosslinking telopeptide of type II collagen
14. COMP: Cartilage oligomeric matrix protein
15. ELISA kit: enzyme-linked immunosorbent assay kit
16. WOMAC: Western Ontario and McMaster Universities Arthritis Index
17. VAS: Visual analog scale
18. NRS: Numerical rating scale
19. RCTS: Randomized control trials
20. EQ-5D: European Quality of Life-5 Dimensions
21. CT: Control trial
22. US: Ultrasound
23. ES: Electrical stimulation
24. NMES: Neuromuscular electrical stimulation
8.1 Bibliography


