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Osteoarthritis: pathophysiology and current treatment modalities

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ABSTRACT

Osteoarthritis (OA) is accepted as a major public health problem. It is one of the major causes of impaired function that reduces quality of life (QOL) worldwide. OA is a very common disorder affecting the joint cartilage. As there is no cure for OA, treatments currently focus on management of symptoms. Pain relief, improved joint function, and joint stability are the main goals of therapy. The muscle weakness and muscle atrophy contribute to the disease process. So, rehabilitation and physiotherapy were often prescribed with the intention to alleviate pain and increase mobility. However, as exercise has to be performed on a regular basis in order to counteract muscle atrophy, continuous exercise programs is recommended in people with degenerative joint disease. Therapeutic exercise regimes either focus on muscle strengthening and stretching exercises or on aerobic activity which can be land or water based. This article presents on overview of the current knowledge on OA and focuses on biomechanics, etiology, diagnosis and treatment strategies, conservative treatment including the physical therapy management are discussed. This information should assist health care practioners who treat patients with this disorder.

Keywords: OA; Strengthening exercises; Stretching exercises; Pain severity; Hamstrings / quadriceps ratio, knee osteoarthritis, cartilage degeneration, non-inflammatory arthritis, intra-articularinjections, corticosteroids

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Introduction

Osteoarthritis (OA) is a common chronic condition resulting in pain, fatigue, functional limitations, increased healthcare utilization and high economic costs to society [1]. The burden of OA is projected to increase, due in part to obesity and population aging [2]. While the prevalence of OA increases with age [3], there is a growing recognition that OA affects people at younger ages. Recent US data demonstrated that half of people with symptomatic knee OA are diagnosed by age 55 [4].

Quadriceps strength deficits have been reported in 20%–70% of patients with knee OA. Any improvement in muscle strength or peak power of the lower extremities with decreased levels of particular pain may be important and is a strong predictor of functional ability [5]. As lower limb musculature is the natural brace for the knee joint, potentially important muscle dysfunction may arise from either quadriceps weakness or relative weakness of the hamstrings in comparison to the quadriceps, usually assessed as the hamstrings: quadriceps (H:Q) ratio. An H:Q ratio of greater than or equal to 0.6 is considered to be normal [6]. Thus, evaluation of muscle dysfunction in relation to the knee joint should examine both quadriceps strength as well as the balance of muscle strength [6].

The etiology of OA is related to repetitive mechanical loads and aging. Recent studies have separated the etiological factors into three main sub-groups: sex, anatomy, and body mass. The clinical manifestations are joint pain, stiffness; decreased range of joint movement, muscle weakness of the quadriceps and alterations in proprioception [7]. Decreased strength in the muscle groups involving the joints is significant because it causes progressive loss of function. These symptoms significantly restrict the individual's ability to get up from a chair, walk, or climb stairs [3]. Walking with a limp, poor alignment of the limb, and instabilities can also be observed in individuals with OA. During movements, crepitating can be heard because of arthritis of the irregular joint surfaces [2]. Clinical knee OA usually is managed in primary care [8] with analgesics and non-pharmacological options, such as exercise [6]. Exercise has been shown to improve function, strength, walking speed, and self-efficacy and to reduce pain and the risk of other chronic conditions [9, 10]. Also, prevent or retard progression of the disease using physical and occupational therapy and exercise programs [3]. Plain radiographs are commonly used to

classify OA subjects for the purposes of clinical studies and joint space narrowing is often used as a measure of disease progression. Although plain radiography is at present, the "gold standard" for evaluation of OA progression, it is brimful with problems related to the accurate reproduction of measurements of joint space width, especially in subjects who have knee OA [11]. A self-reported physical disability or assessment questionnaire most commonly used to assess the outcome of exercises for OA. The most popular specific questionnaire for knee OA is the Western Ontario and McMaster Universities OA index questionnaire (WOMAC) which reports pain, stiffness and daily function difficulties experienced by OA subjects [12].

Several muscle groups support the knee. The two main muscle groups that control knee movement and stability are the quadriceps and the hamstrings. The quadriceps and hamstrings muscles have the potential to provide dynamic frontal-plane knee stability because of their abduction and/or adduction moment arms [13]. Using a neuromuscular biomechanical model, the quadriceps and hamstrings not only have the potential to support frontal-plane moments but also actually do provide support to abduction-adduction moments [14]. In the frontal plane, balanced co contraction of the quadriceps and hamstrings leads to increased joint compression, which should assist in knee joint stabilization [15]. The diminished co activation between the quadriceps and hamstrings in women may contribute to greater knee joint instability in women than in men. The strength relationship between the quadriceps femories and hamstring muscle have been measured and reported by various researchers [16, 17].

Classification

1) Primary osteoarthritis (idiopathic)-

- Localized
  - Hands – nodal osteoarthritis more than three joint sinvolved
  - Hip – eccentric, concentric, diffuse
  - Knee – medial tibiofemoral, lateral tibiofemoral, pattelofemoral
  - Spine – apophyseal, intervertebral, spondylosis
- Generalized
  - Small (peripheral) joints
  - Large (central) joints
  - Mixed and spine
- Erosive osteoarthritis

2) Secondary-

- Congenital and developmental disorders, bone dysplasias.
- Post-surgery / injury – meniscectomy.
- Endocrine – diabetes mellitus, acromegaly, hypothyroidism, hyperthyroidism, hyperparathyroidism, Cushing syndrome.
- Metabolic – hemachromatosis, ochronosis, Marfan syndrome, Ehler-Danlos syndrome, Paget disease, gout, pseudo gout, Wilson's disease, Hurler disease, Gaucher disease.
- Rheumatologic– rheumatoid arthritis.
- Neurological– Charcot joints.
- Hematological – hemoglobinopathies.
- Iatrogenic – intra-articular steroids.[18]

Knee osteoarthritis

The knee is the largest synovial joint in humans, it is composed by osseous structures(distal femur, proximal tibia, and patella), cartilage (meniscus and hyaline cartilage),ligaments and a synovial membrane. The latter is in charge of the production of the synovial fluid, which provides lubrication and nutrients to the avascular cartilage. Unfortunately, given the high use and stress of this joint, itis a frequent site for painful conditions including OA[19,20]OA is classified into two groups according to its etiology: primary (idiopathic or non-traumatic) and secondary(usually due to trauma or mechanical misalignment). Theseverity of the disease can also be graded according to theradiographical findings by the Kellgren–Lawrence (KL)system described in 1957[21].It was believed that OA was exclusively a degenerative disease of the cartilage, however, latest evidence has proven that OA is a multifactorial entity, involving multiple causative factors like trauma, mechanical forces, inflammation, biochemical reactions, and metabolic derangements[22]. It is also known that the cartilaginous tissue is not the only one involved. Given its lack of vasculature and innervation, the cartilage, by itself is not capable of producing inflammation or pain at least on early stages of the disease. Hence, the source of pain is mainly derived from changes tothe non-cartilaginous components of the joint, like the joint capsule, synovium, subchondral bone, ligaments, and periarticular muscles. As the disease advances, these structure sare affected and changes including bone remodeling, osteophyte formation, weakening of periarticular muscles, laxity of ligaments, and synovial effusion can become evident[23].The role of inflammation is not well-understood and there is an ongoing debate to determine if the inflammatory reaction triggers the OA changes, or instead, the inflammation is secondary to the OA changes. Different from inflammatory arthritis, inflammation in OA is chronic and low-grade inflammation, involving mainly innate immune mechanisms. Synovitis (infiltration of inflammatory cells into the synovium) is a common finding of OA and it can be present in early stages of the disease but is more prevalent towards the more advanced stages and can be related withseverity.1 In OA, the synovial fluid has been found to contain multiple inflammatory mediators including plasma proteins(C-reactive protein, proposed as a marker for development and progression of OA), prostaglandins (PGE2), leukotrienes(LKB4), cytokines (TNF, IL1, IL6, IL15, IL17, IL18, IL21),growth factors (TGF, FGFs, VEGF, NGF), nitric oxide, and complement components[24].Locally, all of these components can induce matrix metallo proteinases and other hydrolytic enzymes (including cyclooxygenase two and prostaglandin E)resulting in cartilage breakdown secondary to proteoglycan and collagen destruction[25].White blood cells are also involved, extracellular matrix breakdown releases certain molecules (damage-associated molecular patterns) that are recognized by the innate immune cells (macrophages and mast cells), usually as a protective mechanism. However, this prolonged and dysregulated degree of inflammation can lead to tissue destruction. In animal studies, macrophages have been found to be involvedin the development of osteophytes that are a pathological feature of OA. The body also has protective molecular mechanisms including various growth factors (insulin-like, platelet derived, fibroblast, and transforming growth factor B) which, unfortunately, are altered in patients with knee OA and may become harmful to the joint[19,25].

Epidemiology

Osteoarthritis (OA) of the knee is the most common form of joint disease and prevalence of both radio graphically evident and symptomatic. The females having higher prevalence than males (11.4% vs 6.8%) [26]. The gender difference in prevalence has recently been emphasized in a meta-analyses, which provides evidence for a greater risk in females for prevalent and incident knee OA [27]. The meta-analysis also reported that females tend to have more severe knee OA radio graphically assessed than males and that the gender differences increase with age > 55 years. The prevalence of OA will increase as the population of the kingdom ages, especially if the incidence of obesity remains at over 50% in the 45+ age group [28].

Etiology & Pathogenesis

Modern imaging approaches recognize that OA is a whole joint disease which may involve multiple tissues which confer different phenotypes; subchondral bone in particular is integral to the pathogenesis and progression of OA. In particular, the area of subchondral bone at the femorotibial articulation is larger in OA knees than healthy controls and correlates with knee joint space narrowing, osteophytes [29].

Pathogenetically, knee OA is characterized by structural changes in and around the knee joint. The predominant structural changes are the loss of cartilage and the formation of osteophytes. These changes are easily demonstrated radio graphically, and objective measures of disease severity are based on the amount of joint space loss (a reflection of cartilage loss) and the presence of osteophytes [30]. Furthermore, the subchondral bone scleroses in the early phases of OA and this process, possibly involving micro fractures has been suggested to be pathogenetic factors in the process of cartilage degeneration . In addition to these structural “hard tissue” changes, a number of changes in articular and periarticular soft-tissue occur with knee OA. These include synovial hyperplasia and joint effusions. Although knee OA is not classified as an inflammatory disease, a common sign of knee OA is synovial inflammation, detected using Ultrasonographic. In addition magnetic resonance imaging as well as orthoscopical inspection of the knee joint has also provided insights to the presence of inflammation in knee OA [31,32].

Structural changes: Mainly are reductions instainable proteoglycan, fibrillation, collagen crumping, chondrocyte multiplication or migration and loss of cartilage. Initially, localized areas of softening present apebbled texture at surface followed by disruption alongcollagen fiber planes (tangential flaking, vertical fibrillation). As deep clefts are formed in cartilage, nearby matrix gets depleted of metachromatic material indicating loss of proteoglycans. Subsequent focalproliferation of chondrocytes occurs as an attempt atlocal self-repair leading to irregularly shaped hyaline and fibro cartilage. Later new bone formation occurs in subchondral bone and at joint margins (osteophytes). Subarticular cysts predominate wherever overlying cartilage is thin or absent. Separated fragments of cartilage and bone may form loose bodies, undergo dissolution or become incorporated into synovium and proliferate locally. Synovium becomes thick and hypertrophied and capsule contracts with infiltration of lymphoid follicles, lymphocytes and macrophages. Calcification may occur as calcium crystals deposit in cartilage with presumed secondary uptake in synovium. Despite loss of bone and cartilage in some parts of joint, net effect of new cartilage and bone formation is an increase in joint size and remodelling of shape.[33,34].

Metabolic and biochemical changes in osteoarthritis cartilage

• Generalized – Increased hydration and swelling with loss of tensile strength is noticed in early OA, whereas increase in type I collagen synthesis and progressive fall occurs in proteoglycan concentration in later stage of OA.

• Specific collagens – Initial swelling of collagen fibrillar network with loss of type II collagen, specific cleavage of collagens and loss of tensile strength with increased content of collagen type IV. Type III and X collagen are also synthesized.

• Proteoglycans – Increased extractability and decrease in monomer size because of specific cleavages by aggrecanases and metalloproteinases.

• Cytokines, proteinases and inhibitors – There is increase in pro-inflammatory cytokines, aggrecanases, MMPs (matrix metalloproteinase), cathepsins and decrease in overall inhibitors (TIMP etc.)[35].

Of the three major MMPs that degradenative collagen, MMPs -13 is most important, as it preferentially degrades type II collagen whose expression is greatly increased in OA. The aggrecanases belong to a family of extracellular proteases known as disintegrin and metalloproteases with thrombo spondinmotifs (ADAMTS). ADAMTS-4 and ADAMTS-5 appearto be major enzymes in cartilage degeneration in arthritis. Whereas, IL-1beta synthesized by mononuclear cells(including synovial cells) in inflamed joint is consideredby many investigators as a prime mediator in cartilagematrix degradation and stimulates synthesis and secretion of many degradative enzymes in cartilage including latent collagenase, stronelysin, gelatinase and tissue plasminogen activator. The balance of active and latent enzymes is controlled to some extent by at least two enzyme inhibitors: TIMP and plasminogen activator inhibitor-1(PAT-1).Which in turn are reglated by TGF-beta. However, the imbalance between proteoglycan synthesis and degradation isimportant in pathogenesis of cartilage breakdown.

Growth Factors and Cytokines Anabolic

- TGF (tissue growth factor beta- 1, 2 & 3) help in chondrocyte proliferation, matrix synthesis, modulate effects of IL-1 and increases proteinase inhibitors.
- Fibroblast and platelet derived growth factors also help in differentiation and proliferation of chondrocytes and MMP production.
- Insulin growth factor-1(IGF-1) increases glycosaminoglycan (GAG) and collagen synthesis.
- Bone morphogenetic proteins increase matrix Synthesis[36].

Catabolic

- Interleukin-I (IL-1) and tumor necrosis factor (TNFa) increase MMPs, inhibit GAG synthesis and can further potentiate the degenerative cascade.
- Oncostatin-M combines with IL-1 and TNF to promote matrix breakdown.
- Others like IL-17 and IL-18 increase expression of IL-1bð and IL-6 and increase MMP.
- NO (nitric oxide) is a major catabolic factor produced by chondrocytes in response to proinflammatory cytokines such as IL-I beta and TNF-alpha. NO can inhibit collagen and proteoglycan synthesis, can

activate MMPs and cause an oxidative injury as well as produce apoptosis leading to degradation of articular cartilage.

- Prostaglandins effects on chondrocytes metabolism are complex and include enhanced type II collagen synthesis, activation of MMPs, and promotion of apoptosis. In cartilage explants, IL-1beta induces COX-2 expression and PGE2 production coordinate with proteoglycan degradation. Moreover, COX-2 inhibition prevents IL-1beta induced proteoglycan degradation [37,38].

Treatment

OA is a progressive and degenerative condition, with unlikely regression and restoration of damaged structures. Thus, current management modalities are targeted towards symptom control unless the degree of severity dictates the necessity of surgical intervention with joint replacement. Currently, different guidelines have been developed by multiple academic and professional societies to standardize and recommend the available treatment options Among these, we can find the Osteoarthritis Research Society International (OARSI), American College of Rheumatology (ACR) and American Academy of Orthopedic Surgeons (AAOS)publications[39,40,41].

Non-pharmacological management

The aim of the management of OA is to control the painful signals originated from these joints, but even more, to improve functionality and quality of life. Non-pharmacological therapies should always be attempted as the first line of treatment for knee OA Inactivity and disuse are deleterious for the health of the knee joint, the absence of mechanical stimulation induces a more rapid cartilage degeneration due to cartilage softening thinning, decrease of glycosaminoglycan content, impaired joint mechanics and flexibility[42,43].Light-to-moderate physical activity provides multiple benefits to this patient population, besides the mechanical and functional improvements, they also offer a risk reduction of diabetes, cardiovascular events, falls, disability, and an improvement in mood, and self-efficacy. Exercise routines should be tailored to every patient's needs/tolerance and preferences, high impact activities should be avoided, and long-term adherence should be maximized to increase success[44,45].There are different exercise modalities shown to have a favorable effect on patients with knee OA, routines should be performed three times a week, and to assess response, the patient should complete at least 12 sessions.

Pharmacological management

The vast majority of OA patients are elderly and most of them will have multiple comorbidities. Hence, special attention should be paid to the possible interactions and adverse effects that systemic medications can induce in this population. Historically, cyclooxygenase inhibitors (acetaminophen and NSAIDs) have been the most commonly used medications. But given the gastrointestinal, renal, cardiac, and hematological adverse effects of these medications, their long-term use is limited. Acetaminophen has shown to be inferior to NSAIDs and not superior to placebo for pain control, leading to some guidelines to abstain to recommend it as an effective medical management strategy for moderate-to-severe OA[45].Topical NSAIDs have shown to be safer, with a comparable, or slightly inferior efficacy than systemic NSAIDs. Onshort follow-up studies, they have shown to be superior to placebo in controlling pain during the first week of treatment but failed to prove benefit after 2 weeks[46].Recently, more and more awareness has been raised regarding the consequences of the chronic use of opioids. Studies also keep providing evidence that opioids are not superior to NSAIDs to improve OA pain or WOMAC scores, and the risks of their use, clearly outweigh the benefits[47,48].If a patient is refractory to other treatments and the use of an opioid is considered, Tramadol, a serotonin and norepinephrine reuptake inhibitor with weak μ opioid receptor agonist properties, has shown some benefit in the treatment of severe and moderate OA. This medication, compared to other opioids, has slightly less risk for abuse potential and respiratory depression[49].Duloxetine is a serotonin and norepinephrine reuptake inhibitor approved by the US Food and Drug Administration (FDA) for treatment of diabetic peripheral neuropathy and fibromyalgia. Recent studies have revealed that when used for more than 10 weeks, this medication is better than placebo controlling pain and improving function in patients with OA[50].

Risk Factors

Knee OA is a multi-factorial disease. The cause of OA remains unknown, thought there is clear evidence for major risk factors, such as age, obesity, joint trauma, and heavy work load . The risk factors can be divided into systemic (for e.g. age, gender, genetics, and overweight) and local biomechanical factors, such as joint injury and malalignment, overweight, and muscle weakness. Abnormal mechanical loading in various sport activities or during heavy work may activate the biochemical cascade that leads to joint degeneration and pain, but also even in normal mechanical loading if the cartilage is impaired.

Aging is the most significant risk factor for knee OA . Knee OA is more common in obese subject than in subjects of normal weight. For example, obese women with body mass index (BMI) of 30- 35kg/m2 had a four times higher risk for knee OA than non-obese women [51]. The corresponding was 4.8 for men. Obesity is also a major risk factor for the incidence of bilateral knee OA, whereas local mechanical factors are more often associated with unilateral OA . The effect of obesity on OA has been thought to be mediated through the increased mechanical loading of the knee and hip. This would lead in cartilage damage in these weight-bearing joints. However, obesity is also associated with hand OA, which has given rise to the hypothesis that both mechanical and metabolic factors may mediate the effects of obesity on joints.

Joint injury increases the risk for knee OA. After knee injury, women had a three-fold and men a 5 to 6 fold risk for developing of knee OA, compared to healthy controls. Injuries to the anterior cruciate ligament associate most clearly with the incidence of knee OA (15-20%). As many as 50-70% of patients with complete anterior cruciate ligament rupture, accompanied by concomitant injuries to the meniscus or other ligaments, exhibit radiographic knee OA changes after 15-20 years[52].. Furthermore, at 10 to 20 years after anterior cruciate ligament or menisci injury, on average, half of those patients have symptomatic knee OA. Total meniscectomy after an isolated meniscus tear has been a significant risk factor for knee OA, the relative risk being 14.0 after 21 years. Partial meniscectomy can also contribute to the development of knee OA.

Heavy physical activity and occupational load are important risk factors for the incidence of knee OA. Heavy physical activity may increase the risk of especially among obese individuals. On the other hand, regular and moderate physical exercise has been shown to be associated with a decrease in the development of knee OA . However, most of the clinical or epidemiological studies have concluded that

jogging exercise at moderate intensity or recreational physical activity do not increase the risk for knee or hip OA, provided that the weight-bearing joints have not been injured. The increased risk for knee OA is also associated with those occupations that entail prolonged or repeated knee bending. The risk may be even higher in those activities containing both knee bending and mechanical loading .with respect to the other mechanical risk factors; knee malalignment has been reported to be associated with the development and progression of knee OA. Furthermore, the severity of malalignment can predict the decline in physical function Genetic factors also seem to account for the existence of knee OA to a degree ranging from 39-65% independently of the known environmental or demographic confounders. This suggests that the articular cartilage of some individuals is congenitally vulnerable to mechanical wear and tear. However, the prevention of OA is still a challenging task although there is a considerable body of evidence about the definite causal risk factors, such as obesity, joint injury and occupational load [54,55].

Regenerative medicine

Aiming to stop and revert the degeneration associated with OA, IA injections of autologous conditioned serum (ACS), platelet rich plasma (PRP), and mesenchymal stem cell (MSC) have been tested[56,57,58].Their mechanisms of action is reduction of inflammatory reactions mediated by cytokines, and the induction of anabolism and chondrocyte differentiation via growth factors and stem cells contained in it. These methods are promising and some studies have reported them to be safe, well tolerated and, in some cases, superior to IA placebo and HA in terms of pain relief and knee function [56,57,58]. This is still a developing field and more research is required in order to define and standardize the optimal retrieval, storage, and preparation methods of these products.

Clinical Findings

There are several signs in knee OA that can be identified during the clinical inspection. These include limping due to joint pain, decreased walking speed as well as reduced stride length and frequency. Squatting may have become difficult for a patient suffering from knee OA. The deformity of the knee joint is usually a sign for advanced knee OA. Clinically detectable varus or valgus instability in the knee joint is regarded as a late sign of the disease. Coarse crepitus is considered to indicate the loss of congruency of the joint [59].

Tenderness can be identified with palpation of the knee joint. Tenderness along the joint-line points to an intra-capsular origin for pain and point-tenderness away from the joint-line is indicative of a periarticular lesion. Reduced range of movement (ROM) easily measured with a goniometer is associated with physical impairment. The decreased ROM is mainly caused by osteophytes formation, remodeling, capsular thickening and can be accentuated by soft tissue swallowing. Muscle wasting and weakness are difficult to examine but can be present in knee OA. The classical signs of inflammation, such as heat, pain and effusion indicate synovitis in knee OA. Laboratory tests do not play any role in the diagnosis of knee OA but they can help in the differential diagnosis [59].

Laboratory Findings

A typical clinical presentation of OA does not require laboratory testing. The erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are usually normal. The full blood count is normal. Rheumatoid factor and antinuclear antibodies are usually negative. Note that these antibodies may be low positive and of no significance in elderly patients and in some chronic condition. Synovial fluid analysis usually indicates a low white cell count <2000ul.

Radiological Findings

The plain radiograph serves as the primary investigation in the diagnosis of knee OA, as well as in assessing the severity of the disease. The advantages of radiography are evident: it is cost-effective and relatively safe and its availability is excellent. However, the subjective pain and radiographic changes do not necessarily correlate with each other.

Typical radiographic features in knee OA include joint space narrowing, osteophytes, subchondral bone sclerosis, cyst formation, osteochondral bodies and bone deformity. Loss of cartilage is an early and cardinal feature of OA leading to joint space narrowing in plain radiographs [60]. The thickness of articular cartilage varies between individuals and joint surfaces [60]. Therefore, no reference values for thickness of joint space exist. The osteophytes are a hallmark of OA, these being formed at joint margins by endochondral ossification. They can be regarded as a repair attempt and indicate redistribution of abnormal joint loading. Cysts are also typical radiographic findings in OA and occur mainly within the areas of bony sclerosis at sites of increased pressure transmission. Disintegration of the joint surface in OA results in the formation of osteochondral fragments. As these fragments are released into the joint space, they appear characteristically with the other established features of OA

Manual Therapy

Taping

Taping the knee, in particular the patella is a physiotherapy treatment strategy recommended in the management of knee OA by some clinical guidelines. Knee taping involves the application of adhesive rigid strapping tape to the patella and/or associated soft tissue structures. The mechanism by which taping reduces pain is not clear, but my include changes in patellar alignment and enhanced function and activation of muscles.

Electrotherapy

Transcutaneous electrical nerve stimulation (TENS) is recommended in most guideline as safe adjunctive modalities for pain relief. Although, acupuncture may provide relief to some patients, there is less universal support for its use [61].

Therapeutic Exercises

In recent years, there have been numerous studies that have demonstrated the effectiveness of exercise and physical activity for individuals with knee osteoarthritis (OA). Although exercise and physical activity programs have been found to be beneficial the overall effects of this intervention have been found to yield small to moderate effects at best for individuals with knee OA. For example a systematic review of the effectiveness of exercise for reducing pain and improving disability.

Therapeutic exercise is a form of physical activity that is provided under the supervision of appropriate health professional for specific treatment goals. Regular physical activity is associated with lower mortality rates for both older and younger adults. Moreover, it is associated with a decreasing risk for a wide range of disease and conditions, such as cardiovascular disease, osteoporosis, falling, cancer, diabetes, blood pressure and osteoarthritis [62].

The main reasons for prescribing exercise in general include (1) achieving therapeutic goals, (2) improving general health and reducing secondary disability, and (3) modifying possible risk factors in disease progression. Minor summarized the potential benefits of physical activity and exercise on OA as follows:

1. Minimizes or slows the pathological process that takes place in the OA joint. Exercise increasing cartilage nutrition and remodeling, increases the synovial blood flow, decreases swelling, and improves muscle strength. Thus, the pathological effect of exercise may include slowing the cartilage degeneration process, decreasing bone stiffness, decreasing joint effusion and improving muscle strength.
2. Decreases impairments that occur from OA by reducing the main impairment factors. Exercise helps in decreasing pain, improving strength and endurance, and improving range of motion and connective tissue elasticity.
3. Decreases functional limitation by improving walking speed, gait and physical activity and decreasing depression and anxiety.

Because muscle weakness plays such an important role in development of OA, it is increasingly evident that exercise plays a critical role in the management of the condition. Although, activity avoidance by knee osteoarthritis patients is common, exercise is an effective non-pharmacological treatment for knee OA. The American College of Rheumatology (ACR) has approved regular exercise as a therapeutic approach for the management of knee OA. Systematic reviews of non-pharmacological interventions have documented the effectiveness of exercise in reducing pain and disability. Evidence suggests that stretching, strengthening and aerobic exercise decrease pain and improve muscular strength, functional ability and psychological well-being . Exercise increases muscle endurance, improves proprioceptive acuity and decrease arthrogenic muscle inhibition of the quadriceps. Quadriceps weakness is one of the most common and disabling impairments seen in individuals with knee osteoarthritis (OA). Sufficient quadriceps and hamstrings strength, both isometric and dynamic, is essential for undertaking basic activities of daily living such as standing and walking. Muscle strength testing has revealed that those with knee OA have a 25% to 45% loss of knee extension strength and a 19% to 25% loss of knee flexion strength, compared with similarly aged controls. There are 3 factors thought to contribute to knee extension and flexion weakness in those with knee OA: muscle atrophy, failure of voluntary muscle activity, and apparent weakness from increased antagonist muscle co-contraction [63,64].

Strengthening

Strengthening exercise is commonly recommended. Patients with knee OA tend to have reduced muscle strength as a consequence of reductions in physical activity and pain inhibition .The and have the greatest potential to generate and absorb forces at the knee. Many clinical studies have shown consistent improvements in knee extension strength after training, as well as reductions in pain and physical disability in people with knee OA.

Strengthening the hamstring muscle has been found to enhance the functional ability of the deficient knee . This is probably due to the fact that, which an overall increase in both the hamstring and quadriceps strength, and increase in the hamstring to quadriceps ratio (H:Q), anterior-lateral subluxation of the tibia may be minimized .

Stretching

Stretching should be carried out in conjunction with strengthening exercises. If a specific muscle group is restricted, more emphasis may be placed on these areas but there must be stretching of all the major muscle groups of the lower limb, because they all have an effect on the biomechanics of the knee. Patients should be instructed to hold a stretch for 20-30 seconds for it to be effective .Stretching includes the quadriceps, hamstring muscles, iliotibial band (ITB), and Achilles tendon. Tightness of the ITB can affect normal patella excursion. The distal ITB fibers blend with the superficial and deep fibers of the lateral retinaculum, and tightness in the ITB can contribute to lateral patellar tilt and excessive pressure on the lateral patella. Because the ITB is a very dense and fibrous tissue, the effectiveness of stretching is questionable [65,66].

Discussion

Osteoarthritis is a complex and multifactorial condition of the joints, affecting mainly the knees. Multiple hypotheses have been proposed but still there is not a clear etiology or understanding of its natural course. Based on those hypotheses, a wide variety of treatments have been developed and tested, some more successful than others, but ultimately all of them are aimed to decrease pain, increase function, and delay the necessity for a surgical joint replacement. All the current guidelines agree that water or land-based exercise should be attempted first for symptom control, slowly escalating towards the other therapies such as topical or oral medications. If they are not effective, then a patient can receive IA therapies, which seem to have a certain degree of benefit over the oral therapies with some contribution of the placebo effect. Among those therapies, one of the most studied has been IA CS, but it seems that the current data might not be clear given that efforts to elucidate the exact mechanism of action, analgesic efficacy, indication, and safety profile are still ongoing. Recent papers have not been able to provide a robust and clear answer on using IR CS by patients. Some authors have mentioned that the presence of joint effusion, synovial membrane thickness, high BMI, psychological factors, and knee tenderness could be an indicator, but there is no conclusive data on this[67].Perhaps white blood cells counts in the synovial fluid and low degree of radiographical changes on the KL score might be related to a better response, but it is not a definite answer. Part of the conflicting data is because of the high variability of the design of the studies that make them hard to be compared. Nowadays with the advancements in technology and ultrasound, we should aim to use this option whenever available to increase the rate of adequate IA placement of the injected substance. On October 2017, the FDA approved the extended-release presentation for TA contained in microspheres, called FX006, which theoretically, compared to IR CS, should provide a longer lasting pain relief and less adverse effects given the marked reduction on the serum levels of the CS. Some animal models also showed to be protective of the cartilage structure, and also some first studies have shown some adequate safety profile, but there are still doubts regarding its duration beyond 13 weeks. The truth is that this new presentation of an old medication will require more research to clarify some doubts regarding the indications and magnitude of the benefits of the IR option. But it seems that it might play a role if there is a concern of HPA axis suppression and hyperglycemia given its pharmacodynamics properties. The regenerative medicine field is developing other non- CS IA therapies, showing

promising results, but more knowledge and standardization of their therapies will be required [68].

Conclusion

Despite being one of the most studied and more prevalent conditions of our population, knee osteoarthritis still does not have a clear pathophysiology or a single most efficacious intervention to treat the symptoms and degeneration associated.

Exercises in early stages are a valuable therapy for these patients and it is recommended by all the medical societies. Other non-surgical treatments have variable efficacy and their success will depend on multiple variables (provider, equipment, patient) and their use has to be selected judiciously according to the specific clinical situation.

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