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Molecular Pathogenesis, Clinical Efficacy and Safety of Therapeutics Used in the Treatment of Osteoarthritis

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Authors' contributions

This work was carried out in collaboration among all authors. Author SS designed and supervised the study, Author AUK wrote the first draft of the manuscript, outline the protocol and performed the statistical analysis while Authors KMF and AUT managed the literature search and analyses of the study. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Osteoarthritis (OA) also known as degenerative joint disease, is the most common form of arthritis which affects all the tissues of the joint, including the cartilage, bone, ligaments, and muscles. It can develop in any number of joints, but most commonly affects the knees, hands, and hips. OA is characterized by progressive cartilage deterioration, subchondral bone remodeling, loss of joint space, marginal osteophytosis, and loss of joint function. The prevalence rate is estimated to about 242 million people in the world. OA results from the disruption of the balance between synthesis and degradation of extracellular matrix components by the chondrocyte in combination with increased uncompensated chondrocyte apoptosis. It is increasingly understood that ageing contributes to the development of osteoarthritis by working in conjunction with a variety of other factors, both intrinsic and extrinsic to the joint. Several abnormalities in components of the healthy

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joints such as meniscus, articular cartilage, subchondral bone and synovial membrane results to manifestation the disease. In an attempt to discover new emerging therapeutic target, certain diagnostic strategies are applied such as X-ray, Ultrasonography, Anthroscopy and Magnetic resonance imaging to have a deep insight on its effect and monitor the progression of the disease. Interestingly, many clinical researches proved efficacy of Therapeutics such as Adamulimab which block TNF-α and plays significant role in the pathogenesis of the disease, Diacerein which inhibit interleukin- 1 β, natural anti-inflammatory compound such as curcumin, bisphosphonate drugs such as alendronate and risedronate and anti-osteoporotic drugs such as strontium ranelate, chondroitin sulfate, intraarticular hyaluronic acids and glucosamine sulfate are reported to be effective and safe in the management of the disease.

Keywords: Osteoarthritis; degenerative joint disease; pathogenesis and therapeutics.

1. INTRODUCTION

Osteoarthritis (OA) also known as degenerative joint disease is the most common form of arthritis which affects all the tissues of the joint, including the cartilage, bone, ligaments, and muscles. It can develop in any number of joints, but most commonly affects the knees, hands, and hips [1]. OA typically occurs later in life, usually after age 50, although may start earlier in the case of joint injury but symptoms may vary in severity, whereby OA in its severe forms restricts mobility, interrupts sleep, and interferes with the sufferer's enjoyment of life [2].

The disease has precisely no cure. However, some of the therapeutics mainly aimed at reducing the pain, improving the joint function, and in some instances delay the progression of the disease [3]. OA occurs when the protective cartilage that cushions the ends of two opposing bones wears down over time, although the articular cartilage and subchondral bone often show the most prominent changes [4]. OA is primarily characterized by progressive cartilage deterioration, marginal osteophytosis, subchondral bone remodeling, loss of joint space, and ultimately loss of joint function [5].

OA is also characterized by a degeneration of articular cartilage whereby the breakdown leads to matrix fibrillation, fissure appearance, gross ulceration, and full thickness loss of the joint surface which is accompanied by hypertrophic changes of bone with osteophyte formation and subchondral bone plate thickening. At the early stage of the disease, there are changes in the synovial membrane together with an inflammatory reactions while at advanced stages, joint contractures, muscles atrophy and limb deformity are commonly observed [6].

2. MATERIALS AND METHODS

Using online databases, we conducted a literature review of Molecular pathogenesis and novel therapeutic potentials of osteoarthritis. The key articles used were retrieved predominantly from NCBI, Google Scholar, MEDLINE, UpToDate, using the terms 'Osteoarthritis, degenerative joint disease, Therapeutics of osteoarthritis as keywords for our search. We included scientific publications from 1st January 2010 to 15th December 2018 Articles focusing on clinical characteristics, epidemiology, symptoms, diagnosis and treatments for Osteoarthritis were eligible for selection.

3. EPIDEMIOLOGY OF OSTEOARTHRITIS

The prevalence of OA is break down based on different demographic criteria. The Age-related demographics shows that Primary osteoarthritis is mostly common in elderly and majority of the patients are often asymptomatic. Approximately 80-90% of individuals older than 65 years have evidence of radiographic primary osteoarthritis.

However looking at the gender variations women are at high risk of the infection than men, this also varies with age where as women older than 55 years have high prevalence rate. OA is a major cause of disability in older adults worldwide, according to World Health Organization (WHO) 9.6% of men and 18.0% of women aged 60 years and above has symptomatic osteoarthritis worldwide, this lead to restriction of movement in 80% of those with osteoarthritis and incapable of performing major daily activities of life in 20% of OA patients [7].

In the United States of America, Knee OA accounts for more than 80% of the disease's total burden and affects at least 19% of

American adults aged 45 years and older [8,9]. According to data produced by the Dutch Institute for Public Health, the prevalence of knee OA in individuals of 55 years and above is reported as 15.6% in men, 30.5% in women, and that of hips OA is 4.4% in men and 7.6% in women [10]. Recent study of individual's ≥60 years of age living in Spain documented a prevalence of 6.7% in men and 8.0% in women having OA [9]. A review of several investigations in Canada has reported the overall prevalence ranges between 7.5 and 14.7% [11].

In addition, the North and East regions of China had the lowest prevalence of symptomatic knee OA 5.4% and 5.5%, respectively, followed by the North-East 7.0%, South-Central 7.8%, and North-West 10.8% regions. Surprisingly, the prevalence was highest 13.7% in subjects living in the South-West region [12]. Furthermore, prevalence of 22% to 39% was reported in India; however it is more common in women than men, whereby approximately 45% of women over the age of 65 years have symptoms while 70% of those over 65 years show radiological evidence of OA [7].

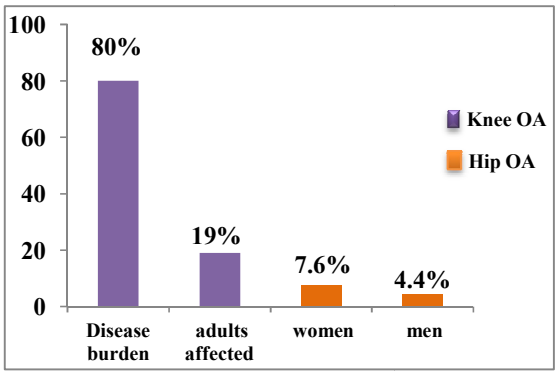

Fig. 1. Prevalence of OA in the united states of America showing the disease burden, adult infected, men and women [8,9]

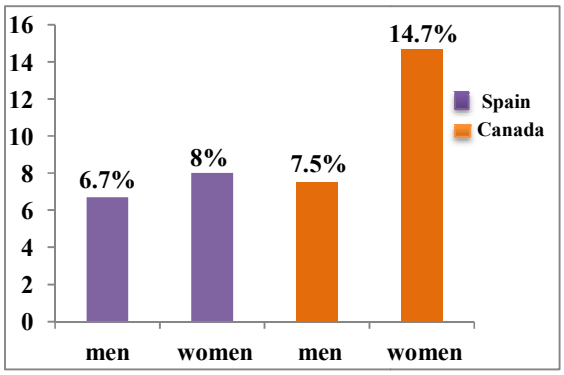

Fig. 2. Shows Spain and Canada infection rate in men and women [9,11]

Fig. 3. Shows overall prevalence rate for different region in china regardless of gender variation [12]

4. DEVELOPMENT OF OSTEOARTHRITIS

There is strong correlation between ageing and development of osteoarthritis where it is increasingly understood that ageing contributes to the development of osteoarthritis by working in conjunction with a variety of other factors, both intrinsic and extrinsic to the joint. It has become distinct that changes that results due to aging in the musculoskeletal system contribute to the development of osteoarthritis by working in conjunction with other factors, both intrinsic (e.g., alignment, overloading) and extrinsic (e.g., genetics) to the joint [13]. The primary changes with osteoarthritis occur in the articular cartilage, followed by associated changes in the subchondral bone [14].

Recently, more focus has been placed on the subchondral bone as the primary cause of symptomatic disease. Understanding of changes at early stages that lead to development of osteoarthritis is important, since these changes could still be reversible, and therefore, preventive treatment could be initiated to halt or reverse further progression of the disease. Biomechanical factors in OA play an important role in the health of diarthrodial joints. Altered joint loading associated to obesity, malalignment, trauma, or joint instability are most common critical risk factor for joint degeneration [15].

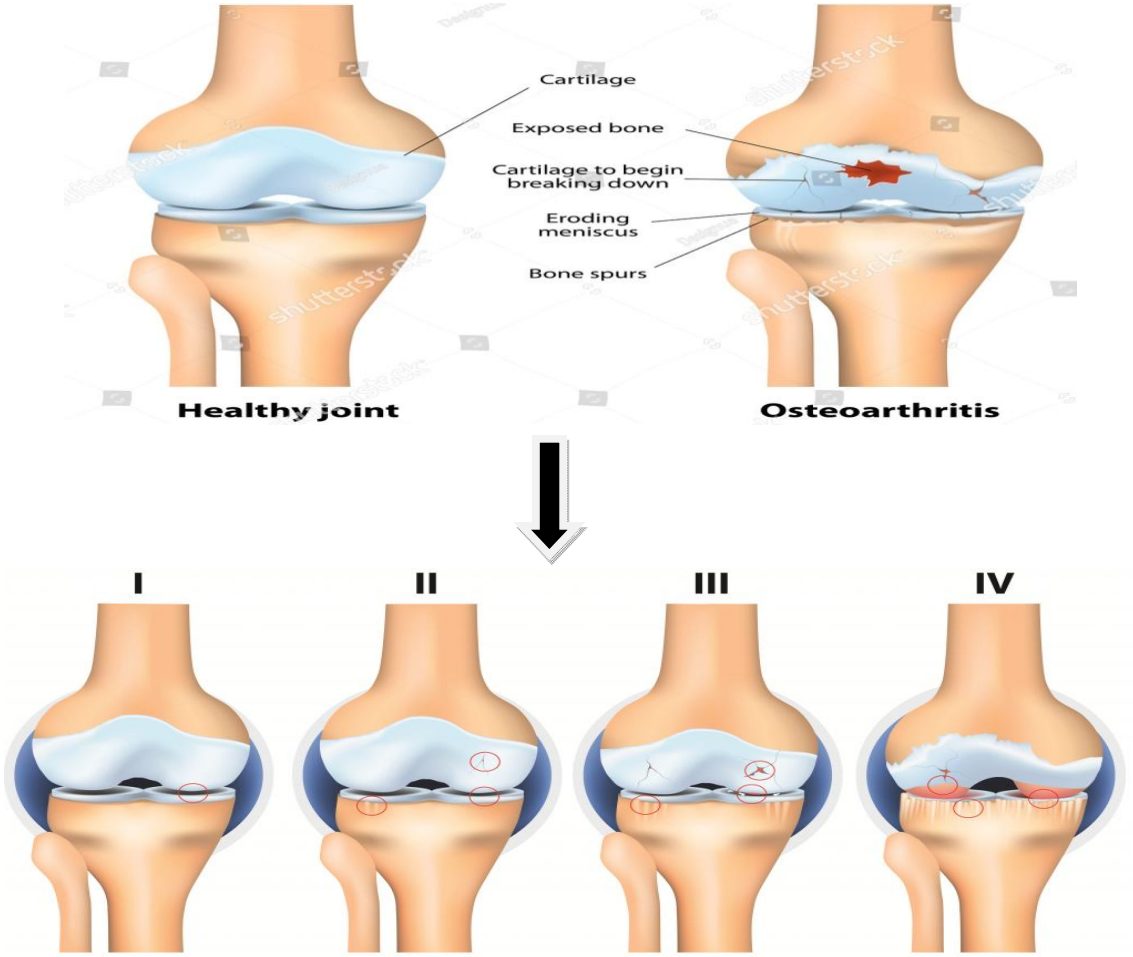

Fig. 4. Shows cartilage breakdown on healthy joint which progresses to several stages of OA development; stage 1 involves minimum disruption accompanied by 10% cartilage lost, Stage 2 involve joint space narrowing where cartilage breakdown begins and characterized by osteophytes formation, in Stage 3 there is moderate joint reduction where gaps in the cartilage expand until they reach bone and lastly stage four which involves 60% cartilage lost and is characterized by large osteophytes [16,17]

5. PATHOGENESIS OF OSTEOARTHRITIS

OA results from the disruption of the balance between synthesis and breakdown of extracellular matrix components by the chondrocyte in addition with increased uncompensated chondrocyte apoptosis [18]. In the young patient, the pathogenesis of knee osteoarthritis is predominantly related to an unfavorable biomechanical environment at the joint, which results in mechanical demand that exceeds the ability of a joint to repair and maintain itself thereby predisposing the articular cartilage to premature degeneration [19]. The pathophysiology of the process by which joint degeneration leads to the clinical syndrome of osteoarthritis remains poorly understood.

However OA mostly involves degeneration of cartilage, abnormal bone remodeling, osteophyte formation and joint inflammation [20]. In healthy joint several components facilitate the proper functioning of joints such as, meniscus (shock absorber) a fibrocartilage which disperse the weight of the body and reduce friction during movement and mainly composed of water, type I collagen, and proteoglycans in its extra cellular matrix [21].

The articular cartilage a hyaline cartilage which decreases friction and distributes loads and mainly composed of water, 90% type II collagen and proteoglycans in the matrix [22]. The subchondral bone which attenuates forces generated through locomotion, with the compact subchondral bone plate providing firm support to the joint and mainly composed of type I collagen. The synovium which produces synovial fluids that functions in reducing friction by lubricating the joint, absorbing shocks, supplying oxygen, nutrients and removing carbon dioxide and metabolic wastes from the chondrocytes within articular cartilage [23]. Synovial membrane composed of two synoviocytes; synovial fibroblast and synovial macrophages. The synovial fibroblast produces the extracellular matrix components of the synovial fluid and thus is important for cartilage integrity and lubrication of the joint, while the synovial macrophages remain relatively quiescent in the healthy joint; they become activated in the inflamed joint and, along with infiltrating monocytes/macrophages, regulate secretion of pro-inflammatory cytokines [24,25].

Several abnormalities such as Mechanical abrasion in the knee have been found to promote OA, which is mostly seen in the older age and can ultimately leads to the progressive degenerative changes in the proper functioning of the joints. Furthermore, the innate immune system plays a role in OA progression through the activation of both the complement and alternative pathways of inflammation, once activated; it leads to an inflammatory response that is a major driver of the disease [25].

6. DIAGNOSIS OF OSTEOARTHRITIS

- X-ray of affected joints will show a loss of the joint space. In more advanced cases, there may be bone spurs or evidence of worn-down ends of the bones in the affected joint [26].
- Magnetic resonance imaging (MRI) has a tomographic viewing perspective and thus provides cross-sectional images of the anatomy free of the projectional limitations of radiography, the technique is uniquely able to depict all the components of the joint, their pathologies, articular cartilage, meniscus, intraarticular ligaments, synovium, effusion, bone attrition, bone marrow lesions, subchondral cysts, and intra- and periarticular cystic lesions [27].
- Arthroscopy: Is a is a surgical procedure orthopedic surgeons use to visualize, diagnose, and treat problems inside a joint by inserting a narrow tube attached to a fiber-optic video camera through a small incision which gives a clear view of the pathological changes inside the joint [28].
- Ultrasonography is a modern ultrasound technique which uses high-frequency sound waves to produce images of internal organs and other tissue [29].

7. THERAPEUTIC TARGETS OF OSTEOARTHRITIS

7.1 TNF-α Blockers

TNF-α is an inflammatory cytokine produced by monocytes/macrophages during acute inflammation, it plays significant role in the pathogenesis of OA. Adalimumab is a human monoclonal antibody bioengineered to prevent the binding of TNF-α to its receptor and inhibit the progression of osteoarthritis. A 12-month randomised, double-blind, placebo-controlled trial evaluate subcutaneous administration of 40 mg adalimumab every two weeks in 60 patients with erosive hand OA, however the tolerability and safety profiles of adalimumab on those patients were very good and resulting to successful

neutralization of the TNFα there by slowing the progression of structural damage in erosive interphalangeal finger joint osteoarthritis [30]. Anti-TNF-α therapy with infliximab (a chimeric monoclonal antibody) was reported to yield effective treatment and reduce the incident of secondary OA via other pathways [31].

7.2 IL-1β Inhibitor

IL-1β also known as leukocytic pyrogen, is a key pathogenic factor in OA. Hence use of Diacerein which is an IL-1β inhibitor, reduces the number of IL-1 receptors, thereby resulting to reduction in functional IL-1 heterodimer receptor complexes and ultimately lowers the disease progression [32]. A study of a symptomatic slow-acting OA drug which accesses the primary outcome for 2 months after the end of a 3 month treatment period shows that diacerein is safe and has a significant effective for the treatment of knee OA [33]. Another study confirmed that symptomatic benefit provided by diacerein in terms of pain reduction is minimal; the small changes observed in the joint space narrowing is of questionable clinical relevance and was observed only for OA of the hip [34]. In vitro and experimental models showed a reduction in cartilage destruction with IL-1 by IL-1 receptor antagonists [35]. One of recent articles shows a possible benefit in using higher doses of Kineret (150-200 mg) in the treatment of osteoarthritis of large joints and suggest it alternativeness to IA steroid [36].

7.3 Curcumin

Clinical trials shows similar efficacy of curcuma formulation with NSAIDS and glucosamine for treatment of osteoporosis [37]. A multicenter study reveal the efficacy and safety of *Curcuma domestica* extracts in pain reduction and functional improvement and further shows it effectiveness, similar to that of ibuprofen [38]. The adjuvant therapy of curcumin with diclofenac has more potential and beneficial effect than individual effect of diclofenac alone [39]. A randomized, double-blind, placebo-controlled, prospective clinical study of a highly bioavailable form of curcumin (theracurmin) in patients with osteoarthritis reveal significant effect of the compound in deceasing pain and its potential in the treatment of human knee osteoarthritis in the future [40]. Meriva (a Curcumin-phosphatidylcholine Complex) is also referred as effective and safe agent for the complementary management of osteoarthritis, leading to better disease control, a decreased use of NSAIDs, and overall improvement in the quality of life [41]. Another study shows that formulation of 500 mg *Curcuma longa* and *Boswellia serrate extract* (CB) administered twice daily demonstrated a greater improvement in the treatment of OA than 100 mg of celecoxib administered twice a day in the scores for pain, walking distance and joint line tenderness. The CB formulation was equally effective as celecoxib in alleviating crepitus, and increasing the range of joint movements with no dose-related toxicity and ultimately the formulation was termed superior to celecoxib (NSAIDs) for the treatment of active OA [42].

7.4 Bisphosphonates

Bisphosphonates are a group of medicines that slow down or prevent bone loss, strengthening bones. They work by inhibiting osteoclasts which are responsible for breaking down and reabsorbing minerals such as calcium from bone. Meta-analysis showed that bisphosphonates therapy is effective in relieving pain and accelerating functional recovery for patients with OA [43]. In another clinical studies, administering alendronate sodium (a bisphosphonate drug) for patients with OA has clinical efficacy in reducing joint complications with significant structural improvement of the joints, and may delay and prevent further disease progression probably through inhibition of leptin activity [44]. Risedronate a bisphosphonate drug in comparison with placebo did not improve signs or symptoms of OA, nor did it alter progression of OA, only reduction in the level of marker of cartilage degradation was observed However sustained clinically relevant improvement in signs and symptoms was observed in all treatment and placebo groups [45]. In a one-year, placebo-controlled trial that included 59 patients with knee OA treated with zoledronic acid 5 mg intravenously as a single infusion, a significant reduction in visual analogue pain scores versus placebo was seen after six months [46].

7.5 Strontium Ranelate

Strontium ranelate (SR) is an anti-osteoporotic drug responsible for balance between bone resorption and bone formation [47]. Clinical trial reveals that treatment with 1 or 2 g of strontium ranelate per day is associated with significant structural changes in patients with knee osteoarthritis; furthermore, there is a beneficial effect on the symptoms specifically at dosage of 2 g/day [48]. Another study shows that dose of 1800 mg/kg/day of SR significantly attenuated

cartilage matrix and chondrocyte loss, and decreased chondrocyte apoptosis, in a medial meniscal tear model using Sprague–Dawley rats [49].

7.6 Chondroitin Sulfate

A 1 Year, Randomized, Double-Blind, Multicenter Clinical Study in Japan, shows that treatment with sodium chondroitin sulfate at a dose of 1560 mg/d is more effective than 260 mg/d more resultant to pain relief in patients with knee OA [50]. However, a 2-year multicentre exploratory study on efficacy of Chondroitin sulfate versus celecoxib on knee osteoarthritis structural changes concluded that chondroitin sulphate is more superior over celecoxib at reducing cartilage volume loss in knee OA patients [51]. Meta-analysis of randomized controlled trials demonstrated that oral chondroitin is more effective than placebo on relieving pain and improving physical function. Although glucosamine showed positive effect on stiffness outcome, further studies are requested to investigate the accurate effectiveness of both the two drugs [52].

7.7 Intra Articular Hyaluronic Acids

A Canadian evidence-based perspective demonstrated that treatment with Intra articular hyaluronic acids is well tolerated, with significantly improved pain, function and stiffness outcomes compared with placebo or noninterventional controls in patients with mild-to-moderate knee OA [53]. Multi-center open perspective study suggests the clinical efficacy of a single intra-articular injection of 3 mL intra-articular hyaluronic acid solution containing 75 mg high molecular weight (>2 MDa) native hyaluronic acid [54].

7.8 Glucosamine Sulfate

Evidence from a real life setting trials and surveys shows that different therapeutic effect are obtained with different formulation of glucosamine. Therefore, not all formulation of glucosamine should be afforded same level of recommendation [55]. Glucosamine supplements composed of different chemical components and have become a mainstay in management of OA due to their symptom-relieving effects, cost effectiveness, important structure-preserving and relatively non-toxic adverse effect profiles. However, researches are required to fully understand the concept [56].

8. CONCLUSION

Many studies on osteoarthritis gave more insight on the inflammatory processes, biochemical changes and abnormalities in some of the component of healthy joint. In this review we have highlighted clinical efficacy and safety of some therapeutics used in the treatment of OA. However, extensive clinical trials should be taken to critically elucidate the efficacy of the therapeutics.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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