Review Article

UNDERSTANDING THE ROLE OF INFLAMMATION IN SECONDARY OSTEOARTHRITIS

Abstract:

Osteoarthritis (OA) is the most seen form of arthritis, affecting a population of about 3.3 to 3.6% worldwide. In the ranking, it is the 11th most incapacitating disease worldwide, and in about a 43million people, it causes mild to severe disability. Estimated that 80% of the population In the United States over 65 years old have radiographic evidence of OA, although only 60-70% of this subset has symptoms. There were about 1 million hospitalizations for OA in 2011, with a cumulative cost of nearly $15 billion. This makes A the second most expensive disease seen in the United States. [1, 2] Secondary OA can affect older adults, and it could also affect younger people, usually those under 35 years of age.

Secondary OA has been regarded more as a mechanically-driven disease than an inflammatory disease. However, low-grade inflammation plays some part in cartilage degeneration and repair at many stages of arthropathy. In the past years, many published scientific papers on both animal models and human studies have indicated an increased role for both synovial inflammations and the activation of the membrane attack complexes of the complement system in the pathogenesis of secondary OA. There is also increasing evidence that significant risk factors for secondary OA have been linked with changes in systemic and local (at the articular cartilage chondrocyte level) cytokines and inflammatory mediators. However, it remains controversial whether or not the inflammatory mediators are primary or secondary regulators of the damage to the cartilage or defective repair mechanisms present in secondary Osteoarthritis because the pathways for signaling involved in

inflammatory and biomechanical stress are very much similar. So, these pathways could also induce and increase the expression of cytokine and chemokine genes.

Although research on the inflammatory mediators associated with Osteoarthritis has been done and much knowledge has been gained in the last decade, more studies are needed to define better the mechanisms by which these factors tip the balance between homeostasis and activation to promote cell death and matrix destruction. In response to stress and inflammatory insults, osteoarthritis chondrocytes produce a variety of matrix-degrading enzymes, including metalloproteinases and aggrecans. The expression of most of these enzymes of degradation is dysregulated in chondrocytes of patients with Osteoarthritis, and their increased activities and aberrant expression are the main contributors to cartilage degradation during osteoarthritis development and progression. [3] This student project aims to understand the role of inflammation in secondary Osteoarthritis.

INTRODUCTION

Osteoarthritis (OA) occurs when the protective cartilage that cushions the end of the bones is worn down over time. OA can damage any joint, but the disorder is most commonly associated with joints of the hips, knees, hands, and spine.

Osteoarthritis begins with the breakdown of the joint's cartilage. The bone ends may thicken and form spurs (bony growths). These abnormal bony growths interfere with the movement of the joint affected. Cartilage and bone's bit may float in the joint space, and cysts filled with fluid may form in the bone, leading to the joint's limited movement. Osteoarthritis can be categorized as primary or secondary. Primary Osteoarthritis has no known cause. Secondary Osteoarthritis is caused by another disease, inflammation, infection, deformity, or injury. Conditions leading to secondary OA include joint conditions at birth (congenital abnormalities), repeated joint surgery or trauma to a joint structure, metabolic disorders, and/or inflammatory arthritis. [1, 71]. Likewise, OA can be secondary to immunological diseases such as Rheumatoid arthritis (RA), Ankylosing spondylosis, Reactive arthritis, Psoriasis, Gout, Pseudogout, Ulcerative colitis, and mild inflammation of the soft tissues around the joints (synovitis). [3]

Clinical features of Osteoarthritis

Both types of OA, primary and secondary, involve the breakdown of joint cartilage, which causes bone-on-bone pain caused by the rubbing together of bones. The more commonly experienced symptom of OA is pain in the affected joints, especially after repetitive use. OA might not cause symptoms early on because its symptoms tend to occur slowly, affecting one or more joints in its progression.

In the past decades of teaching and medical practice, most patients with Osteoarthritis have subtle symptoms managed with local remedies and over-the-counter analgesics. Most patients aged 55 years, especially females, have lower limb manifestations. Males over 60years usually present with low back pain, which prompted the investigation of the patients for the possible presence of prostate cancer, multiple myeloma, bad egonomy, and metastatic tumor that could manifest as back pain. In some cases, when symptoms of OA appear, there is joint swelling (Bouchard's and Heberden's nodes). Pain that worsens with inactivity, tenderness or warmth in affected joints, difficulty moving affected joints, decreased muscle mass, cracking or grating of joints (crepitus), and joint stiffness.

Etiology and risk factors

Secondary OA risk factors include malaligned bones or abnormal joint structure, being over 50 years of age, multiple or recurrent bone fractures, overly using the same joints (which may happen as a result of specific occupations or sports), obesity (excess body weight can put extra stress on joints and increase inflammation), previous ligament or cartilage tear/or other joint injuries, muscle weakness, female, and family

history. Below are primary conditions that are major risk factors for developing secondary OA.

Joint Injuries

Multiple and recurrent bone fractures significantly increase an individual's chances of developing secondary OA and could also bring on the early onset of arthropathy in joints. This is most commonly seen in certain occupations where people repeatedly stress a group of joints. A person's place of work and the type of work they do has been shown to be significant risk factors for secondary Osteoarthritis.

Congenital Joint Deformities

Sometimes, an individual can be born with congenital abnormalities involving or affecting their bone. These could lead to abnormally formed joints vulnerable to early degeneration, injury, joint damage, or cartilage loss.

Congenital joint deformity, e.g., hip dysplasia, is an abnormal condition that makes the socket portion of the hip joint not totally cover the ball portion, resulting in an increased risk for joint dislocation. Because of this, the hip joint would either completely or partially dislocate.[4] Later in life, someone with hip dysplasia could develop severe hip osteoarthritis.

Autoimmune Inflammatory Arthritis

Autoimmune diseases occur when healthy tissues of the body are attacked by the immune system. Some autoimmune diseases can lead to inflammation in cartilage, which would eventually cause damage to joints and lead to Osteoarthritis. One of such autoimmune disease is rheumatoid arthritis (RA).

RA is most closely knitted with secondary OA. It is an autoimmune disease that can affect a person's joints and other body systems, like the blood vessels, skin, eyes, lungs, and heart. [5, 72, 73]

The connection between rheumatoid arthritis and secondary OA begins with inflammation of the soft tissue lining the joints (synovium) caused by RA. This would eventually cause a reduction in the joint's stability and damage the cartilage.[6]

Diseases of Cartilage or Bone

Any condition that affects the structure of bone or cartilage can trigger the onset of secondary Osteoarthritis. These would include but are not limited to; acromegaly, Onchronosis, and Paget's disease.

- ***Acromegaly*** causes a gradual increase in the hands, feet, head, face, head, and organs due to excessive secretion of human growth hormone. Problems of the bone and cartilage caused by acromegaly can result in inflammation and gradual degeneration, which may stimulate the onset of secondary Osteoarthritis.[4]
- ***Paget's disease*** is a condition that disrupts the normal formation of the bone; it makes bones weak and deformed with time. According to a study by the National Institutes of Health, Osteoarthritis is frequently seen in people with Paget's disease. [4,12] Paget's disease leads to secondary OA if the disease exerts stress on joints, changes the curvature of the spine, causes long bones to bend or bow,

changes bone shape, and softens the pelvis which would reduce joint stability of the hip.

Metabolic disorders

These are results of changes in the chemical reactions in the body that are meant to modify the normal metabolic process. A study by the Journal of orthopedics published in 2016 reported on an earlier published National Health and Nutrition Examination (NHANE) analysis, finding that 59% of the population has a metabolic disorder along with secondary OA. [7]

Examples of metabolic disorders leading to secondary OA include hypertension and diabetes mellitus (DM). It has been noted that hypertension causes OA by narrowing blood vessels and causing subchondral ischemia, which would lead to cartilage degradation [8,9]

DM is a chronic metabolic disorder associated with the body's inability to use or produce insulin, also called hypoglycemia [10,11]. Type 2 DM is a metabolic disorder associated with significantly increased glucose levels due to the body's resistance to insulin or a relative deficiency in insulin production [10, 11]. Disorders that affect glucose metabolism would lead to alterations in the extracellular matrix components of the connective tissue, affecting those tissues' cell function and leading to tissue damage, thereby favoring the development or progression of secondary OA. A study evaluated the ability of chondrocytes in extreme conditions of extracellular glucose (insufficient/excessive) to regulate their glucose transport capacity. It was observed that the normal chondrocytes could adjust to variations of extracellular glucose concentrations (modulating the glucose transporter 1 [GLUT-1] synthesis). However, osteoarthritic patients' chondrocytes were incapable of downregulating GLUT-1, which resulted in the build-up of glucose and increased production of the reactive oxygen species. The findings of this study may constitute a pathogenic mechanism by which conditions such as DM could promote degenerative changes that facilitate the progression of OA [10,13].

A study done by Georg Schett in 2010 had a cross-section in which patients with prevalent diabetes (n = 74) were more likely to have received a replacement of the knee and hip joint (implanted for alleviation of OA symptoms) than non-diabetic individuals (knee arthroplasty, intervention proportion 10.8 vs. 3.3%, P = 0.006; hip arthroplasty, intervention proportion 9.5 vs. 5.0%, P = 0.167). Several ancillary cross-sectional analyses were performed to highlight further the relationship between type 2 DM and secondary OA.[14] Evaluation of the clinical symptoms of OA by total WOMAC score, a validated patient-related measure of signs and symptoms of OA, showed significantly more severe OA symptoms in subjects with type 2 diabetes than in controls (Fig 1). Results were consistent in unadjusted (P = 0.034) and fully adjusted models (P = 0.030). [14] Moreover, WOMAC subscales for joint pain and function were lower (i.e., more pathologic in type 2 diabetic patients than controls) (P values from multivariable analyses 0.014 and 0.004; Fig 1). Finally, results were replicated when applying another validated score for quantifying clinical disease activity in OA, the KOOS questionnaire (pain score, P-value from multivariable analyses 0.001; Fig 1). [14]

	Participants without type 2 diabetes (n = 304)	Participants with type 2 diabetes (n = 43)	P value[a]	P value[b]
WOMAC and KOOS (n = 347)[c] [median (IQR)]				
KOOS Pain Score	97.2 (88.9–100)	91.7 (69.4–100)	0.001	0.001
KOOS Symptoms Score	96.4 (85.7–100)	89.3 (78.6–100)	0.211	0.160
WOMAC Pain	100 (90.0–100)	95.0 (77.5–100)	0.011	0.014
WOMAC Stiffness	100 (75.0–100)	100 (62.5–100)	0.495	0.603
WOMAC Function[d]	98.5 (90.9–100)	94.1 (79.4–100)	0.005	0.004
WOMAC Total Score	97.8 (89.6–100)	93.8 (79.2–100)	0.034	0.030
Joint ultrasonography (n = 438)[c]	n = 391	n = 47		
Effusion				
No [n (%)]	138 (35.3)	7 (14.9)	0.001	0.007
Unilateral [n (%)]	132 (33.8)	16 (34.0)		
Bilateral [n (%)]	121 (30.9)	24 (51.1)		
Synovitis				
No [n (%)]	209 (53.5)	13 (27.7)	< 0.001	0.004
Unilateral [n (%)]	112 (28.6)	17 (36.2)		
Bilateral [n (%)]	70 (17.9)	17 (36.2)		
Effusion and synovitis				
Neither criterion [n (%)]	133 (34.0)	6 (12.8)	< 0.001	0.003
All other [n (%)]	193 (49.4)	25 (53.2)		
Both criteria in both knees [n (%)]	65 (16.6)	16 (34.0)		
Synovitis Score [median (IQR)]	2 (0–4)	3 (0–6)	0.003	0.016

A total of 488 individuals participated in the 2010 follow-up exam, and a random subsample of 347 completed the KOOS questionnaire including the WOMAC Osteoarthritis Index. Specific subscores were calculated as follows: KOOS Activities of Daily Living Score, Pain Score, and Other Symptoms Score, WOMAC Pain Score, Stiffness Score, and Function Score. All scores were transformed to a scale of 0–100, with higher values indicating better function and fewer symptoms, respectively. Knee US was performed in a representative subsample of 443 individuals and focused on effusion and synovitis. A US synovitis score was calculated and had a range of 0–20. Five subjects with rheumatoid or psoriatic arthritis of the knee joints were excluded, leaving 438 for the current analysis. [a]P values from unadjusted analyses (t test and χ^2 test [for trend in case of more than two categories]/Fisher exact test). Clinical scores were $\log_e$-transformed for computation to approximate a normal distribution. [b]P values from adjusted analyses (general linear models and logistic regression analysis). Adjustment was performed for age, sex, BMI, social class, smoking, alcohol consumption, physical activity score, and levels of uric acid, creatinine, LDL cholesterol, $\log_e$-transformed hsCRP, and ferritin. Clinical scores were $\log_e$-transformed for computation to approximate a normal distribution. [c]Effusion and synovitis was coded present in case of previous arthroplasty due to severe OA. Supplementary analyses that exclude subjects with previous total knee replacement yielded virtually identical results. The target variable effusion and synovitis differentiates three categories: 1) neither effusion nor synovitis in both knees; 2) both effusion and synovitis in both knees; and 3) all other. [d]The WOMAC Function Score is identical to the KOOS Activities of Daily Living Score.

Fig 1: Cross-sectional association of type 2 diabetes with clinical scores (WOMAC Osteoarthritis Index and KOOS) and US measures of knee OA (Bruneck Study 2010)

Hemochromatosis is another metabolic condition that occurs due to too much iron in the body, and it could lead to secondary OA in common joints like the knees. It could also affect joints that are not commonly affected with primary OA, such as joints of the ankles, shoulders, or metacarpopharyngeal joints (MCP), which are the large knuckles of the hand [15]

PATHOLOGY OF SECONDARY OA

Secondary Osteoarthritis has long been considered predominantly, a non-inflammatory biomechanical degenerative pathology because systemic manifestations of inflammation and neutrophils are absent in the synovial fluid. [2] Hence, secondary Osteoarthritis has been chosen more preferably by many clinicians to make a point of the lack of primary inflammatory processes in this disease. However, periarticular and articular inflammation are prominent early features of secondary OA, and they are present at a point in the course of the disease in many patients with OA. The involvement of inflammatory components in secondary Osteoarthritis, which is marked by symptoms such as stiffness, swelling, and joint pain, is now widely recognized.

Putting the joint as a whole organ would provide a clinician with a complete understanding of secondary OA, i.e., everything, including the bone, the cartilage, the synovium, the menisci, the muscles, and the adipose tissues. The newest data on this topic indicates that all components of the joint, including the subchondral bone, menisci, cartilage, and synovium, play a part in the inflammatory process. The inflammation of the synovial membrane, also called synovitis, can occur in response to joint injury. However, an occurrence of synovitis could also be the predisposing event that initiates the development of secondary OA. Most often, an inflammation involving the subchondral bone, which is located underneath the cartilage, has been seen on MRI as cysts, bone marrow lesions, or bone bruises. It is important to note that the subchondral bone becomes thickened way before there is an evident loss of articular cartilage. Lining the cysts are inflammatory cells that release molecules into the joint space, which initiate the remodeling of the bone and the development of synovitis. Circularly, factors released from the synovium and bone can also promote joint cartilage degradation. Several proteins, including hyaluronic acid, fibronectin, and collagen, can stimulate and activate various inflammatory pathways, which would then lead to the initiation of the breakdown of cartilage and the onset of secondary OA. [4,59]

Chondrocytes could also mediate inflammation once they become damaged due to trauma or abnormal wear and tear. Some evidence shows that chondrocytes produce specific pro-inflammatory molecules that help initiate the low-level inflammation in Osteoarthritic joints. Chondrocytes are also susceptible to mechanical stress that may trigger a repair response. Stimulating this repair response is necessary; however, excessive or extended inflammation would lead to much more tissue damage. Anti-inflammatory agents help to protect the cartilage from further damage by inhibiting an excessive inflammatory response. [4]

The most common mechanism is that chondrocytes react in response to direct biomechanical disturbances by upregulating the production of inflammatory cytokines or increasing their synthetic activity. Expression is activated in response to a trauma to the bone or an injury; this leads to an

increased expression of stress-induced intracellular signals, cartilage-degrading proteinases, and inflammatory mediators. High impact injuries stimulate the release of reactive oxygen species (ROS) that upregulate MMP-13, ADAMTS-5, and TNF-α, activate stress-induced kinases and induce chondrocyte death. [16, 17]

Secondary OA inflammation differs significantly from the inflammation noted in a standard inflammatory joint disease like rheumatoid arthritis (RA). Secondary OA inflammation is categorized as an innate immune response, which typically comprises cells and mechanisms that defend us against infection by other organisms in a non-specific manner. [3, 4]

Studies show a part of the innate immune system called the complement pathway to be involved in secondary OA. The complement system has a biochemical cascade of the immune system that helps clear body pathogens and other toxic materials. It has been reported that the inflammatory pathways involved with secondary OA are activated in response to joint injury and the repair process which follows, rather than an infection. In contrast to the inflammation seen in RA, RA is specified to be an autoimmune response, in which the body attacks self-tissues; because of this, secondary OA has become the standard compared to other inflammatory arthropathies are made as though secondary OA is not an inflammatory disease. [4,7]

Fig 2: Radiographic knee showing joint deformity Secondary Heterogeneity of surrounding soft tissues (early phase). [18]

The activity of chemokines in the inflammatory process

Chemokines are proteins that act as chemo-attractants to assist cells in moving to sites of injury. Many of these chemokines have gained recognition in the development of secondary OA. A few of them, including their receptors, such as CCL19, CCL5, CCR2, CCR3, CCR5, CCR1, and IL-8, may prompt chondrocytes to manufacture MMP-3 when they bind to their ligands and enhance the breakdown of components in the cartilage matrix, which would precipitate the onset of secondary OA [19, 20]. A few chemokines may play a protective role in secondary OA, such as CXCL12 (also called stromal cell-derived factor-1), which has the main function of recruiting mesenchymal stem cells to the injured tissue encouraging the repair of the injured [17][20]. Some of the chemokines observed to be overexpressed in secondary OA (GROα/CXCL-1, IL-8/CXCL-8, MCP- 1/CCL-2, MIP-1β/CCL-4, MIP-1α/CCL-3, and RANTES/CCL-5) were found to be stimulated by IL-1β, whose production is increased in patients with secondary OA [20]. Levels of CXCL-10, also known as INF-γ- inducible protein 10 (IP-10),

in synovial fluid and plasma have been greatly associated with radiographic OA of the knee. A study comparing OA patients with healthy patients noted that CX3CL1, a fractalkine usually found in the serum, was increased in patients with OA. [21]

it has been observed that macrophages play a significant role in the inflammatory response of secondary OA. It has been reported that chemokine ligand-2 (CCL2), also called MCP-1, helps macrophages migrate into atherosclerotic lesions and adipose tissue [21]. MCP-1 and INF-γ levels in synovial fluid and serum have been linked with disability and self-reported pain in the knee of patients with OA. [22] [23] Also, it has been observed that in patients with severe knee OA, the levels of IP-10 and macrophage-derived chemokine (MDC) in synovial fluid were increased. In contrast, eosinophil chemotactic protein (eotaxin) levels were lower when compared with healthy patients.[24][25]

The activity of cytokines in the inflammatory process

The function chemokines play in the initiation and progression of secondary OA has been thoroughly deliberated. It has been found that they can stimulate inflammatory and tissue destructive responses and promote tissue repair. [22,73] Many cytokines were noted to have a part in the progression of secondary OA; these include IL-1β, IL-6, TNF, IL-18, IL-4, IL-15, IL-17, and IL-10. Their exact mechanism of action is yet to be wholly understood. It has been proposed that they inhibit anabolic processes and induce catabolic events, thereby influencing the hemostasis of the cartilage. [24]

IL-1β and TNF

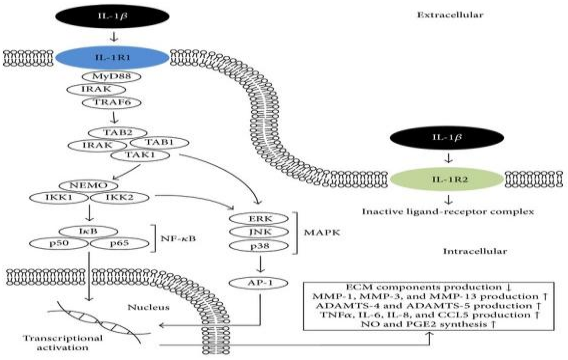

Fig 3: Schematic diagram showing cascades of cytokines interplay in the inflammatory process of Secondary OA

Interleukin (IL)-1β and Tumor necrosis factor (TNF) are the primary mediators in the pathophysiology of secondary OA. They are secreted by osteoblasts, immune cells (especially mononuclear cells), and chondrocytes. [25] It is important to note that these cytokines are elevated in osteoarthritic joints' membrane and synovial fluid. They drive the inflammatory cascade, and an increase in their expression induces catabolic events as they upregulate MMP, as shown in Fig 3/4. [25][26] IL-1β and TNF downregulate the production of major extracellular matrix (ECM) components by reducing the production of collagen type II and inhibiting the anabolic activities of the chondrocytes (Fig 4).[25][27]

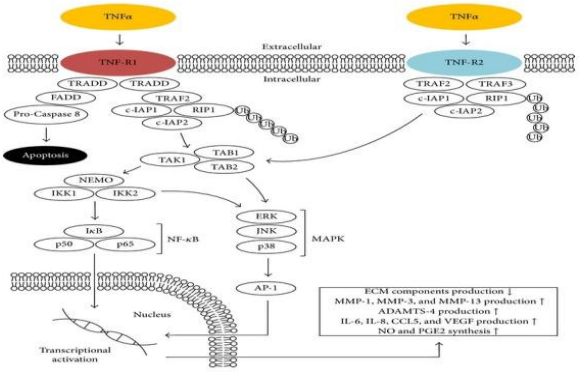

Fig 4: Schematic diagram showing cytokines interplay and ECM components production.

In secondary OA, TNF and IL-1β worsen the arthritic condition by inducing the production of pro-inflammatory cytokines, like monocyte chemo-attractant protein 1 and IL-8 and IL-6. It was also noted that chondrocytes that were treated with TNF and IL-1β increased the production of prostaglandin E2 (PGE2), nitric oxide (NO), and cyclooxygenase 2 (COX-2), which contributed to cartilage destruction and articular inflammation as they inhibited the upregulation of anabolic products such as proteoglycan and collagen, induced chondrocyte apoptosis and enhanced MMP activity.[27]

IL-17

Due to the inflammatory effects of IL-17, it has been observed to play a part in secondary OA [28]. IL-17 is majorly produced by mast cells, and CD4+ T cells, usually present in the cellular infiltrates seen in Osteoarthritic joints [29]. IL- 17 mainly targets fibroblast-like synoviocytes and chondrocytes within the joints, which express IL-17 receptor (IL- 17R) on their surface [30]. It was noted that IL-17 could increase the production of MMPs and inhibit the proteoglycan synthesis by chondrocytes [31]. Additionally, increased IL-17 in both synovial fluid and serum were shown to correlate with the radiographic lesions seen in secondary OA. [32]

The genetic relation between IL-17 and secondary OA has implied polymorphism in the gene IL-17A G-197A. This could be associated with susceptibility to develop secondary OA [33]. Also, a specific T cell lineage known as T helper 17 produces IL-17. These T helper cells can cause synovial membrane hypertrophy as their presence could lead to the formation of excessive blood vessels by influencing the secretion of vascular endothelial growth factor (VEGF) [34]. The T helper cells can affect cartilage indirectly by upregulating cytokines like IL-1β, TNF, IL-6, NO, and PGE2, which are responsible for the degradation of tissue (Fig 5). [35]

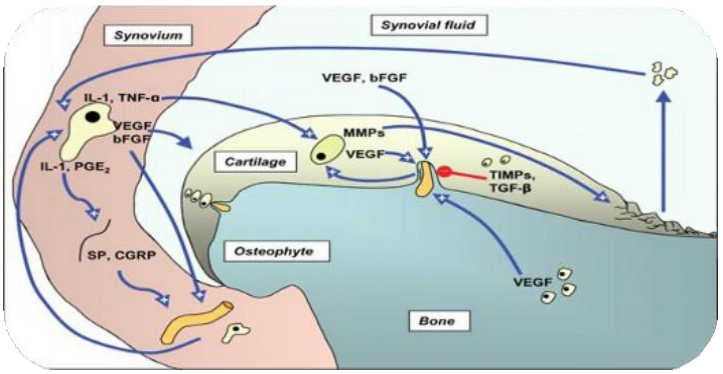

Fig 5: Synovial fluid pathway shown is the interplay of mediators of inflammation in secondary OA

IL-18

IL-18 (active form) comes from the activation of caspase-1 from pro-caspase-1, which is increased in the synovium and articular cartilage of secondary OA. IL-18 production is determined mainly by macrophages, osteoblasts, and chondrocytes [36]. This cytokine affects cartilage by stimulating excessive production of MMP- 13, -1, and -3 and enhancing the stimulation of IL-18Rα on the surface of the chondrocyte [36]. IL-18 inhibits proteoglycan, aggrecan, and type II collagen production and could cause morphological changes typically seen in apoptotic processes. [37, 38]

The high levels of IL-18 observed in cartilage, synovium, blood serum, and synovial fluid from patients with secondary OA have been shown to correlate with severe lesions observed in radiographic imaging [39]. Studies have associated lumbar disc degeneration and development of secondary OA with polymorphisms in the gene encoding numerous cytokines like IL-18 and its receptor (IL- 18R). [32, 61, 62]

Some anti-inflammatory cytokines play a role in the maintenance of secondary OA. IL-4 has been shown to have chondroprotective effects, and it has been reported

IL-4

to inhibit proteoglycan breakdown and reduce MMP production in articular cartilage [40]. Chondrocytes from osteoarthritic joints have been observed to have a decreased susceptibility to the protective effects of IL-4, thereby leaving the cartilage unprotected and hastening the degeneration of the cartilage through the action of pro-inflammatory cytokines that were listed above [41]. Additionally, polymorphisms in the gene encoding IL-4 and its receptor (IL-4Rα) could stimulate OA development in knee and hand joints [42,39]. It has also been observed that, compared to healthy patients, patients with secondary OA present with increased levels of soluble IL-4Rα (sIL-4Rα) [43].

IL-4 activation depends on the transduction of an intracellular signal by the gradual phosphorylation of IL-4Rα, which causes many pro-inflammatory genes to be expressed [44]. Production of IL-4 is majorly stimulated by T cells, especially T helper cell 2, which is usually present in cellular infiltrates seen in OA.[45] It has been noted that IL-4 on its own or combined with IL-10 can significantly downregulate the production of some other pro-inflammatory mediators, such as TNF-α receptors, IL-1β, COX-2, IL-6, and PGE2 [46,47,48]

IL-10

IL- 10 is also a cytokine that presents chondroprotective effects due to its anti-inflammatory features, and it has been associated with IFN release [49]. In vitro studies have reported that after the administration of IL-10 in chondrocytes, there was an increase in levels of proteoglycan and an increase in the synthesis of type II collagen [49]. IL-10 has protective effects, which could be due to a tissue inhibition of MMP-1 (TIMP-1) and enhancement of the production of the antagonist of IL-1β [50]. Additionally, IL-4, and IL-10, both reduce apoptosis in chondrocytes and MMP production [51,52].

Bone morphogenetic protein-6 and -2 (BMP6 and BMP2) expression are induced by IL-10; these proteins belong to the TGF- β family and are linked to chondrogenesis [53]. IL-10, along with BMP production, activates the signaling pathways, like SOX9/NKX-3.2. These pathways induce mesenchymal stem cells to differentiate into chondrocytes [54]. Also, IL-10 can weaken TNF-α effects on synovial fibroblasts by reducing TNF-α receptor expression. The same study also reported that IL-10 caused a decrease in the production of COX-2 [55].

Physical exercises can influence IL-10 secretion. Periarticular and synovial tissue was harvested from the knees of patients with OA and patients without OA before, during, and after they exercised for 3 hours. After the exercise, an increase in levels of IL-10 was observed in osteoarthritic patients. It is not clearly stated what mechanism created this result. However, the observed findings could be linked to pressure increase in intra-articulate areas and subsequent effects on cellular secretion [56,57].

Lipid mediators

The COX-2 enzyme produces lipid mediators, such as leukotrienes and Prostaglandin E2 (PGE2). These enzymes have been noted to be upregulated in osteoarthritic joints. Additionally, an increase in the production of TNF, IL-1β, and IL-6 through toll-like receptors has been associated with the overexpression of COX-2 in secondary OA [58].

PGE2 has been linked to apoptosis and the structural changes associated with arthritic diseases [59].

Leukotrienes are converted from arachidonic acid, which stimulates PGE2 production through the activity of the phospholipase A2 enzyme [60]. Leukotrienes, majorly leukotriene B4 (LTB4), are present in the synovium, cartilage, and bones of patients with secondary OA. Also, it has been shown that LTB4 stimulates the production of TNF and IL-1β in arthritic synovium [61,62].

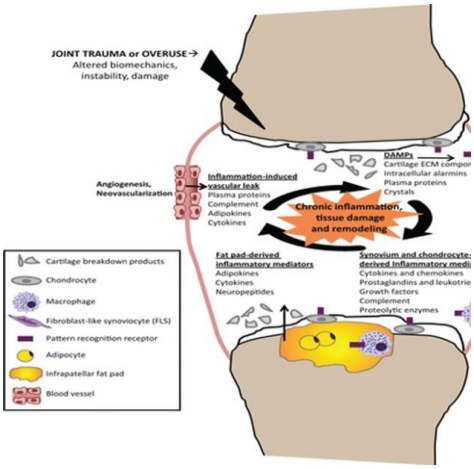

Fig 6: Schematic diagram the showing etiology of chronic inflammation in secondary OA

Apart from the roles of cytokines and chemokines concerning damage to the joint, non-injurious cyclical loading of sufficient magnitude can also inhibit IL-1-induced cartilage matrix degradation [63]. So, even in the absence of overt inflammation, chondrocytes may respond to mechanical stress by inducing inhibitors that serve as feedback modulators or by increasing the activities or expression of inflammatory mediators.

A few cases in which inflammation may be associated with the genesis or progression of secondary OA are listed below.

Obesity

The mechanical impact of obesity correlates with an increased risk of secondary OA. Studies on animals have shown evidence that body weight on its own may not be the only causative factor. If there are low levels of pro-inflammatory cytokines even though bodyweight is high, damage to the joint would be minimized. In studies done on humans, it has been observed that in obese individuals, there is an increased risk of disease in both weight-bearing and non-weight-bearing joints. [64,65] The link between secondary OA and obesity can be explained partly by increased levels of circulating pro-inflammatory cytokines, including those released from adipose tissue. Adipokines like visfatin, leptin, resistin, and adiponectin are cell-to-cell signaling proteins secreted by adipose tissue, and the roles they play in the development of secondary OA are starting to be more highlighted and made clear. [66,67]

Post-Joint Injury

Joint injury has been observed to lead to an increase in the production of catabolic cytokines and anabolic growth factors at the site of the lesion, which could lead to large regions of damage over time. Studies of a mouse model of joint destabilization have shown complement proteins to play an essential part in developing secondary OA. Various molecules have also been cited as possible influencers that help prevent cartilage damage post-injury damage, such as caspases, interleukin-1 (IL-1), reactive oxygen species, and tumor necrosis.

Factor. While animal data and in vitro studies that demonstrate the response of cartilage to the inhibition of these inflammatory mediators exist, only short-term studies with relatively few indicators of plausible long-term clinical outcomes have been done in humans. [68]

Aging

The figure below (Fig 7) shows the detailed risk factors for interacting with the aging process and secondary OA. Inflammatory mediators have been reported numerously as factors in the development of secondary OA, mostly noticed in the early stages. However, there are still questions on how these other risk factors can interact with the aging process in all the related tissues. There are so many mechanisms that initiate inflammatory responses that are also specific to aging joint tissues. These are crystal deposition, cellular senescence, deficiencies in cellular homeostasis mechanisms, and extensive post-translational modification of the extracellular matrix. [63,69]

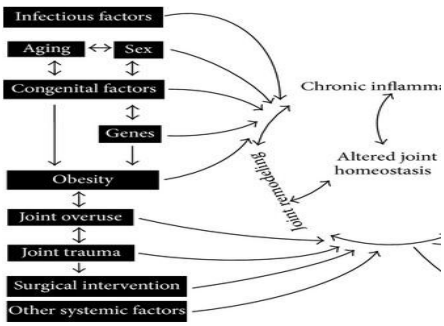

Fig 7: Diagram showing interactions of different risk factors on Secondary OA.

MANAGEMENT

The treatment methods for secondary OA typically begin with identifying the underlying factor that led to the onset of the disease, managing it, and getting it under control. Management begins with non-invasive therapies that are also simple, and these therapies usually involve a mix of the therapies depending on the type and location of joints (or joint) affected and other individual factors to be considered. Though not limited to the list below, the options include surgery, lifestyle modifications, and home remedies like surgical joint replacement, exercise, hot therapy, cold therapy, prescription drugs, and/or over-the-counter (OTC) pain medications.

The therapies/treatments listed above may work together or separately to alleviate the underlying inflammation and the symptoms of Osteoarthritis the patient may be experiencing; swelling, stiffness, joint pain, and sometimes immobility of the joint. Additionally, secondary osteoarthritis treatment aims to preserve joint function, improve quality of life, improve joint function, and minimize disability. [15][70][74]

Over-the-Counter (OTC) Pain Relievers

OTC medications like Tylenol (acetaminophen), commonly the first-line OTC pain reliever, can help relieve symptoms of OA. It is important to note that Tylenol does not help with inflammation, but it has potent effects in relieving pain, and its abuse can lead to liver damage.

Drugs that have both pain relief and anti-inflammatory functions are non-steroidal anti-inflammatory drugs (NSAIDS). These include naproxen, aspirin, and ibuprofen.

Abuse of these drugs can lead to various side effects like cardiovascular diseases, stomach problems, bleeding problems, and kidney or liver damage. However, using a topical NSAID (applied to the skin) would reduce the risk of side effects.[4]

Lifestyle modifications

OA symptoms can be controlled with basic lifestyle changes such as taking a rest when joints are swollen and hurting, using cold or hot therapy to relieve pain and swelling of joints, losing weight, staying active, and ceasing smoking. [4]

Steroids therapy

Steroid therapy with corticosteroids relieves pain and reduces swelling by reducing the inflammation in joints.

Physical Therapy

Physical therapy helps strengthen muscles, reduce joint pain and stiffness, increase the range of motion in joints, and improve gait and balance. Assistive devices such as braces, splints, a cane, or a walker can also be recommended. They can help manage OA by taking pressure off the injured joints, providing support for weakened joints, and reducing pain. [60]

Surgery

More severe cases of OA would need surgery to repair or replace damaged joints. Several types of surgery are available to patients who fit this category, including bone realignment, replacement of joints, arthroscopic surgery, and bone fusion. [15]

CONCLUSION

Osteoarthritis is the most common form of arthritis, but secondary Osteoarthritis is often underdiagnosed. It is largely involved in wearing down of the cartilage at the bone ends that commonly affects the hips, knees, hands, and joints of the spine, with primary having an unknown cause and secondary being the result of an initial condition or comorbidities like inflammation, repeated trauma, obesity deformity, injury, or infection.[71][72]

Symptoms of OA tend to occur slowly, or patients may initially be asymptomatic early into the disease course. Many risk factors for OA, with rheumatoid arthritis and Paget's disease, are commonly associated. Other factors include joint injuries, congenital joint deformities (i.e., hip dysplasia), acromegaly, and metabolic disorders. Furthermore, it has been a finding that many people of the population with OA, approximately 59%, also have a metabolic syndrome.

The pathogenesis of OA involves overexpression and mediation of pro-inflammatory cytokines in response to injury, with TNF and IL-18 considered the major cytokines that induce catabolic events and inhibit anabolic effects leading to MMP production that contributes to chondrocyte breakdown and apoptosis. However, evidence shows that certain cytokines have protective properties for the cartilage, such as IL-4, which can inhibit the cartilage degradation of the joints. IL-10 aids bone growth and CXCL12 recruits stem cells to the injured area to promote tissue repair. [71][72][73]

Management of OA starts with the management of the underlying cause. Simple, non-invasive therapies are first that include home remedies and lifestyle modifications before moving on to prescription drugs, over-the-counter medications, and surgical joint replacement. [74] These treatments may synergistically relieve OA symptoms and preserve or improve joint function, reduce dysfunction and improve the person's quality of life.

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