Review Article

UNDERSTANDING THE ROLE OF INFLAMMATION IN SECONDARY OSTEOARTHRITIS

Abstract:

Osteoarthritis (OA) is the most common form of arthritis and it affects about 3.3 to 3.6% of the population globally. It is the 11th most incapacitating disease worldwide causing moderate to severe disability in 43 million people. It is estimated that 80% of the population In the United States, over 65 years old have radiographic evidence of OA, although only 60% of this subset has symptoms. There were almost 1 million hospitalizations for OA in 2011, with an aggregate cost of nearly $15 billion, making it the second most expensive disease seen in the United States. [1,7] Secondary OA can affect old people and it also occurs in younger people, usually those under 35 years of age.

Secondary OA has been regarded as a more mechanically-driven disease rather than an inflammatory disease. However, it has been known for a while now that low-grade inflammation plays some role in the processes of cartilage degeneration and repair at many stages of arthropathy. In the past several years, many scientific papers have been published in both animal models and human studies indicating an increasingly important role for both inflammations of the synovium, and activation of the inflammatory complement system (the membrane attack complexes) in the pathogenesis of secondary OA. There is also increasing evidence that major risk factors for secondary OA are associated with alterations in systemic and local (at the articular cartilage chondrocyte level) cytokines and inflammatory mediators. However, it remains controversial whether inflammatory mediators are primary or secondary regulators of cartilage damage and defective repair mechanisms in secondary osteoarthritis because the pathways for signaling involved in inflammatory and biomechanical stress are similar. So, these pathways may also induce and amplify the expression of cytokine and chemokine genes.

Although research about inflammatory mediators in osteoarthritis has been done and much knowledge gained in the last decade, more studies are needed to better define 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 these degradative enzymes is dysregulated in osteoarthritis chondrocytes, and their increased and aberrant expression and activities are major 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 occurs when the protective cartilage that cushions the ends of the bones wears down over time. Although osteoarthritis can damage any joint, the disorder most commonly affects joints in your hips, knees, hands, and spine.

Osteoarthritis starts with the breakdown of cartilage in the joint. As the cartilage wears down, the bone ends may thicken and form spurs (bony growths). Bone spurs interfere with the movement of the joint affected. Bits of bone and cartilage may float in the joint space. Fluid-filled cysts may form in the bone and limit joint movement.

Osteoarthritis can be classified as primary or secondary. Primary osteoarthritis has no known cause. Secondary osteoarthritis is caused by another disease, inflammation, infection, deformity, or injury. Examples of conditions leading to secondary OA include repeated trauma or surgery to a joint structure, congenital abnormalities (joint conditions at birth), inflammatory arthritis, and metabolic disorders. [1,14]

Osteoarthritis Symptoms

Both primary and secondary OA involves the breakdown of joint cartilage, which causes bones to rub together, called bone-on-bone pain. The most common symptom caused by OA is a pain in the affected joints, especially after repetitive use.

Symptoms in OA tend to occur slowly and affect one or more joints. However, early on, OA might not cause symptoms.

When symptoms of OA do appear, you may experience joint swelling and stiffness, difficulty moving affected joints, pain that worsens with inactivity, Warmth, and tenderness in affected joints, loss of muscle mass, crepitus (grating or cracking sounds in the joints).

When osteoarthritis is secondary to a type of autoimmune arthritis, such as rheumatoid arthritis (RA), synovitis (mild inflammation of the soft tissues around the joints) is common.[3]

Risk factors

Secondary OA risk factors include: having an abnormal joint structure or unusually aligned bones, being over the age of 50 years, having had a bone fracture, overly using the same joints (which may happen as a result of certain occupations or sports), having obesity (excess body weight can put extra stress on joints and increase inflammation), having had a ligament or cartilage tear/or other joint injuries, having muscle weakness, being female, having a family member with OA

Causes

The following are primary conditions that are risk factors associated with secondary OA.

- Joint Injuries

Repetitive bone fractures increase a person’s chance of developing secondary OA and can also bring about the early onset of arthropathy. This is common in people who repeatedly stress one joint or a group of joints, such as in certain occupations. Occupation is a major risk factor for knee osteoarthritis, especially in jobs where repetitive knee bending is required.

- Congenital Joint Deformities

Sometimes, a person is born with abnormally formed joints—called congenital abnormalities—that are vulnerable to early degeneration, injury, and joint cartilage loss.

An example of a congenital joint deformity condition is congenital hip dysplasia. Hip dysplasia is an abnormality of the hip joint where the socket portion does not fully cover the ball portion, resulting in an increased risk for joint dislocation, causing the hip joint to become either partially or completely dislocated.[10] A person with hip dysplasia may develop severe osteoarthritis in their hip later in life.

- Autoimmune Inflammatory Arthritis

Some autoimmune diseases cause inflammation in cartilage, eventually damaging joints and leading to osteoarthritis. One such autoimmune disease is rheumatoid arthritis (RA).

Rheumatoid arthritis is most commonly associated with secondary OA. [20,35] RA is an autoimmune disease that can affect more than just a person's joints. In some people, it also affects other body systems, including the blood vessels, heart, eyes, lungs, and skin.

Rheumatoid arthritis occurs when the immune system mistakenly attacks its own body's healthy tissues. Its connection to secondary OA starts when RA causes inflammation to the synovium (the soft tissue lining the joints) eventually damaging the cartilage and reducing joint stability.[25]

- Diseases of Cartilage or Bone

Any number of conditions affecting the structure of cartilage or bone may trigger secondary osteoarthritis. This can include acromegaly and Paget's disease.

- **Acromegaly** causes excessive secretion of human growth hormone, resulting in a gradual increase in the hands, feet, head, face, and/or organs. Bone and cartilage problems from acromegaly can lead to inflammation and gradual degeneration and this may eventually result in secondary osteoarthritis.[10]
- **Paget's disease** is a condition disrupting normal bone formation, it causes bones to be weak and become deformed over time. According to the National Institutes of Health, people with Paget's disease frequently have osteoarthritis as well. [10,11] Paget's disease causes secondary OA if it places stress on the joints, changes the curvature of the spine, changes the shape of bones, causes long bones to bow and bend, and/or softens the pelvis, which reduces the stability of the hip joints.

- Metabolic disorders

Metabolic disorders are the result of abnormal chemical reactions in the body that modify the normal metabolic process. In 2016, a study was published in the Journal of Orthopaedics that reported on an earlier published National Health and Nutrition Examination (NHANE) analysis, finding that 59% of the population has metabolic syndrome along with OA.[12]

Examples of metabolic disorders associated with secondary OA include and hypertension. Hemochromatosis is another metabolic condition that occurs as a result of too much iron in the body and it can predispose a patient to secondary OA in common joints like the knees. It could also affect joints that are not commonly affected with primary OA, such as the large knuckles of the hand (MCP joints), shoulders, or ankles.[8]

Overview of secondary OA

Secondary osteoarthritis has long been considered to be predominantly a non-inflammatory biomechanical degenerative pathology because neutrophils are absent in the synovial fluid, as are systemic manifestations of inflammation. [2] Hence, the term secondary osteoarthritis has been preferred by some clinicians to emphasize the lack of a primary inflammatory process in this disease. However, articular and periarticular inflammation is an early and sometimes prominent feature of secondary OA and is present at some point in the disease course of the majority of patients with the disease. The involvement of inflammatory components in secondary osteoarthritis, which is marked by symptoms such as joint pain, swelling, and stiffness, is now well recognized.

A complete understanding of secondary OA requires the joint as a whole organ to be put into consideration i.e., the synovium, cartilage, bone, menisci, adipose tissue, and muscle. Emerging data suggests that all components of the joint, including the cartilage, synovium, menisci, and subchondral bone, participate in the inflammatory process. The development of synovitis (inflammation of the synovial membrane which lines the joints) may occur as a response to joint injury, but could also be the initiating event that leads to the development of OA. Inflammation of subchondral bone, located just below the cartilage, has been seen as bone bruises, bone marrow lesions, or cysts on MRI. In the development of OA, the subchondral bone becomes thickened, even before there is a loss of articular cartilage. The cysts are lined with inflammatory cells that release molecules into the joint space which drive bone remodeling and the development of synovitis. Circularly, factors released from the bone and synovium can also promote the degradation of joint cartilage. A variety of proteins, including fibronectin, hyaluronic acid, and collagen can activate and stimulate the inflammatory pathways, which can then set the stage for the initiation of cartilage breakdown and the onset of secondary OA. [10,33]

Inflammation may also be mediated by the chondrocytes once they become damaged due to abnormal wear and tear or trauma. There is some evidence that chondrocytes make specific pro-inflammatory molecules that help to initiate and perpetuate the low-level inflammation in the Osteoarthritic joint. Chondrocytes are also susceptible to mechanical stress which can trigger the repair response. Stimulation of this repair response is necessary; however, excessive or extended inflammation can also lead to more tissue damage. Anti-inflammatory agents may help protect the cartilage from further damage by inhibiting an excessive inflammatory response. [10]

The most often mechanism is that chondrocytes respond to direct biomechanical disturbances by increasing synthetic activity or by upregulating the production of inflammatory cytokines, which are also made by other joint tissues. In response to traumatic injury, gene expression is activated, which leads to an

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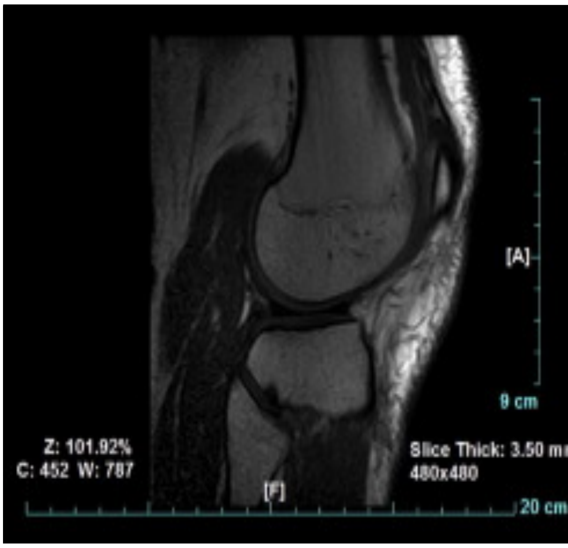
increased expression of cartilage-degrading proteinases, stress-induced intracellular signals, and inflammatory mediators. Impact injury stimulates the release of reactive oxygen species (ROS) that activates stress-induced kinases that upregulate MMP-13, ADAMTS-5, and TNF-α [4,5] and induce chondrocyte death.

Inflammation in secondary OA is very different from the inflammation seen in the standard inflammatory joint disease rheumatoid arthritis (RA). Inflammation in secondary OA is characterized as an innate immune response, typically comprised of the cells and mechanisms that defend us from infection by other organisms in a non-specific manner. [10,3]

Recent studies indicate that a part of the innate immune system called the complement pathway is involved in secondary OA. The complement system is a biochemical cascade of the immune system that helps the body clear pathogens and other toxic materials. It is thought that the inflammatory pathways in secondary OA are activated in response to joint injury and the repair process which follows, rather than an infection. In contrast, the inflammation in RA is characterized as an autoimmune response, in which the body attacks its tissues. Because of this, secondary OA has become the standard by which to compare other inflammatory arthropathies as if the secondary OA were not inflammatory. [10,12]



[13] Fig 1: Xray image

The activity of chemokines in the inflammatory process

Chemokines are small proteins that act as chemo-attractants to assist cells to migrate to injured tissue. Many chemokines have gained attention in the development of secondary OA. Some of them including their receptors, such as CCL19, CCL5, CCR2, CCR3, CCR5, CCR1, and IL-8, may induce the production of MMP-3 by chondrocytes and increase the breakdown of cartilage matrix components, which trigger the onset of secondary OA [52, 45]. However, some chemokines might present a protective role in secondary OA, such as stromal cell-derived factor-1 (also called CXCL12), whose main function is to recruit mesenchymal stem cells to the injured area in order to promote tissue repair.

Several chemokines were reported to be overexpressed in secondary OA, such as GROα/CXCL-1, IL-8/CXCL-8, MCP-1/CCL-2, MIP-1β/CCL-4, MIP-1α/CCL-3, and RANTES/CCL-5. Some of these chemokines are stimulated by IL-1β, which is upregulated in secondary OA, and they induce MMP production upon binding to their ligands, causing tissue degradation [45]. Levels of INF-γ-

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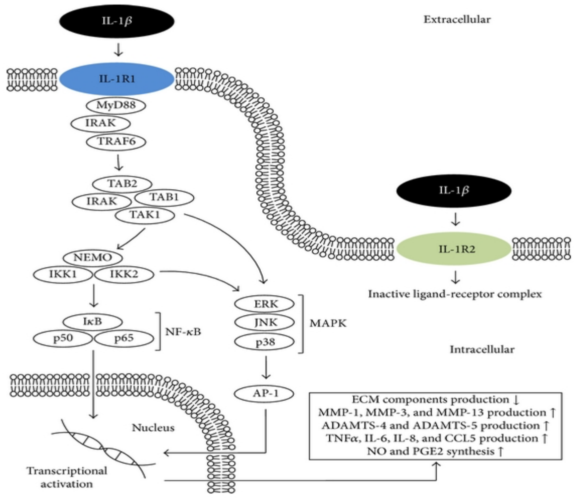
inducible protein 10 (IP-10), also called CXCL-10, in synovial fluid and plasma have been correlated with radiographic knee OA. CX3CL1, a serum fractalkine, has also been reported to be significantly elevated in severe knee OA in a study that compared OA patients with healthy patients.

The role of the macrophage in the inflammatory response has been observed in secondary OA. MCP-1, also known as chemokine ligand-2 (CCL2), has been reported to recruit macrophages into adipose tissue and atherosclerotic lesions [64]. Also, MCP-1 levels in both serum and synovial fluid have been associated with self-reported pain and disability in patients who present knee OA [53] In addition, it was observed that in severe knee OA, the levels of macrophage-derived chemokine (MDC) and IP-10 in synovial fluid were elevated, while eotaxin levels, an eosinophil chemotactic protein, were lower when compared with healthy patients.

The activity of cytokines in the inflammatory process

The role of cytokines in the initiation and progression of secondary OA has also been well studied. Cytokines can produce both pro-inflammatory and tissue destructive responses, but they can also promote the repair process in tissues. [72,34] Several cytokines have been noted to play a role in the progression of secondary OA, such as IL-1β, IL-6, TNF, IL-18, IL-4, IL-15, IL-17, and IL-10. Although their precise mechanism of action has not been completely highlighted yet, it has been proposed that their presence influences cartilage homeostasis as they inhibit anabolic processes as well as induce catabolic events.[17]

- IL-1β and TNF



[69] Fig 2:Cytokines in the inflammatory process

Tumour necrosis factor (TNF) and Interleukin (IL)-1β are considered the major mediators in the pathophysiology of secondary OA. They both are secreted not only by immune cells, especially mononuclear cells but also by osteoblasts and chondrocytes. In Osteoarthritic joints, these cytokines are increased in both the membrane and synovial fluid. They are known to drive the inflammatory cascade, and their increased expression induces catabolic events as they enhance MMP [39]. IL-1β and TNF downregulate the synthesis of major extracellular matrix (ECM) components by reducing type II collagen production and inhibiting anabolic activities of chondrocytes [40].

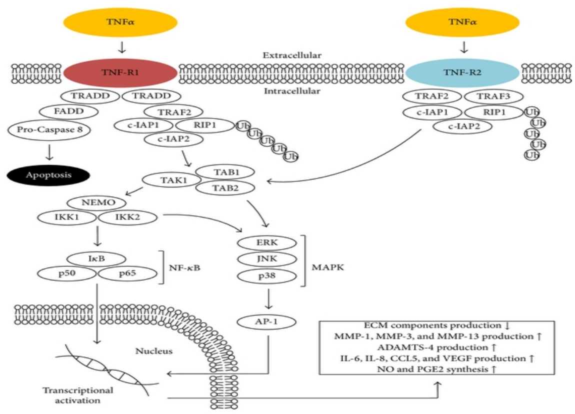


Fig 3: ECM components production

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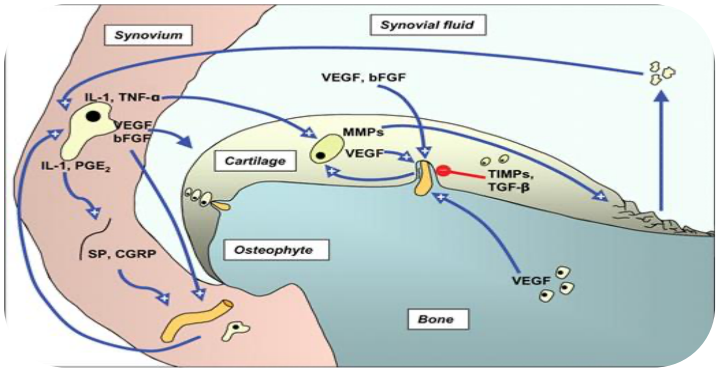
[69]

In secondary OA, IL-1β and TNF amplify the arthritic condition by inducing the production of proinflammatory cytokines, such as monocyte chemoattractant protein 1 and IL-6, and IL-8. In addition, chondrocytes treated with IL-1β and TNF increase the production of cyclooxygenase 2 (COX-2), nitric oxide (NO), and prostaglandin E2 (PGE2), which contribute to cartilage destruction and articular inflammation as they inhibit the production of anabolic products such as collagen and proteoglycan, enhance MMP activity and induce chondrocyte apoptosis.

- IL-17

IL-17 family, due to its inflammatory effects, has been implied to play a role in secondary OA [51]. IL-17 is mainly stimulated by mast cells and CD4+ T cells, which are present in the cellular infiltrates observed in Osteoarthritic joints [76]. IL-17 primarily targets chondrocytes and fibroblast-like synoviocytes within the joints, which express IL-17 receptor (IL-17R) on their surface [36]. It was reported that IL-17 can inhibit proteoglycan synthesis by chondrocytes and increase the production of MMPs [37]. Additionally, high levels of IL-17 in both synovial fluid and serum were correlated with radiographic lesions in secondary OA [38].

The genetic correlation between IL-17 and secondary OA has suggested: a polymorphism in the gene IL-17A G-197A could be associated with the susceptibility to the development of secondary OA [63]. Also, IL-17 is produced by a specific T cell lineage called T helper 17, and it can cause synovial membrane hypertrophy as its presence influences the secretion of vascular endothelial growth factor (VEGF), which leads to excessive blood vessel formation [71]. It can also indirectly affect cartilage by inducing the production of cytokines responsible for tissue degradation, such as IL-1β, TNF, IL-6, NO, and PGE2 [54]



[69] Fig 4:Synovial fluid pathway

- IL-18

The active form of IL-18 results from the activation of caspase-1, which has been noted to be elevated in articular cartilage and synovium of secondary OA, leading to the great promotion of IL-1β and IL-18. The production of IL-18 in joints is mainly determined by osteoblasts, chondrocytes, and macrophages [66]. IL-18 affects cartilage by upregulating the production of IL-18Rα on the chondrocyte surface and stimulates excessive production of MMP-1, -3, and -13 [65]. Also, IL-18 negatively influences the production of proteoglycans, aggrecan, and type II collagen and may cause morphological changes typically observed in apoptotic processes [41,42].

The increased concentration of IL-18 observed in cartilage, synovium, synovial fluid, and even blood serum from patients with secondary OA has been correlated with the severity of lesions seen in radiographic imaging [73]. Also, studies have correlated the development of secondary OA and lumbar disc degeneration with polymorphisms in the gene encoding IL-18 and its receptor (IL-18R) [61,62].

- IL-4

Anti-inflammatory cytokines also present a role in the maintenance of secondary OA. IL-4 is associated with chondroprotective effects as it is reported to reduce MMP production and, consequently, inhibit the breakdown of proteoglycans in the articular cartilage [56]. However, chondrocytes from OA joints have shown a decreased susceptibility to this IL-4 protective effect, leaving the cartilage unprotected, and quickening the degeneration via the action of the proinflammatory cytokines cited above [60]. Additionally, a polymorphism in the gene encoding IL-4 and its main receptor (IL-4Rα) could predetermine the development of OA in hand and knee joints [23,73]. It was also observed that, when compared with healthy patients, secondary OA patients present an elevated level of soluble IL-4Rα (sIL-4Rα) [67].

The activation of IL-4 depends on intracellular signal transduction by gradual phosphorylation of IL-4Rα, which leads to the expression of several pro-inflammatory genes [70]. IL-4 production is mainly determined by T cells, especially Th2, which are present in the cellular infiltrates observed in OA [55] It was noted that IL-4 alone or in combination with IL-10 can reduce the production of diverse proinflammatory mediators, such as IL-1β, TNF-α receptors, IL-6, PGE2, and COX-2 [48,49,50]

- IL-10

Due to its anti-inflammatory features, IL-10 is another cytokine that presents chondroprotective effects, and it is linked to the release of IFN [51]. In vitro studies have reported increased proteoglycan and type II collagen syntheses after the administration of IL-10 in chondrocytes [51]. The protective effects that IL-10 exhibits are likely due to a tissue inhibition of MMP-1 (TIMP-1) and stimulation of the synthesis of IL-1β antagonist [24]. Additionally, IL-4, as well as IL-10, reduces apoptotic events in chondrocytes and the production of MMP [57,58].

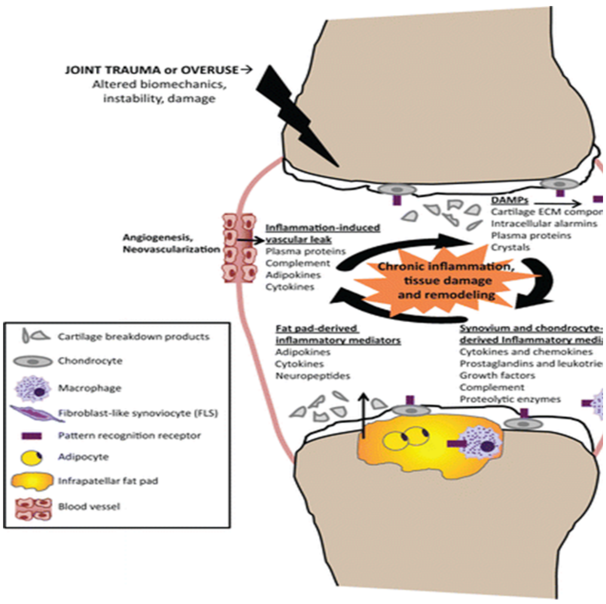
IL-10 induces the expression of bone morphogenetic protein-2 and -6 (BMP2 and BMP6), which are related to chondrogenesis as they belong to the TGF-β family [88]. Together with BMP production, IL-10 activates signalling pathways, such as NKX-3.2/SOX9, that induce the differentiation of mesenchymal stem cells into chondrocytes [46]. Also, by reducing the expression of TNF-α receptors, IL-10 can attenuate the effect of TNF-α on synovial fibroblasts. A decrease in COX-2 production was also reported in the same study [47].

The secretion of IL-10 can be influenced by physical exercises. Patients with and without OA had synovial fluid and periarticular tissue harvested from their knees before, during, and after they underwent exercise to practice for 3 hours. A significant increase in IL-10 levels was observed in these patients after the exercise. Although it is not clear what exact mechanism led to this result, this observation is likely attributed to an increase in intra-articular pressure and subsequent effects on cellular secretion [28,29].

- Lipid mediators

The COX-2 enzyme is responsible for the production of lipid mediators, including PGE2 and leukotrienes, and it is also upregulated in OA joints. In addition, the overexpression of COX-2 in secondary OA has been associated with the increased production of IL-1β, TNF, and IL-6 via toll-like receptor-4 (TLR-4) [59]. Besides assisting the production of MMPs and other functions already cited above, PGE2 is also involved in structural changes and apoptosis that characterize arthritic disease [33].

Leukotrienes have also been investigated for their role in OA. These mediators are converted from arachidonic acid, which also produces PGE2 via the activity of the enzyme phospholipase A2 [18]. Leukotrienes, mainly leukotriene B4 (LTB4), are present, to a lesser extent, in secondary OA synovium, cartilage, and bone. Also, LTB4 has been shown to stimulate the production of IL-1β and TNF in arthritic synovium [19,32].



[69] Fig 5: Chronic inflammation

Apart from the roles of cytokines and chemokines concerning damage of the joint, non-injurious cyclical loading of sufficient magnitude can also inhibit IL-1-induced cartilage matrix degradation [6]. So, even in the absence of overt inflammation, chondrocytes may respond to mechanical stress by inducing inhibitors that serve as feedback modulators or by stimulating the expression and/or activities of inflammatory mediators.

Several circumstances where inflammation may be involved in the genesis and/or progression of secondary OA are described below.

- Obesity

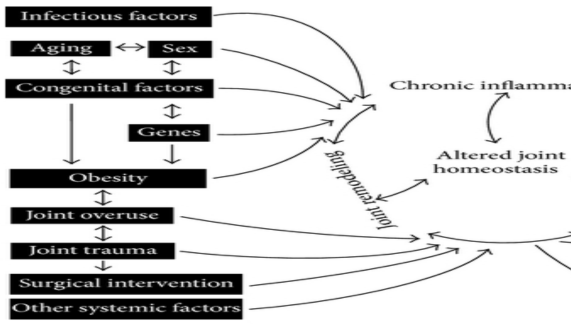
While the mechanical impact of obesity is associated with an increased risk of secondary OA, there is evidence from animal studies that body weight itself may not be the only causative factor. If bodyweight is high, but pro-inflammatory cytokines are low, joint damage is minimized. Also, human studies have shown that there is an increased risk of disease in both non-weight-bearing joints and weight-bearing joints of obese individuals. [80,81] The close link between obesity and secondary OA may be explained, in part, by the high levels of circulating pro-inflammatory cytokines, including those released from adipose tissue. Adipokines are cell-to-cell signalling proteins secreted by adipose tissue. The role of several adipokines, including visfatin, leptin, resistin, and adiponectin, in the development of secondary OA is beginning to be clarified. [83,85]

- Post-Joint Injury

Injury to the joint has been shown to result in the production of anabolic growth factors and catabolic cytokines at the site of the lesion, which over time can lead to broad regions of damage. Recently, complement protein has been shown to play a major role in the development of secondary OA in a mouse model of joint destabilization. Numerous other molecules have been suggested as possible targets to prevent cartilage damage post-injury, such as caspases, interleukin-1 (IL-1), reactive oxygen species, and tumour necrosis factor. While animal data and in vitro studies exist demonstrating the cartilage response to inhibition of these inflammatory mediators, only short-term studies have been carried out in humans, with relatively weak indicators of long-term clinical outcomes. [68]

- Aging

There are interactions between the described risk factors for secondary OA and the aging process. While inflammatory mediators have been implicated in secondary OA, particularly in the early stages of the disease, under the circumstances noted above, questions remain about how these other risk factors interact with the aging process in all the related tissues. Several mechanisms that initiate inflammatory responses, such as cellular senescence, extensive post-translational modification of the extracellular matrix, deficiencies in cellular homeostasis mechanisms, and crystal deposition, are specific to aging joint tissues. [6,7]



[69] Fig 6:Inflammatory mediators

Treatment

Treatment for secondary OA begins with managing the underlying cause and getting it under control. Treatment usually starts with simple and non-invasive therapies and is usually multi-faceted depending on the joint (or joints) affected and other individual factors. Options include (but aren't limited to) home remedies and lifestyle modifications such as hot or cold therapy and exercise; over-the-counter (OTC) pain medications or prescription drugs; and surgical joint replacement.

These treatments can work together to relieve the underlying inflammation and the symptoms of osteoarthritis—joint pain, stiffness, and swelling. Additionally, goals of secondary osteoarthritis treatment include preserving or improving joint function, minimizing disability, and improving quality of life. [8,9]

- Over-the-Counter Pain Relievers

Several types of OTC medications can help in relieving OA symptoms. Tylenol (acetaminophen) is an OTC pain reliever. While it can help reduce pain, it does not help with inflammation, and taking too much can cause liver damage.

Nonsteroidal anti-inflammatory drugs (NSAIDs) can help with multiple OA symptoms, including pain and inflammation. OTC NSAIDs include aspirin, ibuprofen, and naproxen.

They are known for a range of side effects such as stomach problems, bleeding problems, cardiovascular diseases, and liver or kidney damage. Using a topical NSAID (applied to the skin) may reduce the risk of side effects.[10]

- Lifestyle Changes

Many people can control OA symptoms with basic lifestyle changes. This can include using hot and cold therapy to relieve pain and swelling, losing weight, resting when joints are swollen and hurting, staying active, and not smoking. [10]

- Corticosteroids can help reduce inflammation, which improves pain and swelling.
- Physical Therapy

Physical therapy can be useful for managing OA as it can help with strengthening muscles, reducing joint pain and stiffness, increasing range of motion, and improving balance and gait. A physical therapist can also recommend assistive devices—such as braces, splints, a cane, or walker—to provide support for weakened joints, take the pressure off the injured joints, and reduce pain.[18]

- Surgery

Severe cases of OA may require surgery to replace or repair damaged joints. There are several surgery types, including bone realignment, joint replacement, arthroscopic surgery, and bone fusion.[8]

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