Online Journal of Biological Sciences

Literature Review

Correlation of Atherosclerosis and Osteoarthritis, the Role of Inflammation in the Pathogenesis of Osteoarthritis and Atherosclerosis

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Article history
Received: July 27, 2024
Revised: August 31, 2024
Accepted: September 05, 2024

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Abstract: Cardiovascular Diseases (CVD) rank among the leading causes of death globally, accounting for a substantial proportion of mortality rates and affecting millions of individuals. Risk factors such as ageing, obesity, diabetes and a sedentary lifestyle contribute significantly to the prevalence of CVD. Osteoarthritis (OA), on the other hand, is one of the most common joint disorders, affecting a large segment of the population, particularly the elderly. While OA is characterized by the degeneration of joint cartilage and underlying bone, leading to pain and functional impairment, it is not directly fatal. However, OA significantly diminishes quality of life and is increasingly recognized as a contributing risk factor for CVD, possibly due to shared mechanisms such as chronic Inflammation and metabolic dysregulation. Understanding the interplay between these two conditions is essential for improving patient management and outcomes, highlighting the urgency of interdisciplinary research in this area. This review aims to elucidate the relationship between atherosclerosis and Osteoarthritis, focusing on the roles of inflammatory processes, metabolic disruptions and cholesterol in the pathogenesis of both conditions. A comprehensive analysis of existing literature was conducted, synthesizing findings from epidemiological studies that explore the inflammatory linkages and metabolic pathways connecting OA and CVD. Our review highlights that chronic Inflammation, previously underappreciated in both diseases, plays a critical role in their development. Furthermore, emerging evidence suggests that dysregulated cholesterol metabolism aligns with the exacerbation of OA symptoms, potentially driving atherosclerotic pathways. The findings reveal a multidimensional relationship wherein OA susceptibility may heighten cardiovascular risk, underscoring the need for interdisciplinary approaches in prevention and management strategies aimed at these interconnected diseases.

Keywords: Cardiovascular Disease, Atherosclerosis, Osteoarthritis, Inflammation, Autoimmunity

Introduction

Cardiovascular Disease (CVD) is a leading cause of morbidity and mortality worldwide, influenced by factors such as ageing, genetic predisposition, lifestyle choices (e.g., tobacco use, high cholesterol diets) and physical activity levels. CVD encompasses various heart and vascular conditions, including coronary artery disease, angina, congenital heart defects and heart attacks, each with distinct etiologies and risk factors (Rodgers *et al*., 2019).

While CVD encompasses various heart and vascular conditions, the role of Osteoarthritis, often seen as a non-fatal ailment, reveals a deeper interplay that warrants further investigation. Recent studies highlight that OA is characterized by chronic low-grade Inflammation, which is relevant not only to joint health but also to cardiovascular risk. One significant but often overlooked contributor to CVD risk is Osteoarthritis (OA), a chronic degenerative joint disease. Previously regarded as a non-inflammatory condition, recent studies have revealed that chronic low-grade Inflammation characterizes OA throughout its progression. This Inflammation, while less acute than in other rheumatic diseases, can lead to significant tissue damage as a result of joint injury or overload, activating Damage-Associated Molecular Patterns (DAMPs) and inflammatory cytokines that contribute to cartilage degradation (Piva *et al*., 2015).

Approximately a quarter of the global population suffers from OA, which can stem from natural ageing, genetic factors, or joint injuries. Despite its prevalence, the interplay between OA and CVD remains insufficiently explored, warranting further investigation. Understanding their relationship is essential for improving diagnostic processes and treatment strategies (Hunter *et al*., 2008).

This review aims to integrate emerging evidence linking OA and CVD, emphasizing the roles of chronic Inflammation and metabolic dysregulation, particularly in cholesterol metabolism. By highlighting these shared mechanisms, this study seeks to inform interdisciplinary approaches to prevention and management, ultimately enhancing intervention efficacy for individuals affected by both conditions.

Previous research has explored various aspects of Osteoarthritis (OA) and Cardiovascular Disease (CVD) independently. For instance, studies have established that chronic Inflammation is a major driver of CVD, detailing its role in atherosclerosis and other heart-related conditions. However, these investigations often overlook the potential interactions between OA and CVD.

Several studies have linked OA to increased cardiovascular risk but typically focus on traditional CVD risk factors, such as obesity and diabetes, rather than exploring the underlying biological mechanisms connecting the two conditions. In particular, a 2008 meta-analysis found a correlation between radiographically evident OA and elevated cardiovascular events but did not delve into the inflammatory pathways or lipid metabolism that might explain this association.

Moreover, while the role of metabolic syndrome in OA has been documented, often emphasizing dyslipidemia's effects on joint health, limited research has examined how these metabolic disturbances may also influence cardiovascular risk.

Notable studies, such as those by Zhang *et al*. (2014) have highlighted an association between elevated systemic inflammatory markers and both OA severity and cardiovascular events. Yet, these works usually treat OA and CVD as isolated conditions rather than acknowledging their potential interdependency.

The present review distinguishes itself by providing a comprehensive exploration of the shared inflammatory and metabolic pathways between OA and CVD, emphasizing how dysregulated cholesterol metabolism specifically links the two. By synthesizing existing literature and addressing gaps regarding their combined effect on patient outcomes, this research aims to promote interdisciplinary approaches for effective management and highlight the need for integrated public health strategies. This underscores the novelty of our findings in the context of existing literature and the urgency for further interdisciplinary research in this critical area.

Methods

To explore the relationship between Osteoarthritis (OA) and Cardiovascular Diseases (CVD), we conducted a comprehensive literature review utilizing several key databases, including PubMed, Scopus and Google Scholar. The search strategy employed relevant keywords such as "osteoarthritis," "cardiovascular diseases," "inflammation," "cholesterol metabolism," and "metabolic syndrome," alongside Boolean operators to refine results.

Inclusion and exclusion criteria: Studies were included if they focused on the association between OA and CVD, specifically addressing mechanisms of Inflammation, metabolic pathways and any role of cholesterol dysregulation. Both clinical studies and epidemiological data published in peer-reviewed journals were considered. We excluded studies that solely addressed OA or CVD in isolation without examining their interrelationship. Articles not available in English or those focused on animal models without human implications were also excluded.

Data extraction and synthesis: Data was extracted from selected studies regarding the methodologies used, key findings and conclusions drawn about the interplay between OA and CVD. Findings were categorized according to themes, including the role of chronic Inflammation, metabolic dysregulation and specific inflammatory markers linked to both conditions. A systematic approach was applied to synthesize results, identifying recurring patterns and gaps in the existing literature.

Quality assessment: The quality of the included studies was assessed using established criteria, such as the Newcastle-Ottawa Scale for observational studies. This

assessment ensured that only high-quality evidence was integrated into the review, providing a reliable foundation for our conclusions.

To illustrate the research methodology employed in this study, we present a flow diagram that outlines the sequence of steps involved in our research process.

Biology and Metabolism of the Osteoarthritis Joint

The human body features three primary types of joints: Fibrous, cartilaginous and synovial. While fibrous and cartilaginous joints permit minimal to no movement, synovial joints provide a wide range of motion (Sanchez-Lopez *et al*., 2022).

Among these, synovial joints are the most frequently encountered in human anatomy. They are characterized by a synovial capsule that encases the joint and contains synovial fluid, which serves as a lubricant to minimize friction between the bones during motion (Kurowska-Stolarska & Alivernini, 2022).

Inside the synovial capsule, several key structures contribute to the joint's functionality. These include articular cartilage, which offers a smooth surface for bone movement; a synovial membrane that lines the capsule and produces synovial fluid; and subchondral bone, which lies beneath the articular cartilage. This subchondral layer is typically more robust than the surrounding bone, playing a critical role in the overall health and function of the joint (Tamer, 2013).

Articular cartilage, a crucial element of synovial joints, consists mainly of collagen and proteoglycans. Understanding the metabolism of these components is essential, as their degradation plays a central role in the development of Osteoarthritis (OA) and its associated inflammatory responses. This type of cartilage is a sophisticated tissue composed of various biochemical elements that work together to provide a low-friction, load-bearing surface for joints. The matrix contains three primary types of substances: Collagen proteins, non-collagen proteins and various glycoproteins (Eschweiler *et al*., 2021).

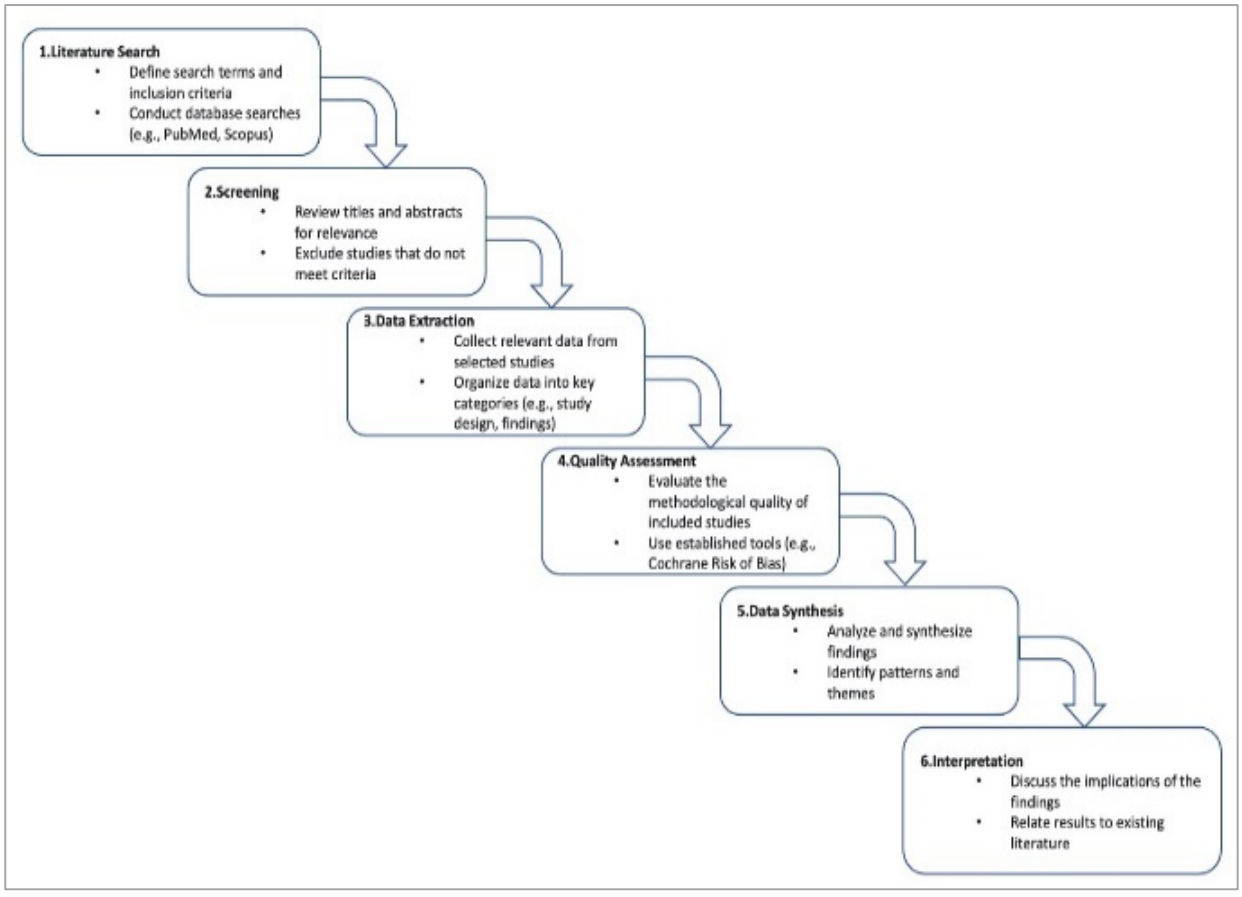

Fig. 1: Research Process Flowchart

Cartilage also comprises several proteases and hyaluronidases. Matrix metalloproteinases (MMPs) are the main proteases involved in breaking down extracellular matrix components, such as collagen and proteoglycans, during matrix turnover. Key MMPs identified in cartilage include MMP-3, MMP-8, MMP-9, MMP-13, along with aggrecanase-4 and aggrecanase-5. To counterbalance these effects, tissue inhibitors of metalloproteinases (TIMPs) help prevent excessive degradation of the extracellular matrix (Tokuhara *et al*., 2019).

The interaction among these components is crucial for effectively functioning articular cartilage. Collagen fibres provide structural support, while proteoglycans, including aggrecan, help resist compressive forces. Other glycoproteins, such as COMP and PRELP, also contribute to the tissue's mechanical properties (Han *et al*., 2011). The presence and activity of proteases and hyaluronidases, including MMPs, are necessary for the proper turnover of the extracellular matrix, which is regulated by TIMPs (Niland *et al*., 2021).

Osteoarthritis is characterized by the degradation of articular cartilage due to changes in the composition and structure of the matrix. This condition involves a decrease in proteoglycan concentration, particularly aggrecan, leading to reduced water content and impaired lubrication properties of the cartilage. The levels and activity of matrix metalloproteinases (MMPs) also increase, intensifying the degradation of collagen and other matrix components (Roughley & Mort, 2014). The most prominent MMPs involved in osteoarthritis progression include MMP-3, MMP-8, MMP-9 and MMP-13, as well as aggrecanase-4 and aggrecanase-5. Elevated MMP activity often surpasses the protective effects of Tissue Inhibitors of Metalloproteinase (TIMPs), resulting in further matrix degradation. Consequently, the cartilage becomes thinner, more brittle and less capable of shock absorption, which leads to pain, stiffness and decreased joint function in Osteoarthritis (Luchian *et al*., 2022).

As the cartilage matrix breaks down, chondrocytes responsible for cartilage production and maintenance become activated and start releasing inflammatory cytokines and chemokines such as IL-1β and TNF-α. These cytokines stimulate the production of MMPs and aggrecanases, perpetuating a cycle of cartilage degradation and Inflammation (Molnar *et al*., 2021).

Additionally, another factor contributing to cartilage degradation in Osteoarthritis is the imbalance between anabolic and catabolic signals in chondrocytes. Anabolic signals, mediated by insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β), foster the synthesis and maintenance of the cartilage matrix. However, in Osteoarthritis, elevated catabolic signals such as those from IL-1β and TNF-α disrupt this balance, leading to increased matrix degradation (Shi *et al*., 2019; McClurg *et al*., 2021).

These changes are thought to represent a compensatory response from chondrocytes attempting to restore the matrix to its normal components. The aberrant behaviour of chondrocytes in Osteoarthritis is evidenced by the emergence of fibrils, matrix depletion, cell accumulation and changes in the quantity, distribution, or composition of matrix proteins. Evidence of phenotypic modulation includes the presence of collagens not typically found in adult articular cartilage, such as the hypertrophic chondrocyte marker, collagen type X and other differentiation genes, indicating a reversion to developmental programs (Danalache *et al*., 2019). In the later stages of Osteoarthritis, the dysregulation of catabolic and anabolic enzymes and cytokines leads to softening, fibrillation, ulceration and progressive loss of articular cartilage. Catabolic mediators like metalloproteinases, ADAMTS and various interleukins (IL-1β, IL-17, IL-18) increase cartilage degradation while inhibiting the synthesis of metalloproteinase inhibitors like TIMPs (Boehme & Rolauffs, 2018). Degradation fragments from proteins such as fibronectin and type II collagen may also contribute to cartilage breakdown. Conversely, anabolic mediators like TGF-β, IGF-1, Fibroblast Growth Factors (FGFs) and Bone Morphogenetic Proteins (BMPs) promote cartilage synthesis and repair. While growth factors such as TGF-β, BMPs, IGF-1 and basic FGF can enhance chondrocyte proliferation and extracellular matrix synthesis, the regenerative capacity of cartilage is quite limited, making the repair of damaged cartilage a challenging process (Mariani *et al*., 2014).

Metabolic Activity of Articular Cartilage

The metabolic functions of articular cartilage are primarily carried out by chondrocytes, which are the sole cell types found within this tissue. Chondrocytes play a crucial role in the synthesis and maintenance of the extracellular matrix (ECM), which is composed of water, proteoglycans and collagen fibres. Proteoglycans, such as aggrecan, contribute to the cartilage's high water retention and its ability to withstand compressive forces, while collagen fibres impart tensile strength to the overall structure (Vincent *et al*., 2022).

Chondrocytes mainly derive energy from glucose through anaerobic glycolysis to meet their ATP requirements. In addition to glucose, they metabolize other molecules like amino acids and fatty acids, which are important for protein synthesis and membrane production, respectively. Chondrocytes also produce lactate as a glycolytic byproduct, which can be converted back into glucose through the Cori cycle (Su *et al*., 2022).

Furthermore, they generate important metabolites such as glycosaminoglycans, which are significant components of the cartilage extracellular matrix, along with various proteoglycans (Silva *et al*., 2019).

Recent research suggests a connection between chondrocyte metabolic activity and metabolic syndrome, indicating that the components of this syndrome are linked to a heightened risk of developing Osteoarthritis (Konstari *et al*., 2021).

Studies indicate that individuals with metabolic syndrome are more susceptible to Osteoarthritis, particularly in weight-bearing joints like the knees and hips. This increased risk may result from the higher mechanical stress on these joints caused by excess body weight, leading to expedited degradation of articular cartilage (Sun *et al*., 2021).

Additionally, dyslipidemia, a frequent aspect of metabolic syndrome, may also play a role in the onset of Osteoarthritis. Elevated levels of Low-Density Lipoprotein (LDL) cholesterol and triglycerides have been associated with a higher risk of Osteoarthritis, likely due to their impact on Inflammation and oxidative stress (Xiong *et al*., 2020).

Stiffening and degradation of cartilage are key features of Osteoarthritis. Chondrocytes (Cartilage Cells) may be exposed to various factors contributing to cartilage degradation, including cholesterol molecules, oxidized LDL (oxLDL), glucose, Reactive Oxygen Species (ROS), Advanced Glycation End-Products (AGEs) and lipopolysaccharides (LPS) from the bacteria of microbiome. These factors lead to the development of oxidative stress, Inflammation and dyslipidemia, as evidenced by increased matrix-degrading enzymes, proinflammatory cytokines secretion (IL-1B, IL-6, TNF-A) and a decrease in paraoxonase and arylesterase activities. The involvement of Toll-Like Receptors (TLR) and the reduction in the expression of cholesterol efflux genes (ABCA1, ApoA1, LXR) further exacerbate cartilage damage.

Association Between AS and OA

Numerous studies have explored the possible link between atherosclerosis and Osteoarthritis, given that both conditions are characterized by chronic low-grade Inflammation. For instance, a 2008 study that utilized data from the Rotterdam Study, a comprehensive prospective cohort investigation, revealed that participants with radiographic signs of Osteoarthritis faced a greater risk of developing cardiovascular diseases and experiencing increased mortality, even when controlling for conventional cardiovascular risk factors (Naranjo *et al*., 2008).

In another investigation conducted in 2013, researchers examined the connection between atherosclerosis and Osteoarthritis in the hand joints of postmenopausal women. The findings indicated that those with more advanced atherosclerosis were more likely to also have Osteoarthritis in their hand joints, which suggests a possible relationship between the two conditions (Koutroumpas *et al*., 2013).

Additionally, a systematic review and meta-analysis demonstrated a positive correlation between Osteoarthritis and atherosclerosis, showing a higher occurrence of atherosclerosis in individuals diagnosed with Osteoarthritis compared to those without (Macêdo *et al*., 2022).

Possible Ways of Cholesterol Involvement in the Pathogenesis of OA

Cholesterol may play a role in the development of Osteoarthritis (OA) through several potential mechanisms. Firstly, as previously noted, cholesterol can promote Inflammation in various tissues, including articular cartilage. In vitro studies have demonstrated that when chondrocytes are exposed to cholesterol, there is an increase in the production of proinflammatory cytokines such as interleukin-1 beta (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α). The release of these cytokines can initiate a series of events that contribute to cartilage degradation (Terkawi *et al*., 2022).

Secondly, particularly in relation to metabolic syndrome, research suggests that abnormalities in cholesterol metabolism may be linked to the onset of OA. For instance, dyslipidemia, characterized by elevated levels of Low-Density Lipoprotein (LDL) cholesterol and triglycerides, along with decreased levels of High-Density Lipoprotein (HDL) cholesterol, has been correlated with a higher risk of developing OA. Furthermore, studies indicate that genes associated with cholesterol metabolism show different expression patterns in osteoarthritic cartilage compared to healthy cartilage (Yanai and Yoshida, 2021).

Triglycerides, High-Density Lipoproteins and Osteoarthritis

Alterations in lipid metabolism are recognized as crucial factors in the progression of Osteoarthritis (OA). Studies have indicated that changes in the subchondral environment occur prior to the manifestation of OA, and lipid abnormalities may serve as indicators for the development of bone marrow lesions in women who have not previously experienced OA (Papathanasiou *et al*., 2021). In those with OA, the expression levels of genes involved in the process of cholesterol efflux, such as ATP-binding cassette transporter A1 (ABCA1), Apo lipoprotein A1 (ApoA1) and Liver X Receptors (LXR), are found to be lower than in healthy cartilage. When OA chondrocytes are

treated with the LXR agonist TO-901317, there is an increase in the expression of ApoA1 and ABCA1, which promotes cholesterol efflux and reduces intracellular lipid accumulation (Tsezou *et al*., 2010). These observations imply that the diminished expression of cholesterol efflux regulatory genes is significant in OA pathogenesis, and the use of LXR agonists might offer a promising therapeutic avenue for OA management. Furthermore, reduced paraoxonase and arylesterase activities in OA patients, along with lower high-density lipoprotein levels, may indicate heightened oxidative stress, potentially leading to atherosclerosis (Tsezou *et al*., 2010). Oxidative stress is also considered a factor affecting chondrocyte survival, as elevated amounts of 4-hydroxynonenal (HNE) have been associated with increased expression of Fas/CD95 and p53, a process that can be mitigated by the antioxidant N-acetyl-cysteine (Vaillancourt *et al*., 2008).

LDL Receptor 1 and Oxidation of LDL in the Pathogenesis of AS

An imbalance of cholesterol inflow and outflow in tissues is one of the main factors in the development of atherosclerosis. Cholesterol transport is provided by cell surface receptors, including CD36 and ABCA1. CD36, which also interacts with a number of ligands, is recognized as a binding and internalizing factor in oxLDL. It is also a regulatory scavenger receptor during oxLDL uptake and recognizes lipid molecules in oxLDL. Ox-LDL can lead to endothelial dysfunction when injected into the blood vessel walls (Poznyak *et al*., 2021).

The LDL receptor 1 (LOX-1), derived from cultured bovine vascular endothelial cells, is a type II membrane protein with a long C-terminal extracellular domain and a short N-terminal cytosolic domain. It is structurally distinct from the CD36 and CD68 receptors. The potential role of LOX-1 in thermogenesis is not yet known, but it is suggested that the uptake of oxy-LDL via this receptor is involved in endothelial dysfunction in the pathogenesis of atherosclerosis (Yoshimoto *et al*., 2011).

Fat Metabolism

The process involves the absorption of lipids from the bloodstream into cells, where they are broken down into smaller units, including fatty acids and glycerol. These components are subsequently transported to the mitochondria, where they undergo oxidation to generate energy in the form of ATP (Alves-Bezerra & Cohen, 2017).

Recent studies suggest that lipid imbalances may be significant in the onset of both Osteoarthritis and atherosclerosis. Specifically, changes in the subchondral environment appear to occur prior to the onset of osteoarthritis and lipid dysregulation, which may predict the emergence of bone marrow lesions in women who have not previously experienced the condition. Additionally, the expression of genes responsible for cholesterol efflux is diminished in osteoarthritic cartilage compared to healthy cartilage, indicating that inadequate expression of these genes could be a key contributor to the progression of Osteoarthritis (Haubruck *et al*., 2021).

In osteoarthritis patients, reduced paraoxonase and arylesterase activity, along with lower levels of High-Density Lipoprotein (HDL), may indicate increased oxidative stress. This condition may exacerbate the risk of atherosclerosis by making lipid peroxidation more likely. Moreover, higher concentrations of 4-Hydroxynonenal (HNE) can stimulate the expression of Fas/CD95 and p53 in chondrocytes, an effect that can be countered by antioxidants. Low-density lipoprotein (LDL) particles are absorbed by peripheral tissues, including adipose tissue, through receptor-mediated endocytosis (Ertürk *et al.,* 2012). Within adipocytes, cholesterol is esterified and stored in lipid droplets, while excess fatty acids are also converted into triglycerides for storage. In relation to Osteoarthritis, LDL may facilitate the formation of lipid droplets and fatty infiltration within articular cartilage, contributing to cartilage damage and Inflammation (Thiriet, 2019).

The Innate Immune System

The innate immune system is essential in the advancement of both Osteoarthritis (OA) and Atherosclerosis (AS). Toll-like receptors (TLRs), a type of receptor within the innate immune system, are vital for detecting and responding to harmful substances. In the case of OA, TLRs are found on chondrocytes, synovial cells and cells in the subchondral bone, where they identify and react to Damage-Associated Molecular Patterns (DAMPs) released by injured tissues (Barreto *et al*., 2020). The activation of TLRs triggers the production of proinflammatory cytokines and enzymes that degrade the extracellular matrix, contributing to cartilage breakdown and the progression of OA.

Similarly, in AS, TLRs are present in vascular cells, including endothelial and smooth muscle cells, where they recognize Danger-Associated Molecular Patterns (DAMPs) like oxidized low-density lipoprotein (oxLDL). When activated by oxLDL, TLRs induce the release of proinflammatory cytokines, chemokines and adhesion molecules, promoting the recruitment of monocytes to the arterial wall and the development of atherosclerotic plaques (Blagov *et al*., 2023).

Low-density lipoprotein (LDL) is a significant factor in atherosclerosis, as it can be oxidized and subsequently taken up by macrophages within the arterial wall, resulting in the formation of foam cells and the development of plaques. Additionally, oxidized LDL activates TLRs on vascular cells, further stimulating the

release of proinflammatory cytokines and attracting immune cells to the arterial wall (Blagov *et al*., 2023).

Changes in Collagenous Properties/Ages

The reduction in estrogen levels in women after menopause is linked to alterations in the collagen structure of several tissues, including cartilage, blood vessel walls, bone, skin, muscles and ligaments. These alterations can weaken muscles and ligaments, leading to decreased joint stability, which may contribute to the development of Osteoarthritis (OA). Furthermore, postmenopausal women tend to exhibit heightened cartilage turnover, resulting in compromised cartilage quality. The deterioration of vascular wall integrity can also trigger plaque formation, which may become unstable due to a weakened fibrous cap surrounding the plaque (Chidi-Ogbolu & Baar, 2019; Peshkova *et al*., 2022).

Advanced Glycation End-products (AGEs) arise from nonenzymatic modifications of proteins and lipids due to glucose, which accumulate in the serum and extracellular matrix. These AGEs can alter cross-linking, modifying the mechanical properties of tissues. While the specific role of AGEs in Ankylosing Spondylitis (AS) remains somewhat ambiguous, a connection has been established. AGEs are also implicated in the destabilization of atherosclerotic plaques (Perrone *et al*., 2020). Circulating AGEs exert proinflammatory effects that may further exacerbate Cardiovascular Disease (CVD) by binding to the receptor RAGE. The accumulation of AGEs in cartilage can cause stiffening and disrupt normal metabolism, potentially affecting the process of OA. The mechanism behind cartilage stiffening is illustrated in Fig. (2). Research using a mouse model of post-traumatic OA indicates that targeting cross-linking can influence the progression of OA (He *et al*., 2022). Although levels of pentosidine, a specific AGE, do not change following menopause, sex hormones appear to affect the AGE-RAGE system, which has been linked to an elevated risk of CVD in postmenopausal women (Zhao *et al*., 2018).

Microbiome

Recent research has suggested that the microbiome may play a significant role in the development of Osteoarthritis (OA). It has been proposed that lipopolysaccharide (LPS), a component of the cell membranes of gram-negative bacteria found in the microbiome, could act as a potential risk factor for OA.

LPS can enter the bloodstream, triggering the innate immune response and resulting in low-grade Inflammation that may contribute to the progression of OA. A study involving 25 patients revealed a correlation between LPS levels and various structural and clinical indicators of knee OA (Chisari *et al*., 2021; Wei *et al*., 2022).

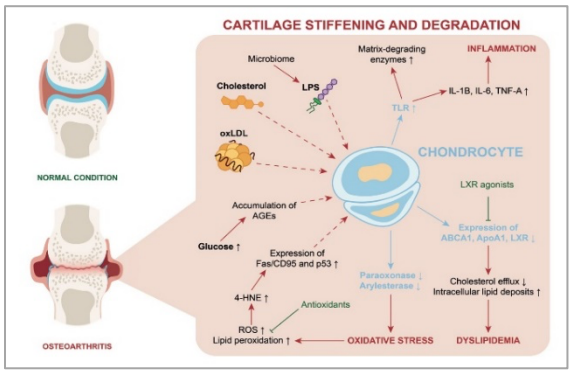

Fig. 2: Mechanisms of cartilage stiffening and degradation in Osteoarthritis

In the context of Atherosclerosis (AS) and Cardiovascular Disease (CVD), there is growing evidence supporting the idea that the microbiome may also be a relevant risk factor. Bacterial DNA from oral and gut microbiota has been detected in AS plaques, with the amount of this DNA correlating with markers of the disease. Additionally, the composition of the gut microbiome has been associated with the long-term risk of CVD, where specific bacterial genera have been linked to an increased risk, while others may offer protective benefits (Shen *et al*., 2021). Microbial-associated molecular patterns, such as LPS, along with microbiota metabolites that activate the innate immune system, have further been linked to AS.

Various factors can affect the composition of the gut microbiome, including female sex hormones. The microbiome's makeup differs between males and females and undergoes changes in women following menopause (He *et al*., 2021). Figure (3) illustrates the differences in hormonal profiles, fat distribution and disease risk across genders.

Role of Hormones Common Aetiology

Hormones significantly influence fat distribution, which in turn affects the risk of developing Osteoarthritis (OA) and Cardiovascular Disease (CVD). Men generally accumulate more visceral fat compared to premenopausal women with normal estrogen levels, potentially explaining the higher incidence of CVD in men. In contrast, premenopausal women may benefit from hormonal protection against heart conditions (Steiner and Berry, 2022). After menopause, however, reduced estrogen levels lead to increased visceral fat accumulation, resulting in an elevated risk of CVD. Additionally, there is a greater prevalence of OA among postmenopausal women, indicating that premenopausal estrogen may have a protective effect on musculoskeletal health (Ko & Kim, 2020). Research by Hoeven and colleagues highlighted a notable rise in atherosclerosis risk among women,

especially those with knee OA [OR 17 (11-27, p<0.05)] and hand OA (OR 14, 12-17, p< 0.0001). This finding could help explain the heightened CVD risk observed in women compared to men, particularly around the age of menopause when estrogen levels drop and OA incidence rises (Hoeven *et al*., 2015).

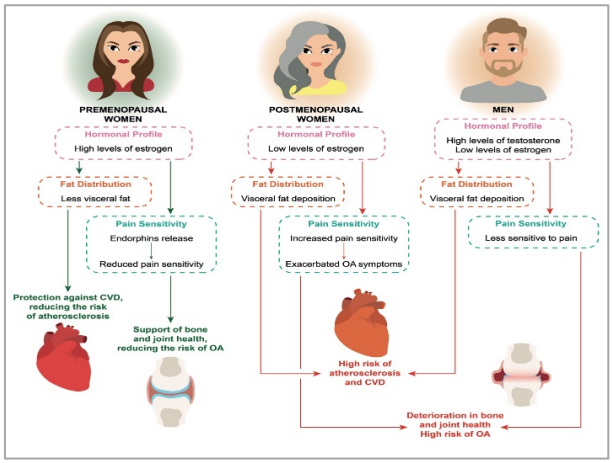

Fig. 3: Gender

In premenopausal women diagnosed with CVD, estrogen is thought to slow down atherosclerosis progression. However, after menopause, the risk of CVD increases, often accompanied by weight gain, obesity, elevated cholesterol and hypertension, all of which are also risk factors for OA. Rising estrogen levels can activate the brain's natural pain-relieving systems by promoting the release of endorphins (Ryczkowska *et al*., 2023). With the onset of menopause, this process may decline, potentially leading to increased pain sensitivity in women. Studies show that women report higher pain levels and greater pain intensity compared to men, suggesting that hormonal factors may contribute to these differences (Ali *et al*., 2020).

Hormonal differences influence fat distribution and pain sensitivity, thereby affecting the risk of atherosclerosis, Cardiovascular Diseases (CVD) and Osteoarthritis (OA) among different genders and hormonal statuses. Premenopausal Women have high levels of estrogen, resulting in less visceral fat, enhanced endorphin release and reduced pain sensitivity, providing protection against CVD and supporting bone and joint health, thereby reducing the risk of OA. In contrast, Postmenopausal Women have low levels of estrogen that leads to increased visceral fat deposition, heightened pain sensitivity and exacerbated OA symptoms, contributing to a higher risk of atherosclerosis, CVD and deterioration in bone and joint health. As for Men, they have higher levels of testosterone and are prone to atherosclerosis, CVD and OA development but to a lower degree compared to postmenopausal women.

The increased incidence of Osteoarthritis (OA) among women compared to men over the age of 50 can be linked to hormonal influences, genetic factors and variations in pain sensitivity. While both men and women possess testosterone receptors in their chondrocytes, the precise impact of testosterone on cartilage in males remains unclear. More research is needed to clarify the roles of estrogen and testosterone in OA development (Tschon *et al*., 2021). Women are known to experience pain more acutely than men, which may contribute to the higher number of women exhibiting OA symptoms. Additionally, although women are equally likely as men to succumb to heart disease, a greater proportion of women develop hypertension after the age of 65. In light of this, a new risk classification algorithm was introduced in 2007, categorizing Cardiovascular Disease (CVD) risk in women based on factors such as lifestyle, exercise and diet. There is growing evidence to suggest that OA and CVD in postmenopausal women may stem from overlapping causes (Maas and Appelman, 2010).

Conclusion

Identifying shared risk factors between Cardiovascular Disease (CVD) and Osteoarthritis (OA) is essential for advancing our understanding of these interconnected conditions. Future research should prioritize large-scale, longitudinal epidemiological studies that clarify the causal relationships between OA and CVD. By tracking patient outcomes across diverse populations, we can better identify specific risk factors.

Employing Mendelian Randomization (MR) will be crucial in establishing definite causal links between genetic variants, LDL cholesterol levels and the development of both diseases. This approach can help distinguish correlations from true causal mechanisms and enhance our understanding of the pathophysiology involved.

Moreover, intervention studies that target pain and mobility issues in OA patients could reveal significant impacts on CVD risk reduction. Evaluating treatment strategies such as physical therapy, dietary changes, and pharmacological interventions can provide insights into effective management.

Research into the shared pathways of low-grade Inflammation is also vital. By exploring specific inflammatory markers related to both conditions, we may develop more effective, targeted therapies.

Ultimately, this research emphasizes the importance of integrating care for OA and CVD. By addressing shared risk factors and underlying mechanisms, we can improve treatment strategies while reducing morbidity and mortality in the elderly population. The findings from this study highlight the need for comprehensive public health

policies that encompass both conditions, significantly enhancing the quality of life for affected individuals.

Acknowledgement

The author(s) would like to thank all individuals and institutions who contributed to the completion of this study. Their valuable support, guidance, and cooperation are gratefully acknowledged.

Funding Information

This research was funded by Russian Science Foundation, grant number 24-15-00217

Author's Contributions

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All authors have read and agreed to the published version of the manuscript.

Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and no ethical issues involved.

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