



The interplay between osteoarthritis and cardiovascular disease: shared pathophysiological mechanisms

La interacción entre la osteoartritis y la enfermedad cardiovascular: mecanismos fisiopatológicos compartidos

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Abstract

The relationship between osteoarthritis (OA) and cardiovascular disease (CVD) is complex. Epidemiologically, both OA and CVD have displayed rising trends in the last decades, largely attributed to consistent increases in the prevalence of overlapping risk factors. Furthermore, subjects with OA appear to have a greater cardiovascular risk. As a result, these conditions are associated with a significant burden for public health systems. Both OA and CVD have traditionally been studied as distinct conditions, yet growing epidemiological and molecular evidence suggests these two highly prevalent chronic diseases are linked not merely by shared risk factors such as aging, obesity, and sedentary lifestyle, but also by deeply interconnected biological mechanisms. In ensemble, a plethora of pathophysiological phenomena, such as chronic inflam-

mation, oxidative stress, adipokine dysregulation, endothelial dysfunction, and extracellular matrix remodeling form a complex and overlapping network of processes that can jointly drive both articular degradation and vascular injury. Bridging the gap between musculoskeletal and cardiovascular research offers the promise of innovative therapies and integrated care strategies that can improve both mobility and longevity for millions of patients worldwide by improving clinical outcomes of both OA and CVD. In this narrative review, we revise the pathophysiological interconnections between OA and CVD.

Keywords: Osteoarthritis, cardiovascular disease, chronic inflammation, oxidative stress, adipokines, endothelial dysfunction, extracellular matrix.

La relación entre la osteoartritis (OA) y la enfermedad cardiovascular (ECV) es compleja. Desde el punto de vista epidemiológico, tanto la OA como la ECV han mostrado tendencias crecientes en las últimas décadas, atribuibles en gran medida al aumento sostenido de la prevalencia de factores de riesgo superpuestos. Además, las personas con OA parecen tener un mayor riesgo cardiovascular. Como resultado, estas condiciones se asocian con una carga significativa para los sistemas de salud pública. Tradicionalmente, la OA y la ECV se han estudiado como entidades distintas; sin embargo, la creciente evidencia epidemiológica y molecular sugiere que estas dos enfermedades crónicas, altamente prevalentes, están vinculadas no solo por factores de riesgo compartidos como el envejecimiento, la obesidad y el sedentarismo, sino también por mecanismos biológicos profundamente interconectados. En conjunto, una multitud de fenómenos fisiopatológicos —como la inflamación crónica, el estrés oxidativo, la desregulación de adipocinas, la disfunción endotelial y la remodelación de la matriz extracelular— conforma una red compleja y superpuesta de procesos que pueden impulsar simultáneamente la degradación articular y el daño vascular. Tender puentes entre la investigación musculoesquelética y la cardiovascular ofrece la promesa de terapias innovadoras y estrategias de atención integradas que mejoren tanto la movilidad como la longevidad de millones de pacientes en todo el mundo, al optimizar los resultados clínicos de la OA y la ECV. En esta revisión narrativa, revisamos las interconexiones fisiopatológicas entre la OA y la ECV.

Palabras clave: osteoartritis, enfermedad cardiovascular, inflamación crónica, estrés oxidativo, adipocinas, disfunción endotelial, matriz extracelular.

Osteoarthritis (OA) is a chronic degenerative disorder which features deterioration and loss of joint cartilage, as well as deleterious structural changes in periarticular bone¹. The epidemiologic impact of OA is in rising trend, in consonance with the increasing life expectancy of the general population worldwide. In 2021, 595 million people worldwide were estimated to have OA, equating to a prevalence of 7.6%, and marking a 132.2% increase from 1990². Knee OA appears to be the most common³. Numerous risk factors for OA have been identified beyond older age, including black ethnicity, genetic predisposition, overweight and obesity, prior joint injury, and excessive articular loading⁴. Notably, several of these factors are shared between OA and cardiovascular disease (CVD), as well as other chronic non-communicable disorders (CNCD).

On the other hand, CVD has been the cause of death during the last three decades, corresponding to roughly a third of all mortality globally⁵. In a similar trajectory to OA, both mortality and incidence also grew substantially between 1990 and 2021, with relative increases of 92.3% and 57.5%, respectively⁶. These trends have been largely attributed to a striking and consistent increase in the prevalence of cardiovascular risk factors, such as insufficient physical activity, atherogenic dietary patterns, smoking, obesity, dyslipidemia, diabetes and hypertension⁷.

The relationship between OA and CVD is complex. The prevalence of CVD in subjects with OA has been estimated at 38.4%; and individuals with OA have shown an almost tripled risk of heart failure or ischemic heart disease in comparison to those without OA⁸. OA and CVD share risk factors, and some of these may even synergistically worsen the progression and outcomes of both conditions, such as reduced physical activity⁹. There also appears to be a significant overlap in the biological mechanisms underlying the development of OA and CVD, such as chronic inflammation (CI), oxidative stress (OS), adipokine dysregulation, and vascular dysfunction. In this narrative review, we revise the pathophysiological interconnections between OA and CVD.

KEY PATHOPHYSIOLOGICAL ELEMENTS IN THE DEVELOPMENT OF OSTEOARTHRITIS BEYOND BIOMECHANICS

A wide array of pathogenic mechanisms beyond the classical biomechanical views has been proposed to be present in both OA and CVD, with CI appearing to be one of the most prominent. Indeed, long-term low-grade

inflammatory states have been recognized as ubiquitous in the pathogenesis and maintenance of a myriad of CNCD¹⁰. In the context of OA, inflammation may be classified as mechanoinflammation and meta-inflammation. The former refers to the result of abnormal loading in joints, which trigger signaling pathways sensitive to mechanical stimuli, such as JAK/STAT, MAPK and NF- κ B, and ultimately activate proteases and extracellular matrix (ECM) degradation¹¹. In contrast, meta-inflammation occurs due to metabolic stress related to a persistent positive energy balance, and it involves the activity of multiple pro-inflammatory cytokines and adipokines, both systemically and locally in the joint¹².

The innate immune response appears to be especially important in OA. A key step in the functionality of this response is the activation of pattern-recognition receptors, such as toll-like receptors, by pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs)¹³. Both of these stimuli indicate the requirement to initiate an innate immune response. In the context of OA, these DAMPs include byproducts of ECM deterioration such as fibronectin and hyaluronan, among others¹⁴. These have been observed to induce the production of pro-inflammatory cytokines like necrosis factor α (TNF α) and IL-1 β , along with matrix metalloproteinases MMP1 and MMP3, which are involved in cartilage breakdown¹⁵.

This tissue damage can lead to local dysregulation of vascular dynamics, resulting in extravasation of plasma proteins which may act as DAMPs. These include fibrinogen, Gc-globulin, α 1-microglobulin, and α 2-macroglobulin, which are able to promote TNF α , IL-6, IL-1 β production from macrophages via activation of TLR4¹⁶. Another source of DAMPs may be intracellular alarmins, which are intracellular proteins that are released from stressed or damaged cells¹⁷. In OA, the main alarmins seem to be the high-mobility group box 1 protein (HMGB-1) and the S100 family of proteins, which have been associated with increased expression of IL-6 and MMPs 1, 3, 9 and 13, as well as downregulation of type II collagen and aggrecan, which are key constituents of the ECM¹⁸.

In the articular microenvironment, synovial macrophages appear to be the epicenter for innate immune response activation, yet many other types of cells have the ability to respond to DAMPs, including fibroblast-like synoviocytes (FLS) and chondrocytes¹⁹. Notably, macrophages treated with LPS and cocultured with exosomes secreted by chondrocytes showed predominant polarization to the M1 phenotype, with augmented release of TNF α , IL-6, IL-1 β and IL-12²⁰.

In a parallel and synergistic fashion with CI, OS has also been identified as a key element in the development of OA, with antioxidant defenses being insufficient to cover pro-oxidative events²¹. Chondrocytes have been reported to produce elevated levels of reactive oxygen species

(ROS) in OA cartilage, and in the proximity of lipid peroxidation and nitrosylation products in both the synovial fluids and the cartilage²². Greater OS has been directly correlated with worse collagen degradation in the ECM; and nitric oxide (NO), along with hydrogen peroxide (H₂O₂), appear to be able to significantly inhibit cartilage ECM synthesis²³.

There is a complex crosstalk between CI and OS that ultimately promotes the maintenance and progression of the diseased state in OA, and which can extend to CVD as well. The expression of inducible nitric oxide synthase (iNOS) has been observed to be upregulated by pro-inflammatory cytokines, such as TNF α , IFN- γ and IL-17, among others²⁴. Furthermore, NO can also activate NF- κ B, augmenting release of IL-1 β and TNF α , adding to the pro-inflammatory milieu²⁵. Excessive amounts of ROS in the articular microenvironment can also act as local signals for the induction of the expression of several MMP, as well as promoters of chondrocyte apoptosis²⁶.

In addition to the classic soluble messengers of the immune system, such as cytokines and chemokines, adipokines—immunologically active mediators derived from adipose tissue—may also play an important role in the pathophysiology of OA. This group includes molecules such as leptin, adiponectin, resistin, visfatin, omentin, vaspin, and retinol binding protein 4²⁷. In the context of OA, the adipokines active in the diseased cartilage may originate both from local periarticular fat pads, or from systemic circulation stemming from fat tissue elsewhere, visceral adipose tissue especially²⁸. Through an array of heterogeneous pathways, adipokines can modulate many aspects of immunometabolism in the joint, including the activity of cytokines, chemokines, MMP, cell growth and differentiation factors, prostaglandin production, and expression of vascular cell adhesion molecule-1 (VCAM-1)²⁹.

Altered joint perfusion may also contribute to articular degeneration in OA. Endothelial dysfunction (ED), similar to that observed in atherosclerotic disease, has been observed in periarticular blood vessels in OA³⁰. Disturbed perfusion has been related to synoviocyte hyperplasia, hypertrophy and fibrosis, as well as increased secretion of IL-1, IL-6, TNF α , and Vascular Endothelial Growth Factor (VEGF)³¹. These effects may be potentiated in subjects with hypertension, highlighting the overlap between OA and CVD. Higher blood pressure may increase intraosseous pressure, leading to hypoxia in subchondral bone, and a resulting disturbance of bone remodeling and ECM maintenance³².

UNDERSTANDING THE OVERLAP IN THE PATHOPHYSIOLOGIC MECHANISMS OF OSTEOARTHRITIS AND CARDIOVASCULAR DISEASE

The epidemiological link between OA and CVD is powerful: In a meta-analysis of observational studies on 358,944 participants, the risk of CVD was significantly higher, at 24%, in subjects with OA³³. One of the main connecting elements in this scenario is CI. Low-grade inflammation is a well-established component associated with CVD, and acts as a trigger and aggravator of several other pathophysiologic phenomena which are closely related, such as insulin resistance, mitochondrial dysfunction, and appetite dysregulation³⁴. In ensemble with these factors, CI also promotes other related disturbances—overweight and obesity, dyslipidemia, hypertension, dysglycemia and diabetes, and a prothrombotic status—which reinforce the pro-inflammatory environment and consequent deterioration in the cardiovascular system and the joints³⁵.

The role of CI in OA is clearly multifaceted. Potent pro-inflammatory mediators, such as TNF α , IL-1 β , IL-6, NF- κ B and iNOS may be upregulated by several stimuli, including mechanical stress to chondrocytes, and signaling from both periarticular and visceral adipose tissue, among others³⁶. In CVD, particularly atherosclerosis, these same cytokines act on endothelial cells and macrophages within the arterial wall, promoting leukocyte adhesion, foam cell formation, and plaque development³⁷. The aforementioned circulating messengers also drive higher levels of C-reactive protein (CRP), a shared biomarker associated with both OA severity and cardiovascular event risk³⁸. Importantly, the NLRP3 inflammasome, a cytosolic multiprotein complex involved in the functionality of IL-1 β and IL-18, is implicated in both joint degradation and vascular inflammation. Thus, it has been identified as a pivotal molecular bridge between the OA and CVD³⁹.

Likewise, ROS, including H₂O₂, superoxide anions (O₂⁻), and hydroxyl radicals (\cdot OH), play central roles in tissue damage in both OA and CVD. In OA, mitochondrial dysfunction in chondrocytes increases ROS production, activating mitogen-activated protein kinases (MAPKs) such as p38 and JNK. In turn, these upregulate ECM-degrading enzymes like MMP-13 and aggrecanases (ADAMTS-4/5)^{40,41}. ROS also suppress the anabolic activity of chondrocytes by downregulating SOX9, a key transcription factor for collagen type II and aggrecan synthesis⁴².

In CVD, OS is an important driver of atherogenesis. ROS and uncoupled endothelial nitric oxide synthase (eNOS) activity contribute to ED, oxidation of low-density lipoprotein (LDL), and vascular smooth muscle proliferation⁴³. This oxidative modification of lipids and proteins within atherosclerotic plaques further destabilizes lesions, increasing the risk of rupture and thrombosis⁴⁴.

On the other hand, adipokines derived from adipose tissue, including leptin, adiponectin, and resistin, exert both local and systemic effects linking obesity, OA, and CVD. Leptin, which is elevated in obese individuals, promotes the expression of pro-inflammatory cytokines (IL-1 β , IL-6), NO, and MMPs in chondrocytes, accelerating cartilage catabolism⁴⁵. Leptin also promotes vascular inflammation and smooth muscle proliferation through JAK/STAT signaling, enhancing atherogenesis⁴⁶.

Conversely, adiponectin, an adipokine with anti-inflammatory properties, is reduced in obesity and metabolic syndrome. This has been associated with increased cartilage degradation and heightened cardiovascular risk⁴⁷. On the other hand, resistin, secreted by macrophages and adipocytes, has been implicated in amplifying CI and insulin resistance, contributing to both OA and CVD pathogenesis through ED⁴⁸.

The latter is a hallmark of early CVD and may also contribute to OA progression. NO, produced by eNOS, plays a central role in maintaining vascular homeostasis by promoting vasodilation, inhibiting platelet aggregation, and suppressing inflammation⁴⁹. In CVD, OS reduces NO bioavailability, leading to impaired vasodilation, leukocyte adhesion, and plaque formation⁵⁰.

Furthermore, subchondral bone vasculature may also experience microvascular rarefaction and perfusion abnormalities, impairing local nutrient delivery and exacerbating mechanical stress⁵¹. In OA, cartilage-derived iNOS upregulation leads to excessive NO production, paradoxically promoting chondrocyte apoptosis and ECM degradation, illustrating a complex tissue-specific role for NO in both systems⁵².

Lastly, the role of MMPs is paramount, as they play an essential role in both joint and vascular tissue remodeling. In OA, MMP-1, MMP-3, and particularly, MMP-13, cleave type II collagen and aggrecan, weakening cartilage structure⁵³. In the vasculature, MMPs degrade the fibrous cap of atherosclerotic plaques, increasing vulnerability to rupture and acute coronary events. Both conditions exhibit dysregulated tissue inhibitor of metalloproteinase (TIMP) activity, further facilitating ECM degradation⁵⁴.

Both OA and CVD have traditionally been studied as distinct conditions, yet growing epidemiological and molecular evidence suggests these two highly prevalent chronic diseases are linked not merely by shared risk factors such as aging, obesity, and sedentary lifestyle, but also by deeply interconnected biological mechanisms. CI, OS, adipokine dysregulation, ED, and ECM remodeling form a complex and overlapping network of processes driving both joint degradation and vascular injury.

Recognizing the interplay between OA and CVD carries important clinical implications. Patients with OA are often at increased cardiovascular risk, yet this risk may go underrecognized in musculoskeletal care settings. Understanding these interconnectedness opens the door for novel therapeutic strategies, including the use of novel anti-inflammatory interventions, such as IL-1 β or TNF α inhibitors; as well as antioxidants, or metabolic modulators that may exert beneficial effects across both disease domains.

The interwoven nature of OA and CVD challenges us to move beyond organ-specific models of disease and embrace a more holistic, systems-based understanding of CNCD. Bridging the gap between musculoskeletal and cardiovascular research offers the promise of innovative therapies and integrated care strategies that can improve both mobility and longevity for millions of patients worldwide.

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