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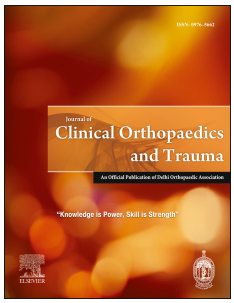

Metabolic syndrome and subchondral bone alterations: The rise of osteoarthritis – A review

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ABSTRACT

Metabolic syndrome (MS) has become one of the top major health burdens for over three decades not only due to its effects on cardiovascular health but also its implications in orthopedics. Extensive research has shown that MS is tightly linked to osteoarthritis and inflammation, a process which appears to primarily occur in the subchondral bone via the incidence of bone-marrow lesions (BMLs). Numerous studies identify obesity, dyslipidemia, insulin resistance and hypertension as the top metabolic risk factors, the so-called “deadly quartet”. These factors are responsible for the disruptive physiological processes that culminate in detrimental alterations within the subchondral bone, cartilage damage and, overall, the predominant pro-inflammatory joint microenvironment. Although it has long been thought that osteoarthritis was limited to the cartilage component of the joint, other studies indicate that the disease may originate from the harmful alterations that occur primarily in the subchondral bone, especially via means of vascular pathology. Since metabolic risk factors are manageable to a certain extent, it is therefore possible to decelerate the progression of OA and mitigate its devastating effects on the subchondral bone and subsequent articular cartilage damage.

METHODS

Literature was reviewed using PubMed and Google Scholar in order to find a correlation between metabolic syndrome and osteoarthritic progression. The investigation included a combination of nomenclature such as: “metabolic syndrome”, “obesity”, “insulin resistance”, “hypertension”, “dyslipidemia”, “low-grade systemic inflammation”, “osteoarthritis”, “subchondral bone”, “cartilage” and “inflammatory biomarkers”.

CONCLUSION

Based on several studies, there seems to be a significant association between The Deadly Quartet (metabolic syndrome), dysregulation of both pro- and anti-inflammatory biomarkers, and osteoarthritic progression arising from unbridled systemic inflammation.

Keywords: metabolic syndrome; inflammation; osteoarthritis; subchondral bone; cartilage

INTRODUCTION

Metabolic syndrome is a major health condition that continues to escalate and challenge public and clinical health on a global scale as a result of urbanization, increased calorie intake, increasing obesity and sedentary life habits [1]. This is a complex condition which is tightly connected to multiple biochemical and physiological pathways, often directly associated with the development of cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and cause mortality. There are many risk factors which promote the aggravation of MS. Common examples include: insulin resistance, accumulation of visceral adipose tissue, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, hypertension, hypercoagulable state, and chronic stress [2]. Interestingly, there appears to be a significant link between MS and inflammatory musculoskeletal disorders, namely, osteoarthritis (OA). It is well known that OA is the most common degenerative joint disease affecting not only the cartilaginous component but the majority of the joint and surrounding tissues. It has long been thought that OA was solely limited to chondral lesion and degeneration. More recently, however, voluminous evidence indicates that persistent, low-grade systemic inflammation also acts as a key mediator driving the pathogenicity of the disease by initially affecting the subchondral bone [3]. Additionally, it has been suggested that in order to treat OA, the subchondral bone must also be targeted [4]. The development and progression of OA is a multifactorial process in which biomechanical and biochemical factors are centrally involved in the structural and functional alterations of the whole joint [5]. Conventional therapeutics such as non-steroidal anti-inflammatory

drugs (NSAIDS) for the management of knee osteoarthritis (KOA) are usually prescribed, however, they are not the best alternative as they do not actually arrest the progression of the disease and may in turn cause undesirable side effects [6]. Being one of the top five most physically incapacitating conditions, OA is normally recognized by joint inflammation and a reparative bone response. KOA, in particular, is more commonly associated with aging and obesity and has doubled in prevalence since the mid-20th century [7]. It usually entails a set of conditions such as continuous loss of articular cartilage, thickening of the subchondral bone, formation of osteophytes and significant inflammation of the synovium.

The most widely cited risk factors for OA encompass joint injury, obesity, aging and even genetic predisposition [8, 9]. The hands are another site of common peripheral joint involvement in OA. Contrary to knee OA, which is frequently linked to mechanical overload, hand OA is often underestimated as a cause of disability. In some cases, it may even predict a shift towards systemic OA, which may compromise the locomotor apparatus, causing stress to the weight-bearing structures, particularly the coxofemoral and patellofemoral joints [9, 10].

Regarding the subchondral bone compartment, its involvement in the pathophysiology of KOA does not seem so simple and should therefore not be bluntly dismissed and left untreated. The studies cited in this review indicate that bone and cartilage are tightly linked in the progression of KOA rather than in isolation. The cellular “crosstalk” between chondrocytes and bone cells within the subchondral bone is a critical process in the joint homeostasis [11]. Some authors argue that large molecules traverse between both compartments, in either healthy or diseased joints [11]. Therefore, it is not impossible for dysregulated circulatory “inflammokines” (inflammatory cytokines) to reach the joint compartment and interfere with regular cell signalling and metabolic activity (figure 1). Speaking of cytokines, upon navigating the literature, it was noted that particular attention is directed towards a specific set of biomarkers pertaining to MS clusters which have been previously discussed in many studies. These biomarkers and their roles in systemic inflammation have been summarized in table 1.

The purpose of this manuscript is to review the link between MS and OA by acknowledging the harmful alterations that may primarily jeopardize the subchondral bone, giving rise to generalized osteoarthritis.

1. SUBCHONDRAL BONE ALTERATIONS

This section will discuss the principal alterations that affect the subchondral bone in the onset of OA. The early changes that occur beneath the articular cartilage at the osteochondral junction are highly relevant as they become possible mediators of pain and structural progression in OA and may aggravate pathology elsewhere in the joint [11]. These modifications include augmented subchondral bone thickness, diminished flexibility and trabecular bone density beneath the subchondral plate. Once osteochondral integrity becomes fragilized, the barrier between intra-articular and subchondral compartments is lost. This exposes the subchondral bone and its nerves to imbalanced biochemical and biomechanical influence. The loss of demarcation between bone and articular cartilage and the inevitable fusion of tissue compartments across the junction is associated with invasion of articular cartilage by blood vessels and sensory nerves as well as advancing endochondral ossification [11]. Moreover, exacerbated subchondral bone turnover is also closely linked to these alterations at the osteochondral junction [11]. Continuous biomechanical and biochemical stress applied to articular cartilage contributes to chondropathy. This subsequently promotes additional subchondral bone alterations, such as microfractures which, in turn, may aggravate pain [11]. Furthermore, the increased turnover of subchondral bone in both human and animal studies has led scholars to believe that the various cytokines and growth factors expressed during this process may interact with articular cartilage. This interaction would then trigger a positive feedback loop as a result of multiple unsuccessful attempts to repair cartilage and bone tissue, eventually resulting in OA [11, 12]. To illustrate, Kadri et al. learned that administration of osteoprotegerin prevented the loss of trabecular bone and cartilage degradation after surgically inducing OA in mice [12]. A similar in vivo study reported that aggrecanase-2 deficient mice, protected from cartilage degradation, displayed only mild subchondral bone alterations in comparison to wild type controls after surgically-induced joint instability [13]. Furthermore, an *in-vitro* study [14] demonstrated that subchondral bone osteoblasts

from osteoarthritic patients promoted hypertrophic differentiation and matrix mineralization of normal chondrocytes, suggesting the potential for cellular cross-talk between the subchondral bone and articular cartilage.

It is understood that OA is responsible for alterations in the structural and material properties of joint tissues [4]. More specifically, vascular channels or microfractures, which have been identified in osteoarthritic joints, can act as transport conduits for many biomolecules [15, 16], including certain dysregulated inflammatory cytokines (table 1) linked to the disease. Pan and colleagues illustrated the potential [17] for molecular interaction between the subchondral bone and articular cartilage in normal mature joints via the use of fluorescence loss induced by photobleaching (FLIP). After quantifying matrix permeability, vessel invasion, and overall joint morphology in both surgically-induced and age-related spontaneous OA models, the authors compared the parameters to controls. The disorder was not found to be associated with significant changes in tissue matrix permeability in either case. On the other hand, the condition did cause thinning of the subchondral bone and an increase in blood vessel invasion which perforated the calcified cartilage in both models. It appears that the potential for cellular cross-talk between the subchondral bone and articular cartilage becomes elevated in OA due to overall joint morphology alteration.

2. THE DEADLY QUARTET

2.1 OBESITY

It is understood that OA pathogenesis is mainly attributed to both excessive joint loading and the subsequent irregular biomechanical and biochemical patterns, such as hormone and cytokine dysregulation which arise from increased adipose tissue, a rich source of pro-inflammatory endocrine factors [18]. This disorder affects the musculoskeletal system, particularly, by triggering degenerative and pro-inflammatory conditions, which may eventually dictate the development of OA [19]. One of the most prominent features of obesity is the manifestation of low-grade systemic inflammation, affecting many organs and anatomical structures. The exact metabolic pathways through which

obesity contributes to structural damage of joints do not seem to be fully elucidated. It is believed that the elevated adipokine expression from adipose tissue elicits direct and downstream effects which lead to the destruction and remodelling of the joint as whole [20, 21]. Leptin and adiponectin are the most abundantly secreted adipokines, and their corresponding receptors have been detected on the surfaces of subchondral osteoblasts, chondrocytes and synoviocytes [22, 23]. Leptin has reportedly been able to elevate the levels of catabolic enzymes, such as matrix metalloproteinases (MMPs), and increase the synthesis of other pro-inflammatory cytokines [23, 24].

The increased concentration of adipokines in obese patients is noteworthy as the biochemical environment in these individuals may challenge regular cellular responses. As an example, chondrocytes from obesity-related OA patients have demonstrated a response pattern to leptin that differs from normal or overweight patients [25]. In regards to adiponectin and its participation in joint disorders, it has been reported that this cytokine bears conventional anti-inflammatory properties under standard metabolic conditions. However, when not adequately regulated, it may shift towards a more pro-inflammatory role [21, 22]. One particular investigation showed that significant weight loss in obesity-related OA patients caused a decrease in the circulatory levels of leptin while increasing the levels of adiponectin [26]. Speaking of weight loss, a study of an adult population without clinical KOA concluded that elevated fat mass was associated with increased bone marrow lesions (BMLs) and cartilage defects, indicative features of primary stage KOA [27]. As previously mentioned, excessive weight applies greater physical stress to the weight-bearing joints. Knee adduction moment is an important mechanical variable linked to the development of OA. Obese individuals have greater absolute knee adduction moments due to excessive body mass and therefore engage in compensatory gait patterns as seen with slower walking velocity and increased toe-out angle [18, 28]. Articular cartilage suffers impaired signalling response due to higher levels of absolute knee adduction moment during gait in comparison to normal weight patients [29]. Interestingly, however, increased joint loading in normal weight individuals does not show strong association with OA [30].

2.2 DYSLIPIDEMIA

Increased dietary fat intake and sedentarism are part of modern society's main health issues. This shift towards western-type diet is also accompanied by many other metabolic irregularities previously introduced [31]. Dyslipidemia is strongly involved the pathophysiology of OA by aggravating subchondral bone damage due to BMLs [32].

BMLs are known to be associated with knee pain and structural alterations in the knee of OA patients [33–36] and subsequently culminate in increased joint space narrowing and cartilage erosion in symptomatic populations [36]. On the other hand, in asymptomatic cases, their presence is linked to systemic factors such as dietary lipids but are more likely to resolve [37, 38]. This may be attributed to the histological profile of BMLs being heterogeneous, encompassing osteonecrosis, oedema, trabecular abnormalities and bony remodelling [37]. A previous study [37] aimed to investigate the correlation between serum lipids and baseline prevalence of BMLs in 176 women between the ages of 40 to 67, adjusting for lifestyle habit variables. The researchers concluded that, in their population of asymptomatic individuals with no clinical KOA, there was no significant relationship between serum lipids and the presence of BMLs at baseline or change in knee cartilage over 2 years. However, it was observed that greater levels of total cholesterol and triglycerides were associated with the incidence of BMLs in knees free of BMLs at baseline. This runs parallel with conclusions from a similar study led by Wang and colleagues, who also found dietary lipids to be associated with the risk of BMLs [39].

Further contributions also explore the link between lipid profile and development of new BMLs. An in vivo study [40] demonstrated the deleterious effects of long-term exposure to western-type diet in the high-density lipoprotein (HDL cholesterol) metabolism of mice. It was found that perturbations in the metabolic pathway due to the administration of a high-fat diet predisposed murine subjects to KOA [40]. Antony et al. analyzed the correlation between physical activity, cartilage defects and clinical status of BMLs in younger adults, aiming to determine whether cholesterol levels measured 5 years prior were associated with current lesions in recruited participants [41]. Moderate physical

activity and HDL cholesterol levels appeared to be more benevolent towards patients in terms of BML development. Conversely, other authors [42] analyzed the association between dietary factors, serum lipids and knee BMLs, revealing that dietary factors and lipids were not significantly associated with BMLs. However, energy, carbohydrate, and sugar intake were positively associated with a change in BML size, consolidating another link between MS and subchondral bone alterations. Lastly, the authors concluded that HDL cholesterol, in particular, tended to be inversely related with BMLs, proposing a rather protective role for this specific lipoprotein.

2.3 INSULIN RESISTANCE

Insulin resistance (diabetes) is debatably the central feature of MS and is usually entailed by additional metabolic irregularities previously introduced, which collectively aggravate musculoskeletal disorders. For instance, Yoshimura and colleagues demonstrated that the accumulation of metabolic risk factors predisposes individuals to osteoarthritic progression in the knee [43]. A meta-analysis conducted by Louati and colleagues indicates a strong correlation between diabetes mellitus and osteoarthritis, with an odds ratio of 1.46 for OA in T2DM populations [44]. After taking BMI into consideration, a solid association between OA and T2DM was observed in many publications since 2009. This might be attributed to an increase in the prevalence of other metabolic risk factors that often follow the incidence of T2DM, illustrating the association of the deadly quartet and aggravated OA progression.

The pro-inflammatory effect of diabetes in KOA can be explained in the sense that diabetic individuals experience more effusion synovitis, which does not rely on BMI [45]. Speaking of inflammation, there is recent evidence connecting the expression of synovial tumour necrosis factor alpha (TNF-α) and insulin resistance to OA pathology [46]. A causal role for TNF-α in OA, especially in obesity- and diabetes-related OA, has been proposed. Hamada et al. used a high-fat diet mouse model of obesity and glucose intolerance to demonstrate that TNF-α gene expression and protein levels were elevated in synovia adjacent to osteophytes, indicating an early pathogenic feature [46]. TNF-α did not only induce the expression and secretion of OA-related proteinases, including

ADAMTS4 (a disintegrin and metalloproteinase with thrombospondin motifs), MMP1, and MMP13 but it also stimulated the expression of OA-associated pro-inflammatory biomarkers, such as IL-1β, IL-6, and TNF-α itself (table 1). Additionally, the authors studied TNF-α and development of osteophytes in knockout mice. It was found that elimination of the TNF-α gene significantly reduced high-fat diet-induced development of osteophytes and synovial hyperplasia. Lastly, this strategy lowered weight and glucose intolerance derived from the high-fat diet, indicating the local and systemic benefits of TNF-α inhibition on overall joint remodelling and metabolic regulation in this particular instance. Unsurprisingly, a clinical study reported that diabetic rheumatoid arthritis patients benefited from anti-TNF-α therapy, which significantly ameliorated insulin resistance, β-cell function and insulin signalling [47].

On a cellular perspective, enriched insulin receptor expression in murine and human synovia has also been previously identified [46]. In fibroblast-like synoviocytes (FLS) isolated from non-diabetic OA patients, insulin stimulation resulted in autophosphorylation of the insulin receptor as well as phosphorylation of the Akt pathway. Conversely, in synovium samples extracted from diabetic OA patients, insulin-induced autophosphorylation of the insulin receptor and phosphorylation of Akt were significantly dampened. Much like other insulin sensitive tissues, the synovium is susceptible to the insulin resistance syndrome.

2.4 HYPERTENSION (VASCULAR PATHOLOGY)

It is known that bone is generously supplied by blood vessels and its vasculature is intimately involved in its growth, repair and metabolic processes [48]. As such, there are many ways for vascular pathology to deplete subchondral bone integrity and culminate in the development of OA. Bone extremities, for example, are very susceptible to vascular invasion. Venous occlusion and the subsequent small-vessel stasis underlying the cartilage plate, joint hypertension, hypercoagulability and microemboli are factors which may all contribute to subchondral bone ischemia [32]. Logically, dysregulated nourishment of the subchondral bone and impaired repair processes may then sabotage the delivery of nutrients and oxygen to the overlying cartilage. Bone ischemia deals additional

damage via the death of osteocytes, generating an unstable, inflammatory and catabolic microenvironment leading to eventual bone resorption. This set of biological events significantly reduces skeletal robusticity and, subsequently, joint strength [32].

The subchondral regions of long bones are well vascularized, indicating an elevated nutritional demand. Elevated blood flow rate, in turn, is associated with increased rate of bone remodelling [49, 50]. It must be noted that at the epiphyseal region of long bones, the “backup” system of nutrients and periosteal arteries is absent due to the presence of cartilage at the site. This means that the epiphyses and articular surfaces are likely to be affected by circulatory insufficiency, to begin with [51]. Irregular blood flow may cause perturbation to osteocytes, leading to apoptosis, attraction of osteoclasts and excavation of non-viable bone [32]. As these events occur repeatedly at the extremities of long bones, there is an increased likelihood of disrupting the standard remodelling process, altering bone morphology. Furthermore, this could also cause partial or total collapse of the subchondral bone, as is the case with avascular necrosis [32].

Previous studies have pointed out bone marrow oedemas (BMO) as potential risk factors for structural deterioration of the knee [52, 53]. Enlargement of BMLs are significantly linked to extended cartilage loss, whereas reduction in the extent of bone marrow abnormalities appears to be associated with decreased cartilage degradation [52, 53]. It has also been demonstrated that subchondral cysts, typically found in severe OA, arise from regions of BMO [53].

The origins of this type of bone marrow injury have not been completely investigated. However, it has been hypothesized that they may be attributed to the generation of intramedullary pressures surpassing peak arterial pressure during strenuous exercise, for example [54].

The consequential effects of hypertension also encompass insufficient capacity for vascular growth and angiogenesis, which is due to endothelial cell damage or dysfunction [55–57]. Although there is some variation amongst the endothelia of different vascular beds, they all suffer reduced capacity to synthesize nitric oxide (NO) in hypertensive environments [58]. Other agents involved in vascularization, such as the vascular endothelial growth factor (VEGF), for example, appear to be

involved in the pathogenicity of this disorder. Enomoto et al. demonstrated that VEGF and its receptors are expressed in osteoarthritic cartilage, indicating the possible participation of this growth factor in catabolic processes via increased synthesis of MMPs [59].

CONCLUSION

The authors propose some of the complex mechanisms through which the components of metabolic syndrome may disrupt the regular biological processes in adults and promote musculoskeletal complications. Supported by numerous appreciable studies, the evidence gathered thus far may satisfactorily illustrate the association between metabolic syndrome, inflammatory cytokine dysregulation and systemic inflammation. This creates a predominant pro-inflammatory microenviroment, which can interfere with normal cellular processes in joints and promote OA.

The most obvious and perhaps cheapest strategy to protect the subchondral bone and bring OA to a halt would be to simply modify lifestyle habits, since the majority of MS risk factors are quite manipulable. For instance, steering clear of high-fat, high-carbohydrate diets and purine-rich foods whilst engaging in moderate physical activity might eliminate the devastating effects brought on by metabolic syndrome.

Pain physicians, rheumatologists, orthopedists and sports medicine experts alike should target musculoskeletal infirmities with conservative treatments and surgical alternatives, as required. Instead of diverting all of their attention towards the exclusive treatment of cartilage, practitioners should be twice as vigilant about the patient's metabolic status. Therefore a full panel of the concentration of the biomarkers cited in table 1 would facilitate conservative treatments, allowing experts to strategically choose the best outcome in order to halt the destruction of the subchondral bone safely and effectively.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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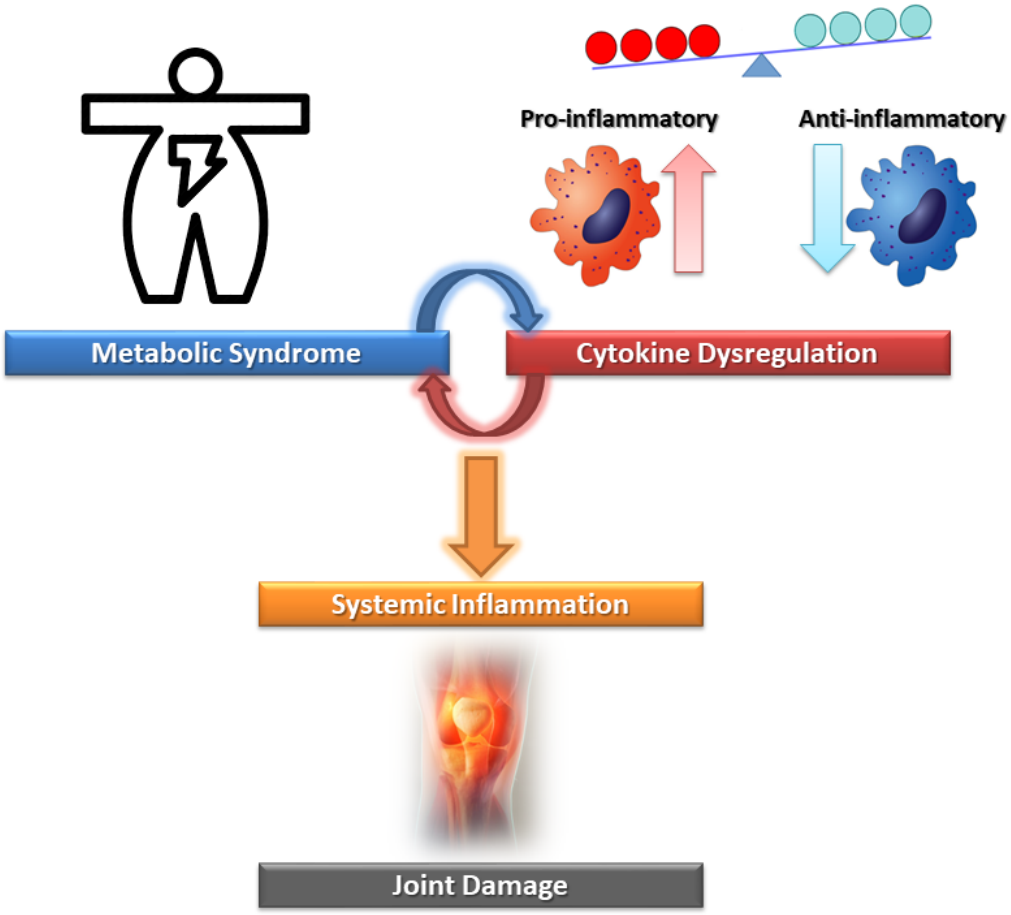
Table 1 – Summary of the principal MS-associated inflammatory biomarkers

Author	Inflammatory Biomarkers	Role	Principal Site of Secretion	Effects
Dong and Ren (2014) [60]	Leptin	Protective (Regulated)	Adipose tissue (adipocytes)	Facilitates glucose utilization and improves insulin sensitivity
Lara-Castro, Fu and Garvey (2007) [61]	Adiponectin	Protective (Regulated)	Adipose tissue (adipocytes)	Positive effects on insulin sensitization. Protects against T2DM
Varela et al. (2011) [62]	Ghrelin	Protective (Regulated)	Stomach	Protects vasculature by antagonizing vasoconstrictors and stimulating lypolysis
Malgorzewicz, Skrzypczak-Jankun and Jankun (2013) [63]	Plasminogen Activation Inhibitor – 1	Protective (Regulated)	Endothelial cells	Regulates ECM remodelling, fibrinolysis and cell-associated proteolysis
Viazzi et al. (2014) [64], El Ridi (2017) [65]	Uric Acid (hyperuricemia)	Pro-inflammatory	Liver (purine catabolism)	Promotes increased expression of inflammatory mediators
Bălăşoiu et al. (2014) [66]	Tumor Necrosis Factor – Alpha	Pro-inflammatory	Abdominal adipose tissue	Systemic inflammation associated with insulin resistance and hypertriglyceridemia
Chedraui et al. (2014) [67]	Interleukin – 6	Pro-inflammatory	Immune cells (M1 macrophages)	Vascular damage and impaired glucose metabolism
Nishida, Moriyama, Sugita and Yamauchi-Takihara (2007) [68]	Interleukin – 10	Anti-inflammatory	Immune cells (M2 macrophages)	Modulates systemic inflammation Promotes tissue remodelling
Landar et al. (2006) [69]	Oxidized LDL	Pro-inflammatory	Product of lipid oxidation	Cell damage and apoptosis Dyslipidemia Vascular pathology
Krzystek-Korpacka et al. (2013) [70], Litvinov (2012) [71]	Paraoxonase – 1	Antitoxic and Antioxidant	Liver	Reduces lipid peroxidation Protects tissues against oxidative stress


Pro-inflammatory
Anti-inflammatory
Metabolic Syndrome
Cytokine Dysregulation
Systemic Inflammation
Joint Damage

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