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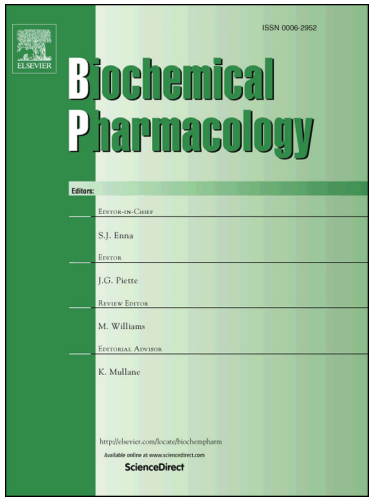

Review

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Adipokines: linking metabolic syndrome, the immune system, and arthritic diseases

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Abstract:

Metabolic syndrome (MetS) represents a cluster of metabolic and cardiovascular complications, including obesity and visceral adiposity, insulin resistance, dyslipidemia, hyperglycemia and hypertension, which directly increase the risk of cardiovascular diseases (CVD) and diabetes mellitus type 2 (DM2). Patients with arthritic diseases, such as rheumatoid arthritis and osteoarthritis, have a higher incidence of CVD. Although recent advances in the treatment of arthritic diseases, the incidence of CVD remains elevated, and MetS has been identified as a possible link between CVD and arthritic diseases. Chronic low-grade inflammation associated with obesity has been established as a significant contributing factor to the increased prevalence of MetS. Adipokines, which play important physiological roles in metabolic activities contributing to the pathogenesis of MetS, are also involved in the regulation of autoimmune and/or inflammatory processes associated with arthritic diseases. Therefore, MetS and dysregulated secretion of pro-inflammatory adipokines have been recognized as a molecular link between CVD and arthritis diseases. In the present paper, we review recent evidence supporting the role played by adipokines, in particular leptin, adiponectin, and lipocalin-2, in the modulation of the immune system, MetS and arthritic diseases. The underlying cellular and molecular mechanisms are discussed, as well as potential new therapeutic strategies.

Keywords: adiponectin, inflammation, leptin, lipocalin-2, metabolic syndrome, obesity, osteoarthritis, rheumatoid arthritis.

1. Introduction

Metabolic syndrome (MetS) refers to a cluster of metabolic abnormalities including obesity, insulin resistance (IR), dyslipidemia, hyperglycemia, and hypertension. These factors directly increase the risk of cardiovascular morbidity and mortality, by approximately two times as those without the syndrome [1], as well as diabetes mellitus 2 (DM2), with around five-fold greater risk [2]. MetS lacks a universally accepted definition since different medical associations disagree with diagnostic criteria [3]. In 2009, the International Diabetes Federation and the American Heart Association/National Heart, Lung, Blood Institute (AHA/NHLBI) have developed a unified clinical definition. Accordingly, insulin resistance is not a crucial factor for MetS diagnosis, but a patient should have at least 3 among the 5 following criteria: visceral obesity, elevated blood pressure, high triglyceride levels, low high-density lipoprotein cholesterol (HDL-C) levels and/or elevated fasting glucose [4]. It is estimated that MetS concerns 10%-40% of the population varying according to the diagnostic criteria, gender, age, genotype, ethnicity, lifestyle, diet, and physical activity [5]. Moreover, MetS prevalence is rapidly increasing with lifestyle modifications, such as increased calorie intake, reduced physical activity, and sedentary conduct, and has been related to high incidence pathologies related to obesity, including fatty liver disease, polycystic ovary syndrome, osteoarthritis or rheumatoid arthritis [5]; thus, becoming one of the major health problems in industrialized countries.

As denoted, MetS underlies a complex and diverse range of pathologic conditions. However, the etiology and the cellular and molecular mechanisms of MetS and its components still need to be clearly understood. Chronic inflammation associated with obesity has been established as a significant factor underlying the pathophysiology of insulin resistance and MetS [6]. Obesity, and especially the expansion of visceral fat depots, leads to a 'chronic low-grade inflammatory state' [7] characterized by a deregulated secretion of adipose tissue-derived factors, i.e. adipokines. Altered synthesis and secretion of adipokines are associated with cellular changes in adipose tissue, namely adipocyte hypertrophy, phenotype and localization of immune cells, vascular and structural cells [7]. Moreover, the expression of these biologically active proteins varies with the site of WAT depot. In particular, the expansion of visceral WAT is associated with increased levels of adipokines [8]. High-calorie diets can also promote a pro-inflammatory state and thus adipokine production in WAT multi-depot organ, such as heart, kidneys or adventitia of major blood vessels [8]. Interestingly, adipokines secretion by epicardial adipose tissue has been associated with coronary artery disease, MetS, and DM2 [9]. Adipokines have also been described to affect the insulin sensitivity in liver, skeletal muscles and adipose tissue itself, and to be involved in the regulation of the innate and adaptive immune system. Moreover, pro-inflammatory adipokines are involved in endothelial dysfunction and atherosclerosis, being pointed out as important players in cardiovascular disease (CVD) [10]. Thus, adipokines provide a connection between the inflammatory state of MetS, IR and endothelial dysfunction.

There is increasing evidence demonstrating a higher incidence of CVD in patients with

arthritic diseases, namely osteoarthritis (OA) [11] and rheumatoid arthritis (RA) [12]. Although the recent advances in the treatment of arthritis diseases, the CVD incidence in these patients remains elevated, and MetS has been pointed as an underlined responsible. Moreover, as important modulators of bone and cartilage metabolism as well as immune responses, adipokines have been described as key factors in the pathophysiology of arthritis diseases [13]. The present review discusses the recent data on the inter-relations between arthritis diseases and metabolic syndrome or CVD, evidencing adipokines as molecular linkers (Figure 1). A better understanding of pathophysiologic mechanisms of MetS and arthritis diseases is mandatory to develop efficient and safe treatments against the progression of these diseases and their associated comorbidities.

2. Metabolic syndrome and arthritis diseases

Osteoarthritis, the most common form of arthritis, is a progressive degenerative and multifactorial disease of the entire joint, affecting the articular cartilage, meniscus, ligaments, bone, and synovium. It is characterized by molecular, anatomic, and/or physiologic derangements, including abnormal metabolism of joint tissues, cartilage degradation, bone remodeling, osteophyte formation, inflammation and loss of normal joint function [14,15]. It has been verified that the prevalence of MetS is higher in OA subjects [16,17]. Inflammation, oxidative stress, common metabolites, and endothelial dysfunction were proposed to link metabolic OA aetiologically to MetS [18]. Moreover, Zhuo and co-workers proposed that metabolic OA should be a new facet of MetS definition, evidenced by the strong associations and shared mechanisms with MetS components, such as hypertension, dyslipidemia, hyperglycaemia and obesity [18]. Furthermore, obesity, the main MetS risk factor, is also a well-known risk factor for OA incidence, progression, and disability. Besides the patent biomechanical effect of overweight on the joint, there is increasing evidence that a metabolic component links obesity with OA [19]. In particular, adipokines have been highlighted as important modulators of joint homeostasis implicated in the pathogenesis of OA [20,21].

Rheumatoid arthritis is a chronic inflammatory joint disease defined by synovial membrane inflammation and hyperplasia ("swelling"), destruction of cartilage and bone ("deformity"), production of autoantibodies (rheumatoid factor and anti-citrullinated protein antibody) - autoimmune disease, and systemic features like pulmonary, skeletal, cardiovascular, and psychological complications [22,23]. It was verified that MetS is commonly present in RA patients [12,24] and that the risk of developing moderate-to-severe RA was higher in patients with MetS than those without it [25]. Furthermore, the disease activity was related to the number of MetS parameters present, indicating that MetS might have inflammatory milieu that promotes the occurrence of more severe RA [25]. These data indicated the presence of common modulators cross-linking MetS and RA. Accordingly, adipokines have been indicated as modulators of metabolic disorders as well as autoimmune rheumatic diseases [13,20].

Given the great evidence on the pleiotropic roles of adipokines, here we summarized the

actions of leptin, adiponectin, and lipocalin-2 in immunity as well as in MetS and arthritis diseases. A schematic representation of adipokines as molecular linkers between metabolic syndrome, immune system, and arthritic diseases can be found in Figure 1, while Table 1 overviews their biological activity in multiple organs.

3. Leptin

Leptin, the forerunner and best-characterized member of the adipokine family, is a 16 kDa non-glycosylated cytokine-like hormone encoded by the obese (*ob*) gene, the murine homolog of human *LEP* gene [26]. Leptin is mainly produced by adipocytes and thus, its levels are mostly dependent of the white adipose tissue (WAT) mass and body mass index, but some inflammatory factors can also modulate leptin synthesis [27]. This hormone regulates food intake and energy consumption by inducing anorexigenic factors and suppressing orexigenic neuropeptides on hypothalamic nuclei [28]. In fact, mutations in either *ob* or *db* gene (encoding leptin and leptin receptor, respectively) result in severe obesity in murine models. Moreover, leptin is also implicated in other physiologic functions, like insulin secretion, atherosclerosis, bone and cartilage metabolism, inflammation, infection and immune responses [20,29]. Accordingly, leptin receptors [LEPR; or Ob receptors (Ob-R)] is expressed throughout the cells of innate and adaptive immune system, blood vessels, as well as cardiomyocytes, suggesting leptin as an important linker of neuroendocrine, cardiovascular and immune systems [29,30].

Leptin receptors , are a class I cytokine receptor family from diabetes (*db*) gene [31]. There are at least six Ob-R isoforms that possess identical extracellular binding domains but differ in the length of the cytoplasmic domain: a soluble isoform (Ob-Re), four short isoforms (Ob-Ra, Ob-Rc, Ob-Rd and Ob-Rf), and a long isoform (Ob-Rb), which has a full intracellular domain that allows the transduction of signal via Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathways [32]. Alternatively to the canonical JAK/STAT pathway, leptin receptors also signal via extracellular signal–regulated kinases (ERK) 1/2, p38 mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinases (JNK), Protein kinase C (PKC), Src homology region 2-containing protein tyrosine phosphatase 2 (SHP2)/ Growth factor receptor-bound protein 2 (GRB2) and Phosphoinositide 3-kinases (PI3K)/Akt pathways [20,28]. In humans, common obesity is frequently characterized by hyperleptinemia and unresponsiveness to exogenous leptin administration. This leptin resistance state is possible derived by a decreased in the levels of cell surface Ob-Rb, down-regulation of positive regulators or up-regulation of negative regulators, including suppressor of cytokine signaling 3 (SOCS-3) and protein tyrosine phosphatase 1B (PTP1B) [20,28,31]. Therefore, it is important to take into account leptin responsiveness when interpreting the leptin effects in peripheral tissues as well in the development of leptin-directed therapeutic approaches.

3.1. Leptin in innate and adaptive immunity

Leptin has been described as a potent regulator of the immune system (extensively reviewed in [20]). In innate immunity, leptin can augment the cytotoxicity of natural killer (NK) cells, and the activation of granulocytes, namely neutrophils, basophils and eosinophils, as well as macrophages and dendritic cells (DCs), thus exacerbating and perpetuating inflammatory conditions [20]. Leptin enhanced immature NK survival through Bcl-2 and Bax gene modulation [33] and increases NK cytotoxicity via STAT3 activation and expression of IL-2 and perforin [34]. In neutrophils, leptin mediates chemotaxis and infiltration via p38 MAPK and Src kinases [35], and induces survival by delaying the cleavage of Bid and Bax, mitochondrial release of cytochrome C and activation of caspase-3 and -8 through PI3K, NF-κB and MAPK pathways [36]. Leptin enhances the release of pro-inflammatory mediators IL-1β, IL-6, IL-8, and MCP-1, up-regulates the expression of cell surface adhesion molecules ICAM-1 and CD18 while down-regulates ICAM-3 and L-selectin [37] in eosinophils. Moreover, this hormone acts as an eosinophil survival factor by delaying their apoptosis via JAK, NF-κB and p38 MAPK signaling pathways [37]. In basophils, leptin-induced migratory activity promoted IL-4 and IL-13 secretion, increased the cell surface expression of CD63, and augmented basophils degranulation in response to aggregation of IgE or its high-affinity receptor FcεRI [38]. Thus, leptin has a positive action in cell survival, cytokines release and chemotaxis of neutrophils, eosinophils, and basophils. Accordingly, in obese hyperleptinemic individuals, neutrophils have increased superoxide release and chemotactic activity [39], and eosinophils demonstrate greater adhesion and chemotaxis towards eotaxin and CCL5 [40]. Moreover, in these individuals, NK function is impaired compared to lean subjects, likely due to the development of leptin resistance [41],

In macrophages, leptin treatment promoted phagocytic activity, via modulation of cAMP levels [42], intracellular ROS generation [43], and chemotactic responses, through intracellular calcium influx, JAK/STAT, MAPK and PI3K pathways [44]. Furthermore, leptin-treated human macrophages had increased M2-phenotype surface markers but were able to secrete M1-typical cytokines, like TNF-α, IL-6, IL-1β. IL-1ra, IL-10, and MCP-1, indicating a role for leptin in the determination of the adipose tissue macrophages phenotype [45]. Leptin acts as an activator of human DCs by up-regulation of IL-1β, IL-6, IL-12, TNF-α, and MIP-1α production, increasing the immature DC migration and their chemotactic activity, licensing them towards Th-1 priming [46]. Moreover, leptin induces DC survival by reducing apoptosis via modulation of NF-κB, PI3K/Akt, Bcl-2 and Bcl-xL [47,48]. The role of leptin in DC activation, chemoattraction, and survival, with further implications on DC maturation ad migration was also verified in *Lepr*-deficient (*db/db*) and leptin-deficient (*ob/ob*) murine models [47,49,50].

The functions of leptin in adaptive immunity were first evidenced using *ob/ob* and *db/db* mice, which demonstrated thymus atrophy, T-cell lymphopenia, and reduced delayed-type hypersensitivity, which were reversed by leptin administration in *ob/ob* mice [49–51]. Later on, the effect of leptin in T and B cell biology have been extensively studied. Leptin promoted the proliferation of human naïve (CD45RA+)CD4+ T cells [51], whereas it negatively affected the

proliferation of Foxp3+CD4+CD25+ T regulatory (Treg) cells [54]. Accordingly, morbidity obese children (congenitally leptin-deficient) had decreased number of circulating CD4+ T cells, and impaired T cell proliferation and cytokine release, which were rescued by treatment with recombinant human leptin [55], and obese subjects demonstrated a reduced number of CD4+CD25+CD127-Foxp3+ Treg cells [56]. Leptin also promoted CD4+ T cell polarization towards a pro-inflammatory Th1 phenotype, which secretes IFNγ and IL-2, rather than anti-inflammatory Th2 response, which secretes IL-4 [57]. Furthermore, articular injection of leptin enhanced Th17 cells in joint tissues in collagen-induced arthritis mice model, leading to the exacerbation of inflammation and early onset of arthritis [58]. It was verified that leptin modulated Th17 cells differentiation via retinoic acid-related orphan receptor (ROR)γt and STAT3 activities [59]. Thus, leptin diminishes Treg proliferation, whereas it augments Th17 cell proliferation and responsiveness, pointing out the therapeutic potential of the leptin system in autoimmunity and inflammation. In B lymphocytes, leptin promoted cell homeostasis via suppression of apoptosis and induction of cell cycle entry via activation of Bcl-2 and cyclin D [60], and mediated the release of pro- (TNF-α and IL-6) and anti-inflammatory (IL-10) cytokines through JAK/STAT and p38MAPK-ERK1/2 pathways [61]. Accordingly, *db/db* and *ob/ob* mice had a reduced number of peripheral blood and bone marrow B lymphocytes. Moreover, fasted mice, characterized by low serum leptin levels, presented a decreased number of pro-B, pre-B and immature B cells and increased levels of mature B cells in bone marrow, all reversed after leptin administration [60–62].

3.2. Leptin and metabolic syndrome

It is widely accepted that elevated leptin levels -hyperleptinemia- are correlated with MetS and cardiovascular diseases, including atherosclerosis, hypertension, stroke and myocardial infarction [65] (Figure 2). The high-fat induced rodent model of metabolic syndrome presented hyperleptinemia, hyperinsulinemia, increased body weight and energy intake, impaired glucose tolerance, as well as cardiovascular complications, like endothelial dysfunction, cardiac fibrosis, and cardiac hypertrophy [66,67]. Accordingly, hyperleptinemia was observed in both male and female patients with metabolic syndrome [68], and variations on leptin concentrations were correlated with MetS score in Taiwanese adults [69]. In fact, leptin levels were pointed out as an obesity-independent predictor of MetS development, which could be related to the development of glucose intolerance and insulin resistance [70]. Moreover, leptin levels were positively correlated with insulin resistance and triglycerides concentration, and negatively correlated with HDL-cholesterol, typical parameters for early signs of MetS [71]. The leptin-deficient *ob/ob* mice model developed cardiomyopathy evidenced by impaired cardiac relaxation and contractility, partially due to augmented apoptosis and deregulation of intracellular Ca2+ reuptake in sarcoplasmic reticulum [72]. In patients with acute ischemic stroke, elevated leptin levels were more often present in patients with metabolic syndrome, being pointed as an independent risk factor for stroke in obese individuals [67]. Patients with coronary heart disease also demonstrated elevated leptin levels,

which were as an independent risk factor for disease development [73]. Noteworthy, in a 20-year follow-up study, little association was found between leptin, the prevalence of metabolic syndrome and cardiovascular death [74]. Moreover, some studies evidenced a cardioprotective role for leptin by attenuation of cardiac apoptosis and thus protecting against experimental and clinical ischemia, likely through JAK/STAT3 and AMPK activation [73–75]. Altogether, these findings indicated that leptin may be a double-edged sword for the cardiovascular system and further studies are needed to clarify the actions mechanisms of leptin and the role of hyperleptinemia in CVD under obesity and MetS.

3.3. Leptin and arthritic diseases

Besides to its well-known role on immune responses, leptin has been described as a central factor in the pathophysiology of arthritic diseases due to its ability to modulate bone and cartilage metabolism [20] (Figure 2).

3.3.1. Osteoarthritis

Leptin has been extensively associated with cartilage metabolism and OA. OA human chondrocytes produced higher levels of leptin than from normal cartilage[78], being the pattern of leptin expression related to the grade of cartilage destruction [79,80]. Moreover, the leptin levels were found elevated in serum, IPFP, synovial tissues and cartilage of OA patients compared with healthy controls [81,82]. Very recently, the leptin-induced OA phenotype was correlated with the up-regulation of inflammatory mediators, MMPs, growth factors and osteogenic genes [83]. Accordingly, the NEIRID lab demonstrated that leptin, in synergy with IL-1β, induced the expression of pro-inflammatory factors, such as IL-6, IL-8, NO, NOS2, PGE2, and COX2 in chondrocytes [84]. Recently, it was demonstrated that leptin also regulates the production of IL-6, IL-8, and CCL3 by CD4+ T cells in OA patients, but not in healthy individuals [85], revealing new action mechanisms of leptin in the immune system and OA pathophysiology. Besides regulating pro-inflammatory mediators expression, leptin also leads to OA-related joint destruction by inducing MMPs expression. In particular, MMP-1, -2, -3, -8, and -13, ADAMTS4 and S5, while proteoglycan and FGF2 were reduced [86]. Leptin is also responsible for the perpetuation of cartilage degradation through VCAM1 induction in human primary chondrocytes, which induces the migration of leukocytes and monocytes to inflamed joints via chemoreceptors activity [27]. Of late, the role of microRNA miR-27, which directly targets the 3'-untranslated region of leptin, in OA has been evidenced. OA chondrocytes presented low levels of miR-27 and the overexpression of this microRNA in a preclinical model of OA in rats led to increased levels of IL-6, IL-8, MMP-9 and MMP-13. This indicated the potential protective role of miR-27 likely by targeting leptin [87]. Leptin also modulated osteoblast function and thus bone metabolism leading to joint destruction in OA patients [21,88]. Altogether, this data pointed out leptin as an important modulator of inflammation, cartilage catabolic activity, as well as cartilage and bone remodeling, all associated with OA

pathophysiology.

3.3.2. Rheumatoid arthritis

Leptin has been implicated in RA development; however, there are contradictory results and large cohort studies are necessary. It was verified that leptin levels were elevated in RA patients, being its synovial fluid and serum levels correlated with disease duration, radiographic joint damage, and parameters of RA activity (Olama, Senna, and Elarman 2012). However, leptin has also been associated with reduced radiographic joint damage [90], which could be related to the anabolic action of leptin [78]. Leptin-deficient mice evidenced a less severe antigen-induced arthritis, reduced levels of TNF-α and IL-1β, a defective cell-mediated immunity, and a shift towards Th2 cell response [91]. Interestingly, the reduction of leptin levels by fasting in RA patients improved the RA clinical symptoms [92]. Clinical studies evaluating the effect of PPARγ agonists () are ongoing to target inflammation and cardiovascular complications associated with RA [93]. Of note, these agonists are modulators of insulin sensitivity, which is affected by leptin levels. Moreover, leptin protein mutants with antagonist action as well as monoclonal antibodies against leptin and LEPR have been pointed out as promising therapeutic strategies for RA [94]. Therefore, deep knowledge of the leptin action mechanisms would be crucial for the treatment of RA.

4. Adiponectin

Adiponectin, also called GBP28, apM1, Acrp30 or AdipoQ, is a 244-residue protein with structural homology to collagen type VIII and X, as well as complement factor C1q. This adipokine is mainly produced in adipose tissue and it is found in different molecular forms: the globular adiponectin (gAPN), the full-length adiponectin (fAPN), the low MW (LMW) adiponectin, the medium MW (MMW) adiponectin, the high MW (HMW) adiponectin, and the serum albumin bonded LMW form (Alb-LMW) [95,96]. Adiponectin acts specifically through two receptors, the AdipoR1, predominantly present in the skeletal muscle, and AdipoR2, mainly found in the liver. Binding to Adipo receptors leads to activation of AMPK, PPAR-α and -γ, among other signaling pathways [96]. In morbidly obese patients, circulating levels of adiponectin tend to be low and increase after weight loss or treatment with thiazolidinediones (PPAR agonists), which enhance insulin sensitivity [96]. In fact, adiponectin works as an endogenous insulin sensitizer by stimulating glucose uptake via an increase of fatty acid oxidation and reduction of glucose synthesis in the liver. AMPK signaling has been implicated in the insulin-sensitizing activity of adiponectin in the liver, while AMPK, PPAR-α, and Ca2+ are involved in adiponectin ability to modulate fatty acid and glucose metabolism [96]. Adiponectin knockout mice develop severe insulin resistance and exhibit lipid accumulation in muscles when placed on a high-fat/sucrose diet, however, no dramatic effects were observed when placed in a normal diet [97]. In fact, adiponectin is encoded by the ADIPOQ gene located on the chromosome 3q27, a locus linked with susceptibility to develop diabetes and CVD [97]. Additionally, there is increasing evidence revealing the importance of adiponectin in

inflammation-related diseases, namely CVD, T2DM, MetS, OA and RA, likely due to its action on the innate and adaptive immune system [98] (Figure 2).

4.1. Adiponectin in innate and adaptive immunity

Adiponectin has been recognized as an important modulator of the immune system, but whether it acts as pro- or anti-inflammatory adipokine is still a matter of intense debate. In macrophages, adiponectin was demonstrated to suppress differentiation and classical M1 activation via down-regulation of pro-inflammatory cytokines, like TNF-α, IL-6, and CCL2, whereas it promotes M2 proliferation and activation leading to the expression of anti-inflammatory cytokines, namely arginase-1, IL-10 and MgI-1 [98]. This adipokine also regulates the activity of neutrophils, eosinophils, NK cells and DCs [98,99]; however, it remains unclear if the cell's functions are positively or negatively regulated by adiponectin. These apparent paradoxical, dual effects might be related to different adiponectin configurations [95]. In particular, gAPN but not fAPN adiponectin impaired LPS-induced ERK1/2 activation in Kupffer cells, while gAPN and HMW but not MMW or LMW augments NF-κB activation in monocytic cells [95].

In adaptive immunity, adiponectin was described to activate plasma B cells and stimulate B cell-derived peptide PEPITEM secretion, thus inhibiting the migration of memory T cells [100]. Adipo receptors are up-regulated after T cells activation and adiponectin leads to decreased antigen-specific T cell proliferation and cytokine production through augment of T cell apoptosis [101]. Furthermore, adiponectin enhances Th1 differentiation and DCs, treated with adiponectin, induced both Th1 and Th17 responses in allogenic T cells, contributing to enhanced pro-inflammatory responses [101]. A deeper understanding of the adiponectin's effects and mechanisms in innate and adaptive immune cells will be of relevance for developing new therapeutic strategies directed against adiponectin system.

4.2. Adiponectin in metabolic syndrome

Unlike most of the other adipokines, adiponectin seems to have a protective role in MetS and T2DM. Circulating adiponectin levels are decreased in patients with obesity, coronary artery disease, diabetes, and hypertension, as well as in IR and diabetic animals [100–103], and increased with weight loss [106], physical training [107], and the use of insulin-sensitizing drugs [106]. This suggests that obesity-related hypoadiponectinemia is reversible [108]. Moreover, adiponectin secretion is inhibited by pro-inflammatory factors, like IL-6 and TNFα [109], indicating the potential role of inflammation in the development of hypoadiponectinemia associated with IR and obesity. Adiponectin was also negatively correlated with triglyceride levels whereas positively associated with plasma HDL levels, even in the absence of other MetS risk factors [110,111]. In fact, several studies indicated adiponectin as MetS biomarker. A strong negative correlation between the MetS score and serum adiponectin levels has been verified [112]. In a prospective cohort study, decreased adiponectin levels were progressively been associated with increasing

incidence of MetS [113]. Patients with nascent MetS, and thus without confounding CVD and/or T2DM, presented lower adiponectin levels than controls [114]. Moreover, low adiponectin plasma levels have been demonstrated to predict IR and T2DM [102,115,116]. Consequently, normal or even elevated adiponectin concentrations are considered to be protective against MetS and T2DM [117]. Adiponectin administration reduced the plasma glucose levels by improving the insulin action in diabetic and healthy mice [115–117].

As mentioned above, obesity, the major risk factor of MetS, is characterized by altered secretion of adipokines. Accordingly, adiponectin gene expression and circulating levels were inversely correlated with adiposity and waist circumference (WC) in patients with MetS, where intra-abdominal fat mass was found to affect the levels of circulating adiponectin [1,120]. Lower adiponectin levels were also found in obese patients with MetS, and in visceral obesity, which is negatively associated with IR [116,121], and in [122]. Adiponectin concentrations have also been inversely associated with endothelial dysfunction, hypertension, and markers of vascular inflammation, and thus, with CVD [121–123]. In particular, epidemiological data pointed hypoadiponectinemia as a predictor of imminent myocardial infarction [126,127] or hypertension development [128]. Furthermore, patients with arthritis and MetS demonstrated lower levels of adiponectin that arthritic patients without MetS. In RA patients, low adiponectin levels were suggested to be implicated in the development of RA-associated CVD [129]. Moreover, it was verified that in RA patients undergoing anti-TNFα therapy, the adiponectin concentrations were independently and inversely correlated with high-grade inflammation, via a mechanism not likely to be mediated by TNF-α [129].

4.3. Adiponectin in arthritic diseases

4.3.1. Osteoarthritis

Adiponectin has been evidenced to be implicated in the pathophysiology of OA. Serum and plasma levels of adiponectin were increased in OA patients, compared to healthy subjects [130], being higher in patients with radiologically most severe OA disease [131], as well as in patients with erosive OA in relation to non-erosive OA [132]. In fact, adiponectin was proposed as a biomarker for OA [133]. Moreover, adiponectin serum levels have been correlated with OA biomarkers and local synovial inflammation [131,134]; however, no association with radiographic hand OA was observed [135]. This adipokine could be expressed by synovial fibroblasts, IPFP, osteophytes, cartilage, and bone tissues within the joint [136], and its levels in OA synovial fluids were correlated with aggrecan degradation [137]. Most of the results indicated a pro-inflammatory and catabolic action of adiponectin by increasing the production of NO, IL-6, IL-8, VCAM-1, TIMP-1, MMP-1, -3, and -13 [82,129,136–138], which lead to cartilage degradation and OA pathogenesis. Nevertheless, a protective role for adiponectin in the OA pathogenesis has also been reported. In particular, this adipokine down-regulated IL-1β-induced MMP-13 expression and increased TIMP-2 production in human chondrocytes [141], while its serum concentration was

lower in a spontaneous animal OA model (STR/Otr mice) than in controls [142]. This contradictory evidence could be derived from patient heterogeneity, different study protocols, or the significance of adiponectin accordingly to the phase and severity of OA. Furthermore, exercise and mechanical loading were indicated as positive modulators of adiponectin levels, with potential effect in preventing bone loss [143,144]. Adiponectin was demonstrated to stimulate osteoclast proliferation and mineralization through bone morphogenetic protein (BMP)-2 and activation of p38 MAPK signaling [145,146], but there are contradictory results [147]. Altogether, the present data indicated that adiponectin modulated cartilage and bone metabolism, as well as biomechanical properties of the joint. However, further studies are necessary to clarify the exact role of this adipokine in OA pathogenesis.

4.3.2. Rheumatoid arthritis

Adiponectin has also been evidenced as a modulator of RA pathophysiology. RA patients demonstrated increased serum and synovial adiponectin levels compared with healthy individuals, being its baseline levels predictive of RA radiographic progression [90,148,149]. Accordingly, it has been verified that adiponectin, alone or in combination with IL-1β, increases the production of inflammatory mediators, including IL-6, IL-8, and PGE2, in RA synovial fibroblasts [86,149]. The IL-6 production induced by adiponectin is dependent on Adipo1R/AMPK/p38MAPK/NF-κB signaling pathway [86,149]. Interestingly, the anti-IL-6 receptor monoclonal antibody has been approved to RA treatment in several countries. Moreover, adiponectin induced the expression of MMP-1, MMP-13, and VEGF in synovial cells and boosts joint inflammation through the induction of cytokine production and recruitment of immune cells into the synovium [86]. Therefore, adiponectin was pointed out as an important player contributing to synovitis and joint destruction in RA. However, *in vivo* data indicated that this adipokine demonstrated quite different actions in RA. In a preclinical model of collagen-induced mice arthritis, adiponectin administration mitigated arthritis severity along with a decrease in pro-inflammatory markers, such as TNF-α IL-1β, and MMP-13, in the joint [150]. Thus, further data from basic research and clinical observations in large-scale cohort studies will be fundamental to better elucidate the action of adiponectin in RA.

5. Lipocalin-2 (LCN2)

Lipocalin-2 (also called neutrophil gelatinase-associated lipocalin-NGAL, p25, 24p3, migration-stimulating factor inhibitor, α-1-microglobulin-related protein, human neutrophil lipocalin, siderocalin or uterocalin) is a glycoprotein encoded by a gene located at the chromosome locus 9q34.11 [151]. Initially identified in human neutrophils granules and mouse kidney cells [152,153], WAT is its major source. However, LCN2 is also expressed in immune cells, liver, spleen, and chondrocytes [154]. LCN2 circulates as a 25 kDa monomer, 46 kDa homodimer or as a covalent complex with MMP-9, blocking MMP-9 auto-degradation [155,156]. Two receptors have been proposed to LCN2: the megalin/glycoprotein GP330, an LDL receptor that also binds human LCN2,

and the transporter protein SLC22A17 (24p3R) that binds to mouse LCN2 [157]. Although less studied than leptin or adiponectin, LCN2 has been suggested as an important modulator of the immune system with potential implications in the pathophysiology of metabolic syndrome and arthritis diseases [13,21,158] (Figure 2).

5.1. LCN2 in immune system

The members of lipocalin family posses a hydrophobic ligand binding pocket that confers the ability to bind and transport LPS, steroids, fatty acids, iron, and in the case of LCN2, siderophores [159,160]. By this way, LCN2 binds to enterobactin, a siderophore of Gram-negative bacteria responsible for iron transport. By depleting bacterial iron stores, which is essential for bacterial growth, LCN2 exhibits bacteriostatic activity with potential effects on the gastrointestinal tract protection against pathogens [161]. Besides its role in transport small lipophilic molecules, LCN2 has been implicated in the induction of hematopoietic cells [162] and in the modulation of the immune system. The promoter region of LCN2 comprises binding sites for key inflammatory transcription factors, namely NF-κB, C/EBP, STAT-1 and -3 [163]. In accordance with this, LCN2 was described as an anti-inflammatory regulator of M1/M2 polarization through NF-κB/STAT3 loop activation [164]. Moreover, in adaptive immunity, LCN2 was described to induce human leucocyte antigen G (tolerogenic mediator) on CD4+ T cells, and to increase the expansion of T reg cells in healthy individuals [151]. Taking into account the immunoregulatory activity of LCN2, further studies should evaluate the therapeutic potential of LCN2 in immunosuppressive therapy efficacy, tolerance induction in transplants, and in immune system disorders, including MetS, CVD, OA, and RA.

5.2. LCN2 in metabolic syndrome

The LCN2 concentrations have been associated with various metabolic and inflammatory parameters [149, 156, 163]. In particular, LCN2 circulating levels are positively correlated with adiposity, hyperglycaemia, insulin resistance, and hypertriglyceridaemia, but negatively associated with HDL cholesterol [165]. The LCN2 expression is generally increased in obesity and is reduced by thiazolidinedione treatment [151]. Moreover, there is increasing evidence suggesting that LCN2 contributed to the development of obesity-related pathologies, like T2DM and CVD. Circulating LCN2 levels were increased in coronary heart disease patients [165]. Since LCN2 inhibits MMP9 inhibition, its increased levels might lead to increased proteolytic activity and collagen degradation turning on atherosclerotic plaques into vulnerable plaques [165]. MetS patients demonstrated a significant correlation between insulin resistance and LCN2 levels [165]. Accordingly, serum LCN2 levels were suggested as a useful biomarker for evaluating the clinical outcomes of obesity-related metabolic and cardiovascular complications [165].

5.3. LCN2 in arthritic diseases

LCN2 can be produced at joint tissues in response to inflammatory mediators as well as to mechanical loading. In particular, LCN2 expression is augmented by IL-1β, LPS, dexamethasone, adipokines leptin, and adiponectin, as well as osteoblast conditioned medium in chondrocytes. Of note, NO controls the LCN2 expression in chondrocytes, indicating a feedback loop regulation of its expression. In osteoblasts, LCN2 is induced by TNF-α and IL-17, and by the absence of mechanical loading, likely contributing to bone metabolism through stimulation of osteoclastogenic factors, receptor activator of NF-κB ligand and IL-6, and inhibition of the osteoclastogenic factor osteoprotegerin [151].

In OA patients, the synovial fluid is enriched with LCN2/MMP9 complexes that have been involved in the reduction of chondrocyte proliferation, as well as matrix and cartilage degradation [151,166]. Of late, glucocorticoids (commonly used in OA and RA treatment), alone or in combination with IL-1, have been demonstrated to increase LCN2 expression via corticoid receptor and PI3K, ERK1/2 and JAK2 pathways in immortalized mouse chondrocytes [167]. Moreover, transcription factor E74-like factor 3 and NF-κB also modulated LCN2 expression in chondrocytes [168]. Although these data indicated the involvement of LCN2 in joint pathophysiology, one study verified that LCN2 overexpression in mouse cartilage did not induce OA pathogenesis and that knockout of LCN2 did not affect cartilage destruction induced by medial meniscus destabilization in mice [169]. Therefore, even though LCN2 could contribute to OA pathophysiology, it is not sufficient by itself to initiate OA cartilage destruction. Further studies will be important to elucidate the action of LCN2 in the development of OA in humans.

RA patients displayed higher LCN2 levels than OA patients in synovial fluid [170]. Using proteome approaches, it has been verified that GM-CSF contributed to RA pathophysiology by increasing LCN2 expression in neutrophils, with consequent induction of transitional endoplasmic reticulum ATPase, cathepsin D and transglutaminase 2 in synoviocytes, which have potential implications in synovial cells proliferation and infiltration of inflammatory cells into the synovium [170]. However, the role of LCN2 in RA etiology and development remains largely unknown.

6. Current and forthcoming therapeutic prospects

Currently available treatments for arthritis diseases show low efficacy, are frequently associated with adverse effects, and as far to achieve disease remission. Due to the lack of self-healing capacity of articular cartilage, OA therapy is challenging and traditional pharmacologic therapies, such as acetaminophen, non-steroidal anti-inflammatory drugs, and opioids, are limited to pain relief [171]. Link MetS with OA evidenced the possibility of introducing new pharmacological interventions. Accordingly, thiazolidinedione and statins are being evaluated as supplements to symptom-alleviating NSAID treatment in OA [18]. However, well-designed, controlled studies for this novel use of conventional drugs are needed.

Currently, there is no cure for RA and treatment strategy focus on early diagnosis and rapid achievement of a low disease activity state. In the last years, several biological disease modifying

anti-rheumatic drugs (DMARD) have emerged, including TNF-inhibitor, anti-CD20 antibody, IL-6 receptor antibody, RANKL antibody, and JAK inhibitor. But, long-term disease remission is not reached for many patients and therefore new therapeutic options are necessary [172]. Some RA treatments have been demonstrated to modulate adipokines levels. In particular, some studies indicated that TNF blockade increased adiponectin levels, but did not change circulating leptin levels [173]. Consequently, the leptin/adiponectin ratio, which is a marker of MetS and insulin resistance, can significantly decrease during biologic therapy [173].

The relationships between MetS and rheumatic diseases are complex, encompassing a variety of influencing factors including obesity, cardiovascular function, metabolic status, and immune system. Accordingly, the treatment of arthritis pathologies seems to influence the risk of developing MetS and vice-versa [12]. Here, we evidenced adipokines as potential links between MetS, the immune system, and arthritis diseases (Figure 1). Thus, a better understanding of adipokines actions and mechanisms is of utmost relevance for developing effective therapies allowing to stop the progression of arthritic diseases as well as MetS and CVD, thereby improving the quality of life of the aging population. So far, the prevention of excessive weight gain must be the first line approach in the prevention of these high-incidence degenerative diseases. This strategy should be a social priority and require deep sociocultural changes, as well as international coordinated medical instructions.

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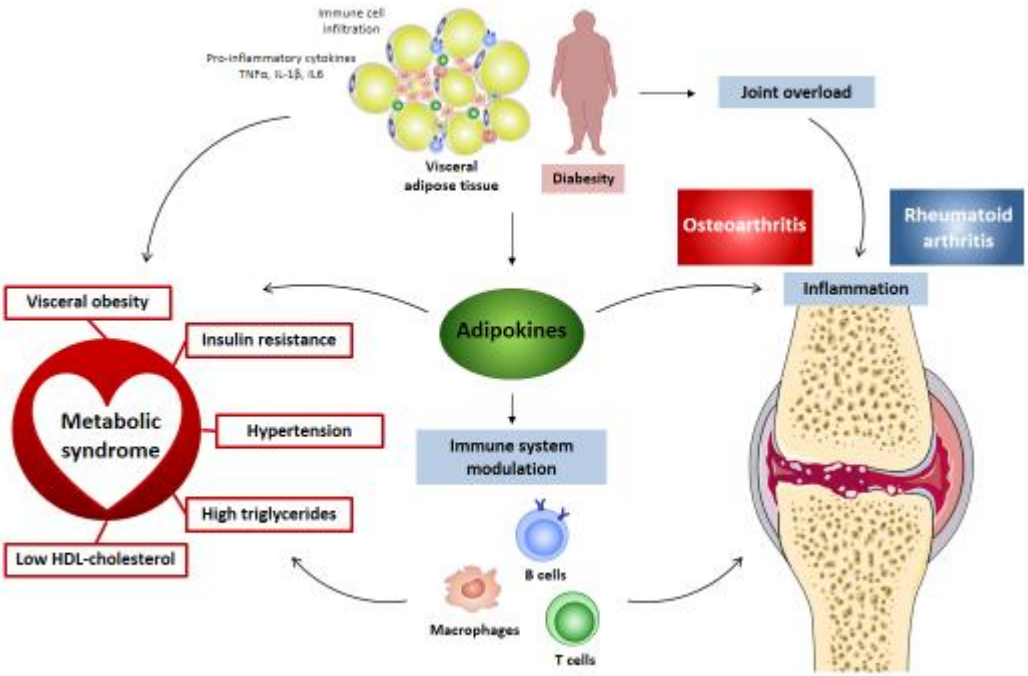
Figure's legend:

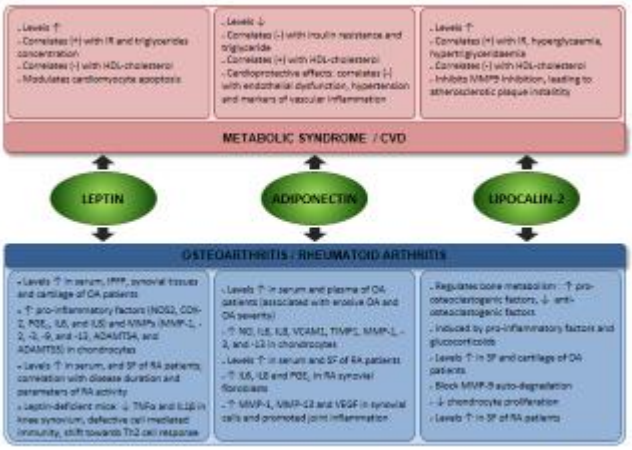
Figure 1. Adipokines as molecular linkers between metabolic syndrome, immune system, and arthritic diseases. Body weight gain, accompanied by white adipose tissue expansion, lead to diabetes, obesity and associated chronic low-grade inflammation. Adipose tissue-derived adipokines cause cartilage degradation and osteoblast dysregulation in subchondral bone, thus promoting joint destruction. Adipokines also play important physiologic roles in metabolic activities contributing to the pathogenesis of metabolic syndrome. By inducing pro-inflammatory cytokine release from innate and adaptive immune cells, adipokines generated an inflammatory environment that prompts metabolic syndrome and arthritis diseases.

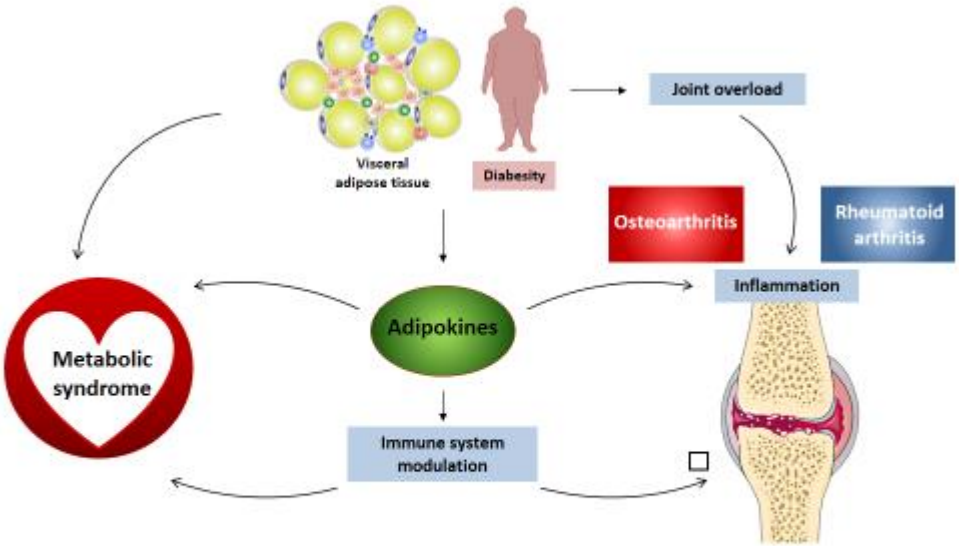
Figure 2. Schematic representation of the biological effects of adipokines in metabolic syndrome and associated cardiovascular disease (CVD), as well as in arthritis diseases (osteoarthritis and rheumatoid arthritis).

Table 1. Effects of leptin, adiponectin, and lipocalin-2 in multiple organs.

	LEPTIN	ADIPONECTIN	LIPOCALIN-2
LIVER	▪ (+) correlation with IR and triglycerides concentration ▪ (-) correlation with HDL-cholesterol	▪ (-) correlation with IR and triglycerides concentration ▪ (+) correlation with HDL-cholesterol	▪ (+) correlationwith IR, hyperglycaemia, hypertriglyceridaemia ▪ (-) correlation with HDL-cholesterol
VASCULAR CELLS	▪ ↓ cardiac apoptosis, through JAK/STAT3 and AMPK activation	▪ (-) correlation with endothelial dysfunction, hypertension and markers of vascular inflammation	▪ ↑ MMP9 proteolytic activity and collagen degradation leading to vulnerable atherosclerotic plaques
IMMUNE CELLS	▪ ↑ NK cytotoxicity ▪ Activation of granulocytes, macrophages and DCs ▪ Polarization of TH cells towards Th1 (pro-inflammatory phenotype) ▪ ↓ Treg cells, ↑ Th17 cells	▪ Modulation of innate immune cells activation ▪ ↑ B cell activation and PEPITEM secretion ▪ ↓ T cell proliferation and cytokine production ▪ ↑ Th1 cells differentiation	▪ Bacteriostatic effect via depletion of iron stores ▪ Anti-inflammatory regulation of M1/M2 polarization ▪ ↑ Treg cell proliferation
JOINT	▪ ↑ pro-inflammatory factors (NOS2, COX-2, PGE_2, IL6, and IL8) in chondrocytes ▪ ↑ MMPs (MMP-1, -2, -3, -9, and -13, ADAMTS4, and ADAMTS5)	▪ ↑ NO, IL6, IL8, VCAM1, TIMP1, MMP-1, -3, and -13 in chondrocytes ▪ ↑ human osteoblast proliferation and mineralization ▪ ↑ IL6, IL8 and PGE_2 in RA synovial fibroblasts ▪ ↑ MMP-1, MMP-13 and VEGF in synovial cells and promoted joint inflammation	▪ Regulates bone metabolism: ↑ pro-osteoclastogenic factors, ↓ anti-osteoclastogenic factors ▪ Induced by pro-inflammatory factors and glucocorticoids ▪ Block MMP-9 auto-degradation ▪ ↓ chondrocyte proliferation


Immune cell infiltration
Pro-inflammatory cytokines TNFα, IL-1β, IL6
Visceral adipose tissue
Diabesity
Joint overload
Osteoarthritis
Rheumatoid arthritis
Inflammation
Visceral obesity
Insulin resistance
Metabolic syndrome
Hypertension
High triglycerides
Low HDL-cholesterol
Adipokines
Immune system modulation
B cells
Macrophages
T cells


- Levels ↑
- Correlates (+) with IR and triglycerides concentration
- Correlates (-) with HDL-cholesterol
- Modulates cardiomyocyte apoptosis
- Levels ↓
- Correlates (-) with insulin resistance and triglyceride
- Correlates (+) with HDL-cholesterol
- Cardioprotective effects: correlates (-) with endothelial dysfunction, hypertension and markers of vascular inflammation
- Levels ↑
- Correlates (+) with IR, hyperglycaemia, hypertriglyceridaemia
- Correlates (-) with HDL-cholesterol
- Inhibits MMP9 inhibition, leading to atherosclerotic plaque instability
METABOLIC SYNDROME / CVD
LEPTIN
ADIPONECTIN
LIPOCALIN-2
OSTEOARTHRITIS / RHEUMATOID ARTHRITIS
- Levels ↑ in serum, IPFP, synovial tissue and cartilage of OA patients
- ↑ pro-inflammatory factors (NOS2, COX-2, PGE2, IL6, and IL8) and MMPs (MMP-1, -2, -3, -9, and -13, ADAMTS4, and ADAMTS5) in chondrocytes
- Levels ↑ in serum, and SF of RA patients, correlation with disease duration and parameters of RA activity
- Leptin-deficient mice ↓ TNFα and IL1β in knee synovium, defective cell mediated immunity, shift towards Th2 cell response
- Levels ↑ in serum and plasma of OA patients (associated with erosive OA and OA severity)
- ↑ NO, IL6, IL8, VCAM1, TIMP1, MMP-1, -3, and -13 in chondrocytes
- Levels ↑ in serum and SF of RA patients
- ↑ IL6, IL8 and PGE2 in RA synovial fibroblasts
- ↑ MMP-1, MMP-13 and VEGF in synovial cells and promoted joint inflammation
- Regulates bone metabolism: ↑ pro-osteoclastogenic factors, ↓ anti-osteoclastogenic factors
- Induced by pro-inflammatory factors and glucocorticoids
- Levels ↑ in SF and cartilage of OA patients
- Block MMP-9 auto-degradation
- ↓ chondrocyte proliferation
- Levels ↑ in SF of RA patients


Visceral
adipose tissue
Diabesity
Joint overload
Osteoarthritis
Rheumatoid
arthritis
Inflammation
Metabolic
syndrome
Adipokines
Immune system
modulation