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Review Article

Adipokines as Potential Biomarkers in Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by severe joint injury. Recently, research has been focusing on the possible identification of predictor markers of disease onset and/or progression, of joint damage, and of therapeutic response. Recent findings have uncovered the role of white adipose tissue as a pleiotropic organ not only specialized in endocrine functions but also able to control multiple physiopathological processes, including inflammation. Adipokines are a family of soluble mediators secreted by white adipose tissue endowed with a wide spectrum of actions. This review will focus on the recent advances on the role of the adipokine network in the pathogenesis of RA. A particular attention will be devoted to the action of these proteins on RA effector cells, and on the possibility to use circulating levels of adipokines as potential biomarkers of disease activity and therapeutic response.

1. Introduction

An emerging body of evidence suggests that the white adipose tissue (WAT) plays more than just the role of energy storage compartment and thermal and mechanical insulator. WAT is now recognized as a pleiotropic organ specialized in endocrine functions being able to produce several hormones and other proteins involved in both physiological and pathological processes, including immunity and inflammation [1]. The biological active substances secreted by WAT contribute to the systemic "low-grade inflammatory state" associated with obesity [2, 3]. Indeed, increased circulating levels of several markers of inflammation occur in obese subjects, such as IL-6, TNF-α, C-reactive protein (CRP), and plasminogen activator inhibitor I (PAI-I) [4, 5]. It should be also considered that infiltrating macrophages represent an important source of inflammatory mediators which further promote and sustain inflammation [6]. The term "adipokines" is applied to all the biological active substances synthesized by WAT which function as regulators of energy homeostasis and metabolism; the same mediators are also involved in chronic inflammation and metabolic dysfunctions [7].

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder characterized by synovial inflammation, cartilage damage, and bone erosion, with 1% prevalence worldwide [8]. Although the pathogenesis of this disease is poorly understood, several observations indicate that adipokines affect tissues and cells involved in RA, including synovium, cartilage, bone, and immune cells [9]. In the present review we will describe the information available on the role of adipokines in RA pathogenesis, focusing on the role of adiponectin, leptin, chemerin, visfatin, resistin, lipocalin 2, SAA3, and a few others, in light of their possible consideration as new potential circulating biomarkers of disease activity and therapeutic response.

2. Adiponectin

Adiponectin (also called GBP28, AdipoQ, ApM1, and Acrp30) is a collagen-like protein with a structure similar to the complement factor C1q. Adiponectin is mainly produced by adipocytes and is present, in different molecular isoforms, at high levels (3–30 μg/mL) in the blood [10, 11].

Two adipokine receptors were recently identified, AdipoR1, mainly expressed in skeletal muscles, and AdipoR2 which is expressed in the liver [12]. The signaling transduction pathways of adiponectin receptors involve the activation of the adaptor protein APLL1 [13] and many signaling molecules, including AMPK, p38 MAP kinases, and PPAR-α and PPAR-γ [10, 14]. The main functions of adiponectin are, in the muscle, the increase of fatty acid oxidation and glucose uptake and, in the liver, the reduction of glucose synthesis.

Low levels of circulating adiponectin, as those observed in obesity, type 2 diabetes, atherosclerosis, vessel inflammation, and metabolic syndrome, suggest a protective function. Accumulating evidence supports a potential role of adiponectin in controlling inflammation. For instance, adiponectin was reported to inhibit the transformation of macrophages into foam cells [15], to stimulate the production of the anti-inflammatory cytokine IL-10 [16], to reduce the production of TNF-α [17], to induce tolerance in response to TLR ligands [18], and to promote the anti-inflammatory M2 macrophage polarization (Figure 1) [19]. The anti-inflammatory effects of adiponectin have been, to some extent, ascribed to its capacity to alter ceramide metabolism and to promote sphingosine-1-phosphate synthesis [20]. However, evidence that adiponectin may act as a proinflammatory mediator promoting extracellular matrix degradation and joint disruption is also available. Indeed, in cultured chondrocytes, adiponectin increases the expression of MMP-3 [21] and the secretion and activity of proinflammatory mediators, such as nitric oxide synthase type II (NOS2/iNOS), MMP-9, IL-6, MCP-1, and IL-8 [22, 23]. Similarly, adiponectin is able to stimulate the production of PGE2, IL-6, IL-8, vascular endothelial growth factor (VEGF), MMP-1 and MMP-13, cyclooxygenase 2 (COX-2), and microsomal prostaglandin E synthase 1 (mPGES-1) [24, 25] in RA synovial fibroblasts (Figure 1). In RA, the cellular targets of adiponectin may also include lymphocytes and endothelial cells, further supporting the role of adiponectin in this pathology [26].

In RA patients, the serum/plasma levels of adiponectin, as well as the levels in the synovial fluid, are associated with radiographic damage [27] and are increased compared to osteoarthritis patients (OA) and healthy donors [28, 29]. Increased adiponectin levels positively correlate with the disease activity score 28 (DAS28), the erythrocyte sedimentation rate (ESR), and the rheumatoid factor (RF) [30]. Recently, Klein-Wieringa et al. reported that the baseline levels of adiponectin can also predict radiographic progression over a four-year period independently of the presence of anticyclic citrullinated peptide (CCP) antibodies and body mass index (BMI) [31]. In addition, the elevation of total and high molecular weight adiponectin was described in patients with RA treated with anti-TNF agents (e.g., infliximab and etanercept) [32, 33] (Table 1). Finally, considering the detrimental effects of this adipokine in perpetuating joint inflammation, the use of adiponectin as a potential therapeutic target of blocking therapies has been proposed [34].

3. Leptin

Leptin, the product of *ob* gene, is a 16 kDa nonglycosylated hormone peptide [35] which binds the OB-Rb long form leptin receptor coupled to a JAK/STAT signaling pathway [36, 37]. Leptin is considered the major regulator of body weight, since it induces the decrease of food intake and increases energy consumption [38]. Leptin is mainly produced by WAT and the circulating levels of leptin correlate positively with the amount of adipose tissue and BMI [39]. However, leptin synthesis is also regulated by the action of inflammatory mediators [40]. Leptin is generally considered a proinflammatory adipokine. In fact, leptin stimulates the production of proinflammatory cytokines, such as TNF-α and IL-6, and reactive oxygen species in cultured monocytes. In addition, it induces the production of CC-chemokines by macrophages and alters the Th1/Th2 balance favoring the Th1 phenotype (Figure 1) [41–43]. Moreover, leptin null mice are protected in experimental models of T cell mediated hepatitis and experimental autoimmune encephalomyelitis [44, 45].

Leptin has been associated with autoimmune diseases, in particular with RA. However, there are conflicting observations concerning the circulating levels of leptin in RA patients, since some studies suggested a correlation between leptin levels and disease activity [28, 46, 47], while others failed to detect changes in circulating leptin levels [48]; interference of concomitant pharmacological treatments might be responsible for these apparently contrasting results. In experimental models of arthritis, leptin deficient mice showed a milder form of antigen-induced arthritis associated with the reduction of IFN-γ production and the increase in IL-10 secretion by in vitro reactivated lymph node cells [49]. In contrast, leptin-deficient and leptin receptor-deficient mice exhibited a delayed resolution of the disease [50]; the administration of leptin ameliorated disease activity [51]. These conflicting results do not allow coming to a clear conclusion on the role of leptin in RA. To note, leptin circulating levels apparently are not modulated in patients treated with anti-TNF-α therapy [52–54] (Table 1). Recently, the serum/synovial fluid ratios of leptin levels were associated with disease duration and erosion [55]. In addition, several in vitro studies sustained the pathogenic role of leptin in RA. In human and murine chondrocytes, leptin synergizes with IL-1β and IFNγ for the activation of type 2 nitric oxide synthase (NOS) and the induction of IL-8 and metalloproteinases via a JAK2, PI3K, and MAP kinase-dependent signaling pathway [23, 56–58]. Leptin also induced IL-8 in human synovial fibroblasts with a NFκB-dependent pathway [59]. Furthermore, leptin can also modulate the activities of several immune cells [60]. For instance, in murine dendritic cells, leptin increases CD40 expression and T cell priming (Figure 1) [61]. Matarese et al. showed that leptin-null and leptin receptor-null mice have increased levels of Treg cells and are protected in experimental models of autoimmune diseases [45]. In keeping with this observation, high leptin levels are associated with a reduction of Treg and with the activation of proinflammatory effector T cells [62–64]. Recently, it was shown that the leptin-induced state of overexpression of the mTOR pathway, in freshly isolated Treg cells, is

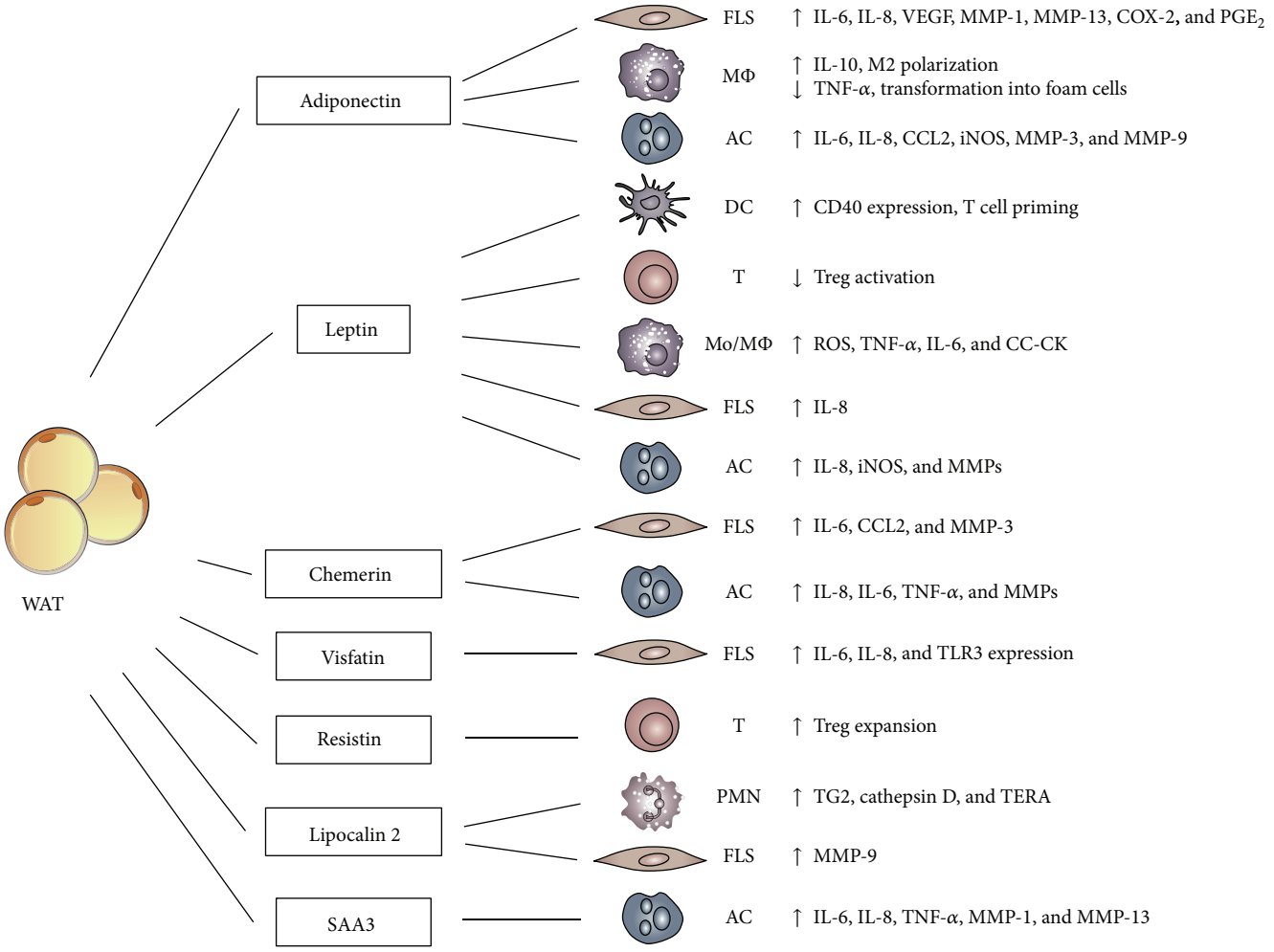

Figure 1: Role of adipokines on RA effector cells. The role of different adipokines on RA target cells is illustrated in the figure. WAT: white adipose tissue, SAA3: serum amyloid A3, FLS: fibroblast-like synoviocytes, AC: articular chondrocytes, PMN: neutrophils, MMP: metalloprotease, COX-2: cyclooxygenase 2, ROS: reactive oxygen species, iNOS: inducible nitric oxide synthase, CC-CK: CC-chemokines, TG2: transglutaminase 2, and TERA: transitional endoplasmic reticulum ATPase.

responsible for their state of hyporesponsiveness. Therefore, it is conceivable that Treg activation is dependent on the dynamic regulation of mTOR activity by the composition of the extracellular milieu, such as the concentrations of leptin and cell nutrients [65]. These results clearly depict leptin as a pleiotropic molecule placed at the crossroads of immune tolerance, metabolism, and autoimmunity. Further studies are needed in order to clarify whether leptin might represent a new disease activity biomarker and to explore its therapeutic potential in autoimmune diseases.

4. Chemerin

Chemerin is a 16 kDa protein, originally described as the product of the Tazarotene-induced gene 2 (Tig2) [66] and purified from ascitic fluids of ovarian cancer patients and synovial exudates of rheumatoid arthritis patients [67]. Chemerin is secreted as an inactive precursor protein which is subsequently converted into a bioactive protein following the proteolytic removal of the last six or seven amino acids from the C-terminal end [68]. Chemerin was first described as the functional ligand of the chemotactic receptor ChemR23. Dendritic cells, macrophages, and NK cells express ChemR23 and a role for chemerin in their recruitment into inflammatory sites was described in lupus erythematosus, oral lichen planus, and psoriasis [69–72]. More recently, the adipokine function of chemerin was proposed, since chemerin is mainly produced by WAT and plays important regulatory role in adipogenesis in vitro [73]. In addition, chemerin is considered a biomarker of adiposity, because chemerin levels strongly associate with BMI [74], markers of inflammation (e.g., TNF-α, IL-6, and CRP) [75], and metabolic syndrome [76]; chemerin circulating levels decrease with weight and fat loss [77]. Human articular chondrocytes express chemerin and its receptor ChemR23 and secrete proinflammatory cytokines, such as IL-6, IL-8, and TNF-a, and metalloproteases, in response to chemerin stimulation (Figure 1) [78].

Table 1: Correlation of adipokines with disease activity parameters and therapeutic response.

Adipokine	Correlation with					
	DAS28	BMI	IL-6/TNF/ESR	Anti-CCP	Radiographic progression	Therapeutic response
Adiponectin	pos [30]	neg [31]	pos [30]	neg [31]	pos [27, 31]	Anti-TNF: pos [32, 33]
Leptin	pos [46]	neg [46]	neg [31]	no [31]	neg [98]	Anti-TNF: neg [52]
Chemerin	pos [80]	neg, pos [80]	pos [78]	ND	ND	Anti-TNF: pos [81]
Visfatin	neg [102]	neg [149]	pos [31]	pos [31], neg [102]	pos [100]	Anti-TNF: neg [101], pos [91] Anti-CD20: pos [102]
Resistin	pos [30]	pos [31]	pos [31, 118]	No in serum but pos in SF [111]	ND	Anti-TNF: pos [118]
Lipocalin 2	ND	ND	ND	ND	ND	ND
SAA3	ND	ND	ND	ND	ND	ND
Vaspin	SF pos [150]	pos [147]	SF neg [150]	SF neg [150]	ND	ND
Omentin	SF neg [150]	neg [152]	SF neg [150]	SF pos [150]	ND	ND
Apelin	ND	ND	ND	ND	ND	DMARDs: neg [158]
Adipsin	ND	pos [31]	pos [31]	ND	neg [31]	DMARDs: pos [160]

Abbreviations: pos: positive; neg: negative; SF: synovial fluid; ND: not determined. Where not specified, the correlations are referred to serum levels. Positive correlation with therapeutic response is assumed when the adipokine levels are modified (either they increase or decrease) by the treatment.

In RA patients the expression of chemerin and ChemR23 in fibroblast-like synoviocytes (FLS) was found increased compared to OA patients. Chemerin was reported to mediate direct proinflammatory and stimulatory effects on the RA-FLS [79], suggesting a pivotal role of the chemerin/ChemR23 axis in the pathogenesis of RA. A recent study reported that RA patients have increased levels of circulating chemerin and chemerin levels positively correlated with disease activity (DAS28, ESR, and CRP) [80]. Circulating chemerin levels are negatively regulated by the anti-TNF therapy (adalimumab) in parallel with the reduction of disease activity markers, such as DAS28, ESR and CRP, and IL-6, and the macrophage migration inhibitory factor (MIF) levels [81] (Table 1). These results nominate chemerin serum levels as a biomarker for disease activity and therapeutic response.

5. Visfatin

Visfatin, also known as pre-B-cell colony-enhancing factor (PBEF) and nicotinamide phosphoribosyltransferase (Nampt), was originally described as a cytokine involved in early B-cell development and was later renamed visfatin since it is secreted mainly by visceral fat [82]. In addition, leukocytes, in particular granulocytes and monocytes/macrophages, from obese patients produce high levels of visfatin [83–85]. Visfatin is also produced by endotoxin-challenged neutrophils, where it functions as an antiapoptotic molecule acting at level of caspases 3 and 8 [86]. Visfatin was also suggested to have insulin-like functions [87, 88]. A specific receptor for visfatin has not been identified yet. Nevertheless, the proinflammatory action of visfatin was described to be mediated by the insulin signaling pathway through Akt phosphorylation [89].

Circulating levels of visfatin correlate with obesity and type 2 diabetes and are reduced after weight loss [90]. Visfatin was also proposed to promote atherosclerosis and to cause plaque destabilization through the induction of proinflammatory mediators and adhesion molecules in endothelial cells [91–93]. Several observations sustain the hypothesis that visfatin may play a major role in the pathogenesis of RA. Recent studies reported the upregulation of visfatin in activated RA-SFs in response to proinflammatory stimuli, such as IL-6 and the activation of TLR3 [94, 95] with visfatin acting as an autocrine positive feedback mechanism for IL-6 production [96]. In RA synovium, visfatin was predominantly expressed in the lining layer, lymphoid aggregates, and interstitial vessels. In RA-SFs, visfatin induced high amounts of chemokines such as IL-8 and CCL2, proinflammatory cytokines (i.e., IL-6), and matrix metalloproteinases (i.e., MMP-3) (Figure 1). Visfatin promoted fibroblast migration and induced phosphorylation of p38 MAPK; of note, inhibition of p38MAPK strongly reduced visfatin effects [97]. Finally, visfatin inhibition significantly reduced the severity of the disease and TNF-α circulating levels in the experimental model of collagen-induced arthritis [98, 99].

In RA, circulating levels of visfatin are increased [28], as well as its expression in synovial fluids and inflamed synovium [94–96]. Visfatin serum and synovial fluid levels correlated with the degree of inflammation, with the severity of the disease, and with joint damage [31, 95, 100]. Contradictory results are available on visfatin levels in patients undergoing anti-TNF-α therapy. In one study no significant changes were observed [101], while in others a negative correlation with therapy was found [91]. In general, visfatin serum levels better correlated with the number of circulating B cells rather than with the disease activity and were profoundly affected after B-cell depletion therapy with rituximab. The lack of change in

serum visfatin levels is suggested to predict worsening disease activity [102] (Table 1).

6. Resistin

Resistin is a cysteine-rich protein of 12.5 kDa also known as adipocyte-secreted factor (ASF) or "found in inflammatory zone 3" (FIZZ3) [103]. In RA experimental models, resistin promotes insulin resistance, while the function in humans is still unclear [104]. Even if resistin was originally described to be produced only by WAT, subsequent studies demonstrated that, in humans, resistin mainly derives from circulating monocytes and macrophages [105]. The resistin receptor is still unknown and recently TLR4 was proposed to mediate resistin proinflammatory functions in human cells [106]. Resistin has a strong impact on immune functions. It can enhance the expansion of Treg cells through an effect on dendritic cells (Figure 1) [107]. Proinflammatory mediators increase resistin expression; in turn, resistin induces TNF-α, IL-12, IL-6, and IL-1β production [108, 109]. These findings, together with the observation that the intra-articular injection of resistin in the knee joints induces arthritis, sustain the involvement of resistin in RA pathogenesis [110]. Several reports have demonstrated that serum resistin levels are significantly higher in RA than in OA patients or healthy controls [111–113]. The increased serum levels of resistin correlated with markers of inflammation, such as CRP, ESR, IL-1Ra, and total leukocyte count [47, 114–117], disease activity (DAS28), and joint destruction [112]. However, these results were not confirmed by other groups [111], and conflicting results were reported on the association between resistin and radiographic progression signs [27, 31, 100]. Recently, the anti-TNF-α therapy was reported to modulate resistin levels in RA patients [118, 119] (Table 1). Resistin levels in synovial fluids and in the sublining layer are higher in RA than in OA patients [29, 110, 112]. These results strongly suggest that resistin production is elevated at the site of inflammation and accumulates in the synovial fluid of RA patients. In anti-CCP positive patients, synovial fluid resistin levels, but not serum levels, correlated with disease progression suggesting resistin as a disease progression marker [111].

7. Lipocalin 2

Lipocalin 2 (LCN2), also known as siderocalin, 24p3, uterocalin, and neutrophil gelatinase-associated lipocalin (NGAL), is a recently identified glycoprotein stored in neutrophil granules [120] but mainly produced by WAT [121, 122]. LCN2 has been isolated in different isoforms and its functions are carried out by the activation of the cellular receptor megalin [123]. LCN2 binds and transports small lipophilic substances, such as retinoids, arachidonic acid, steroids, iron, and fatty acids [124–126]. Other functions that have been attributed to LCN2 are the induction of apoptosis in hematopoietic cells [127], the inhibition of bacterial growth [128, 129], regulation of iron metabolism [130], and insulin resistance [131]. LCN2 is induced by inflammatory stimuli through the activation of the NFkB pathway [132]; however dexamethasone promotes LCN2 production in chondrocytes [133, 134]. LCN2 is involved in the allosteric activation of MMP-9 [135] and levels of MMP-9 are higher in the serum and synovial fluid of RA patients [136]. Recently, LCN2 synovial fluid levels were found to be increased in RA compared to OA patients [137]. Through a proteomic approach, GM-CSF was found to induce LNC2 upregulation in neutrophils, which in turn can influence synoviocyte behavior through the release of several enzymes, such as transglutaminase 2 (TG2), cathepsin D, and transitional endoplasmic reticulum ATPase (TERA) (Figure 1), which contribute to both inflammation of synovium and proliferation of synovial cells, promoting the RA state [137].

8. SAA3

The serum amyloid A3 (SAA3) belongs to the family of acute phase serum amyloid A proteins produced by hepatocytes [138] and other cell types, including adipocytes [139, 140]. SAA3 was associated to altered metabolic and immunocompromised conditions [141, 142]. Several stimuli, such as TNF-α, IL-1β, dexamethasone, IL-6, and LPS, can increase SAA3 expression [139, 140, 143]. Recently, SAA3 was suggested to directly activate the MyD88-dependent TLR4/MD-2 pathway [144].

In a rabbit Ag-induced arthritis model, upregulation of SAA3 transcripts was detected in cells infiltrating into the inflamed joint, in the area where pannus formation starts and, most notably, also in chondrocytes. In vitro, recombinant human SAA induces matrix metalloproteinase transcription in human chondrocytes (Figure 1). Further, SAA is highly expressed in human RA synovium [145]. Recently, Geurts et al. proposed that a SAA3-promoter report may have a diagnostic value in the classification of RA molecularly distinct forms with different degree of synovial tissue inflammation [146].

9. Other Adipokines

Vaspin, visceral adipose tissue-derived serine protease inhibitor, is expressed predominantly in visceral adipose tissue [147]. Expression of the vaspin gene positively correlates with BMI and administration of the protein to obese mice improved glucose tolerance and insulin sensitivity [147, 148]. Vaspin levels are increased in the serum and synovial fluid of RA patients [149, 150] (Table 1).

Omentin, also known as intelectin, is a protein secreted by omental adipose tissue and highly abundant in human plasma [151]. Both circulating protein levels and mRNA levels in adipose tissue decrease in obese subjects and correlate negatively with markers of obesity, such as BMI, waist circumference, and circulating leptin [152] (Table 1). Expression of the omentin gene was reported in omental adipose tissue of patients with Crohn's disease, suggesting a role in chronic inflammatory diseases [151]. The levels of omentin were found significantly reduced in the synovial fluid of patients with RA compared to OA patients [150]. On the contrary, circulating

levels of omentin were significantly higher in patients with juvenile idiopathic arthritis compared to healthy controls [153].

Apelin is a bioactive peptide, originally identified as the endogenous ligand of the G-protein coupled receptor APJ [154]. Apelin is mainly produced by adipocytes, its expression is upregulated by insulin, and TNF-α and its levels are increased in obesity [155, 156]. Apelin has been implicated in the pathogenesis of OA, since high circulating levels are increased in the sera and synovial fluids of OA patients [157]. In early-stage RA patients serum apelin levels were found to be decreased but were insensitive to pharmacological treatment [158] (Table 1).

Adipsin, also known as complement factor D, is highly expressed in adipose tissue and in activated monocyte/macrophages [159]. Circulating levels of adipsin did not predict the radiographic progression of early-stage disease [31]; however, increased adipsin levels were found to be associated with a higher remission rate in early RA patients treated with DMARD [160] (Table 1).

10. Conclusions

The discovery of adipokines has profoundly changed our understanding of the functions of adipose tissue. The adipokine network is involved in the interplay between WAT, metabolic disorders, and immune-mediated diseases. Adipokines have shown to be able to modulate several aspects of inflammation as well as both innate and adaptive immune responses. Although in the past few years the implications of the adipokines in autoimmune diseases, including rheumatoid arthritis, have greatly increased, a clear picture of the role of these proteins in the pathogenesis and in the progression of this disease is still missing. Nevertheless, accumulating evidence on the modulation of serum and synovial fluid levels of many adipokines encourages their future exploitation as soluble biomarkers of disease activity and therapeutic response. Further studies are needed in order to translate the increasing number of experimental and clinical observations to the use of adipokines as clinical diagnostic markers.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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