

Obesity, adipose tissue and rheumatoid arthritis: coincidence or more complex relationship?

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ABSTRACT

In the last two decades we have witnessed a boost in scientific interest and knowledge of adipose tissue biology to such an extent that it was promoted to an active endocrine organ. Adipose tissue is not just related to body weight and appetite regulation. It is also implicated in obesity, a low-grade inflammatory state, as well as inflammatory conditions including rheumatoid arthritis (RA), an autoimmune disease where anti- and pro-inflammatory cytokine balance is critical. All major adipose derived products, simply termed adipokines, like leptin, adiponectin, visfatin and resistin, reportedly participate in inflammation and immunity. In this review we explore in depth the relationship between adipose tissue and RA, with focus on possible mechanisms, beyond observations about circulating or synovial levels, and special reference to future perspectives and clinical implications.

Introduction

Over the past 40 years, changes and trends towards a westernised diet and lifestyle have led to alarmingly heightened obesity prevalence. Concomitantly, the complications of obesity have had greater impact: increased body weight and fat mass correlate with increased risk of developing cardiovascular disease (CVD), type 2 diabetes, hypertension and dyslipidemia, all of which are major public health problems (1). Epidemiological evidence and observational studies have also identified obesity as a risk factor and a prognostic marker of rheumatoid arthritis (RA) (2-7), and adipose tissue as a possible governor of inflammation in RA.

RA is a chronic inflammatory autoimmune disease that leads to progressive joint destruction. It is characterised by synovial hyperplasia, cell activation,

articular inflammation, invasion of synovium to adjacent bone and cartilage. Extra-articular manifestations include nodular lesions, anemia, as well as pulmonary, heart, eye and kidney involvement. It affects about 0.3–1% of the population in developed countries, women 2–3 times more often than men, although it may be present with certain oddities among different populations (8–10). Its prevalence has also risen during the last decades, at least in some countries (11, 12). These countries are also confronted with the obesity epidemic simultaneously.

Furthermore, both RA and obesity are characterised by increased CVD risk, as well as chronic inflammatory cytokine production (13–18). This common feature they share, in conjunction with the fact that adipose tissue is no longer thought of as solely a triglyceride storage compartment and neighboring tissue insulator, but rather as an active endocrine organ, with multiple functions (19), implies that this relationship is complex. The purpose of this review is to present the complexity of relationship between obesity and RA, to explore in depth the relationship of adipose tissue derived products with RA and discuss any clinical implications they may have.

Adipose tissue as endocrine organ: metabolism and adipokines

As noted above, adipose tissue is now far from being considered as an energy storage depot (19). It consists primarily of adipocytes. Present are also preadipocytes, fibroblasts, endothelial cells and immune cells such as neutrophils (20), macrophages (21, 22), mast cells (23), CD4 and CD8 T lymphocytes (24–26). It is characterised by a rich vasculature and nerve network, and appears to be in constant interaction with other organs and tissues, such as liver, muscle,

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Table I. Adipokines specifically and non-specifically produced by white adipose tissue.

Adipose tissue specific proteins	Adipose tissue non-specific proteins
Leptin	Tumour necrosis factor α
Adiponectin	Soluble tumour necrosis factor receptor
Resistin	Interleukin 1
Visfatin	Interleukin 1 receptor antagonist
Vaspin	Interleukin 6
Omentin	Interleukin 8
Retinol binding protein 4	Interleukin 10
	Sex hormones/enzymes
	Matrix metalloproteinases

brain, reproductive system, pancreas, bone and vasculature (27). In addition, not only can one discrete a specific adipose tissue depot from various others (28), but also differentiate small from large adipocytes (29). Such anatomical and morphological variations may confer significant functional variation and different responses to nutrient, hormonal and stress stimuli (28-30).

Hence, briefly focusing on adipocyte, prior to presenting specific adipose tissue proteins referred to as adipocytokines or adipokines is essential. Lipolysis, triglyceride and glucose uptake which have been extensively discussed elsewhere (31, 32), are not the scope of this review and will be not covered herein. White adipocyte, as opposed to brown adipocyte, whose role is primarily thermogenesis (33), is a 25 to 200 nm in diameter cell characterised by the central dominance of a single triglyceride containing lipid droplet (34). The nucleus, the endoplasmic reticulum and few mitochondria are confined to periphery. Preadipocyte differentiation is a complex procedure dependent on hormonal and nutrient adequacy, which involves the successive activation of certain transcription factors (35). Interestingly, adipocytes share the same stem cell precursor with osteoblasts and chondrocytes (36, 37) and under certain conditions their precursor can differentiate to osteoblasts and macrophages (36, 38). Inducers of adipogenesis inhibit osteoblastogenesis and the opposite. Inter-conversion has also been reported, where mature adipocytes may undergo transformational changes to osteoblasts and vice versa (39). Mature adipocytes and osteoblasts express and secrete common fac-

tors, such as leptin and adiponectin (40, 41). Macrophages and adipocytes also share common features and it is suggested that they have overlapping biology: macrophages express many adipocytes-characteristic genes and store lipids to progressively turn into foam cells, while adipocytes produce macrophage cytokines like tumour necrosis factor (TNF) α and preadipocytes exhibit phagocytotic and anti-microbial properties (42). In addition, pathophysiology of RA involves cell types, some of which, such as T cells (43), mast cells (44) and macrophages (43), are common to adipose tissue pathophysiology as well (21-25). These common features suggest that there might be a link between the two.

Adipose tissue functions as an endocrine organ, producing adipose tissue-specific proteins, collectively termed adipocytokines or adipokines. Major adipokines are leptin, adiponectin, resistin, visfatin, vaspin, omentin and retinol binding protein 4 (27, 34, 45). Other important adipose tissue derived proteins, though not exclusively produced by adipose tissue, are included in Table I, (27, 34, 46-56).

Leptin

Leptin, to start with, is the most widely studied adipokine, a 16-kd protein encoded by the *ob* gene that belongs to the type 1 cytokine superfamily (57, 58). Its receptor (Ob-R), encoded by the diabetes (*db*) gene, is expressed in central nervous system (CNS), choroid plexus, kidney, gonads, liver, lung and vascular endothelium, jejunal epithelium, pancreatic β cells, ovarian follicular cells, CD34+ haematopoietic bone marrow precursors, and T

lymphocytes. Leptin cascade involves activation of Janus kinases (JAK2) and signal transducers and activators of transcription (STAT) proteins and also tyrosine phosphorylation of insulin receptor substrate 1 (IRS-1), phosphatidylinositol 3-kinase (PI 3-kinase) activity and extracellular signal-regulated kinases 1 and 2 (ERK1/2) activation. It is predominantly produced from adipocytes and its primary role is appetite suppression and down-regulation of food intake (Fig. 1) (57, 58). Mice lacking the leptin gene or leptin receptor gene are massively obese. In humans though only few cases are described and the common form of obesity is presented with high leptin levels, indicating a condition of leptin resistance. Insulin resistance and diabetes are also associated with higher leptin levels (57, 58). Presence of leptin receptor in various tissues explains why leptin has also been found to possess a role in lipoprotein metabolism, acute phase reactants, sex hormones and glucocorticoid metabolism, and immune function: Its synthesis and levels increase in response to overfeeding, infection, sepsis and secretion of inflammatory mediators as interleukin (IL)-1, TNF- α and during bacterial infection, or lipopolysaccharide challenge. It protects T lymphocytes from apoptosis, regulates their proliferation and activation, by driving T-cell differentiation towards a Th-1 response, and also influences response, for instance phagocytosis and cytokine production, of other immune cells: monocytes, neutrophils, basophils, eosinophils, natural killer (NK) and dendritic cells (59).

Adiponectin

Adiponectin has gained considerable attention in the last years. As suggested by its name, it is also mainly produced from adipose tissue, like leptin. In fact, it is the most abundant adipokine secreted by adipocytes (0.01% of total circulating protein in plasma) (60, 61). It is a 30-kD protein whose tertiary structure shares homology to TNF- α and C1q, and binds to C1q receptor (62). It possesses unique properties by acting as an anti-diabetic and anti-atherogenic adipokine (Fig.

2). Adiponectin levels are decreased under conditions of obesity, insulin resistance and type 2 diabetes and it has even been proposed that low circulating levels are indicative of increased CVD risk. Adiponectin circulates in various forms: globular trimers and full length trimers, hexamers and polymers. Adiponectin isoforms bind to two distinct types of receptors, Adipo-R1 and -R2. These are widely expressed in the whole body, mainly though in the muscles and liver respectively. Globular adiponectin binds primarily to Adipo-R1 and full length to Adipo-R2. Via its receptors, adiponectin exerts beneficial anti-atherogenic function, improves insulin sensitivity and reduces circulating fatty acid concentration and triglyceride levels in muscle and liver. Endothelium beneficial effects include nitric oxide (NO) upregulation from human aortic endothelial cells *in vitro*, NO synthase (NOS) increase, inhibition of adhesion molecules and anti-platelet properties. It attenuates the inflammatory response mediated by TNF- α , inhibits macrophage phagocytic activity and TNF- α production, induces IL-10 production, facilitates uptake of early apoptotic bodies and inhibits oxidised low-density lipoprotein (LDL) uptake from macrophages (60, 61, 63, 64). Recently it was shown to induce a macrophage shift towards an M2 profile, which is divergent from classically activated M1 cells (65). In addition, it inhibits B-cell lymphopoiesis (66) and induces the production of anti-inflammatory factors by monocytes and dendritic cells (64, 67). It reduces T cell recruitment in atherogenesis (68), and possibly in other inflammatory conditions. Recently though, adiponectin-related pro-inflammatory actions have been demonstrated and involvement in autoimmune conditions has been found (see adipokines and RA section). The exact molecular pathways have not been fully elucidated yet, but most likely include peroxisome proliferator-activated receptor α (PPAR α), AMP-activated protein kinase (AMPK), and p38 mitogen-activated protein kinases (MAPK) activation. The complexity of adiponectin action is perhaps due

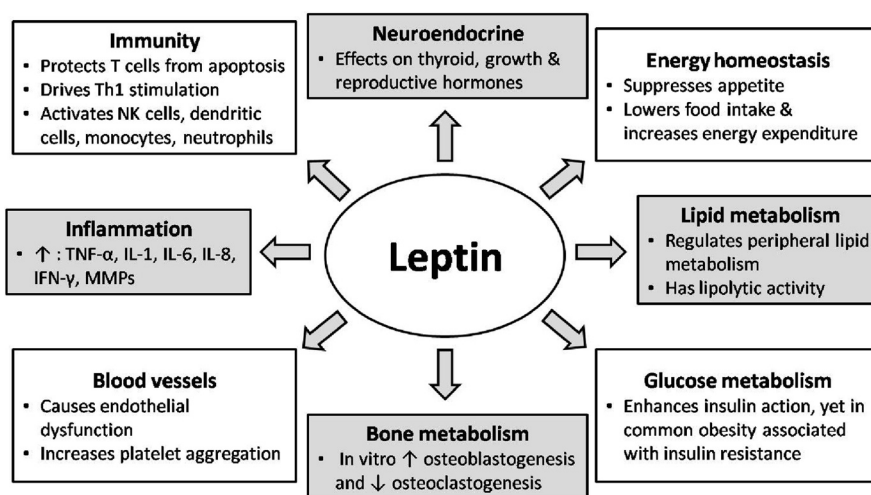


Fig. 1. Major leptin actions. NK: natural killer; TNF- α : tumour necrosis factor-alpha; IL: interleukin; IFN- γ : interferon-gamma; MMP: matrix metalloproteinases.

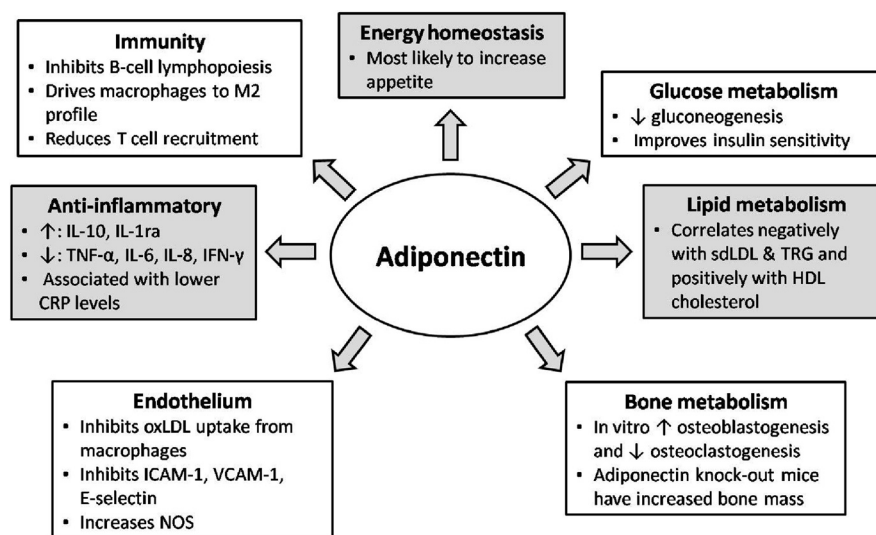


Fig. 2. Major adiponectin actions. IL: interleukin; IL-1ra: interleukin 1-receptor antagonist; TNF- α : tumour necrosis factor-alpha; IFN- γ : interferon-gamma; CRP: C-reactive protein; sdLDL: small-dense low density lipoprotein; TRG: triglycerides; HDL: high density lipoprotein; oxLDL: oxidised low density lipoprotein; ICAM-1: inter-cellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule-1; NOS: nitric oxide synthase.

to the many forms, ie globular or high molecular weight (HMW) polymer and the existence of two receptors in various tissues and cells.

Visfatin

Visfatin was initially identified as a growth factor for early B-cells, termed pre-B-cell colony enhancing factor (69). It is also discovered to act as an enzyme referred to as nicotinamide phosphoribosyl transferase (Namp1). Although present in various tissues, probably its main producer is visceral fat (69). It is encoded as 52 kD protein.

Visfatin exerts insulin-mimetic effects *in vivo* and *in vitro* and is upregulated in obesity, metabolic syndrome and diabetes (69, 70) (Fig. 3). It is also implicated in dyslipidaemia, hypertension and generally atherosclerotic-related diseases. Immunohistochemistry revealed presence of visfatin in carotid plaques from symptomatic patients and was found to induce MMP-9 from monocytes and be increased by TNF- α and oxidised LDL (69). It has also been shown to stimulate the release of cytokines as well as to be widely induced by inflammatory stimuli in other cells

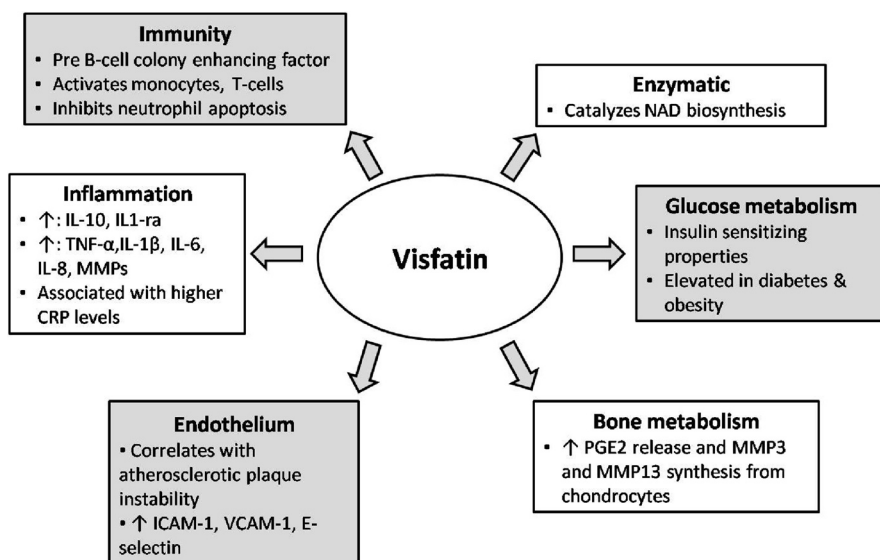


Fig. 3. Major visfatin actions.

IL: interleukin; TNF- α : tumour necrosis factor-alpha; MMP: matrix metalloproteinases; CRP: C-reactive protein; ICAM-1: inter-cellular adhesion molecule 1; VCAM-1: vascular cell adhesion molecule-1; PGE2: prostaglandin E2.

involved in innate immunity, such as monocytes and macrophages (69, 71). Other studies suggested that visfatin exerts a mainly intracellular role, as an enzyme (69, 71). Visfatin catalyses the rate-limiting step in nicotinamide adenine dinucleotide (NAD) biosynthesis, the conversion of nicotinamide to nicotinamide mononucleotide. NAD can be detected at nanomolar levels in human serum, and there is increasing evidence that extracellular NAD can modulate the function of cells of the innate immune system (69, 71). Taken together these results suggest a link between visfatin and inflammation.

Other adipokines

Other important adipokines include resistin, vaspin and omentin. Briefly, resistin, also referred to as ADSF (adipocyte-specific secretory factor) and FIZZ3 (found in inflammatory zone), is a 12 kDa peptide (72, 73). It was shown to be produced by adipocytes in rodents; its administration resulted in hyperinsulinemia and glucose intolerance in mice and inhibition of glucose uptake from adipocytes and myocytes *in vitro*. In humans, though, controversy exists as to which cells produce resistin and if it is a true inducer of insulin resistance. Vaspin is a serine protease inhibitor predominantly secreted from visceral

adipose tissue (74). It was initially isolated from visceral adipose tissue in a rat model of abdominal obesity and diabetes and was considered as an adipokine with insulin sensitising properties. Human vaspin consists of 395 amino acids and shares 40% structural homology to alpha-1 anti-trypsin. Vaspin mRNA expression and serum levels are upregulated in diabetics and are associated with parameters of obesity, insulin resistance, and glucose metabolism (74-76). Thus, it could be claimed that vaspin increase may be a compensatory mechanism of adipose tissue in obesity associated conditions, with more studies required to back-up such a claim.

Omentin is another depot specific adipokine alleged to possess insulin sensitising properties. Omentin gene encodes a peptide of 313 amino acids, containing a secretory signal sequence and a fibrinogen-related domain and is expressed by stromal cells of omental adipose tissue (45). Omentin levels are decreased in insulin resistant states such as obesity, polycystic ovary syndrome and diabetes (77, 78). It supposedly possesses vasodilatory properties via phosphorylation of NOS (79), may regulate insulin action in adipocyte cultures (80) and was suggested to protect against intestinal bacterial translocation in Crohn's disease (45).

Hence, adipose tissue stands out for the production of adipokines, but is also a potent producer of other proteins and despite adipocytes presiding in the tissue, other cells possess important role therein. It is now evident that recent advances in adipose tissue physiology revealed and upgraded its role, establishing it as a key player in immune response, additionally to other important aspects of adipose functions (59).

Obesity as a risk factor for RA and a marker for disease progression

Obesity is among one of the major risk factors for RA according to some, but not all studies (2-4). It is also associated with known CVD risk factors both in normal and in RA populations (81). Surprisingly, obesity, as defined by body mass index (BMI) higher than 30 kg/m², has emerged as a protective risk factor for radiographic joint damage (5-7) and lower BMI as a predictor of increased CVD and total mortality in RA (82, 83). Certainly, observational-longitudinal studies should be carefully evaluated, as care and therapy of RA has been through considerable change and progress over the last 30 years. Indeed a recent report from the QUEST-RA study associated increasing BMI with disease activity in women (84). Still, these are unexpected findings indeed, considering the well characterised role of obesity contribution to CVD, via the effects of adipose tissue on lipid profile, carbohydrate metabolism, insulin resistance, blood pressure, endothelium and inflammation (34). However, BMI as an indicator of obesity should be carefully evaluated both in clinical practice and in the above mentioned observational/epidemiological studies, since disease progression and severity in RA are associated with a condition of increased resting energy expenditure, fat-free mass loss and relative fat gain, termed rheumatoid cachexia (85). Based on body composition studies, dissociating fat actually present, as a percentage of body weight in RA patients, from BMI cut-off points used in general population, Kitas's group (86) have proposed lower cut-off points for defining normal, overweight and obesity in RA. Some issues arising are crucial. Pos-

sibly, it is RA that causes low body weight, via rheumatic cachexia, and increased mortality. Hence, we might hypothesize that increased adipose tissue and energy stores may confer a significant survival benefit in the context of the increased resting energy expenditure and inflammation of RA. Secondly, we ask: should strategies manipulating weight gain or loss be used in order to improve physical activity (87), quality of life, slow disease progression and maybe even extend life expectancy in RA (81, 88)? So far, no definite answer is given and studies aiming at answering this are required (see clinical implications section). It would be reasonable to seek via which mechanisms can adipose tissue possibly modulate or confer to disease activity and progression.

Adipokines and RA

Leptin

Starting with the last question put forward, investigating the relationship of RA with adipokines is necessary and may assist in answering all and even give rise to new ones. TNF- α is found to increase leptin *in vivo* and *in vitro*. It is also a major target in RA. Leptin's possible role in RA deserves and justifies investigations. Although no difference in serum leptin levels among RA patients and controls was found in initial and subsequent studies, irrespective of BMI and body fat, and no correlation with disease activity (89-93), further studies showed otherwise (94-98) (Table II). Various explanations can be offered: differences in race, sex, age, age at disease onset, disease duration, BMI and BMI variation, as well as body fat distribution, cardiovascular disease risk factors and medication used between the studies. We favour increased leptin levels in RA, based on our results (98) and on evidence from studies in other auto-immune diseases (99-102). Interestingly, synovial leptin levels have also been found elevated in RA patients compared to control group and even to patients with lower disease activity (103). Leptin synovial levels were higher compared to serum levels in a study and correlated with synovial white blood cell counts (94). In a small group of 19 patients followed over 2

years, changes in leptin correlated well with changes in disease activity for 28 joints score (DAS-28) and IL-17(97). Patients with longer disease duration also showed correlations between leptin and disease markers like DAS-28, erythrocyte sedimentation rate (ESR) and the number of tender joints (104). Other studies (93, 103, 105) though, did not confirm these findings. Additionally, erosive RA compared to non-erosive was found co-existent with lower synovial leptin levels, which was attributed to "leptin consumption" on the joint (94). A recent study linked leptin with insulin resistance in RA and showed that paradoxically it attenuated the proatherogenic effects of insulin resistance on coronary calcification (106). The same group linked leptin with reduced joint damage (107). The fact that leptin has a diurnal pattern with higher levels in the early morning hours (108) which might relate to morning stiffness in RA, could be an interesting assumption warranting proof. In a mouse model of RA, impaired leptin signalling via leptin or leptin-receptor deletion in mice attenuated adjuvant induced arthritis (109). This finding is very important but does not present the full extent of leptin actions and results cannot be extrapolated in humans, since the majority is faced with leptin resistance, especially as BMI increases, rather than rare leptin gene deletions or mutations. To summarise, leptin is a pro-inflammatory adipokine up-regulated in RA (110), yet, future studies need to further address leptin's role in RA and also answer whether it acts via a CNS indirect pathway, directly or both (111, 112); alone, synergistically or dependent on other adipokines. Overall, mounting evidence suggests leptin blockade, preferably in synovial fluid, could also be a potential therapeutic target (110).

Adiponectin

– *Pro-inflammatory role*

Adiponectin is a rather unique adipokine. It possesses highly desirable properties as noted previously. Surprisingly, its levels have been found to be elevated in RA, both systemically and in synovium in most (92, 98, 113-116) but not

all studies (117) (Table II). Adiponectin is also implicated in other autoimmune conditions (118, 119). In addition, radiographic joint damage has been found to be positively correlated with adiponectin serum levels (120, 121). Correlation with disease parameters, positive (96) and negative (122, 123), have been reported in some studies, whereas others report no correlations at all (92, 124) (Table II). Adiponectin and its receptors have been found to be expressed in synovial fibroblasts from RA patients (RASFs) (115, 125-127), in lymphocytes (128) and chondrocytes (129) in culture. Adiponectin possibly contributes in arthritis via p38 MAPK, protein kinase C (PKC) and NF-KappaB pathways by enhancing gene expression and/or release of interleukins, metalloproteinases (MMPs) monocyte chemoattractant protein 1 (MCP-1) and other chemokines (115, 126, 127, 130-133). It also enhances prostaglandin E2 (PGE2) production from RASFs *in vitro* (125, 131) (Table II). Pro-inflammatory effects are also encountered in chondrocytes, lymphocytes and endothelial cells (132), that entirely confront anti-inflammatory properties mentioned earlier in the introductory section for adiponectin.

– *Anti-inflammatory properties*

Yet, to further complicate the picture, in adjuvant induced arthritis, adiponectin was surprisingly found to alleviate symptoms and inflammatory markers when injected to mice knees (134); and when its gene was transferred by adenovirus it suppressed progression of arthritis (144). It also down-regulated cartilage C1q and C3 deposition and leukocyte infiltration (144). Finally, it significantly decreased mRNA of inflammatory markers IL-1 β , IL-6, cyclooxygenase-2 (COX-2), interferon-gamma (IFN- γ) and TNF- α (135). In addition, it facilitates uptake of early apoptotic body by macrophages *in vitro*, by interacting with calreticulin receptor (136). This task is considered an additional anti-inflammatory mechanism which might also prove helpful in understanding calreticulin's presence and role in RA synovial tissue, as well as inhibition of T cell apoptosis (137). An-

Table II. Major adipokines in rheumatoid arthritis, correlations in clinical studies and effects in animal or cell studies.

Adipokine	Serum levels	Synovial levels	Correlations in clinical studies	Effects in animal/cell studies
Leptin	↑, – (89-98, 103)	↑ (103)	DAS-28*, ESR [†] , number of tender joints, IL-17, reduced joint damage (97, 104, 107)	Leptin knock-out mice present with attenuated adjuvant induced arthritis (109)
Adiponectin	↑, – (92, 98, 113-117)	↑, – (113, 115)	Positive: Radiographic joint damage, C-reactive protein (96, 120-121) Negative: DAS-28, C-reactive protein synovial leukocyte count (122, 123)	Induces expression of IL-6, IL-8, IL-11, MMPs** 1, -10, -13, prostaglandin 2 from RA [‡] synovial fibroblasts (115, 125-127, 130-133) Adiponectin injection or viral gene transfer alleviates adjuvant induced arthritis in mice (134-135)
Visfatin	↑ (96, 106, 107, 152, 153)	↑ (152, 154)	DAS-28, functional capacity, radiographic joint damage, CRP, TNF-α [§] , IL-6 (107, 152)	Induces IL-6, IL-8, MMPs from RA synovial fibroblasts (152) Activates monocytes (151) Inhibits neutrophil apoptosis (157) Visfatin inhibition mitigates adjuvant induced arthritis (161)
Resistin	↑, – (96, 105, 107, 162-164)	↑, – (105, 113, 162)	DAS-28, CRP, ESR [§] , synovial leukocyte count, radiographic joint damage, TNF-α, IL-6, IL-1ra*** (105, 107, 113, 155, 163-164)	Induces TNF-α and IL-6 expression from synoviocytes (162) Causes arthritis in mice (162)

*Disease activity for 28 joints score; [†]Erythrocyte sedimentation rate; [‡]Interleukin; ^{**}Matrix metalloproteinases; [‡]Rheumatoid arthritis; [§]Tumour necrosis factor-alpha; [§]Erythrocyte sedimentation rate; ^{***}Interleukin 1-receptor antagonist.

other potential bone-protective mechanism maybe osteoclast inhibition, osteoblast induction (138), and induction of tissue inhibitor of metalloproteinase-2 (139), contrary to negative effects reported elsewhere (132). These results should be carefully evaluated since they refer to different disease models. However, in terms of physiological effect of adiponectin they denote a relevant function in the cartilage. Obesity is associated with reduced number and activation of NK cells (140) that in turn are identified as attractive targets in autoimmune diseases (141). Adiponectin is reported of being a regulator of NK cytotoxicity (142) and possible participation, negative or positive, via NK cells in RA (143-145) needs to be elucidated and clarified.

In summary, contradictory results and confutational actions rather complicate the role of adiponectin. A possible explanation is that perhaps they are not mediated solely by Adipo-R1/2, as mentioned earlier. Other receptors like C1q receptor (62), calreticulin receptor (136) or a new, yet unknown receptor (146) may be implicated. Different receptor activation may trigger different pathways. Another explanation could be actions through entirely different pathways such as binding to other chemokines

(147), or just simply variation in doses used. Adiponectin increase in more pronounced bone erosion could be a physiological mechanism to counteract the damage, based on bone protecting effects and explain this correlation with joint damage. Certainly, all these are speculations that need to be tested. Different forms, receptors and dual role dependent on time-point of inflammation (136, 148) are findings that, in conjunction with the consideration of adiponectin as beneficial in terms of CVD risk, a relationship though not established in RA, brings us faced with a dilemma: Should we design therapeutic strategies to increase or decrease adiponectin, or better a specific form of it, activate or block its receptors, and with what specific side-effects? Overall, its role in RA warrants further investigation and more studies in humans are urgently needed to upgrade adiponectin from a marker in RA into a real therapeutic target, either negative or positive.

Visfatin

Visfatin's role is under investigation, particularly with regard to whether it is a true adipokine, if it exerts insulin mimetic properties and as to if it is an enzyme, a cytokine or a hormone. What we know for sure is that it is up-regulat-

ed in insulin resistant states, like obesity, metabolic syndrome and diabetes, in inflammatory situations like acute lung injury and in autoimmune diseases (149-151). Otero *et al.* first reported elevated plasma levels in RA (96). These findings were in accordance to future studies also presenting increased circulating (106, 107, 152, 153) and synovial (152, 154) visfatin levels (Table II). Visfatin was positively correlated with disease parameters, functional capacity and radiographic joint damage, but not BMI (107). It was also reported to be higher in seropositive patients (107). Similarly, another group showed strong correlation of both serum and synovial levels with C-reactive protein (CRP) and DAS-28 (152). Another study curiously reported lower levels in RA patients with abdominal obesity (155). These findings, despite lack of a control-healthy group, suggest that perhaps inflammation is the main link or reason for increased visfatin levels in RA. Gonzalez-Gay *et al.* (156) in a smaller scale study found no correlation of visfatin with disease activity. Their results could be biased due to prior anti-TNF treatment. Visfatin is not only produced by adipocytes and strong evidence exists to support that it is not a simple bystander in RA: macrophages (151),

lymphocytes, monocytes, neutrophils (157), RA synovial fibroblasts (152, 154), osteoblasts (158) and chondroblasts (159, 160) also produce visfatin. Its expression is predominant in synovial lining and at sites of attachment and invasion of RA synovial fibroblasts into bone (152). *In vitro* it induces IL-6, IL-8 and MMPs production from RA synovial fibroblasts (152), IL-1 β , IL1-receptor antagonist (IL-1ra), IL-6, IL-10 and TNF- α from monocytes (151, 152), MMPs from chondrocytes (159). It activates monocytes (151) and inhibits neutrophil apoptosis (157). Furthermore, IL-6, TNF- α and visfatin seem to be interrelated in a positive loop (151, 154). To further strengthen the notion that visfatin is implicated in RA, Busso *et al.* (161) pharmacologically inhibited visfatin and mitigated inflammation and arthritis in collagen-induced arthritis mice. Future studies in humans should be expected with anticipation.

Resistin

Resistin has emerged as an important adipokine in low-grade inflammatory conditions and evidence of resistin role in RA has propagated in the last few years: Initially, synovial resistin levels were found elevated by as much as 10 times compared to osteoarthritis patients (113). This study was followed by others showing increased synovial (105, 162) and serum levels (105, 107, 162, 163), with some exceptions (96, 164) (Table II). Resistin correlated positively with disease parameters and inflammatory molecules (105, 107, 113, 155, 163, 164), (Table II). In support of the inflammatory role of resistin, other studies also found higher circulating resistin in inflammatory bowel disease (165) and salivary resistin in Sjögren's syndrome (166). Pathophysiological involvement of resistin in RA was explored and revealed production from macrophages, B cells and synovial fibroblasts (105, 162), especially after inflammatory stimulation by TNF- α (162). Resistin, in turn, induces TNF- α and IL-6 mRNA expression and release from human peripheral blood mononuclear cells and synoviocytes via NF- κ B signaling and dose-dependently causes arthritis in mice, even when

TNF- α is blocked (162). The presence of resistin in inflamed tissue and its involvement in RA may promote resistin to a therapy-target candidate, especially for those who do not respond to anti-TNF treatment (167).

Other adipokines

To conclude with adipokines implicated in RA, vaspin and omentin have recently been reported to be higher and lower respectively in synovium of RA patients compared to osteoarthritis patients (168). A comparison of serum levels with those in healthy individuals or/and osteoarthritis patients would be useful. Vaspin but not omentin correlated with DAS-28 ($r=0.320$, $p=0.070$), whereas omentin with serum levels of anti-citrullinated peptide antibodies ($r=0.398$, $p=0.029$) and IgM-rheumatoid factor ($r=0.592$, $p<0.001$). More studies are required to clarify their role in obesity and inflammation and elucidate possible implication in RA.

Perspective on clinical implications

Adipokines, especially the more studied leptin and adiponectin, function well beyond triglyceride storage messengers. They possess pleiotropic effects, direct and indirect. Assuming that adipokines could be potential RA therapeutic targets in the future, it is

worth elaborating on factors affecting their levels and exploit existing drugs with adipokine modulating properties (Table III).

Methotrexate, meloxicam and corticosteroids

Methotrexate and corticosteroids, used as first-line treatment anti-rheumatic drugs, can potentially modulate adipokine levels. *In vitro* and *in vivo* studies showed corticosteroid use and glucocorticoid metabolism potency towards adipogenesis and altered adipokine gene expression and release (56, 169, 170). We are not aware of any study in RA examining corticosteroid use and adipokine levels. Interestingly, in a small study of 7 patients with polymyalgia rheumatica, prednisone treatment increased total adiponectin and leptin, but not HMW adiponectin after 1 month. In that time, inflammatory marker change was greater; and by 3 months, as that change tended to reach the initial levels, adiponectin, but not leptin levels, fell, thus suggesting adiponectin-drive by inflammation (171). Low-dose methotrexate is allegedly believed to reduce vascular event rates based on anti-inflammatory properties (172). In support of this, a prospective study reported reductions in vascular events and cardiovascular deaths among RA patients re-

Table III. Pharmacological agents and strategies to modulate major adipokines in rheumatoid arthritis.

Adipokine	Pharmacological agents in rheumatoid arthritis
Leptin	Meloxicam no effect in rats (175) Anti-tumour necrosis factor treatment no effect (92, 98, 177, 179) Lowered by statins (211, 213, 214) Lowered by glitazones (237) Lowered by weight loss and dietary modification (229, 265, 273, 285)
Adiponectin	Increased by methotrexate by 13% (116) Increased by meloxicam in rats (175) Anti-tumour necrosis factor treatment reported to lower, increase or not affect adiponectin levels (92, 98, 117, 122, 124, 177, 178, 180-182) Increased by statins (212, 215, 218, 219) Increased by fibrates (227, 231) Increased by glitazones (233, 235-237) Increased by weight loss and dietary modification (261-266, 273)
Visfatin	Anti-tumour necrosis factor treatment no effect (156) Lowered by statins (216, 220) Lowered by weight loss (229)
Resistin	Anti-tumour necrosis factor treatment lowers serum resistin (183) Lowered by statins (214, 218) Lowered by glitazones (72, 73) Lowered by weight loss and dietary modification (73, 265, 273)

ceiving methotrexate (173). To the best of our knowledge, only one study has so far investigated thoroughly possible changes of adiponectin in early RA after treatment initiation with methotrexate plus low dose cortisone (116). Adiponectin increased by 13% in drug naive RA patients after methotrexate treatment. In contrast, *ex vivo* adiponectin release from mesenteric adipose tissue was reduced after methotrexate in a mouse model of experimental colitis (174). Meloxicam, a COX-2 inhibitor, is approved for RA treatment. Despite enhanced PGE2 production from synovial fibroblasts after adiponectin incubation (125), meloxicam treatment increased adipose tissue mass and serum adiponectin without an effect on leptin in rats (175). Unfortunately, synovial adipokine levels were not measured in this study (175). The above findings warrant further study and need to be confirmed by others to clarify the relationship between disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids and adipokines in RA.

Anti-TNF treatment

TNF- α has a pivotal role in inflammatory process. Based on this finding, anti-rheumatic drugs neutralising its effects by binding to it, have been developed and for some time now have been proven particularly beneficial in RA and other autoimmune diseases. TNF- α is also produced by adipose tissue (50). The fact that its levels are elevated in obesity and that it is a potent regulator and interacts with most adipokines (34, 176) lead us and others to investigate possibility of these biological agents to modulate adipokine levels. The verdict was not unanimous. Some studies report no change (92, 98, 124, 156, 177-179) and others elevation (117, 122, 180-182) or down-regulation (92, 183) of adipokines. Apart from anti-TNF, effect of co-administration of steroids (56, 92, 169, 170, 184) and DMARDs (185) cannot be excluded. In addition, we cannot exclude short-term fluctuations of adipokines in the first 24 hours after infusion, since TNF- α administration results to subsequent leptin peaks (186). In Crohn's disease, infliximab led to leptin increase early on (187),

without change of weight, but these patients are presented with lower leptin levels (188). In studies of subjects with diabetes and metabolic syndrome anti-TNF therapy had no effect in insulin resistance (176, 189-191), in contrast to short (192) and long-term (193) effect in RA. This might be due to disease differences (194) and drug-specific effect. In these populations, however, TNF- α blockade results in lowering of inflammatory response (191) and adipokine changes, primarily increase in total, but not HMW adiponectin, decrease in resistin and no effect in leptin (176, 191), in the 2 studies with measurements conducted.

TNF- α production by subcutaneous adipose tissue seems to act locally and not contribute to systemic TNF- α levels (195, 196). It mediates its actions via 2 distinct receptors. They are proteolytically cleaved and released in circulation, a phenomenon occurring to a greater extent in obesity (54, 194). This might partly explain why obesity, although considered an inflammatory condition, is linked to higher life expectancy in RA (despite findings in type 2 diabetic women (198)). Adipose tissue release of soluble TNF-Rs may localise the effects of TNF- α within the tissue, enabling it to function as an autocrine/paracrine factor (54). In RA, conversely, it could be hypothesized that it is a defensive mechanism of the tissue against TNF- α from other tissues. Is there a balance between anti-inflammatory and pro-inflammatory cytokines in obesity, leaning the scales over one or other side that may predict better or worse clinical response in the obese RA? We are not aware of the existence of a study aiming at answering this.

IL-1ra

Apart from increased soluble TNF-R, IL-1ra serum levels are also markedly increased in obese subjects, partly due to leptin induction (46, 47, 199). IL-1ra adipose tissue production may reflect an effort to counteract the catabolic, anti-obesity effect of IL-1 in sepsis and RA (IL-1 mediates leptin action and inhibits adipogenesis). IL-1 signalling participates in RA and targeting with synthetic IL-1ra has also been devel-

oped. No study so far, to the best of our knowledge, has examined the effect on adipokines, or whether overweight and obese patients respond better or worse compared to normal weight patients after IL-1ra treatment.

Hypolipidemic therapy

Statins, a class of drugs that block cholesterol synthesis, lower total and LDL cholesterol and effectively protect from CVD, exert a variety of several pleiotropic actions that may result in clinical benefits (200). In RA, which is characterised by increased CVD risk and inflammation, as noted earlier, statins are associated with lower risk of developing RA, in some (201), but not all studies (202), and suggested to improve disease parameters, inflammatory markers and endothelial function initially in animal studies (203, 204) and subsequently in humans, both *in vitro* and in clinical trials (205-210). Their potency to alter adipokine levels and adipose tissue characteristics was shown in cell culture, animal studies and humans (211-220). Hence, some of their beneficial effects, beyond LDL-cholesterol lowering, might be a result of altered adipose tissue biology. Ezetimibe and fenofibrate are two other classes of hypolipidemic compounds that act on cholesterol absorption on the gastrointestinal tract and by activating peroxisome PPAR- α , respectively (221, 222). Reports of beneficial reductions in disease activity and inflammatory markers and improvement of endothelial functions, in parallel to those seen with statins, exist for both, though they are limited (208, 223-226). Their administration and/or their combination may also impact on adipokines (227-231), an effect though probably dependent on weight loss as well, or via adipokines, such as in the case of RASF and adiponectin mediated PGE2 reduction (125).

Thiazolidinediones

Thiazolidinediones or simply glitazones are a class of anti-diabetic drugs. They are peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonists. These receptors are located in the nucleus and bind to DNA. Their

activation leads to expression of various genes (232). In the adipose tissue, PPAR- γ activation is an essential step in adipogenesis and glitazone treatment results in adipokine and adipose tissue physiology changes, with more profound effects on adiponectin and resistin (72, 73) expression and production (233-237). A common problem with glitazone treatment is osteoporosis and bone fractures reported in type 2 diabetics (238). The mechanism is not yet fully understood, but adipose tissue alterations are not solely to blame: they impact on osteoblasts and bone formation (239), while Wan *et al.* (240) provided evidence that points to increased osteoclast differentiation and bone resorption. Adverse effects have been reported with glitazone therapy: A case report in the literature describes RA deterioration after troglitazone, a type of glitazone now withdrawn (241). In rat adjuvant arthritis, on the other hand, glitazone derivative CGP 52608 was shown to have potent anti-inflammatory activity, via activation of retinoic acid receptor-related orphan receptor α (242), in contrast to rosiglitazone, which had a neutral effect, suggesting no effect of PPAR- γ (243). In the following years, more studies, incorporating different glitazones, higher dosages or different administration route, showed beneficial effects (244-247). It is also noteworthy that rosiglitazone ameliorated murine lupus most likely by increasing adiponectin (248). Effects on cell types other than adipocytes that may explain positive effects are reviewed in Fahmi *et al.* (185). In humans, the only evidence comes from an open-label study by Bongartz *et al.* in 10 patients with psoriatic arthritis treated effectively with high dose pioglitazone (60 mg daily) (249). We cannot attribute beneficial or adverse effects to adiponectin changes (30, 250, 251) alone (note, *e.g.* soluble TNF-R increase and IL-1ra decrease in Halvorsen *et al.* (251)), nor can we exclude such a possibility; with activation of PPAR- γ by prostaglandins, already present due to inflammation (185), providing another possible explanation on adiponectin presence in the site of inflammation.

Even more advanced therapeutic approach was implemented by Gonzalez *et al.*, who took advantage of adipose tissue-derived mesenchymal stem cells in order to alleviate T cell inflammatory process in an animal model of arthritis and subsequently in human culture *in vitro* (252, 253). Their findings were, in a way, reproduced in another autoimmune situation (254). This suggests the potency of adipose tissue *per se* to impact on RA and other autoimmune diseases.

Dietary/lifestyle changes

But since this is a step to be taken not in the very near future, other, more tangible and cost-effective strategies could be undertaken: What role can dietary portfolios play, knowing that, for instance, the Mediterranean diet, limiting saturated fatty dietary intake, higher omega 3 fatty acid and weight loss may desirably affect inflammation, on the one hand, and that they are implemented by a large percentage of RA patients (255) who are often on a poor nutrient status (256), on the other? Numerous studies established omega 3 fatty acids as anti-inflammatory lipids and protective against CVD. Based on these effects, they have also been tested as add-ons to RA therapy and proven to be of significant effectiveness in alleviating symptoms (256, 257). Mediterranean diet, characterised by a high consumption of fruit, vegetables, whole grains, legumes, reduced intake of meat, and higher intake of fish, was also put on trial, based on cardioprotective, anti-cancer and anti-inflammatory effects (258). It was found to lead to a reduction in inflammatory activity, an increase in physical function, and improved vitality. Nutrient intake is certainly set to modulate adipokines as well: for instance TNF- α and leptin decrease and adiponectin increases when healthier diet choices are made (259-268). Although there are no data on adipokines, diet and RA, it cannot be claimed that this is merely a coincidence. Clinical studies that will address this question are required. The efficacy of fat soluble vitamin D is not entirely proven, but is an intriguing target for RA treatment (269-272) and may exert

some of its functions via adipose tissue (273, 274). Weight loss, especially in obese insulin resistant subjects, lowers inflammation (275), alters serum adipokines in the same manner as healthier dietary choices do (276, 277) and undoubtedly confers beneficial effects on endothelium and blood pressure, glucose and lipid metabolism (278-280). In RA there is some indication of positive effect of weight-loss interventions. Excluding the cases where dietary support is necessary to deal with protein-energy malnutrition and cachexia (268, 281), weight loss, without lean body mass loss, and acute starvation seem promising (282-286). Some researchers attributed beneficial effects partly on adipokine-mediated changes (285), whereas others do not favour weight loss as a means of improvement (287). Overall, lifestyle changes are easily applied, cost-effective and deserve further research with regard to their role in RA management.

Concluding remarks

Overall, inflammation and insulin resistance reinforce each other via a positive feedback loop and often come together as is the case in both adipose tissue expansion (*i.e.* obesity) and RA. In this review we have attempted to delineate the relationship between adipose tissue and RA. All major adipokines (leptin, adiponectin, visfatin, resistin) bear immune-modulatory properties or obliquely impact on inflammation and solid evidence points to involvement in the pathophysiology of RA. Future research should focus on investigating if inflammation in RA, and maybe other autoimmune diseases, is triggering insulin resistance and the latter is causing adipose tissue to respond by altering adipokine expression and possibly modulating metabolic processes such as lipogenesis and lipolysis that also might be related to rheumatoid cachexia. If so, is visceral or subcutaneous adipose tissue affected the most? Also, can RA involved cells "migrate" from the synovium to other tissues (288) and to what extent, if at all, cells other than adipocytes produce adipokines in the synovium (36, 41, 152), also bearing in mind that we cannot easily dissociate the effects

of one adipokine from another, but rather examine them as a whole. Finally, dietary or pharmacological strategies that modulate adipokine levels might prove beneficial in improving certain aspects of disease, followed by clinical studies incorporating human recombinant adipokines (108) or monoclonal antibodies against them or their receptors (289). In conclusion, adipose tissue biology is an open field and is worth exploring, particularly with regard to immune-modulatory actions and inflammatory processes and diseases like RA.

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