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Adiposity, joint and systemic inflammation: the additional risk of having a metabolic syndrome in rheumatoid arthritis

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Summary

Adiposity is a predisposing condition to atherosclerosis, and rheumatoid arthritis (RA) also predisposes to accelerated atherosclerosis. Adiposity is one of the key features of the metabolic syndrome (MetS) and it is well recognised that a metabolic syndrome (and fat tissue) is a major player in this complex network. Endothelial dysfunction and carotid intima-media thickness, early pre-clinical markers of atherosclerosis which are the main determinants of cardiovascular (CV) morbidity and mortality, occur early on in RA. RA patients have an incidence of CV diseases at least two times higher than the general population.
MetS and RA have a low and a severe-moderate degree of inflammation in common, respectively. Adipose tissue has emerged as a dynamic organ that releases several inflammatory and immune mediators (adipokines). In addition, fat has been recognised as a producer of B cell activating factor (BAFF) and of chemerin, an inducer at the chondrocyte level of IL1β, TNFα, IL6, IL8 and MMP13, thus possibly contributing to cartilage damage. Since fat produces inflammation, to obtain a full control of the CV risk in RA, data suggest that it is therefore mandatory to have a "tight control" of both RA and MetS-related inflammation, especially if RA presents MetS as a co-morbidity.

Key words: *rheumatoid arthritis; adiposity; adipokines; chemerin; remission*

Introduction

Rheumatoid arthritis (RA) pathobiology seems to share some common pathways with atherosclerosis, including endothelial dysfunction which is related to underlying chronic inflammation and presents in the early phases of the disease [1–4]. A possible aggravating risk is represented by the co-existence of a metabolic syndrome (MetS), characterised by a combination of various risk factors that imply additional cardiovascular morbidity that is greater than the sum of the risks associated with each individual component. Several studies have demonstrated that inflammatory processes are involved in the pathogenesis of the metabolic syndrome. On the other hand, there is evidence that components of cardiovascular (CV) risk increase the inflammatory burden in RA.

Cardiovascular risk in RA

A recent, Dutch, cross-sectional study found that age- and gender-adjusted odds ratios for CV diseases derived from these cohorts were 3.1 for RA patients and 2.3 for individuals with type 2 diabetes (T2DM) with respect to healthy subjects, indicating that the CV risk in RA is comparable to diabetes, one of the most relevant CV risk factors. It also showed a prevalence of CV events (coronary, cerebral and peripheral arterial diseases) of 13% in non diabetic RA patients, 12% in subjects with T2DM and 5% in non diabetic individuals [5].
The expected life span of patients with RA is known to be shorter than in healthy controls [6], with a standardised overall mortality ratio of between 1.3 and 3 compared to the general population [7], and it is well recognised that, as in the general population, cardiovascular diseases are the leading cause of death. Large epidemiological studies from the last several decades have confirmed that patients with RA are 30 to 60% more likely to suffer a CV event than subjects from the general population [1, 7].
To assess the incidence of CV events, the Dutch authors prospectively followed two cohorts of 263 non diabetic RA patients and 1492 non diabetic individuals for 3 years [8, 9] and they confirmed that patients with RA have about a 2–fold higher CV diseases risk than the general population. The magnitude of the increased CV risk occurred was at least as that of T2DM patients, and this confirmed the previous data in the literature [10].
Histological data provided evidence that coronary arteries from autopsied RA patients have more inflammation in the media and adventitia and more fragile atherosclerotic plaques, but less atherosclerosis, when compared to coronary arteries from age-and sex-matched controls who died from CV diseases. Despite this, the number of acute coronary lesions and grades of stenosis were similar [11, 12, 13]. A possible interpretation of these differences is that the mechanisms responsible for cardiovascular morbidity and mortality are likely to be different in patients with RA.

When comparing the dramatic improvements in the overall mortality rates of the general U.S. population (from 1.0–1.2 to 0.2–0.3), it seems that RA patients have not experienced improvements in survival over the past 4 decades (1965–2005 mortality rates: 2.4–2.5) despite the progress made in the diagnosis and therapy of RA. Clear-cut data suggest that there is a widening mortality gap between RA patients and the general population [14]. In agreement with this analysis, a retrospective population-based cohort study suggested that, even at the moment of RA diagnosis, the absolute CV risk in RA patients was similar to that of subjects without RA who were 5–10 years older [15].

These data suggest that mortality has not really been modified during the past 50 years [16]. Of note, we must take into account that most of these studies considered patients with a diagnosis made before the 1990s, when disease-modifying anti-rheumatic drugs (DMARDs) were poorly prescribed and only minimal attention was paid to the control of inflammation and the prevention of cardiovascular events. It will certainly be interesting to assess the effects of an early diagnosis, of a "tight control" of disease activity and of the new therapies, in particular of the biological drugs, on CV risk. In agreement with the hypothesis that control of CV risk relies on better disease activity control, preliminary evidence reports an improvement of overall cause mortality, and also of CV mortality, when patients were treated very early on [17] and with a more aggressive therapy [18, 19]. The conclusions are still controversial and more data are really needed, especially because a very recent report showed that the risk of cardiovascular events and survival in patients who received TNF-α antagonists was not different from those who received other DMARDs (with a CV morbidity of 38% in both groups) [20]. The strength of this work was that it was conducted in a cohort of about 20'800 U.S. veterans who were diagnosed with RA over a period of seven years, although the bias is that the data were collected retrospectively from an administrative registry. Data from further prospective long-term studies and in early arthritis registries could really help to elucidate this fundamental issue.

Metabolic syndrome and RA

The prevalence of Metabolic syndrome (MetS) has been assessed in patients with many systemic rheumatic diseases [21]. Recently, Karvounaris *et al* found a prevalence of MetS (defined with NCEP ATP III criteria) in RA patients (40%), comparable with their control population, and documented a relationship between disease activity and the presence of MetS [22]. Another study showed that MetS was significantly more prevalent in American patients with long-standing RA (42% – WHO and NCEP/ATPIII criteria) as well as in early RA patients (31% and 30% – WHO and NCEPIII criteria respectively) than in controls (11% and 22% – WHO and NCEP/ATPIII criteria, respectively) [23].

The same problem can be seen from the alternative angle, and indeed Karvounaris *et al* found that the risk of having a moderate-to-severe RA was higher in patients with metabolic syndrome than in those without, and that disease activity correlated with the number of MetS parameters present [22]. The take-home message might be that MetS has an inflammatory milieu leading to the occurrence of a more severe RA. If this were true, the therapeutic response should differ in RA carriers of MetS versus non carriers.

Up to now no data are available in the literature on the possible effect of MetS on the response to therapy. Our group evaluated a cohort of 115 long standing RA patients with an active disease, for the presence of metabolic syndrome and disease activity at the start of an anti-TNFα drug prescription and after 12 months of follow-up (tables 1 and 2). At baseline, MetS was seen in 27% of our patients. Over time there was a statistically significant increase in the levels of total cholesterol (mean value 184.1 mg/dl at T0 vs. 192 mg/dl at T12) and triglycerides (mean value 122.3 mg/dl at T0 vs. 134.5 mg/dl at T12) without changes of glucose, high-density lipoprotein (HDL), artery pressure levels or body mass index (BMI). Importantly, we observed that RA patients with a metabolic syndrome at baseline had a significantly lower chance to achieve a good response (DAS<2.4) at 1 year of follow-up, compared to patients without a MetS (38% of poor responder in MetS patients vs. 18% in non-MetS, Odds Ratio (OR) 2.36 [Confidence Interval (CI) 1.12–6.25], $p = 0.02$), while the prevalence of a MetS remained unchanged over time. The overall changes in lipid levels in our cohort under TNF blocker therapy are in line with a meta-analysis [24].

These findings suggest that a MetS may contribute to a poorer response to therapy in RA patients. This could be explained by the additive effect of the low-grade components of inflammation present in MetS to the already present inflammatory burden of rheumatoid arthritis, and partly by the pathogenetic processes driving inflammation in the two conditions (RA and MetS) that might involve different pathways and cytokines, thus requiring different therapeutic targets. The presence of a MetS could maintain some degree of chronic inflammation and, on the other hand, the persistence of inflammation associated with rheumatoid arthritis might affect the cardiovascular risk, thus mutually reinforcing each other. These data strongly suggest that it is likely to be necessary in patients with both RA and MetS that maintain a higher disease activity, compared to RA patients without MetS, to treat both conditions simultaneously and effectively in order to have a significant impact on the cardiovascular risk. This hypothesis should be tested when looking at the cardiovascular mortality rate in patients receiving DMARDs and/or biologic therapy. The introduction of new biologic therapies, that potently suppress inflammation, has further improved the outcomes but they have shown some controversial effects, especially on lipid profile. In particular, a great number of studies on anti-TNF agents have found different results, although the majority showed an increase of total cholesterol levels, as well as of HDL cholesterol, thus with an atherogenic index that tends to remain the same. Along this line, patients treated with the anti-IL6 drug, tocilizumab, are likely to experience an increase of total cholesterol, LDL, HDL and triglycerides, even though these are reversible. The long-term effect of these drugs on CV outcomes has yet to be fully elucidated [25, 26], but it is increasingly recommended to normalise cholesterol through statins, taking advantage of the intrinsic anti-inflammatory effects [27–29] . On

a large scale basis, statins do not show any clear-cut effect on RA disease activity [30], even though being on statins has shown a reduced risk of developing RA [31].

Cardiovascular risk factors in RA are not the same as for the general population.

Hypertension, diabetes mellitus or hyperlipidemia levels among RA patients are similar to the general population. Gonzalez et al [32] found that, with the exception of smoking which also increases the susceptibility to RA, the distribution of the other traditional CV risk factors does not appear to differ between RA patients, at the time of the RA onset, and non-RA people. As the prevalence of traditional CV risk factors does not seem to account for the increased risk of CV morbidity and mortality in RA patients, the logical conclusion should be that several RA-related risk factors have to play a crucial role in the course of the disease. These factors certainly include a diminished exercise capacity, but also the possible iatrogenic effects of therapeutic interventions and chronic inflammation.

Since it is well known that disability, as measured by the Health Assessment Questionnaire (HAQ), is a predictor of both overall and cardiovascular mortality [33], the take-home message should be that HAQ remission should be included among the major outcomes for defining remission in all RA cohorts.

All the evidence supports the concept that chronic inflammation characterising RA plays a key role in accelerating atherosclerosis [34, 35]. CV disease mortality is higher in patients with more widespread disease and high levels of systemic inflammation markers [11], and Provan *et al* showed that patients with active RA, but not those in remission, had significantly increased levels of CVD risk markers (NT-proBNP, hypertension, total cholesterol, reactive hyperaemia index (RHI), measures of arterial stiffness and intima media thickness) than the control group [26]. These results indirectly support the notion that remission in RA allows diminished cardiovascular morbidity. The remaining open question is when and how we can define remission in a RA patient. It has previously been said that the increased risk of heart disease precedes the clinical onset of rheumatoid arthritis [11], suggesting that other factors (e.g., environmental or genetic), in addition to those described above, may contribute to this early risk. In this regard, it has already been demonstrated that there is a pre-clinical phase of RA during which inflammatory activity and serological and autoimmune disturbances occur [27], thus triggering the CV risk, and that there may be a consistent delay between the onset of the first RA symptom, diagnosis and the start of an effective therapy. These findings suggest that an untreated systemic inflammation can induce damage to the CV system before it affects the joints, and most importantly that chronic exposure to systemic inflammation increases the risk of CVD [3].

The specific background of RA is clear when one considers that a lower body mass index is also associated with a higher CV mortality in RA, which is very likely related to the increased inflammatory cytokines inducing a catabolic state: the so-called rheumatoid cachexia [36].

To demonstrate that there are important and independent RA-related factors contributing to the CV risk, Solomon *et al* evaluated both traditional CV risk factors and parameters of RA severity (long disease duration, modified HAQ score, Clinical Disease Activity Index-CDAI, seropositivity, radiographic joint erosions, subcutaneous rheumatoid nodules and previous joint replacement) at baseline in predicting CV events. In this large cohort of patients the authors showed that traditional CV and RA related factors were independent predictors of CV diseases and that the risk increased with the number of both types of parameters [37].

Metabolic syndrome and cardiovascular risk

Metabolic syndrome (MetS) represents a cluster of cardiovascular disease risk factors that have insulin resistance and increased visceral adiposity in common. This entity has received great attention as the best known predisposing setting for the development of CV morbidity [38] and represents a condition which has been defined, by the National Cholesterol Education Program's Adult Treatment Panel III Report (NCEP ATP III) from the National Institute of Health, as the situation in which three of five characterist-

Table 1: Behaviour over time of the metabolic variables in the 115 patients treated with a TNFα blocker (Adalimumab).

Baseline disease activity DAS 4.7 ± 1.1	**Baseline**	**T6**	***p***	**T12**	***p***
Glucose	88.1 ± 21	87.5 ± 21.6	0.370	88.3 ± 16	0.390
Glucose abn.	27(19.9%)	23(16.9%)	0.103	22(16.3%)	*0.025*
TGL mg/dl	122.3 ± 67.2	131.6 ± 56.3	*<0.001*	134.5 ± 67.7	*<0.001*
TGL abn	29(21.3%)	31(22.8%)	0.414	32(23.5%)	0.366
HDL mg/dl	54.0 ± 15.3	54.8 ±13.3	0.210	55.3 ± 15.2	0.310
HDL abn	48(35.3%)	42(30.9%)	0.157	41(30.1%)	0.194
Cholesterol mg/dl	184.1 ± 37.7	191.1 ± 40.3	*0.001*	192.8 ± 41.3	*0.002*

Table 2: Low disease activity according to the baseline metabolic abnormalities in the cohort of patients treated with a TNFα blocker.

Variables	**Outcome DAS≤2.4 (54)**	**Outcome DAS>2.4 (61)**	***p***
Age (years)	52 ± 12.9	55.6 ± 11.2	0.170
Sex (male)	11(20.4%)	6(9.8%)	0.120
Dis Duration (years)	8.6 ± 10.8	8.8 ± 9.3	0.640
BMI	25.5 ± 3.2	27.4 ± 4.0	*0.013*
BMI abnormal	23(42.6%)	39(63.9%)	*0.026*
MetS	10(18.5%)	23(37.7%)	*0.025*

ics are present, including obesity, elevated triglyceride, low level of high density lipoproteins (HDL) cholesterol, high systolic and diastolic blood pressure, and elevated fasting glucose [39]. The prevalence of MetS in the general population varies between 17 and 43 % [41, 42] and increases with age. In our cohort of RA patients receiving anti-TNF it was 27%. The MetS-associated increase in CV disease morbidity may depend on the definition used and a recent study showed that CV disease prevalence was more pronounced when the NCEP ATP III and the AHA/NHLBI criteria for MetSyn were used [42].

A recent systematic review and meta-analysis of the literature, involving more than 950'000 patients, has shown that metabolic syndrome is associated with a 2-fold increased risk of cardiovascular disease, CV mortality, myocardial infarction and stroke [43]. These data are even stronger when considering that the CV risk associated with MetS remains the same when patients with type 2 diabetes mellitus are excluded from the analyses. As a whole, MetS is a risk for higher inflammation, higher CV risk and persistence of active disease [44–49].

Adiposity and joint inflammation

Being overweight is a major component of MetS and is associated with an adverse cardiovascular risk profile, characterised by hypertension, insulin resistance and an atherogenic lipid profile. In addition, there is a continuous relationship between BMI and risk of death from coronary artery diseases in middle-aged adults [44]. Obesity is now regarded as a systemic, low-grade inflammatory state, characterised by elevated circulating levels of C-reactive protein, TNF-α, IL-6 and PAI-1 [51]. Obesity is also a recognised risk factor for osteoarthritis and it is thought to be an additive risk for long standing RA [52], while there is a debate as to the possibility that obesity protects the joints in the early years of the disease [53].

Biological data have certainly clarified that adipose tissue is a dynamic endocrine organ that releases several bioactive substances, in common with inflammatory diseases such as RA, including some pro-inflammatory cytokines like TNF-α and IL-6, and specific cytokines, termed adypokines. These include adiponectin, leptin, resistin and visfatin, some of which promote inflammatory responses and metabolic dysfunction, and others which contribute to the resolution of inflammation and have beneficial effects on obesity-linked metabolic disorders [54]. One adipokine which gained upmost importance just recently has been chemerin, which plays a critical role in adipogenesis. Through its receptor ChemR23 it can amplify inflammation and lead to cartilage damage. In obese people it has been shown that adipose tissue presents more inflammatory infiltrate than normal-weight people and is characterised by different regulatory mechanisms and cytokine pattern production [55]. This implies that pro-inflammatory cytokines and adipokines can affect metabolic dysfunction and CV risk on the one hand, and rheumatoid arthritis on the other one. In this regard, an Italian retrospective study first described an approximately 3–fold lower chance to achieve remission in RA, obese patients receiving anti-TNF therapy than in normal-weight RA patients [56]. These data were confirmed by a recent prospective study showing that a high body mass index (BMI) was associated with a poor response to infliximab [57], a drug whose dose should still be proportional to body weight, supporting the fact that adipose tissue may be involved in the pathophysiology of RA. If we consider that obese patients are at increased risk of developing RA, with an adjusted odds ratio of 3.74 [58], then we may conclude that an obese RA patient does have more inflammation than the same RA in a non-obese patient.

Adiposity, adipo-cytokines, joints and vessels

TNF-alpha

In white adipose tissue (WAT), TNF-α is produced by adipocytes and fat infiltrating macrophages and is overexpressed in plasma and adipose tissue of obese human and animal models. TNF-α promotes insulin resistance by decreasing tyrosine kynase activity of the insulin receptor and insulin signalling *via* MAPK pathways *in vitro* and *in vivo*, thereby reducing insulin activity [59, 60]. Studies in mice suggest that the attenuation of TNF activity improves glucose homeostasis [61]. In humans in a small group of obese T2DM patients, a study showed that blocking TNF-α decreased plasma levels of inflammatory markers but did not ameliorate insulin resistance [62], while a recent report found that a prolonged period of TNF neutralisation in patients with a metabolic syndrome improved fasting glucose levels and increased high molecular weight adiponectin levels [63]. Moreover, anti-TNF therapy in "high-grade" inflammatory diseases, such as rheumatoid arthritis, has been reported to promote insulin sensitivity in several small studies [64, 65], suggesting that TNF has an important role in inducing insulin resistance mediated by inflammation.

TNF-α also plays a role in endothelial dysfunction [4, 66], an early marker of atherosclerosis, and as such is already

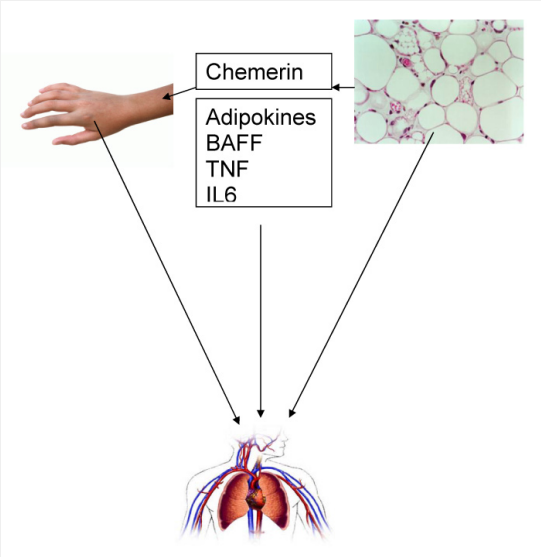

Figure 1

Fat inflammation increases joint inflammation and cardiovascular risk.

present in MetS [67]. There is evidence that TNF-α blockade in RA patients leads to a decrease of biomarkers of endothelial dysfunction and an improvement of endothelial dysfunction [68, 69], especially in the early phases of the disease [4].

IL-6

WAT produces 10 to 30% of circulating IL6, and plasma levels of IL-6 strongly correlate with BMI and insulin resistance [70]. Elevated IL-6 plasma levels predict future risk of cardiovascular events [71] and of T2DM [72], independently of BMI.

In a preliminary study involving a small group of non diabetic RA patients, it seemed that inhibition of IL-6 signalling improved insulin sensitivity [73]. The IL-6 effects on accelerated atherosclerosis are controversial. In an experimental model, administration of exogenous IL-6 in the murine apolipoprotein E–deficient (*ApoE*$^{-/-}$) model of atherosclerosis dramatically enhanced atherosclerotic lesion formation, suggesting a pivotal role for IL-6 in plaque progression [74]. However, a lifetime deficiency of IL-6 in the *ApoE*$^{-/-}$ model enhanced atherosclerotic lesion formation and increased cholesterol levels [75, 76].

In light of these data, it will be interesting to see if antagonising IL-6 in RA positively affects the cardiovascular outcomes, despite the known negative effects on the lipid profile. These data will certainly derive from inception cohorts in registries.

Leptin

WAT also produces the adipokine leptin, the product of the *ob* gene [77]. Leptin is considered a major regulator of body weight by suppressing appetite, thus decreasing food intake, and stimulating energy expenditure via hypothalamic receptors. Plasma levels of leptin are directly correlated with the amount of body fat and obese people have high circulating levels of leptin, indicating the occurrence of resistance to its action [78]. However, leptin is also involved in the inflammatory and immune mechanisms. Leptin synthesis is enhanced during acute infection and inflammation [79], as well as under the action of inflammatory mediators such as TNFα, IL-6 and IL-1. Furthermore, leptin stimulates the production of pro-inflammatory cytokines from cultured monocytes and increases the production of Th1 type cytokines, down-regulating Th2–type cytokines, thus polarising T cells towards a Th1 phenotype [80–81]. High circulating leptin levels have recently been demonstrated in patients with RA [82], both in plasma and in the synovial fluid. The clinical relevance of these findings still needs to be fully elucidated [83, 84].

Resistin

Resistin is a 108 amino acid long protein (12.5 kD) initially related to insulin resistance [85]. In animal models, resistin promotes insulin resistance, while the evidence for this effect in humans is less clear [86, 87]. Resistin was originally identified in adipose tissue. Later, it was observed that resistin production is restricted to adipocytes in mice, while in humans it is mainly derived from circulating monocytes and macrophages [88]. In this regard, several studies demonstrated that pro-inflammatory cytokines increase the expression of resistin [89], which in turn is able to stimulate the production of TNFα and IL12 [90], and to up-regulate the genes of TNF-α, IL-6, IL-1β and, interestingly, resistin itself [91]. Being produced by macrophages, resistin appears to be one of the several enhancers of inflammation produced by these cells. Along this line, it has been suggested that resistin may have a role in the pathogenesis of arthritis, triggering inflammatory synovitis when injected into mice joints [92]. In rheumatoid arthritis, despite conflicting results concerning serum levels, resistin synovial fluid levels were found to be higher in RA when compared to osteoarthritis, and resistin expression in synovial lining layers positively correlated with acute phase reactants and disease activity [93]. Of interest, recent experimental data suggest that resistin, in the presence of dendritic cells (DC), might induce the expansion of functional regulatory T cells (TRegs) [94].

Adiponectin

Adiponectin, encoded by the ADIPOQ gene, is a protein which is almost exclusively synthesised and secreted by adipocytes. It shows anti-inflammatory, insulin-sensitising and anti-atherogenic properties [95]. Adiponectin plasma levels are decreased in obese people compared with normal weight individuals, and also reduced in type 2 diabetes and MetS. These findings suggest that the functional adipocytes of lean subjects express high adiponectin levels, while in the dysfunctional adipocytes of obese individuals its expression is down-regulated. Moreover, weight reduction significantly increases circulating levels.

Adiponectin has shown several "anti-inflammatory" effects: it inhibits the transformation of macrophages into foam cells; it reduces TNF production by macrophages; it promotes the alternative activation of monocytes from a pro-inflammatory M1–type macrophage into an anti-inflammatory M2–phenotype; and it stimulates the production of the anti-inflammatory cytokine IL10 and of Interleukin 1 Receptor antagonist (IL1Ra) by macrophages [96, 97]. Studies in RA found elevated serum and synovial fluid adiponectin levels both in early and established disease, which did not correlate with disease activity nor were affected by TNF blockade, but increased with methotrexate treatment [98]. These data suggest that Adiponectin induces a sort of "natural" tolerance in macrophages to inflammatory stimuli.

Visfatin

Visfatin is a novel 55 kD adipokine that was originally discovered in the liver, skeletal muscle and bone marrow as a growth factor for B lymphocyte precursors (hence pre-B-cell colony-enhancing factor 1, PBEF) with insulin-mimetic actions, preferentially produced by visceral adipose tissue but also found in the liver, bone marrow, skeletal muscle and lymphocytes [99, 100]. Circulating levels of visfatin correlate with obesity and type-2 diabetes, and are reduced after weight loss [101].

Visfatin is also synthesised in response to inflammatory stimuli, and, moreover, it can enhance production of TNF-α, IL-6, IL-1β, as well as of IL-10 and IL-1Ra [102], and could promote atherosclerotic processes (inducing cell adhesion molecules) and plaque destabilisation [103] Visfatin

has been shown to induce chemotaxis and the production of IL-1β, TNF, IL-6 and co-stimulatory molecules by $CD14^+$ monocytes, and to increase their ability to induce all proliferative responses in lymphocytes, effects which are mediated intracellularly by p38 and MEK1 [104]. Inhibiting visfatin reduced circulating TNFα levels during endotoxemia in mice [105] in other inflammatory conditions, and also in rheumatoid arthritis some authors reported increased synovial fluid and plasma levels of this adipokine as well as its expression by rheumatoid synoviocytes at sites of attachment and invasion into cartilage or bone [106]. Additionally in agreement with these findings is the association between radiographic damage and high visfatin serum concentrations [107].

BAFF (B cell activating factor)

BAFF is a 17 kD protein mainly secreted by myeloid cells (but also by bone marrow stromal cells, granulocytes, synovial fibroblasts etc.) that exerts profound effects on B cells leading to their maturation and increased survival. BAFF has three receptors: B cell maturation antigen (BCMA), trans-membrane activator and CAML interactor (TACI), and BAFF receptor (BAFF-R) [108; 109].

It has recently been shown that BAFF and its receptors are synthesised by maturing adipocytes, that TNF increased BAFF synthesis by mature adipocytes, and that BAFF itself increased the synthesis of two of its receptors, namely BAFF-R and BCMA [110]. Whether the expression of the ligand and of its receptors might influence the course or the occurrence of autoimmune disease will only be solved by prospective studies.

Chemerin and ChemR23

Chemerin is a novel 18 kD adipokine that regulates adipocyte development and metabolic function as well as glucose metabolism in liver and skeletal muscle tissues. The chemerin gene, also known as tazarotene-induced gene 2 (TIG2) or retinoic acid receptor responder 2 (RARRES2), was originally identified as a novel retinoid- responsive gene in psoriatic skin lesions. Chemerin is a secreted protein that exerts its functions by binding the G protein-coupled receptor ChemR23. It was first discovered as a chemotactic peptide directing macrophages and dendritic cells expressing ChemR23 towards sites of inflammation, being involved in both adaptive and innate immunity [111, 112].

ChemR23 and chemerin proteins have been detected in chondrocytes *in vitro* by immunocyto chemistry, and ChemR23 and prochemerin transcripts were detected in chondrocyte cultures by reverse transcriptase PCR. It has been shown that Chemerin binding to ChemR23 led to increased phosphorylation of p44/42 mitogen-activated protein kinases (MAPKs) and Akt and blocking of MEK-1/2 signalling prevented phosphorylation of p44/42 MAPKs, but not of Akt. This suggests that intracellular downstream events upon chemerin stimulation occur through the Akt/MEK/MAPK pathway [113]. In chondrocyte cultures, Chemerin regulates the production of pro-inflammatory cytokines, IL-1β, TNF-α, IL-6, and IL-8 as well as MMP-13, thus suggesting that it can lead to cartilage damage and degradation [114]. Indirect evidence for this hypothesis comes from the observation that Chemerin levels are increased in synovial fluid of RA patients and that synovial tissue from RA shows expression of both Chemerin and ChemR23 [115]. Therefore, obesity and joint damage seems to be linked by several possible pathways (Fig. 1). The interesting aspect of this possible pathway is that Chemerin-derived peptides, after protelysis of the precursor protein, can also exert anti-inflammatory effects, thus suggesting that the initial synthesis and the chronic production of Chemerin can have different effects [116]. Whether this might explain why obesity in the early phases of RA seems to exert a protective effect whereas it does have a deleterious effect over the long lasting periods, will be solved by dedicated prospective studies.

Conclusions

In view of the role of adipokines in inflammatory arthritis and the potential modulatory role of TNF on adipokines, some studies have tested the effect of TNF blockade on the plasma levels of some of these adipokines in patients with RA. In particular, with regard to adiponectin, five studies have found that short or long-term TNF blockade had no influence on circulating levels of this cytokine [117], while four showed an increase of adiponectin after anti-TNF administration [118–119]. Additionally, four studies on leptin [120] and one on visfatin [121] showed no changes in plasma concentrations of these adipokines and one study described a decrease of resistin following anti-TNF therapy [122–124]. Only one study showed that a TNFa blocker decreased chemerin levels [115].

The conclusion at this moment is that the biological role of adipokines is not entirely understood, The evidence that obesity represents a negative biomarker for TNFα blockers-treated patients to reach low disease activity or remission, suggests that it represents an amplifying loop on the course of RA. Only an adequate control of obesity and MetS seems to guarantee full control of the systemic inflammation and, as such, of the related CV risk.

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