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ADIPOSITY, JOINT AND SYSTEMIC INFLAMMATION AND THE RISK OF METABOLIC SYNDROME IN RHEUMATOID ARTHRITIS

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Abstract: 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 recognized 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.
Keywords: 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.

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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 standardized 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 diseasemodifying 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.

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 takehome 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-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 or 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]. Table 1. Presents the demographics and metabolic components of the patients

Table 1. Demographics and Metabolic Components of the patients

Demographics and Metabolic Components	Patients	Females	Males
Age (years)	45.5 ± 13	45.3 ± 13	46.5 ± 16
Systolic blood pressure (mmHg)	115 ± 19	116 ± 19	112 ± 13
Diastolic blood pressure (mmHg)	75.1 ± 9	75.5 ± 9	72 ± 9
Weight (kg)	66.9 ± 12	66.4 ± 11	71.5 ± 18
Belt circumference (cm)	92.3 ± 14	91.7 ± 13	97.4 ± 20
BMI (kg/m2)	26.8 ± 4	27 ± 4	25.1 ± 4
FBS (mg/dL)	99.5 ± 40	100.1 ± 43	95.1 ± 14
TG (mg/dL)	105 ± 36	133.4 ± 98	113 ± 61
Cholesterol (mg/dL)	202 ± 180	195 ± 41	176 ± 35
LDL-C (mg/dL)	117 ± 36	116.2 ± 37	122 ± 23
HDL-C (mg/dL)	46.6 ± 11	47.7 ± 11	38.6 ± 11
Smoking (%)	7.2%	5.1%	22.3%
MetS (IDF)(%)	31.4%	42.7%	29.1%
MetS (NCEP–ATP III)(%)	46.7%	39.2%	29.7%

Adiposity and joint inflammation

Being overweight is a major component of MetS and is associated with an adverse cardiovascular risk profile, characterized 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, characterized by elevated circulating levels of C-reactive protein, TNF-α, IL-6 and PAI-1 [51]. Obesity is also a recognized 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.

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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