

METABOLIC SYNDROME, INFLAMMATION
AND ATHEROSCLEROSIS – THE ROLE OF
ADIPOKINES IN HEALTH AND IN SYSTEMIC
INFLAMMATORY RHEUMATIC DISEASESMaria José Santos,^{*,**} João Eurico Fonseca^{*,***}**Abstract**

Cardiovascular (CV) events are among the leading causes of morbidity and mortality in patients with inflammatory rheumatic diseases. It has been hypothesized that, in addition to the traditional CV risk factors, inflammation is a major contributor to atherogenesis. Metabolic syndrome (MetS) stands for a cluster of risk factors associated with insulin resistance and increased abdominal fat. Inflammation and MetS are intimately linked. Inflammatory biomarkers are frequently elevated in people with MetS and, conversely, the prevalence of MetS is higher in patients with chronic inflammatory rheumatic diseases, such as Rheumatoid Arthritis and Systemic Lupus Erythematosus. Inflammatory cytokines impair insulin sensitivity and can induce an adverse lipoprotein profile as seen in MetS. Furthermore, the presence of MetS correlates with increased subclinical atherosclerosis, major adverse CV events and death, making an important contribution to the CV burden in inflammatory diseases.

Adipose tissue has recently emerged as an active organ that produces and secretes numerous mediators – adipokines – particularly relevant in energy homeostasis, inflammation, immune regulation and angiogenesis. These mediators arise as a potential link between MetS, inflammation and atherogenesis. Understanding the complex regulation and function of adipokines in health and disease is a priority since it may lead to new preventive and therapeutic interventions aiming to decrease CV risk.

Keywords: Metabolic Syndrome; Adipokines; Inflammation; Atherosclerosis; Systemic Rheumatic Diseases.

Resumo

Os eventos cardiovasculares (CV) encontram-se entre as principais causas de morbilidade e mortalidade nas doenças reumáticas inflamatórias. Para além da reconhecida importância dos factores de risco CV tradicionais, há evidência que aponta para um contributo *major* da inflamação na aterogénese. A síndrome metabólica (SMet), definida por uma associação de factores de risco que têm em comum a insulino-resistência e o aumento da gordura abdominal, está intimamente ligada à inflamação. Biomarcadores do processo inflamatório encontram-se frequentemente elevados nos indivíduos com SMet e, por outro lado, a prevalência da SMet é maior nos doentes com doenças reumáticas inflamatórias crónicas, tais como a Artrite Reumatóide ou o Lúpus Eritematoso Sistémico. As citocinas pró-inflamatórias diminuem a sensibilidade à insulina e podem induzir um perfil lipídico adverso, tal como se observa na SMet. Além do mais, a SMet associa-se a um aumento da aterosclerose subclínica, dos eventos CV *major* e da mortalidade, significando deste modo um contributo adicional para o risco CV nas doenças inflamatórias. O tecido adiposo é visto actualmente como um órgão activo que produz e segrega numerosos mediadores – adipocinas – particularmente relevantes na regulação do equilíbrio energético, na inflamação, na regulação imune e também na angiogénese. As adipocinas surgem assim como um potencial elo de ligação entre a SMet, a inflamação e a aterogénese. Compreender a complexa regulação e função das adipocinas, tanto em situações normais como na doença é uma prioridade, pois

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pode conduzir a estratégias terapêuticas e preventivas visando a redução do risco CV.

Palavras-chave: Síndrome Metabólica; Adipocinas; Inflamação; Aterosclerose; Doenças Reumáticas sistêmicas.

Introduction

Metabolic syndrome (MetS), previously known as syndrome X or insulin resistance syndrome, represents a cluster of cardiovascular disease (CVD) risk factors that have in common insulin resistance and increased visceral adiposity. This entity has received great attention in the last few years due to its contribution to the burden of cardiovascular (CV) morbidity and mortality. CVD is a major public health problem and the leading cause of death in industrialized nations. In Portugal, nearly 37 000 deaths are annually attributed to ischemic heart disease and stroke, which represents a third of all deaths.¹ Besides, it has also been recognized that patients with inflammatory rheumatic diseases die prematurely largely due to CVD.^{2,3} Almost half of the death causes of rheumatoid arthritis (RA) patients and 26-45% of the mortality of systemic lupus erythematosus (SLE) patients are directly related to CVD.⁴⁻⁸

Atherosclerosis, the main determinant of CV morbidity and mortality, occurs prematurely in RA and SLE.⁹ Although traditional risk factors may arise more frequently among these patients, this does not fully explain their propensity to premature atherosclerosis.⁹ Atherosclerosis is characterized by a persistent low-grade inflammatory state, and systemic inflammation, *per se*, hypothetically further contributes to atherogenesis. However, the interaction between inflammatory mediators and the atherosclerotic process still remains to be fully elucidated. MetS and fat tissue are likely to be additional players in this complex network.

This review describes the pathogenesis, epidemiological data and clinical features associated with MetS, with a special emphasis on inflammatory rheumatic diseases. Moreover, the role of adipose tissue and adipokines in inflammation and atherosclerosis is discussed.

Metabolic syndrome and CVD

The term metabolic syndrome came into use more than forty years ago. It was first employed by Hal-

ler to describe a constellation of abnormalities, which included obesity, diabetes mellitus, hyperlipoproteinemia, hyperuricemia and hepatic steatosis, with a potentiating effect on the risk of atherosclerosis.¹⁰ A decade later, Raven proposed insulin resistance and hiperinsulinemia as the underlying connecting factor.¹¹ Multiple metabolic pathways have been suggested to link insulin resistance and compensatory hyperinsulinemia to the other metabolic risk factors, yet visceral fat accumulation is likely to play a key role in MetS pathogenesis. Moreover, several lines of evidence suggest that genetic predisposition and inflammation add to the risk of MetS.^{12,13}

Despite the great interest on this subject, no consensus has been reached regarding the definition of MetS. Several groups have attempted to establish diagnostic criteria and the most widely used have been provided by the World Health Organization (WHO),¹⁴ the Third report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III),¹⁵ the International Diabetes Federation (IDF),¹⁶ and also by the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI).¹⁷ Regardless of somewhat distinct diagnostic parameters and different cut-offs, all definitions have in common atherogenic dyslipidemia (elevated triglycerides and low high density lipoprotein cholesterol levels), central adiposity, elevated plasma glucose and elevated blood pressure. Other threats that run associated with these risk factors but are not part of the MetS definition are hyperfibrinogenemia, increased plasminogen activator inhibitor-1, low tissue plasminogen activator, nephropathy, microalbuminuria, and hyperuricemia.¹⁸

From a clinical point of view, the relevance of the metabolic syndrome derives from its strong association with the occurrence of subclinical atherosclerosis,¹⁹ major adverse cardiovascular events²⁰ and death.²¹ In fact, clinically healthy men with MetS were found to have significantly increased intima-media thickness (IMT) of the common carotid artery and carotid bulb, a surrogate marker of coronary atherosclerosis, compared with subjects with no risk factors.¹⁹ In patients with premature coronary artery disease aged ≤ 45 years, MetS was present in 31% of men and 73% of women, representing the most frequent coronary risk factor in young women.²² Moreover, a prospective cohort study including men without diabetes or previous CV events showed a 2.6-3.0-fold increased risk for

CVD death and a two-fold increased risk for all-cause deaths in patients with MetS, independently of other risk factors such as smoking, alcohol consumption or serum LDL cholesterol levels.²¹ Patients with MetS are also at increased risk for developing type 2 diabetes.

MetS is widespread through the world and is expected to become increasingly common as a consequence of sedentary lifestyles, excessive caloric intake and the dramatic increase in obesity. The prevalence of MetS differs between populations and ethnic groups. This condition is more common among women and its prevalence increases with age.^{23,24} Some reports sustain a higher prevalence in Hispanics, in the Middle East and among people with low education level and low socioeconomic status, depicting the relevance of modifiable environmental factors as well as a possible genetic basis.²⁵⁻²⁷ Using the NCEP-ATPIII definition the prevalence of MetS varies from 9.8% in Chinese men up to 42% in Iranian women.²⁸ Using the same criterion the estimated prevalence in Portugal is approximately 25%, but varies from 24% to 42% if other definitions are applied.^{23,24}

Systemic rheumatic diseases and the metabolic syndrome

Several groups have documented a high prevalence of MetS in patients with systemic rheumatic diseases. The increased CVD risk associated with RA and SLE place these diseases among the most widely studied.

Rheumatoid arthritis

Cytokines can induce alterations in lipid metabolism and insulin sensitivity during acute inflammation. Both dislipidemia and insulin resistance are components of MetS frequently found in RA patients. An adverse lipid profile characterized by low HDL cholesterol, low apolipoprotein A1 and increased atherogenic index (total/HDL cholesterol ratio) is observed in active RA.^{29,30} Improvement of the lipoprotein profile following suppression of the inflammation has been documented with a number of antirheumatic treatments including steroids, traditional DMARDs, and TNF blockers.³⁵ Insulin resistance correlates with C-reactive protein (CRP) levels and can also be reduced with successful control of RA activity.³³ In addition, effective treatment reduces the burden of CV morbidity and mortality in RA patients. A significant decrease in the rate of acute myocardial infarction has

been documented with the use of traditional DMARDs, including methotrexate, leflunomide, hydroxychloroquine and sulfasalazine.³⁴ There is also some evidence pointing towards a lower incidence of first-ever CV event in patients treated with TNF blockers.³⁵ Moreover, methotrexate use is associated with a decline in overall mortality and particularly with CV mortality, in which there is a 70% decrease after adjusting for potential confounders,³⁶ again emphasizing the importance of halting inflammation.

Metabolic syndrome occurs in up to 45% of RA patients, but its prevalence depends on the definition used.³⁷ A recent study showed that MetS was significantly more prevalent in American patients with long-standing RA (42% - WHO and NCEP/ATPIII criteria) as well as early RA (31% and 30% - WHO and NCEP/ATPIII criteria respectively) than in controls (11% and 22% - WHO and NCEP/ATPIII criteria, respectively). Furthermore, patients with MetS had an increased risk of having coronary artery calcifications and a four-fold increased risk of having CVD.^{37,38} Another study among Mediterranean RA patients also found a higher prevalence of MetS (44% - NCEP/ATPIII criteria) but not significantly different from local population controls (41%).³⁹ In contrast to the general population, MetS in RA is independent of gender and body mass index (BMI).^{38,39} Current corticosteroid use does not increase the risk of MetS^{37,40} whilst methotrexate may even reduce its prevalence.³⁷ On the other hand, the risk of having moderate to severe RA is higher in patients with MetS than in those without.³⁹ In summary, these results stress the intimate relationship between inflammation and the metabolic disorders observed in RA and provide further evidence that links MetS to the increased CV risk in this condition.

Systemic lupus erythematosus

Some groups have examined the occurrence of MetS in SLE and also reported a higher frequency in lupus patients. Chung *et al* using the WHO and NCEP-ATPIII criteria documented the presence of MetS in 32.4% and 29.4%, respectively of American SLE patients. This prevalence was higher than in controls (10.9% defined by WHO criteria and 19.8% according to the NCEP), even if a significant difference was achieved only for the WHO definition.⁴¹ A recent study in Spain observed a frequency of 15.8% for metabolic syndrome as defined by the NCEP/ATPIII in young (≤ 40 years) SLE patients,

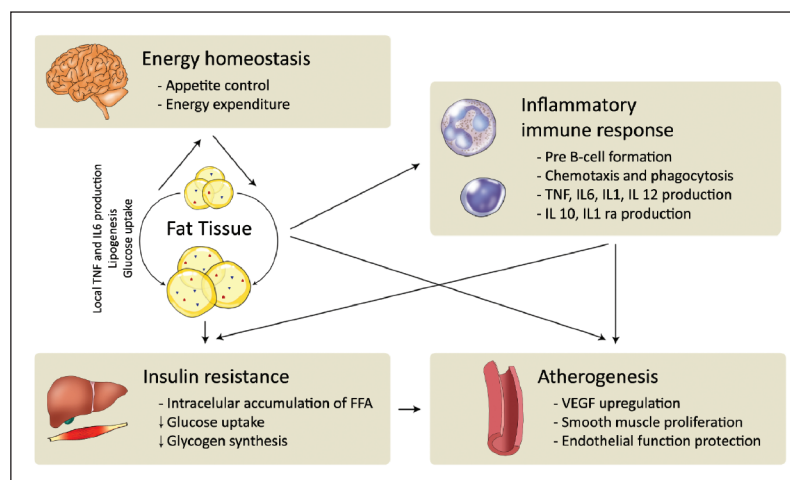


Figure 1. By secreting adipokines, adipose tissue actively modulates several pathways that involve energy intake and expenditure, inflammatory and immune response, insulin-resistance, and atherosclerosis. Adipokines also act as an autocrine/paracrine factor with effects on adipogenesis, lipogenesis and glucose uptake. Adipocytes are able to produce MCP-1 (monocyte chemoattractant protein 1), a potent factor that promotes infiltration of adipose tissue by mononuclear cells. Infiltrating macrophages are responsible for the most part of local production of TNF and IL-6 and are candidate initiator cells of the inflammatory response. VEGF – vascular endothelial growth factor; FFA – free fatty acids; RBP4 – retinol binding protein 4.

which was significantly higher than in controls of the same age (4.2%), and a similar trend was found in Puerto Rico.^{42,43} Even though younger lupus patients have generally been studied, it should be noted that age matched SLE and RA patients present a similar prevalence of metabolic syndrome.⁴⁴ Furthermore, MetS was found to be associated with higher CRP levels⁴³ and higher erythrocyte sedimentation rate (ESR),⁴³ but the studies could not depict any solid association with clinical features, immunologic characteristics or disease activity. The risk of having CVD was three-fold higher in lupus patients with MetS as compared with those without MetS.⁴³

Adipose tissue and inflammation

The pivotal role of adipose tissue in energy homeostasis as well as in inflammation was recently highlighted. In the last few years, fat tissue has emerged as a dynamic organ that releases several inflammatory and immune mediators, termed adipocytokines or adipokines. More than 50 adipokines have been identified including leptin, adiponectin, resistin, chemerin, interleukin 6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), retinol binding protein 4 (RBP4), tumor necrosis factor (TNF) and visfatin, among others.

Obesity has been associated with a chronic in-

flammatory response, characterized by elevated circulating levels of TNF, IL6, CRP and PAI-1.⁴⁵⁻⁴⁷ In view that inflammatory cytokines are key players in the pathogenesis and severity of atherosclerosis⁴⁸ and its complications⁴⁹ some authors now regard obesity as a systemic, low-grade inflammatory state,⁵⁰ and inflammation as a link between obesity, metabolic syndrome and cardiovascular diseases^{51,52} (Figure 1). The association of MetS and atherosclerosis is thought to be partly mediated by altered secretion of adipokines by adipose tissue. The main roles of adipokines are summarized in Table I.

Leptin

Leptin is the protein product of the *ob* gene, identified in 1994.⁵³ This cytokine is mainly produced by white adipose tissue cells and its plasma concentration is directly correlated with the amount of body fat. Leptin is considered a major regulator of body weight by suppressing appetite and stimulating energy expenditure via hypothalamic receptors. Although this feedback regulatory loop is well established in rodents, obese people have unusually high circulating concentrations of leptin as a result of resistance to its action.⁵⁴ Leptin production is mainly regulated by food intake and hormones, but also by inflammatory mediators such

Table I. Summary of the main effects of adipokines

	Leptin	Adiponectin	Resistin	Visfatin	RBP4
Insulin-resistance	↓	↓(?)	↑	↓	↑
Metabolic rate	↑	↑			
Appetite	↓	=;↑(?)			
Adipogenesis	↓	↓	↓(?)	↑	
Inflammation	↑; ↓(?)	↓	↑	↑(?)	↑(?)
Atherogenesis	↑	↓	↑(?)	↑(?)	↑(?)

RBP4 – retinol binding protein 4; ↑ enhances; ↓ decreases ;(?) possible, but uncertain effect; = no effect.

as TNF, IL-6 and IL-1. Acute infection and inflammation enhances leptin synthesis,⁵⁵ while during starvation and dietary fat restriction its levels decrease dramatically.⁵⁶ Interestingly, leptin/leptin receptors have also pro-inflammatory and immunomodulatory effects. It has been recognized that leptin interferes with neutrophil chemotaxis and phagocytic function, stimulates the production of pro-inflammatory cytokines from cultured monocytes and enhances the production of Th1 type cytokines.^{57,58} On the other hand, leptin also shows anti-inflammatory effects by inducing IL-1 receptor antagonist secretion.⁵⁹ The net result of this contradictory immunomodulating functions is still unclear.

Additionally, leptin affects bone metabolism⁶⁰ and promotes angiogenesis. A study in patients with symptomatic atherosclerosis demonstrated that gene expression of the leptin receptor and vascular endothelial growth factor (VEGF) is upregulated in carotid atherosclerotic plaques.⁶¹ High circulating leptin levels have recently been demonstrated in patients with SLE⁶² and RA,⁶³ but the clinical relevance of these findings is not fully elucidated given that leptin levels appear to be independent of body mass index and RA activity⁶⁴ and might have a protective role against radiographic damage.⁶⁵

Adiponectin

Adiponectin is a protein exclusively synthesized and secreted by adipocytes with anti-inflammatory, insulin-sensitizing and anti-atherogenic properties, recently associated with longevity.⁶⁶ Plasma adiponectin concentrations are substantially higher in females and correlate inversely with body fat and with insulin resistance.^{67,68} Despite being produced by adipose tissue, hypoadiponectinemia is observed in obesity, CVD, hypertension, type 2

diabetes, non-alcoholic fatty liver disease and MetS. Moreover, weight reduction significantly increases circulating levels. Adiponectin exerts some weight reduction effects via the hypothalamus, has a direct hepatic and peripheral insulin-sensitizing action and protects from endothelial dysfunction.^{69,70} Furthermore, adiponectin reduces macrophages' TNF secretion and may modulate TNF induced inflammatory response.⁷¹ However, the role of adiponectin in rheumatic inflammatory diseases is uncertain. Unexpectedly, 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.⁷²⁻⁷⁴ Increased levels of adiponectin were also reported in SLE patients,⁷⁵ though not confirmed later on.⁷⁶ The problem of this apparently paradoxical increase of adiponectin in chronic inflammatory conditions remains unsolved.

Resistin

Resistin is a recently discovered adipocyte-derived mediator that negatively influences insulin sensitivity of peripheral tissues. Circulating levels are increased in obesity and are mainly regulated by peroxisome proliferator-activated receptor gamma (PPAR γ). Three physiological roles have been proposed for resistin: 1) mediator for the regulation of metabolism, 2) regulator of adipogenesis and 3) pro-inflammatory.⁷⁷

Animal studies suggest that the major target of resistin action is the liver, causing hepatic insulin resistance; it also affects skeletal muscles and adipose tissue. In skeletal muscle, it seems to reduce the uptake and metabolism of free fatty acids, thus contributing to insulin resistance.⁷⁸ Moreover, resistin enhances secretion of pro-inflammatory cytokines, TNF and IL-12, upregulates IL-6 and in-

duces arthritis when injected into mice joints.^{79,80}

In rheumatoid arthritis conflicting results were reported concerning serum levels.^{63,81} However, resistin synovial fluid levels were found to be higher in RA when compared to osteoarthritis, and positively correlated with acute phase reactants and disease activity.^{73,81} The potential role of resistin in rheumatoid inflammation is further supported by its rapid reduction after infliximab administration.⁸²

Serum resistin levels in patients with SLE were similar to those found in controls,^{83,84} but the influence of corticosteroid therapy on these results cannot be ruled out, as resistin concentration is known to increase in response to glucocorticoids and decrease in response to TNF.⁸⁵

Other adipokines

Visfatin (pre-B-cell colony-enhancing factor, PBEF) is a novel adipokine with insulin-mimetic actions, preferentially produced by visceral adipose tissue but also found in the liver, bone marrow skeletal muscle, and lymphocytes.⁸⁶ Plasma visfatin levels correlate with intra-abdominal fat mass, but not with subcutaneous fat. This adipokine facilitates adipogenesis, improves insulin sensitivity and decreases hepatic glucose release.⁸⁷ Despite the lack of current evidence to support visfatin action in the inflammatory process, some authors reported increased synovial fluid and plasma levels of this adipokine in RA⁶³ as well as its expression by rheumatoid synoviocytes at sites of attachment and invasion into cartilage or bone.⁸⁸ In agreement with these findings a recent report found an association between radiographic damage and high visfatin serum concentrations.⁶⁵

Retinol Binding Protein 4 (RBP4) is predominantly secreted by visceral adipose tissue and by the liver. A large number of studies in rodents and also in humans confirmed an association of increased circulating RBP4 levels with obesity, insulin resistance, type 2 diabetes, dyslipidemia, hypertension and metabolic syndrome.⁸⁹ Moreover, RBP4 gene expression in humans was associated with inflammatory markers and RBP4 levels were associated with inflammatory response in obese individuals.⁹⁰ The role of RBP4 in rheumatic diseases has not yet been established.

Conclusion

Metabolic syndrome is frequently present in pa-

tients with inflammatory rheumatic diseases and represents an important risk for developing atherosclerosis.

Dysregulation of adipokine secretion, non-sterified fatty acid toxicity and the specificities of abdominal fat support the central role of abdominal obesity in metabolic syndrome. Significant advances in the understanding of the relationship between fat tissue and inflammation have been achieved in recent years. Nevertheless, larger studies are needed in order to have a better understanding of the role of adipokines in inflammatory rheumatic diseases. The benefits of lifestyle modifications and other therapeutic interventions with the objective of reducing visceral fat urge to be established. This approach, combined with the adequate control of inflammation, might significantly reduce CV morbidity in patients with inflammatory rheumatic diseases.

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