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Inflammatory markers and cardiovascular risk in the metabolic syndrome

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1. ABSTRACT

Elevated blood glucose, obesity, high blood pressure, elevated triglycerides and low high density lipoprotein (HDL) cholesterol are well accepted risk factors in the development of coronary artery disease. Clustering of at least three of these factors in an individual is defined as metabolic syndrome (MetS). Obesity is a central pathological mechanism in the disease and it is expected that the incidence of this condition will increase dramatically within the next years. The visceral adipose tissue is not only an energy depot but also an endocrine organ which produces a large number of bioactive molecules, the so called adipokines. In the setting of obesity, the over-production of proinflammatory and pro-thrombotic adipokines is associated with insulin resistance. This mechanism represents the pathophysiological basis for the development of MetS. Inflammation has a central role in the pathogenesis of MetS and in mediating its impact on the development of cardiovascular disease. Knowledge of these mechanisms has relevance in the context of preventive and therapeutic strategies.

2. INTRODUCTION

A large amount of epidemiologic data indicates that people with atherosclerotic risk factors like elevated blood glucose, obesity, high blood pressure, elevated triglycerides and low high density lipoprotein (HDL) cholesterol have an increased risk of developing coronary artery disease (1-6). The clustering of at least three of these factors in an individual is defined as metabolic syndrome (MetS) (3-5). Among people with MetS, atherosclerosis is accelerated and the risk of cardiovascular events is increased (6-7). In MetS patients, the risk to suffer from myocardial infarction or stroke is two to three times higher than in patients without MetS (3, 5). Therefore, MetS identifies a high-risk population.

According to results from the National Cholesterol Education Program, the current prevalence of MetS in the adult population of the United States is as high as 24% (3, 6, 8). During the last decades, a striking increase in the number of people with MetS has taken place in industrialized countries, a trend that seems to go parallel

Table 1. Diagnostic criteria of metabolic syndrome Metabolic syndrome can be diagnosed if at least three of the following components are present. (Adapted from 5)

Parameter	Pathological finding
Waist circumference	Population based definitions[1]
Triglycerides	≥ 150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides
HDL-cholesterol	Men ≤ 40 mg/dL (1.0 mmol/L) and women ≤ 50 mg/dL (1.3 mmol/L) or drug treatment for elevated HDL-cholesterol
Blood pressure	Systolic ≥ 130 mmHg and/or diastolic ≥ 85 mmHg or antihypertensive drug treatment
Fasting glucose	≥ 100 mg/dL or drug treatment for elevated glucose

[1]For example the definition from the Word Heath Organization: For Caucasian: waist circumference: men ≥102 cm and women ≥88 cm, For Asian: waist circumference: men ≥90 cm and women ≥80 cm

with the global epidemic of obesity and diabetes (9-10). Moreover, MetS increasingly affects younger generations. In a recent analysis of teenagers aged 12 to 19 from the United States, 60% had at least one component of MetS (11-12). Obesity is a central causative component in the development of MetS. Increased adiposity is associated with many metabolic alterations including insulin resistance, dyslipidemia and arterial hypertension (3, 5). Central pathophysiological mechanisms have their origin in adipose tissue, which produces bioactive molecules that can accelerate inflammation and finally atherosclerosis (13-18). This review will address the link between MetS and inflammation and their impact on atherosclerosis progression, cardiovascular prognosis and therapeutic strategies.

3. THE METABOLIC SYNDROME

3.1. Definition of metabolic syndrome

Several definitions of MetS have been put forth by the International Diabetes Foundation, from the American Heart Association and the National Heart, Lung and Blood Institute or from the Word Health Organization (3, 5, 8, 18-21). All these definitions include obesity, arterial hypertension, elevated blood glucose, raised triglycerides and lowered HDL-cholesterol as diagnostic criteria. However, one major issue is the absence of a unanimous definition of obesity, which is clearly one of the most important components of the syndrome. It has been shown in large studies that the accumulation of adipose tissue in the visceral depot is a more reliable predictor of cardiovascular events than body mass index (BMI) (3, 6, 22). Therefore, waist circumference should be preferred as measurement of adiposity for the identification of MetS. In addition, using waist circumference an easy estimation of abdominal obesity is possible. However, because of differences between ethnic groups, population-based normal values should be used for this parameter (5, 22). In a current scientific statement from the International Diabetes Federation Task Force on Epidemiology and Prevention; the National Heart, Lung, and Blood Institute; the American Heart Association; the World Heart Federation; the International Atherosclerosis Society; and the International Association for the Study of Obesity, an effort is being made toward the harmonization of the various definitions of obesity (5). According to this statement, a diagnosis of MetS should be made if at least three of the following requirements are met: elevated waist circumference, increased triglycerides, lowered HDL-cholesterol, elevated blood pressure or increased fasting glucose (Table 1).

3.2. Metabolic syndrome and cardiovascular prognosis

As described above, patients with MetS have an up to three-fold increased risk of developing cardiovascular diseases (3, 6, 20). In the West of Scotland Coronary Prevention Study (WOSCOPS), a diagnosis of MetS was associated with an 3.7-fold increase in the risk for coronary artery disease; in the Prospective Cardiovascular Münster (PROCAM) study, a similar 2.3-fold increased incidence was reported (2, 19). Importantly, the global cardiovascular risk of patients with MetS is higher than the summation of the risk associated with the single components of the syndrome (20). It has been suggested that obesity is a first step followed by the appearance of associated risk factors like mild elevated blood pressure, slight dyslipidemia or impaired fasting glucose (23). Insulin resistance plays a crucial role in the development of manifestations of MetS in obese individuals. Borderline risk factors can evolve into arterial hypertension, dyslipidemia and finally type 2 diabetes mellitus, which is often associated with a marked increase in the incidence of complications including accelerated atherosclerosis, renal failure, neuropathy and retinopathy (6, 18). In addition, patients with MetS also suffer from many other associated diseases like fatty liver disease, gallstones, gout, cancer, renal failure, lung insufficiency or sleep apnea (3). In conclusion, patients with MetS are multi-morbid and have many reasons for an adverse outcome: not only is the incidence of cardiovascular events higher in these patients, but also that of many other conditions.

4. INFLAMMATION AND ATHEROSCLEROSIS

4.1. Endothelial dysfunction

From the current point of view, atherosclerosis seems to be an inflammatory disease (24-25). In fact, inflammatory mechanisms have been demonstrated to play an important role in all stages of atherosclerosis, and the vascular endothelium appears to play a central role in mediating the deleterious effects of inflammation (24-25). Under healthy conditions, the endothelium is a selective barrier to the diffusion of macromolecules from the vessel lumen to the interstitial space and has multiple protective functions such as regulation of vascular tone, modulation of inflammation, inhibition of vascular growth or modulation of plasma aggregation (26-27). Cardiovascular risk factors like hypercholesterolemia, hypertension, diabetes or smoking lead to endothelial dysfunction, a condition that is characterized by reduced production of endothelium-derived mediators and by an increased synthesis and release of inflammatory markers (28). In addition, an altered endothelial homeostasis promotes platelet aggregation and

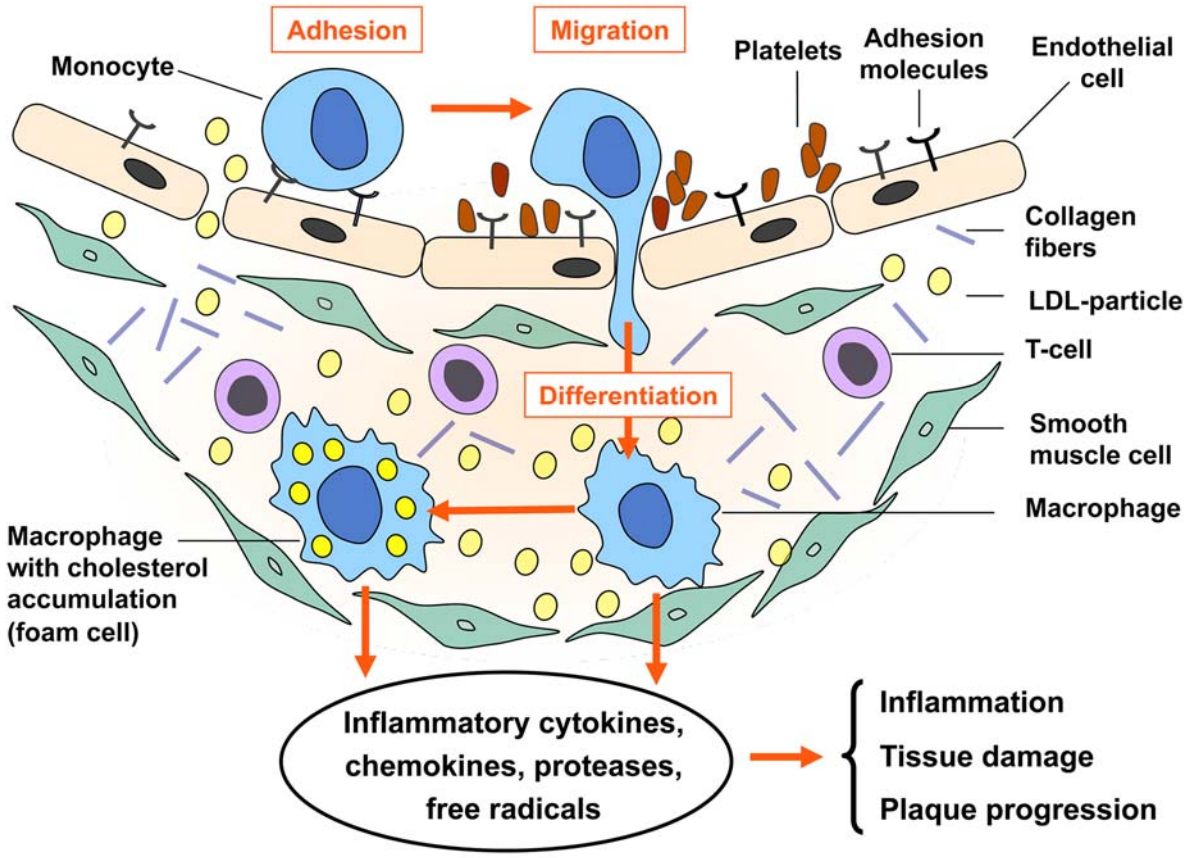

Figure 1. Inflammatory mechanisms in the atherosclerotic plaque.

the release of growth factors from the vessel wall (28-29). In particular, the elevated levels of free fatty acids that are associated with insulin resistance, obesity and diabetes may promote endothelial dysfunction by immune activation and upstream regulation of transcription of nuclear factor–kappa B (30). Therefore, there is a reciprocal relationship between inflammation and endothelial dysfunction, and especially in the presence of insulin resistance, endothelial dysfunction soon becomes a further mechanism that promotes further inflammation.

4.2. Inflammation in the atherosclerotic plaque

Endothelial dysfunction is considered to be a first step in atherosclerosis. In response to elevated levels of oxidized low density lipoprotein (LDL) cholesterol, and in response to local injury or infection, endothelial and smooth muscle cells synthesize pro-inflammatory proteins including chemokines, cell adhesion molecules, cytokines, growth factors and prothrombotic substances. Then, resident or circulating monocytes bind to the vessel wall. In an effort to build up reparatory mechanisms, monocytes begin phagocytosing lipid particles and evolve into macrophages and finally into foam cells, with the development of a macroscopic lesion called fatty streak. Immediately, other inflammatory cells including activated T-cells and mast cells migrate into the atherosclerotic plaque and attract additional immune cells by producing chemotactic enzymes (Figure 1). These inflammatory cells contribute to the formation of an atherosclerotic plaque which consists of a lipid pool protected by a fibrous cap. At the same time, vascular smooth muscle cells migrate into the vessel wall and secrete chemotactic factors which attract additional macrophages. The macrophages release proteolytic enzymes (metalloproteinases) which destroy the collagen contained in the fibrous cap, a process that eventually results in increased plaque instability. As a result of this process, the plaque can rupture and contact between flowing blood and the cholesterol rich core leads to thrombus formation and vessel occlusion (24-25).

5. ROLE OF VISCERAL ADIPOSE TISSUE

5.1. Visceral adipose tissue

Visceral fat accumulation is a sensitive predictor of cardiovascular events (22). Obesity is associated with many cardiovascular risk factors which are also components of MetS like insulin resistance, arterial hypertension and dyslipidemia (3, 5). It can be suggested that inflammation within the visceral adipose tissue may be a causal factor in the development of most of the

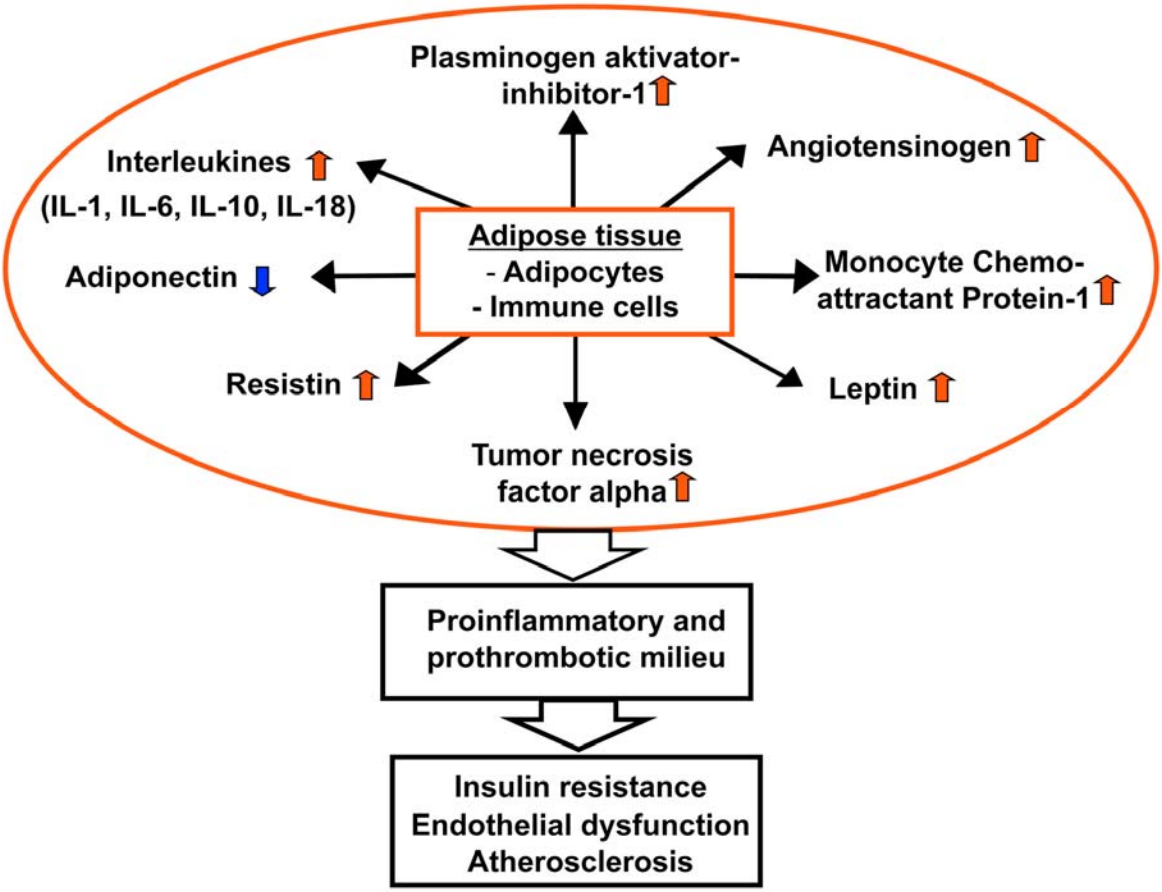

Figure 2. Adipokines secreted by adipose tissue and their impact on atherosclerosis. The Figure shows some of the key adipokines linked to inflammation.

pathological components of MetS resulting in atherosclerosis, and that therefore the visceral adipose tissue plays a key role in the pathogenesis of MetS. Adipose tissue consists of adipocytes and immune cells including macrophages and lymphocytes. Recent studies show that the visceral adipose tissue is a complex and active endocrine organ that plays major roles in the regulation of human metabolic and vascular biology (23, 31-36). The adipose tissue produces several biologically active molecules, so called adipokines, which can induce insulin resistance, and adiponectin which can increase insulin sensitivity (37). Over nutrition leads to an abnormal expansion of visceral adipose tissue followed by increased release of proinflammatory and prothrombotic adipokines and a decreased release of the protective adiponectin (Figure 2) (34, 36). Many adipokines have been discovered so far. The effects of some of the more interesting ones with regard to MetS and inflammation are highlighted below.

5.2. Adipokines

5.2.1. Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNF alpha) is secreted from adipocytes and macrophages accumulated in obese adipose tissue. TNF alpha stimulates lipolysis and is a powerful inducer of other proinflammatory adipokines (31, 38). Increased levels of TNF alpha are associated with insulin resistance, hyperinsulinemia and elevated systolic blood pressure (38). Murine models demonstrated that TNF alpha gene deficiency can counteract obesity-induced insulin resistance (23). Thus TNF alpha might be a mediator of insulin resistance and, potentially, an interesting pharmacological target.

5.2.2. Interleukin-6

Visceral adipose tissue produces a large proportion of the total circulating interleukin-6 (ÌL-6) and circulating IL-6 levels increase in people with obesity and insulin resistance (32-34). IL-6 is a multifunctional cytokine that regulates immune response, haematopoiesis, the acute phase response and inflammation (30-32). Moreover, IL-6 has been demonstrated to inhibit insulin action in muscle, liver and adipocytes *in vivo* and *in vitro* and contributes to hepatic insulin resistance in obesity (39-40). In contrast, IL-6 also has anti-obese effects by central nervous appetite suppression and weight loss (34).

5.2.3. Leptin

Leptin is involved in appetite regulation and plays a role in inflammatory responses (34). It has recently been

shown that leptin enhances cellular immune response and increases blood pressure (41-42). Leptin causes proliferation of macrophages and leads to the activation of neutrophils and natural killer cells resulting in the production of reactive oxygen species and oxidative stress (43). In addition, leptin has been discussed to have procoagulant and antifibrinolytic properties (12). Thus, leptin acts as a promoter of local and systemic inflammation.

5.2.4. Resistin

Resistin is expressed primarily in macrophages and has been involved in the pathogenesis of type 2 diabetes by induction of insulin receptor insensitivity (44). In addition, resistin induces the expression of vascular cell adhesion molecule-1 and intracellular adhesion molecule-1 (33, 44). Therefore, resistin promotes the adhesion of monocytes to vascular endothelium, one of the key events in the development and progression of atherosclerosis. In line with this concept, elevated serum resistin was associated with cardiovascular events in patients with coronary artery disease in prospective studies (44-45).

5.2.5. Monocyte Chemoattractant Protein-1

Chemokines, such as monocyte chemoattractant protein-1 (MCP-1), activate monocytes, stimulate their movement into the vessel wall and promote their conversion to macrophages (31). Experimental data demonstrates that MCP-1 release from adipocytes was greater in obese mice than in normal weight mice (31, 46). Thus MCP-1 seems to be important for the monocyte accumulation in adipose tissue which accelerates further inflammatory processes.

5.2.6. Plasminogen-Activator Inhibitor 1

Plasminogen-activator inhibitor 1 (PAI-1) is a regulatory coagulation protein and TNF alpha is a key mediator of PAI-1 release (46). Elevated levels of PAI-1 are known risk factors for thrombosis in obese patients (46), and it is well accepted that MetS patients are in a procoagulant state, and that they show increased circulating PAI-1 levels. The combination of PAI-1 decrease of fibrinolysis and the obesity-induced increase of clotting factors lead to a hypercoagulative state predisposing to atherosclerosis (46-47). Circulating PAI-1 is produced by the adipocytes and levels of PAI-1 correlate with visceral obesity (48). In addition, PAI-1 influences accumulation of visceral adipose tissue and seem to contribute directly to the development to type 2 diabetes and arterial thrombosis. This explains the results from multiple studies that elevated PAI-1 seem to be a predictor of cardiovascular events (49-50).

5.2.7. Angiotensinogen

The renin angiotensin system is important for the fluid and electrolyte balance and regulates vascular tonus. Several studies have shown that the plasma level of angiotensinogen which reflects activation of the renin angiotensin system in adipose tissue is positively correlated to obesity (34, 51). Angiotensinogen stimulates lipogenesis and preadipocyte differentiation and is therefore involved in increased accumulation of adipose tissue (34, 52). Moreover, elevated levels of angiotensinogen and angiotensin II in obese patients have been associated with vascular inflammation, angiogenesis and arterial hypertension (53).

5.2.8. Adiponectin

In contrast to the other adipokines, adiponectin improves insulin sensitivity and inhibits vascular inflammation (37). Decreased levels of adiponectin are associated with higher BMI, decreased insulin sensitivity, dyslipidemia and increased risk of cardiovascular events (33-34). Studies demonstrate an inverse relation between adiponectin levels and prevalence of MetS (30-35). Genetic studies show a strong relation between decreased adiponectin associated with a genomic locus for adiponectin and manifestation of MetS (54). This suggests that decreased activity of adiponectin can be a causative factor for the development of MetS.

The dysregulation of different adipokines induced by an increased visceral fat mass plays a crucial role in the genesis of a proinflammatory as well as prothrombotic milieu. Adipokines are involved in the development of the individual components of the MetS (23, 31-35). Triggered by inflammation this situation can lead to endothelial dysfunction and the progression of atherosclerosis.

6. INFLAMMATORY BIOMARKERS

6.1. Inflammatory markers and cardiovascular disease

6.1.1. Interaction of inflammatory markers

Activated immune cells in the atherosclerotic plaque can produce inflammatory cytokines (interferon-gamma, interleukin-1 (IL-1), TNF alpha). There is evidence that these inflammatory cytokines can induce the production of the messenger cytokine IL-6 (Figure 3). In several other tissues including the adipose tissue, IL-1, IL-6 and TNF alpha are also released. IL-6 stimulates the production of acute phase reactants in the liver including C-reactive protein (CRP), serum amyloid A and fibrinogen (24, 25). In turn, these acute phase reactants trigger inflammation at the vessel wall. Thus, the activation of a limited number of immune cells can initiate an inflammatory cascade locally and systemically. As a result, elevated levels of inflammatory markers like IL-6 and CRP can be detected in the peripheral circulation.

6.1.2. Inflammatory markers and atherosclerosis

In line with this concept, clinical and experimental studies have shown consistent relationship between various systemically measured markers of inflammation and cardiovascular disease (7, 24, 25, 55-62). These study results have increased the interest in the potential use of systemic inflammatory biomarkers as risk predictors for future cardiovascular events and also raised the possibility to discuss inflammatory biomarkers as targets of therapy.

A number of inflammatory markers have been evaluated as possible predictors of cardiovascular prognosis. Several studies focus on the acute phase reactant CRP, because standardized assays are commercially available, the molecule is quite stable and the test is reproducible. Several authors show associations between elevated levels of highly sensitive CRP and atherosclerosis

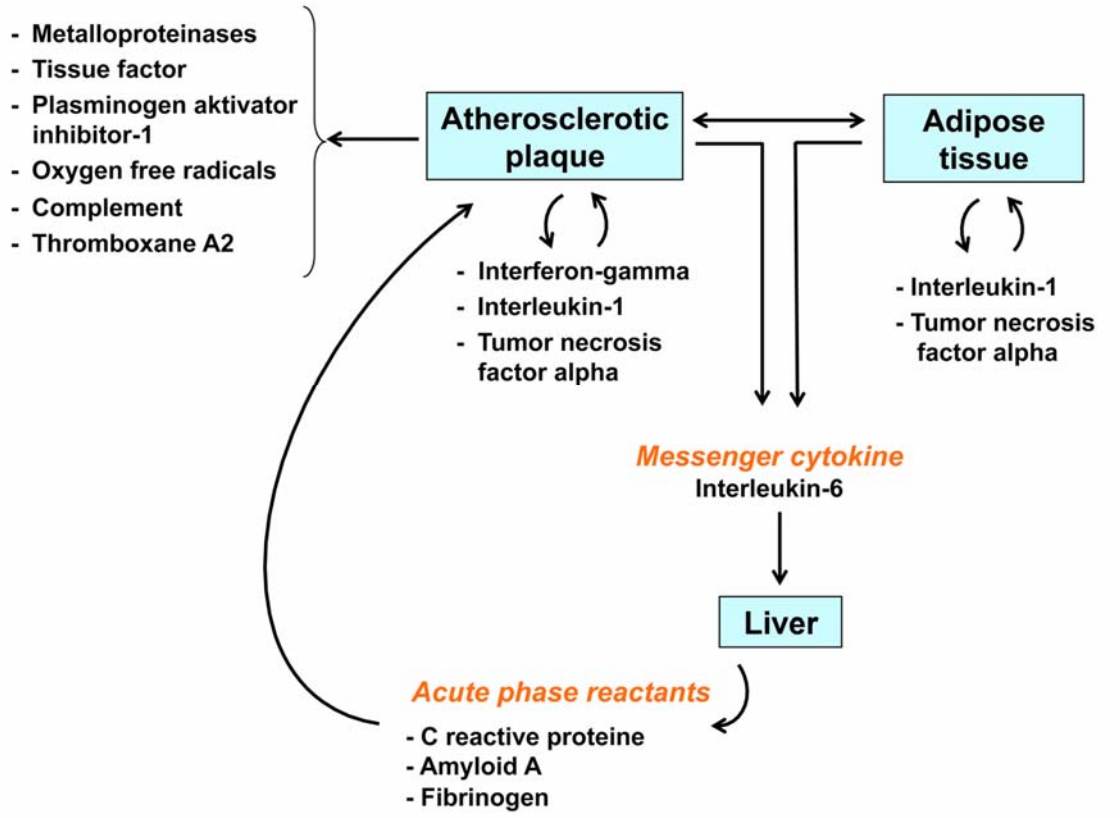

Figure 3. Proinflammatory cytokine release by atherosclerotic plaque and adipose tissue and their systemic impact on the hepatic synthesis of acute phase reactants.

in different vascular beds as well as cardiovascular events (55-61). Many other inflammatory markers in the peripheral blood including TNF alpha, fibrinogen, IL-6, interleukin-18 (IL-18), adhesion molecules and soluble P-selectin are also associated with increased risk of cardiovascular diseases (55, 60-65).

However, up to now it remains unclear whether these systemic measured inflammatory biomarkers are only markers of the atherosclerotic process ("risk indicators") or also contributors of atherosclerosis progression ("risk factors") (24, 25).

6.2. Inflammatory markers in the metabolic syndrome

6.2.1. Metabolic syndrome

Several studies have established that acute phase proteins and proinflammatory cytokines are associated with single components of MetS. Inflammatory markers like CRP, fibrinogen or white blood cell count are associated with dyslipidemia, abdominal obesity, low insulin sensitivity and manifestation of arterial hypertension (68-72). It has been shown that elevation of CRP, IL-6, IL-18 and TNF alpha are associated with obesity (68-71). Moreover, elevation in biomarkers with prothrombotic properties like PAI-1 and fibrinogen are correlated with obesity (72). In addition elevation of inflammatory markers is related to insulin resistance and increased serological markers of endothelial dysfunction (73). This data suggests that obesity is associated with a chronic low-level proinflammatory and prothrombotic state and that the manifestation of cardiovascular risk factors in MetS might be triggered by these processes.

Moreover, some investigations demonstrate an association between the number of components of MetS and the elevation of inflammatory markers. It has been described that elevation of CRP, fibrinogen, IL-6 and IL-18 increase linearly with the number of components of the MetS and addition of inflammatory markers to the definition of MetS has been discussed (67, 73-80). Thus, inflammation seems to increase with the progression of MetS and with its severity (as manifested by the co-presence of an increasing number of the diagnostic factors for this condition). This supports the observation that the cardiovascular risk of patients with MetS is higher than the sum of its components, and supports the hypothesis that an inflammatory cascade triggered by release of proinflammatory adipoklines by the adipose tissue results in a vicious circle of inflammation.

Increased levels of inflammatory markers like the acute phase protein CRP were also associated with the future manifestation of MetS and its components (76, 81).

6.2.2. Prognostic impact in metabolic syndrome

Many different inflammatory biomarkers have been evaluated with regard to their prognostic impact in patients with MetS. For instance, in prospective studies patients with MetS and elevated levels of CRP, fibrinogen

or IL-6 had more cardiovascular events compared to patients with lower levels of inflammatory markers (67, 72-74, 82). Furthermore, elevation of circulating interleukin-18, which is secreted by adipocytes as well, was strongly predictive in MetS patients (67, 79-80). In our own research, IL-18 was the only inflammatory marker which was independently associated with cardiovascular survival in patients with MetS after adjustment for possible confounders (66). It has been suggested that IL-18 can directly cause plaque destabilization. Possible mechanisms of IL-18 are the induction of interferon-γ and metalloproteinases leading to a thinning of the fibrous cap (63). Therefore, IL-18 seems to have a direct impact not only in the development of MetS but also on cardiovascular prognosis.

In sum, a large amount of data show that patients with MetS have elevated levels of systemic inflammatory markers (67-79), and that this has clinical relevance in terms of development of the complication of this disease and the patients´ prognosis. What remains to be seen is whether a reduction in these inflammatory markers translates into reduced number of clinical endpoints in MetS. Therefore, future studies will need to test whether targeted diagnostic and pharmacological interventions may be developed to reduce the burden of this epidemic disease.

7. THERAPEUTIC IMPLICATIONS

In light of these results, an interesting therapeutic strategy for the treatment or even prevention of MetS is to alter the ratio of proinflammatory, insulin –desensitizing adipokines to anti-inflammatory, insulin-sensitizing adipokines to attenuate the pro-inflammatory milieu. In addition, there is some evidence from secondary prevention data demonstrating that anti-inflammatory therapies can improve cardiovascular prognosis after acute coronary syndromes (25). There are several therapeutic strategies including weight loss, exercise of drugs with anti-inflammatory properties which may influence inflammatory processes.

7.1. Life style modifications

Life style modifications are of therapeutic importance in patients with MetS. Effective weight reduction improves many risk factors related to MetS (6). Moreover, reduction in fat mass correlates with a decrease of serum levels of many of the adipokines (59, 83-88). There are two strategies to achieve weight loss: caloric restriction and exercise. Particular beneficial effects have been reported for the combination of diet and exercise. For example, in postmenopausal women at risk of cardiovascular disease (not all included women met the criteria for MetS), a low-fat and high-fiber diet in combination with aerobic exercise significantly reduced glucose (11%), insulin (26%), CRP (2.6+/-2.3 to 1.4+/-0.9 mg/L) and intracellular adhesion molecule-1 (158.8+/-48.3 to 145.6+/-38.2 ng/mL) with an increase of insulin sensitivity (reduction of HOMA-IR 34%) (88). Thus, life style modifications are very effective in the reduction of proinflammatory and prothrombotic mechanisms associated with obesity. With regard to the increasing number of children and adolescents with obesity, it seems important to start with these interventions at an early age with the aim to prevent the final manifestation of MetS (70, 89).

7.2. Drug interventions

In addition, several drug groups could modify the immune mechanism and decrease the levels of inflammatory biomarkers. Statins display many pleiotropic properties including plaque stabilization (90-92). Recent data suggest that statins as well as fibrates decrease the level of inflammatory biomarkers (91-93). Apart from lipid lowering drugs, there are also other medications that can influence inflammatory mechanism. For example, clinical trials of angiotensin-blocking strategies have demonstrated significant decrease in markers of systemic inflammation including IL-6, CRP and TNF alpha (94-95). In addition, glitazones can significantly lower plasma levels of inflammatory biomarkers subjects with hypertension, obesity or diabetes (96). The results of these trials raise the question whether the early drug treatment of obese persons may reduce proinflammatory milieu and potentially prevent the development of MetS with all its complications. However, additional large prospective intervention trials including obese, but otherwise healthy persons will be necessary before this question can be answered.

8. CONCLUSION AND PERSPECTIVE

As a result of excessive caloric intake and over-nutrition, the number of obese people will dramatically increase within the next years. Obesity leads to over-production of proinflammatory and prothrombotic adipokines which leads to insulin resistance and finally the biologic manifestation of MetS. Many inflammatory biomarkers can be systemically measured and elevations in these markers impact the development of MetS and cardiovascular disease. Future therapeutic interventions will have to focus on life style modifications to prevent obesity and this vicious inflammatory circle by diet and exercise. The strategies should start with school children to help prevent the development of the syndrome. The role of drugs in the prevention of the manifestation of MetS should be the aim of future investigations.

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