Mini Review

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Subcutaneous adipose tissue biology in metabolic syndrome

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Abstract:
Metabolic syndrome (MetS) is a common global problem that comprises the cardio-metabolic cluster and predisposes to both diabetes and cardiovascular diseases. Although the pathogenic mechanisms have not been elucidated, both increased inflammation and insulin resistance play a pivotal role. It appears that both monocyte/macrophages and adipose tissue (AT) conspire to accentuate both the pro-inflammatory state and increased insulin resistance. Whilst there are scant data on visceral adipose tissue (VAT) and epicardial adipose tissue (EAT) biology, there are data on subcutaneous adipose tissue (SAT) dysregulation. There is a significant increase in macrophages and crown-like structures in the SAT of patients with MetS. With respect to adipokines, there is an increase in plasma leptin, plasminogen activator inhibitor-1, retinol-binding protein-4 (RBP-4), chemerin, serum amyloid-A, C-reactive protein (CRP), interleukin-1, -6, -8, lipopolysaccharide, fetuin A (FetA) and a decrease in adiponectin and omentin-1. All of the abnormalities in plasma were also confirmed for SAT-secreted adipokines except for adiponectin and RBP-4 which derive largely from VAT. As many of these biomediators correlate with both insulin resistance and increased inflammation, we can posit that dysregulation of SAT is detrimental and contributes to both the pathogenesis of MetS and its sequalae. Furthermore, as future directions, much work is needed with respect to VAT/EAT biology, autophagy, sirtuins, the gut microbiome, browning of AT, to further elucidate this common syndrome and identify potential therapeutic targets to forestall its serious complications.

Keywords: adipokines, inflammation, insulin resistance, macrophages, metabolic syndrome, subcutaneous adipose tissue

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Introduction

Metabolic syndrome (MetS) is a very common disorder that appears to afflict 35% of American adults >40 years of age. Importantly, a joint statement was published by the International Diabetes Federation, American Heart Association and National Heart, Lung and Blood Institute who arrived at a harmonized definition to avoid confusion with the different criteria used by different organizations previously. According to this definition, MetS is diagnosed if three of the five features are present [1]. The five features include an increased waist circumference (WC) which is population and country specific, hypertriglyceridemia (>150 mg/dL), decreased levels of high-density lipoprotein (HDL)-cholesterol <50 mg/dL in females and <40 mg/dL in males, blood pressure >130/85 and an elevated blood glucose >100 mg/dL. Drug treatment for glycemia, hypertension, hypertriglyceridemia and low HDL-cholesterol levels were also considered as criteria. MetS confers an increased risk for both diabetes and cardiovascular disease and hence is a major global cardio-metabolic problem [1], [2].

The pathogenesis of MetS is poorly understood and both insulin resistance and inflammation have been advanced as major potential pathogenic mechanisms [1], [2], [3], [4]. The liver, monocyte/macrophages, muscle and adipose tissue (AT) could all contribute to genesis of the MetS. Previously, we have detailed in a review, the role of the monocyte/macrophages in the genesis of MetS [5]. In this mini review we will focus largely on our studies in patients with nascent MetS uncomplicated by either diabetes or cardiovascular disease as we wish to understand its pathogenesis at the earliest possible stage. We will also discuss other relevant published studies on MetS. Hence, we will review the published studies on AT dysregulation in MetS with a focus on subcutaneous adipose tissue (SAT) biology in human patients.

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Body of review

SAT accounts for around 80% of the AT and is the major provider of free fatty acids to the liver [3]. Using the product of fasting insulin and free fatty acids to define adipose tissue insulin resistance (adipose-IR), we documented increased adipose-IR in MetS independent of adiposity [6]. Furthermore, we showed that adipose-IR correlated significantly and positively with leptin and chemerin and inversely with adiponectin and omentin-1. However, we cannot conclude if the adipokine dysregulation resulted in the adipose-IR or vice versa but we establish in nascent MetS that there is also insulin resistance in AT. Furthermore, there was a 2.4-fold increase in plasma free fatty acids in the patients with MetS versus controls [7].

Adiponectin is a classical adipokine and is the most abundant adipokine secreted exclusively by the AT [8], [9], [10], [11]. Its anti-inflammatory and cardioprotective actions are mediated by the receptors, adiponectin receptor 1 and adiponectin receptor 2. Adiponectin has been shown to be decreased in chronic obesity and/or insulin resistant states in animal models and human subjects and has been shown to reduce atherosclerotic vascular lesions in vivo. Adiponectin is an insulin-sensitizing adipokine, involved in glucose and lipid homeostasis, through the activation of adenosine monophosphate (AMP)-activated protein kinase. In addition, it suppresses tumor necrosis factor (TNF)α, reduces oxidative stress, prevents cell apoptosis and reduces foam cell formation [8], [9], [10], [11]. A strong correlation between low levels of adiponectin and increased insulin resistance has been well established both in vivo and in vitro in animal models and humans. Adiponectin levels are significantly reduced in MetS patients compared to controls [8], [9], [10], [11]. We have shown lower levels of total high molecular weight oligomers and low- and medium-molecular weight adiponectin in patients with MetS versus controls, underscoring the significance of hypoadiponectinemia [12].

Leptin is another adipokine which regulates food intake by inducing satiety and facilitating energy expenditure. Circulating leptin levels directly correlate with adipose mass and adipocyte size. Several studies have shown increased leptin levels and the development of macrovascular complications of diabetes, obesity, cardiovascular risk [13], [14], [15], [16]. Leptin exerts its effect on energy balance mainly by acting on the brain, either directly or indirectly by activating specific centers in the hypothalamus to decrease food intake, to increase energy expenditure, to influence glucose and lipid metabolism, or to alter neuroendocrine function [13], [14], [15], [16]. Leptin is pro-inflammatory and augments cytokine production and T-cell proliferation, however, leptin levels are increased in obese subjects, and cannot regulate energy homeostasis, due to the phenomenon of leptin resistance. In humans, insulin resistance is associated with elevated plasma leptin levels independently of body fat mass. Importantly, leptin is pro-inflammatory and promotes Th1-type cytokine production, induces the expression of pro-inflammatory cytokines by macrophages and monocytes, and acts directly on hepatocytes to promote C-reactive protein (CRP) expression.

Serum amyloid A (SAA) as well as CRP circulating levels are significantly higher in obese subjects compared to normal weight subjects [4]. Many studies report that SAA is a reliable marker of low-grade inflammation in human obesity [17], [18]. A 1-year drastic weight loss resulted in a sustained improvement in inflammation and was associated with a dramatic decrease of serum SAA. With regard to the AT, the expression of inducible isoforms SAA1 and SAA2 is higher in AT, especially in subcutaneous white AT and the adipocyte cell volume and SAA circulating levels were highly correlated, independently of body mass index, validating the strong relationships between AT enlargement and SAA. We have shown a significant increase in both plasma and SAT-secreted CRP and SAA in MetS underscoring further that CRP derives from extra-hepatic sources also [19].

With regard to the AT, the amount of SAT in subjects with MetS positively correlates with increasing MetS factor scores and negatively correlates with circulating adiponectin levels and positively with CRP levels. In one of the first studies on SAT obtained from nascent MetS compared to matched controls, we examined several adipokines in SAT of MetS compared to matched controls. Expressed per gram of SAT, the amount of leptin, CRP, SAA, plasminogen activator inhibitor-1 and monocyte chemotactic protein-1 were significantly higher in subjects with MetS than in controls [19]. Importantly, all these differences persisted even after adjusting for WC as a covariate. There was a trend toward decreased adiponectin and retinol-binding protein-4 (RBP-4) which was not significant. However, as plasma levels were decreased this supports the view that adiponectin and RBP-4 derives largely from visceral adipose tissue (VAT) and not SAT [3], [20].

Chemerin, produced by both the liver and AT, is a chemoattractant for macrophages and appears to induce insulin resistance in skeletal muscle [3], [20]. Also levels are increased in diabetes and obesity [3], [20]. In patients with some features of MetS, chemerin levels are also increased [21]. In a report on both plasma and SAT-secreted chemerin in nascent MetS, we showed that both levels were significantly increased independent of adiposity, and that both plasma and SAT-secreted levels correlated significantly [22]. Furthermore, chemerin correlated significantly with high sensitivity CRP, homeostatic model assessment of insulin resistance (HOMA-IR), hypertriglyceridemia, systolic blood pressure and inversely with HDL-cholesterol. Thus, SAT-secreted chemerin is an adipokine that could contribute to both the pro-inflammatory state and insulin resistance of MetS.

Omentin-1 appears to be derived largely from VAT and is reported to have insulin sensitizer actions (which enhances glucose uptake stimulated by insulin in adipocytes) [20], [23]. Lower levels have been recorded in both obesity and diabetes [20], [23], [24]. In our novel report, we documented both lower plasma and SAT-secreted omentin-1 independent of adiposity [22]. Furthermore, the levels correlated inversely with glucose and hypertriglyceridemia and positively with HDL-cholesterol and SAT-secreted omentin. The latter suggests that omentin derived from SAT also contributes to the circulating levels. Interestingly, it has also been suggested to be a marker for endothelial function [25]. Importantly, low levels of omentin in patients with MetS have been associated with increased severity of coronary artery disease [26] suggesting that it is also a predictor of cardiovascular disease.

With respect to plasma and SAT-secreted resistin and visfatin, we failed to show any significant differences between MetS and controls [22]. The trend toward an increase in plasma resistin following adjustment for adiposity ($p = 0.07$) with no significant increase in SAT-secreted resistin, would suggest that it is being secreted by activated leukocytes in our patients with MetS [5], [22]. Resistin is considered a pro-inflammatorty mediator but does not appear to be an adipokine in human subjects [20], [22], [27]. Norata et al. [28] reported higher resistin levels in females (not adjusted for adiposity) and not in males with MetS but with no differences in obesity or diabetes adding further confusion to the literature on resistin.

Lipopolysaccharide binding protein (LBP) appears to derive exclusively from the liver and is classically considered as an acute phase reactant [29]. Increased levels have been reported in obesity, insulin resistance and MetS [29]. By binding to the lipid A moiety of LPS it escorts lipopolysaccharide to cluster of differentiation 14 (CD14) (both soluble and membrane forms). In patients with nascent MetS, we showed an increase in both plasma and SAT-secreted LBP [30]. SAT-secreted LBP correlated significantly with HOMA-IR. In a report by Moreno-Navaratte et al. [31] they showed increased messenger RNA (mRNA) in both SAT and VAT of obese persons (greater expression in SAT than VAT) and confirmed that it derived predominantly from adipocytes by AT fractionation studies. Also they showed that AT LBP correlated with both insulin resistance and inflammation and increased with weight gain and decreased with weight loss in obese persons. These studies on obesity and MetS collectively support the notion that LBP is also an adipokine as mRNA and the protein are present in AT. Furthermore, LBP is secreted from adipocytes (human and mice), suggesting a role in the pathogenesis of MetS as both plasma and SAT levels were increased and correlated with both insulin resistance and inflammation.

Fetuin A (FetA) is classically considered a hepatokine, which impairs insulin signaling [32]. Levels are elevated in obesity, diabetes and MetS. However, we made the novel observation that FetA secretion is increased from SAT in patients with MetS compared to controls. Furthermore, FetA correlated with HOMA-IR, a measure of insulin resistance and hypertriglyceridemia. Also using the ob/ob mice, an accepted animal model of MetS, we confirm mRNA in AT arguing for FetA to be considered as an adipokine and hepatokine. In this regard, we should point out that Chatterjee et al. [33] also reported an increase in visceral adipose FetA protein in a small number of obese diabetic persons ($n = 5$) and mice models.

Immune cells in SAT in MetS

We have failed to document lymphocytes in SAT using both CD3 and CD5 staining. However, we showed abundant macrophages as evidenced by CD68 staining [19]. Furthermore, we documented around a 3-fold increase in crown-like structures in SAT. The increased macrophages do not appear to be due to the M1 phenotype as there was no correlation with pro-inflammatory mediators. In an attempt to understand the factors that account for macrophage homing to AT we correlated AT macrophage density with various biomediators and found that only resistin, soluble CD14 and monocyte P38-miotgen-activated protein kinase activity correlated significantly [34]. The correlations with interleukin 8 (IL-8), adiponectin (trend toward both, $p = 0.06$) leptin and monocyte chemotactic protein were not significant. Thus, based on these pilot findings, we propose that an activated monocyte is crucial for macrophage homing to SAT in MetS and in the resulting inflammation and insulin resistance of MetS. Recently, we showed both increased fibrosis (sirius red staining) and collagen staining and increased angiogenesis [CD31 and vascular endothelial growth factor (VEGF) staining] in SAT from patients with MetS versus controls [35]. Surprisingly, angiopoetin-2 was not increased and the ratio of Angio 2:1 was decreased. As CD31, VEGF and fibrosis score both correlated with multiple biomediators of inflammation, we hypothesize that both are dictated by the proximal pro-inflammatory state. We speculate that the paradoxical increase in angiogenesis is a protective mechanism in gluteal fat to avoid further dysregulation of SAT biology.

There is a serious paucity of data on other immune cells such as eosinophils, mast cells, neutrophils and different subtypes of lymphocytes in the AT [36]. This should be a major focus of future studies to help unravel the inflammatory burden in AT.

Expert opinion and outlook

In conclusion, in this mini review we provide a status report on SAT biology in MetS. There is a paucity of data on VAT and epicardial adipose tissue (EAT) and this needs to be a major future focus area. We can conclude that SAT contributes via the production of adipokines and cytokines (Figure 1) to both inflammation and insulin resistance of MetS and hence is a co-conspirator with macrophages contributing to both inflammation and insulin resistance. Thus, dysregulation of AT is a crucial factor in the pathogenesis of MetS and has provided some important biomediators that can be potential targets in ameliorating this common global syndrome.

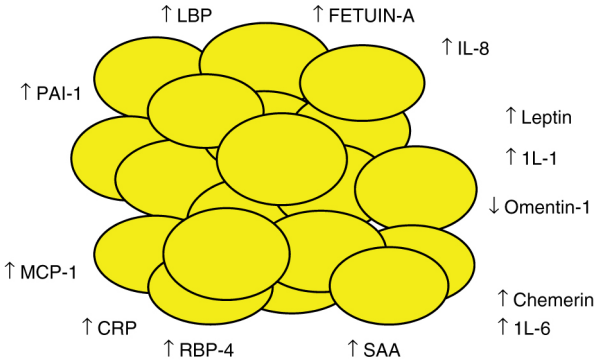

Figure 1: Schema portraying dysregulation in adipokine and cytokine secretion from subcutaneous adipose tissue of patients with MetS.

Significant gaps in our knowledge including the role of VAT/EAT biology, the role of sirtuins, autophagy, the microbiome and browning of fat, etc. in subjects with MetS still exists [37]. Hence, future investigations focusing on these issues will go a long way in elucidating the pathogenesis and identification of potential therapies for MetS. With respect to future enquiry into the role of microbiota, we need to point out that we have documented increased levels of endotoxin in patients with MetS [7] and preliminary studies have shown that infusion of intestinal microbiota from lean healthy donors temporarily improves insulin resistance in patients with MetS [38].

Highlights

- The MetS is a very common disorder that predisposes to increased diabetes and cardiovascular diseases.
- There is increased adipose-IR in MetS independent of adiposity.
- With regards to the AT, the amount of SAT in subjects with MetS positively correlates with increasing MetS factor scores.
- The amount of leptin, CRP, SAA, plasminogen activator inhibitor-1 and monocyte chemotactic protein-1 were significantly higher in AT of subjects with MetS than in controls.
- Levels of chemerin, LBP and FetA are increased while omentin is decreased in adipose tissue of MetS compared to controls and correlated with markers of insulin resistance.
- AT of MetS is characterized by abundant macrophages as evidenced by CD68 staining and increased crown-like structures in SAT. Adipose macrophage density correlated with resistin, soluble CD14 and monocyte P38-mitogen-activated protein kinase activity.
- AT from MetS also exhibited increased fibrosis and increased angiogenesis as a counter regulatory mechanism compared to controls.
- The dysregulation of SAT biology in MetS is a significant factor contributing to the pathogenesis and sequalae.

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