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Review

Metabolic syndrome is an inflammatory disorder: A conspiracy between adipose tissue and phagocytes

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ABSTRACT

Metabolic syndrome (MetS) describes a cluster of cardio-metabolic factors that predispose to type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). While 35% of Americans suffer from this disorder, the specific pathways related to this disease are largely underexplored. The prevailing consensus is that inflammatory pathways contribute to the pathogenesis of this disease, and therefore new research has uncovered how inflammation plays a critical role in the development and progression of MetS. The purpose of this review is to understand the role of major inflammatory mechanisms and their role in MetS. Our review identifies that adipose tissue (AT) contributes to the inflammatory pathways through the release of pro-inflammatory adipokines such as leptin and chemerin and dysregulation of anti-inflammatory adiponectin. Chemokines and cytokines deriving from monocytes are also altered and promote inflammation and insulin resistance. Circulating inflammatory biomarkers including C-reactive protein (CRP), fibrinogen, Serum amyloid A (SAA), cytokines, and chemokines have also been linked to the pathogenesis of MetS. Researchers have identified the significance of CRP levels in predicting future sequelae of MetS such as ASCVD. Mast cells in subcutaneous adipose tissue (SAT) promote both inflammation and fibrosis. Thus, both AT and phagocyte activity define MetS as an inflammatory disorder.

1. Introduction

Metabolic syndrome (MetS) affects approximately 35% of American adults and is expected to increase globally. MetS describes a cluster of cardio-metabolic risk factors that predispose individuals to type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). It is defined by the global harmonized definition as having three of the five following features: increased triglycerides (TG), low levels of high-density lipoprotein (HDL)-cholesterol, plasma glucose > 100 mg/dL, increased waist circumference (WC), and hypertension (HTN). This is depicted in Table 1 [1].Currently, clinicians and researchers have not identified an optimal treatment for MetS, and

Abbreviations: MetS, Metabolic syndrome; BMI, body mass index; T2DM, Type II Diabetes Mellitus; ASCVD, atherosclerotic cardiovascular disease; WC, waist circumference; HDL, high-density lipoprotein; HTN, hypertension; SAT, Subcutaneous adipose tissue; IR, insulin resistance; SFRP5, Secreted frizzled-related protein 5; LBP, lipopolysaccharide-binding protein; PAI-1, plasminogen activator inhibitor-1; TNF-α, tumor necrosis factor- α; IL, interleukin; CAD, Coronary artery disease; CRP, C-reactive protein; MCP-1, Monocyte chemoattractant protein-1; NAFLD, non-alcoholic fatty liver disease; FFA, free fatty acids; MCP-1, monocyte chemotactic protein-1; RBP4, retinol binding protein 4; sTNFR2, soluble tumor necrosis factor receptor 2; CD, Cluster of differentiation; JNK, Jun N-terminal Kinase; TG, triglycerides; AdipoR, adiponectin receptor; AMPK, Adenosine monophosphate protein kinase; PPAR, peroxisome proliferator activated receptor; CCL2, chemokine ligand 2; MI, myocardial infarction; GLUT4, glucose transporter 4; ICAM-1, Intercellular Adhesion Molecule-1; SAA, Serum amyloid A; A-SAA, acute-phase SAA; ATM, Adipose tissue macrophage; PC 34:2, phosphatidylcholine 34:2; IRS-1, Insulin Receptor Substrate-1; NLR, Neutrophil to lymphocyte ratio; GABA, Gamma-aminobutyric acid; PGA, d-pyroglutamic acid; NAT, *N*-acetyl-d-tryptophan; LBP, lipopolysaccharide-binding protein; NAT, *N*-acetyl-tryptophan; CD40L, CD40 ligand; TLR, Toll-Like Receptor; PAMP, pattern-associated molecular pattern; CCR, chemokine receptor; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; HOMA, Homeostatic model assessment; MIP-1β, macrophage inflammatory protein-1β; Nrf-2, nuclear factor erythroid 2-related factor 2; ox, oxidative; GABA, gamma-Aminobutyric acid; ER, endoplasmic reticulum; NADPH, nicotinamide adenine dinucleotide phosphate; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in one minute; MAC-1, Macrophage-1 antigen; HBA1C, Hemoglobin A1C

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Table 1
Harmonized criteria for the clinical diagnosis of metabolic syndrome.

Measure	Categorial cut points
Elevated waist circumference	Population and country-specific definitions
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥85 mm/Hg
Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)	≥100 mg/dL
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)	≥ 150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator)	≤40 mg/dL (1.0 mmol/L) in males < 50 mg/dL (1.3 mmol/L) in females

Adapted from Alberti et al. [1].
*2-fold increased risk of ASCVD and 5-fold increased risk of Diabetes.

consequently, it is critical to identify new ways of approaching this syndrome in order to identify efficacious methods of diagnosing, screening and treating MetS. Numerous studies have suggested that MetS, like its downstream sequelae of ASCVD and T2DM, is largely an inflammatory disease. However, studies have been unable to identify the precise role of inflammation in the pathophysiology of MetS. Therefore, in this review, we assess various aspects of inflammation in MetS including circulatory biomarkers of inflammation, monocyte and neutrophil activity, and adipose tissue biology to identify abnormalities that underscore our predicate that it is an inflammatory disorder. The goal of this review is to identify the role of these inflammatory mediators, both circulating and cellular in MetS to define it an inflammatory disorder.

2. Adipose tissue biology

2.1. Adipokines

Subcutaneous adipose tissue (SAT) makes up 80% of adipose tissue and is a major provider of circulating free fatty acids (FFA) to the liver and other tissues. Dysregulation of SAT is believed to be detrimental and contributes to pathogenesis of MetS and its downstream consequences including T2DM and ASCVD. Studies have reported that increased adiposity results in insulin resistance (IR) and increased macrophages in SAT of patients with MetS [2,3]. MetS was also significantly associated with circulating adipokines in well-functioning adults aged 70–79 years. In a model adjusted for age, race, and gender, MetS was significantly associated with leptin, plasminogen activator inhibitor-1(PAI-1), and lower levels of adiponectin. This association was independent of body fat percentage and visceral adiposity, suggesting that inflammatory pathways may be associated with the development of MetS in older adults [4]. In general, adipose tissue (AT) is integral to the development of obesity induced inflammation by increased cytokines and chemokines and dysregulation of adipokines including tumor necrosis factor- α (TNF-α), interleukin (IL)-6, IL-8, IL-1, monocyte chemoattractant protein-1 (MCP-1), leptin, PAI-1, retinol binding protein 4 (RBP4), chemerin, serum amyloid A (SSA), C-reactive protein (CRP), lipopolysaccharide-binding protein (LBP), fetuin A, and decreased adiponectin and omentin-1 [2,3]. Others have identified enlargement of adipose tissues in obesity as a cause of dysregulation of adipokines and increased release of FFA and pro-inflammatory adipokines, which modify the inflammatory response by increasing cytokines and chemokines and disrupting glucose and lipid metabolism [3]. In states of excessive adiposity there is excess energy, hypoxia, apoptosis, stress, which in turn leads to inflammation and increased risk for metabolic disease. Barchetta et al. have termed this “sick fat” which describes aberrant adipose dysfunction that leads to release of inflammatory mediators including TNF-α, IL-1β, IL-6, CRP, fibrinogen, leptin, MCP-1, chemerin, granzyme B, resistin, wingless-related integration site inducible signaling pathway protein −1, dipeptidyl-peptidase 4, procollagen type II amino-terminal propeptide, apelin, angiopoietin 2, omentin-1, haptoglobin, and vascular adhesion protein-1 [5]. This suggests that dysregulated adipose biology and its associated proinflammatory state may have a larger role in metabolic disease.

Another modulator of adipose biology is PAI-1, an inhibitor of fibrinolysis, which is also made by adipocytes and stromal vascular cells. Low PAI-1 decreases weight gain, improves insulin resistance, and increases total body expenditure in high fat diet fed mice [3]. PAI-1 is also increased when adipocytes are stimulated by TNF-α, transforming growth factor, angiotensin II, glucocorticoids, and insulin, suggesting that PAI-1 can play a role in inflammatory pathways while also affecting MetS directly. It is also associated with thrombotic vascular conditions, suggesting that PAI-1 is an independent risk factor for the development of ASCVD, which is often a downstream sequelae of MetS [6]. Circulating and PA1–1 secreted by SAT are both increased in MetS. Also RBP-4 levels are increased in MetS and correlate with insulin resistance [7].

Visfatin is a modulator of beta cell differentiation. Researchers have reported that it is secreted by adipose tissue and visceral adipose tissue. However, studies failed to confirm visfatin expression in visceral white adipose tissue and identify how visfastin in adipose tissue is correlated with obesity [8]. While serum visfatin does not correlate with insulin resistance in humans, serum levels correlate with IL-6 ($r = -0.27$, $P < 0.001$) and CRP ($r = 0.12$, $P < 0.05$) [9]. The exact role of visfatin in MetS needs further clarification.

Secreted frizzled-related protein 5 (SFRP5) is a new adipokine with properties that suggest a role as an insulin sensitizer and anti-inflammatory biomediator. Its gene and protein are expressed in higher levels in adipose tissue and a deficiency in SFRP5 impairs insulin sensitivity in mice and increases the risk of non-alcoholic fatty liver disease (NAFLD) development. SFRP5 knockout mice had aggravated fat pad inflammation when compared to control mice on the same high calorie diet. Administration of SFRP5 improves metabolic function (glucose levels and insulin sensitivities) and reduces adipose inflammation in obese diabetic mice [10]. SFRP5 levels were lower in adults with glucose intolerance and T2DM with activation of Jun N-terminal kinase (JNK)-1 adipose tissue [3,11].

Researchers have also recently identified that mast cells may have implications in adipose tissue biology and inflammation. SAT biopsied from humans and stained for mast cells including tryptase showed a 2.5 fold increase of mast cells in SAT of MetS subjects compared with controls. Mast cells also correlated positively and significantly with IR, TG, glucose, and WC. Mast cells showed a positive and significant association with leptin and soluble tumor necrosis factor receptor (sTNFR)-2, IL-1β, IL-6, endotoxin, FFA, chemerin, and cluster of differentiation (CD)-31.Also mast cells correlated with markers of fibrosis in SAT including collagen and Sirius red staining. Together, this suggests that adiposity contributes to an inflammatory state, which may be directly linked to metabolic disease [12].

Weisberg et al. also found that accumulation of macrophages in adipose tissue is directly proportional to measures of adiposity in mice and humans. Immunohistochemical analysis of human SAT showed that body mass index (BMI) and adipocyte size were strong predictors of the percentage of CD68- macrophages. Adipocyte volume was also highly correlated with markers of systemic insulin resistance, dyslipidemia, and risk for developing T2DM. Weight loss showed decreased adipocyte

volume and the reduction of metabolic phenotypes [13]. Adipose tissue can also affect the liver, skeletal muscle, heart, and can contribute to insulin resistance, dyslipidemia, and NAFLD [3]. Researchers identified that circulating adipokines are associated with future incidence of MetS in young to middle-aged adults. Metabolically healthy obese individuals had worse adipokine profiles, where higher circulating levels of both RBP4 and fetuin-A are associated with future incidence of MetS and insulin resistance [14]. This suggests that certain adipokines such as RBP4 and fetuin-A, may be used as early biomarkers of MetS and may help screen for high-risk individuals. Focusing on adipokine signaling pathways and intracellular cascades activated by adipose tissue may also be helpful in finding new ways of understanding how adipokines and adiposity relate to the pathology of metabolic disease.

Other observations with respect to SAT dysregulation is the novel finding that Fetuin A, classically considered an hepatokine which promotes insulin resistance, is secreted in increased amounts from SAT in MetS and correlated with insulin resistance. In the same report we showed increased secretion of LBP also correlated with insulin resistance [15]. The findings with respect to LBP was first reported by Moreno-Navaratte et al. [16]. Thus both Fetuin A and LBP can also be classified as adipokines since expression is increased in AT.

2.2. Leptin

Leptin is another adipokine that regulates food intake by inducing satiety and aiding energy expenditure. Leptin levels directly correlate with adipose mass. Leptin is also pro-inflammatory and augments cytokine production and T cell proliferation by increasing Th1 type cytokines secreted by monocytes and acting directly on hepatocytes to increase CRP [2]. Leptin expression can also be increased in response to pro-inflammatory cytokines such as TNF-α, IL-1, and endotoxin, and is inhibited by anti-inflammatory factors such as IL-4. The pathway is bidirectional where proinflammatory cytokines increase release and synthesis of leptin, which in turn contributes to chronic inflammatory states in obese individuals. Leptin also plays a significant role in glucose homeostasis. It improves insulin sensitivity in the liver and skeletal muscle and regulates beta cell function [3]. In humans with nascent MetS, which describes MetS patients without ASCVD or T2DM, leptin is increased independent of adiposity and correlated positively with various amino acids and lipids which were also significantly increased including L-carnitine ($r = 0.4$, $p = 0.02$), phosphatidylcholine 34:2 (PC 34:2) ($r = 0.5$, $p < 0.01$), and isoleucine (r = 0.4, p = 0.02). These metabolites were also directly associated with various inflammatory factors which suggest that they may be affecting leptin levels through inflammatory pathways [17–19]. However, lysine and *N*-acetyl-d-tryptophan (NAT), which are metabolites that have both been profoundly decreased in nascent MetS, did not correlate significantly with leptin [19,20]. More research is necessary to determine if exactly how leptin levels affect the development of MetS.

2.3. Adiponectin

Adiponectin is a 244-residue protein that is structurally similar to collagen type VII and X and C1q. Synthesized in adipose tissue, it acts through adiponectin receptor (AdipoR)-1 and AdiopoR2 on skeletal muscle and in the liver. Its binding leads to activation of adenosine monophosphate protein kinase (AMPK), peroxisome proliferator activated receptor (PPAR)-α and γ, and other signaling pathways [2,21]. Adiponectin is released into the bloodstream in three oligomeric forms: a trimer, hexamer, or high molecular weight multimer, thus making it difficult to accurately measure in the bloodstream.

In obese patients, circulating adiponectin is typically decreased but increases after weight loss and treatment with thiazolidinediones, which enhances insulin sensitivity. Adiponectin works as an endogenous insulin sensitizer by upregulating glucose uptake and promoting fatty acid oxidation. Spiegelman et al. showed that adiponectin expression may be decreased in obesity as decreased adiponectin mRNA was found in adipose tissue from obese mice and humans [22]. Additional studies found a significant inverse correlation between plasma adiponectin and TNFα mRNA expression in vitro. Adiponectin expression from adipose tissue was found to be higher in lean subjects and women, and is associated with greater insulin sensitivity and lower TNFα expression [23]. It is possible that adiponectin itself may affect insulin sensitivity and, considering its role in inflammation, may be also inducing metabolic dysfunction through inflammatory mechanisms.

Research has also identified that adiponectin is implicated in inflammatory diseases including ASCVD, T2DM, MetS, osteoarthritis, and rheumatoid arthritis due to its action on the innate and adaptive immune system. It can suppress TNFα, reduce oxidative stress, prevent cell apoptosis, and reduce foam cell formation. In animals and humans, both in-vivo and in-vitro, there has been a strong correlation between low levels of adiponectin and IR [2].

In MetS, adiponectin may have a protective role. Adiponectin levels are decreased in patients with obesity, coronary artery disease (CAD), diabetes, and HTN. It is increased with weight loss, physical training, and insulin sensitizing drugs. Using Caucasians and Pima Indians, who have a high propensity for obesity and T2DM, researchers found that the adiponectin levels inversely and significantly correlated with percent body fat ($r = -0.4$), log fasting insulin ($r = -0.6$), and log 2 h glucose levels ($r = -0.4$) [24]. Furthermore, adiponectin gene expression and circulating levels inversely correlated with adiposity and WC in MetS patients. Intra-abdominal fat was found to especially affect circulating adiponectin levels and visceral fat depots appear the major sources of adiponectin. Lower levels of adiponectin were also linked to obese patients with MetS and inversely associated with endothelial dysfunction, HTN, and factors contributing to vascular inflammation. Adiponectin has been shown to inhibit pro-inflammatory factors such as macrophage activation and the production of IL-6 and TNFα. In a prospective cohort study, decreased adiponectin was associated with increasing incidence of MetS [21]. This phenomena has also been associated with insulin resistance and T2DM, and therefore normal or increased adiponectin levels may be protective against MetS and T2DM.

In patients who have nascent MetS, there were lower adiponectin levels compared to matched controls [17]. In this same cohort, L-carnitine and phosphatidylcholine (PC) 34:2, which were increased in nascent MetS, were significantly and inversely proportional to adiponectin ($r = -0.4$, $p = 0.02$ and $r = -0.5$, $p \leq 0.01$) and directly proportional to inflammatory factors including *s*TNFR1 ($r = 0.5$, $p < 0.05$), respectively. This suggests that adiponectin and inflammation may have implications in nascent MetS through its association with various lipids and amino acids [17–19]. The combined evidence suggests that adiponectin may have a potential role in mediating inflammation and also alleviating harmful effects in MetS. More research is needed to identify if adiponectin can be used to screen for MetS or if adiponectin replacement can help treat MetS. Although there is compelling evidence for an important role for low adiponectin in obesity and MetS, very little work has been done to validate it as a biomarker in the clinical arena given its multiple circulating forms.

3. Circulating biomarkers: CRP, fibrinogen and SAA

3.1. CRP

CRP, a member of the pentraxin family of proteins, is secreted by hepatocytes, lymphocytes, alveolar macrophages, monocyte-derived macrophages and endothelial cells in atherosclerotic plaques in response to IL-6 and other inflammatory markers. It is considered as the prototypic downstream marker of inflammation. The interaction between CRP and Fc receptors promotes the release of proinflammatory cytokines in the inflammatory response [25]. Because its levels are increased in response to trauma, inflammation, and infection, CRP has been widely used to monitor inflammatory states (25). CRP has been

increasingly linked to MetS and more recently has been characterized as an independent predictor of future cardiovascular events in MetS [26].

In a cross-sectional analysis of 1366 adolescents from the National Health and Nutrition Examination Survey, Ford et al. found that the mean and median concentrations of CRP were higher among subjects with MetS. Additionally, the percentage of subjects with a concentration of CRP > 3.0 mg/L was nearly four times as high in those with MetS compared to those without the syndrome ($p = 0.007$). This observation is significant in that early low-grade inflammation characterized by elevated CRP seen in children with MetS may predispose them to the development of ASCVD and T2DM later in life [27]. Researchers have also demonstrated an association between elevated CRP levels and specific features of MetS. In the nondiabetic population of the Insulin Resistance and Atherosclerosis Study (IRAS), hsCRP directly correlated with BMI, waist circumference, blood pressure (BP), TG, cholesterol, low density lipoprotein (LDL) cholesterol, plasma glucose, and fasting insulin and indirectly correlated with HDL cholesterol and insulin sensitivity index. Notably, a linear increase in CRP levels was associated with an increase in the number of metabolic disorders, and the strongest associations were observed between CRP levels, central adiposity, and insulin resistance ($p < 0.0001$) [26,28].

There is accumulating evidence linking CRP with abdominal adiposity, a key feature of MetS. CRP levels showed a positive correlation with volume of visceral fat determined by magnetic resonance imaging in a group of 14 healthy female subjects ($r = -0.63$, $p = 0.028$) [29]. Abdominal adiposity was also associated with significantly elevated CRP values independent of BMI among healthy, non-obese subjects ($p < 0.01$) [30]. CRP synthesis occurs in adipose tissue, which is present in excess amounts in individuals with increased visceral adiposity, thus predisposing patients to insulin resistance, T2DM, and ASCVD. The widely accepted mechanism linking abdominal obesity to elevated CRP relates to the accumulation of free fatty acid in adipose tissue, which in turn promotes cytokine secretion that causes upregulation of CRP synthesis [5].

Researchers have identified the significance of CRP levels in predicting future sequelae of MetS. In a 9-year follow up prospective study with 14,916 healthy male subjects, baseline levels of CRP and total cholesterol (TC) were measured in 245 participants who developed a first myocardial infarction (MI) and 372 participants who did not have one. The relative risks of future MI in subjects with both elevated CRP and TC (RR = 5.0, $P = 0.0001$) were higher than the risks associated with isolated increases in CRP (RR = 1.5) or TC (RR = 2.3). Thus, baseline CRP levels contributed to the predictive value of TC in predicting the risk of MI [31]. A similar trend was shown in the West of Scotland Coronary Prevention Study, where multivariate analysis demonstrated a graded increase in risk of T2DM across CRP quintiles in middle-aged male subjects. Particularly, the highest quintile (CRP > 4.2 mg/l) was associated with more than a threefold risk in development of T2DM independent of established clinical risk factors, including baseline BMI and fasting triglyceride and glucose concentrations (HR 3.07; 95% CI 1.33–7.10) [32]. Multiple studies have aimed to elucidate the precise role of CRP in insulin resistance. Collectively, their data shows that hrCRP-mediated IRS-1 phosphorylation at Ser307 and Ser612 via JNK and extracellular signal-regulated kinases 1 and 2 (ERK1/2), results in ineffective translocation of glucose transporter 4 (GLUT4) and insulin-stimulated glucose uptake [26,33,34]. CRP plays a role in both MetS and coronary artery disease by impairing insulin signaling and promoting atherothrombosis via endothelial dysfunction [35].

Multiple studies have proposed adding hsCRP as a clinical criterion for MetS given its additive prognostic value in the prediction of development of T2DM [36]. Emerging clinical and laboratory investigations have also shown a significant association between CRP and features of MetS [26]. Notably, investigators argue that the addition of CRP as a clinical criterion of MetS may be an instrumental advancement in preventing the development of adverse sequelae. The role of CRP as an early biomarker in predicting progression to ASCVD and T2DM in MetS patients is an important point of discussion, given that early screening can identify high-risk patients who may require closer medical monitoring and intervention. Also the assay for CRP is reasonably standardized and available in most automated platforms in clinical laboratories. While the correlation between CRP and development of ASCVD and T2DM is universally acknowledged, the molecular role of CRP in the pathogenesis of MetS and its sequelae as well as its vascular effects requires further elucidation. However, hsCRP is not considered as a feature of MetS by any national or global guideline committees.

3.2. Fibrinogen

Fibrinogen is a soluble 340-kDA glycoprotein synthesized predominantly by hepatocytes in the liver. It is most well-known for its role in the final step of the coagulation cascade. The function of fibrinogen in the body is complex as it plays significant roles in inflammation, atherogenesis, and thrombogenesis. Because of its multifaceted function in pathophysiological processes and studies linking hyperfibrinogenemia to cardiometabolic risk and insulin resistance, the relationship of fibrinogen and MetS has been increasingly investigated, although its precise role has been controversial [37].

In the acute phase response, interleukin- 6 (IL-6) upregulates the expression of fibrinogen in hepatocytes. Fibrinogen interacts with leukocytes through 2 main surface receptors: MAC-1, CD11b/CD18, alpha M beta 2) and alpha X beta 2 (CD11c/CD18,). Leukocytes induce conformational changes in the MAC-1 receptor which enhances fibrinogen binding. Fibrinogen also serves as a ligand for intercellular Adhesion Molecule-1 (ICAM-1), which promotes leukocyte adhesion to vascular endothelium by bridging the Mac-1 on monocytes to ICAM-1 on endothelial cells [37,38]. Additionally, the binding of fibrinogen to its receptors on leukocytes induces a chemotactic response which promotes inflammation.

The correlation between hyperinsulinemia and hyperfibrinogenemia has been identified in multiple studies. In a novel investigation exploring the relationship between fibrinogen and insulin resistance, Raynaud et al. sought to determine whether plasma fibrinogen concentrations were linked to plasma insulin levels or to the degree of insulin resistance itself. Data taken from 62 nondiabetic, normotensive male and female patients showed a significant negative correlation between fibrinogen and insulin sensitivity ($r = -0.76$, $p < 0.0001$) and a positive correlation between fibrinogen and basal insulin ($r = 0.56$, $p < 0.0001$). Of note, a multiple regression analysis characterized insulin sensitivity as the only predictive factor of fibrinogen levels. The question as to whether there is a simple correlation between fibrinogen and insulin resistance or a causal association continues to be debated. Imperatore et al. considers the positive correlation between serum fibrinogen and insulin as an epiphenomenon of the condition of insulin resistance underlying hyperinsulinemia. Hyperinsulinemia may serve as a marker of insulin resistance and therefore it shares an indirect relationship with fibrinogen whereas insulin resistance itself represents the pathogenic factor of hyperfibrinogenemia [39]. This hypothesis is consistent with previous literature which showed that insulin itself does not directly stimulate fibrinogen synthesis in cell cultures or regulate fibrinolysis [40,41]. The proposed mechanism of how hyperfibrinogenemia relates to insulin resistance continues to be debated. Some reports postulate that the release of free fatty acids in a state of insulin resistance and T2DM stimulates synthesis of fibrinogen by hepatocytes [42]. Other literature cites TNF-α, a contributor to the pro-inflammatory state of insulin resistance, as the mechanism behind increased hepatic fibrinogen synthesis.

MetS is associated with both hemostasis activation and chronic inflammation. The combination of hypercoagulability, impaired fibrinolysis, and inflammation is believed to heighten potential for thrombosis, ultimately increasing the risk of MetS and insulin resistance

leading to ASCVD. Multiple studies have investigated the relationship between fibrinogen and MetS. One cross-sectional study examined this association in a subset of 1252 non-diabetic males. Imperatore et al. found that age-adjusted fibrinogen levels directly correlated with systolic and diastolic blood pressure, waist-to-hip ratio, BMI, LDL-cholesterol, triglycerides, and insulin. Individuals with MetS also had significantly higher levels of serum fibrinogen compared to their counterparts ($p = 0.0001$). Notably, there was a progressive increase in serum fibrinogen with increasing number of MetS features ($p = 0.0001$). Multivariate analysis showed a significant correlation between fibrinogen, plasma insulin, and MetS [39]. Another study investigating the role of plasma fibrinogen in predicting MetS found conflicting results in a group of Turkish adults. Median fibrinogen concentrations were found to predict newly developing MetS in male subjects (RR 1.32 [95%CI 0.95; 1.83); however, MetS was not significantly predicted by fibrinogen levels in female subjects [43].

In a study examining the association between fibrinogen and MetS in a rural Chinese population, Ma et al. similarly noted an increase in adjusted mean fibrinogen levels with increasing features of MetS. Fibrinogen correlated positively with age, waist to hip ratio, SBP, DBP, triglycerides, and total cholesterol. Significantly higher mean fibrinogen levels were present in individuals with MetS compared to individuals without MetS ($p < 0.001$). This study observed sex differences in fibrinogen and several metabolic features, notably in the waist-to-hip ratio [44]. Likewise, in a study examining gender differences in obesity-related ASCVD in a weight loss program, it was postulated that body fat distribution is a more robust risk factor in obese female patients compared to their male counterparts, which could be due to the higher rate of subcutaneous fat deposition with increasing weight in females.

Cumulatively, these findings suggest that the hyperfibrinogenemia linked to MetS may partially account for the association between insulin resistance and heightened risk of ASCVD. Additionally, inflammatory processes have long been affiliated with plaque rupture and thrombosis; thus, with plasma fibrinogen emerging as a possible new ASCVD risk factor, novel targets for therapy may be devised with further studies on this subject. Germane to this review is the fact that fibrinogen can easily be assayed by standardized automated techniques in clinical laboratories e.g. the clotting assay and has the issues associated with other acute phase reactants.

3.3. Serum amyloid A

Serum amyloid A (SAA) is an acute phase protein released primarily by the liver in response to proinflammatory cytokines including IL-6, TNF, interferon-γ, and transforming growth factor. Plasma levels of acute-phase SAA (SAA) rise drastically in response to acute inflammation and injury, reaching up to 1000 fold the norm in just 5–6 h. Previous investigations have shown that SAA is a potent stimulator for the production and secretion of TNF-α, IL-6, and IL-8 in neutrophils as well as inflammatory cytokines in coronary artery endothelial cells [45]. Although the liver is the primary source of circulating SAA, increased extrahepatic synthesis has been observed in patients with obesity, insulin resistance, atherosclerosis, MetS, and T2DM [46]. Published studies suggest that the low-grade chronic inflammation associated with obesity plays an integral role in the development of MetS and inducible isoforms SAA1 and SAA2 are higher especially in SAT [2] and may be implicated in this process. We have reported increased circulating and SAT secreted SAA in patients with MetS [7]. SAA is a pro-inflammatory adipokine which is expressed in adipocytes. Thus, it is not surprising that obese individuals who naturally have more adipocytes also have higher levels of serum SAA. Interestingly, studies have also found that the average adipocytes from obese individuals secrete higher levels of SAA compared to adipocytes from lean individuals. This observation is significant in that increased adipocyte expression of SAA indicates a potential link between local and systemic inflammation, obesity, and its comorbidities including atherosclerosis and insulin resistance. Several mechanisms have been proposed to better characterize SAA's role as a direct mediator of obesity-associated inflammation and its metabolic consequences. These include upregulation of lipolysis resulting in increased circulating free fatty acids, down-regulation of adiponectin expression, and impaired uptake of glucose by muscle and liver [45]. It is important to note that this is a difficult protein to assay and is not available in clinical laboratories but only in the research setting.

4. Macrophage/monocyte function

MetS can be characterized by monocytes and tissue macrophages that are activated into the proinflammatory phenotype. This novel observation was first made by Natal et al. who demonstrated that monocyte CD40 expression was elevated along with increased interaction with CD40L in MetS patients compared to controls [47]. This CD40L mediated activation of monocytes increases downstream production of inflammatory cytokines such as IL-1 and IL-6 as well as matrix metalloproteinases, cyclooxygenase-2, and tissue factor [48] [49]. The increased interaction between monocyte CD40 and CD40L is thought to play a role in atherosclerosis and subsequent ASCVD as well as worsening insulin resistance [50,51].

Another crucial receptor pathway in monocytes are the Toll-Like Receptors (TLRs). TLRs are found on the surface of macrophages and endosomes and are traditionally activated by pattern-associated molecular pattern (PAMP)s characteristic of microbes, with endotoxin, also known as lipopolysaccharide, being the most well-known of these PAMPs. This leads to downstream signally and translocation of the transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) to the nucleus, resulting in increased transcription of effectors of inflammation and an appropriate immune response to an agonist. This response is co-opted in MetS via upregulation of TLRs, leading to an erroneous inflammatory response. In a 2012 study of 49 patients with nascent MetS vs. 41 controls, Jialal et al. demonstrated significant increases in TLR2 and TLR4 surface expression in the MetS group. This difference remained after correction for waist circumference, implying some inherent differences in the inflammatory profile in MetS independent of adiposity. Additionally, they demonstrated increased NF-κB nuclear binding and increased IL-1β, IL-6, and IL-8. Though both TLR2 and TLR4 correlated with multiple markers of inflammation, only TLR4 significantly correlated with Homeostatic model assessment (HOMA)-IR ($r = 0.26$, $p = 0.020$), suggesting that TLR4 is playing a more prominent role in insulin resistance [52]. Hardy et al. confirmed the major finding of this study in 2013, demonstrating that TLR2 and TLR4 were significantly elevated in nine adolescents with MetS compared to eight BMI-matched controls [53].

Though TLRs are upregulated in MetS even when corrected for waist circumference and in the absence of ASCVD and T2DM, research also suggests that TLRs are activated as a downstream consequence of increasing adiposity. Increased adipose tissue leads to increases in saturated fatty acids that act to directly activate resident tissue macrophages into a persistent M1 inflammatory state by acting as ligands for TLRs [54]. Additionally, obesity may induce changes in the gut microbiota that enhance gut permeability [55] leading to increased absorption of endotoxin, also known as lipopolysaccharide, the primary ligand of TLR4, and observed endotoxemia. Endotoxemia in MetS was first reported by Nakagomi et al. in 2010, where it was observed that Japanese patients with MetS had elevated endotoxin levels compared to controls [56]. In the aforementioned Jialal et al. study of TLRs, endotoxin was also shown to be significantly increased in the MetS patients ($p < 0.001$) and also associated with increased TLR4 ($r = 0.53$, $p < 0.001$), but not TLR2. Free-fatty acids were also increased and correlated with TLRs, supporting the aforementioned theory that saturated fatty acids activate monocytes [52]. In 2014, Chen and Devaraj similarly observed significantly increased endotoxin and free fatty acids

in a group of 15 MetS patients vs. controls [57]. In a 2019 study of 123 hemodialysis patients, Lim et al. found that patients with higher levels of lipopolysaccharide-binding protein,an accessory protein of endotoxin,were more likely to have metabolic syndrome and had higher levels of hsCRP and IL-6 [58].

Monocytic chemokine receptor (CCR)-5 expression is also increased in MetS patients and is thought to further potentiate the inflammatory response. The ligands of CCR5 include eotaxin-1 and macrophage inflammatory protein-1β (MIP-1β), and their action on CCR5 leads to increased production of chemoattractants, including MCP-1. In a study of MetS patients vs. lean controls, Loughrey et al. observed a twofold increase in CCR5 expression in the MetS group in addition to elevated eotaxin-1, MIP-1β, and MCP-1. Though this result indicates macrophage activation via CCR5 in MetS, they did not show increased MCP-1 production from the monocyte itself [59]. Khan et al. also found that CCR5 was increased in MetS patients vs. healthy controls. However, the increase was not statistically significant [60], casting some doubt on the role of CCR5 in MetS inflammation and necessitating future studies.

With regards to monocyte chemotaxis, the role of different chemoattractants must be explored. Chemokines are a cluster of small, highly conserved chemotactic cytokines which recruit leukocytes to areas of inflammation and upregulate production and secretion of inflammatory cytokines via specific G protein-coupled receptors [61]. Increased adipose tissue macrophage (ATM) recruitment via chemokine signals have been hypothesized to enhance the inflammatory activity in obese adipose tissue. ATMs serve as a vital source of pro-inflammatory cytokines, including TNF and IL-6 that oppose the action of insulin in adipocytes and contribute to systemic insulin resistance. Studies show that the interaction between MCP-1 (CCL2) and its receptor CCR2 plays a role in the pathogenesis of obesity-induced insulin resistance. Mice which overexpress MCP-1 have increased infiltration of ATMs into adipose tissue and a higher degree of insulin resistance ($p < 0.05$) [62]. Mice with targeted deletion in genes coding for MCP-1 and its receptor CCR2 were found to have decreased ATM content, decreased inflammation in fat, and improved systemic glucose homeostasis and insulin sensitivity ($p < 0.01$) [63]. However, research is less clear in human studies. In a 2013 study of 45 nascent MetS patients vs. 30 controls, Bremer and Jialal observed that the MetS group had significantly increased MCP-1 in subcutaneous adipose tissue, which also correlated with hsCRP ($r = 0.46, p = 0.03$) [64]. In a 2016 study of 240 young adults, increased levels of MCP-1 were correlated with central obesity and was increased in individuals with 2 or more components of MetS [65]. Conversely, a 2017 study by Pahwa et al. of a predominantly middle-aged female population ($n = 58$) with nascent MetS showed no significant difference in MCP-1 levels between the control and MetS group [66].

CCL2/MCP-1, is known to be an important chemoattractant for macrophages in multiple inflammatory models [67]. In obese states, serum and adipose tissue CCL2 levels are significantly elevated and its ability to recruit ATMs has been proposed to contribute to insulin resistance and development of T2DM in the setting of obesity. The precise role of chemokines in insulin resistance is complex however, as recent investigations have suggested confounding trends. One study predicted that chemokine ligand (CCL)-2 deficient mice would have decreased macrophage content compared with wild-type mice. However, CCL2 deficient mice had no significant reduction in ATM levels even though they had mildly increased plasma glucose, decreased serum adiponectin, and were hyperinsulinemic on high-fat diets compared to wild-type mice ($p < 0.05$). This suggests that CCL2's role in altering metabolic function may be independent of ATM. Further studies are required to acquire a deeper understanding of how chemokines interact with inflammatory cells in the pathogenesis of obesity, inflammation, insulin resistance, and MetS.

IL-6 is another cytokine implicated in the recruitment of macrophages in adipose tissue. In a 2016 study of mice on a high fat diet, blocking the soluble IL-6 receptor reduced accumulation of macrophages into adipose tissue [68]. IL-8 is also expressed by macrophages and adipocytes and exerts chemotactic and proinflammatory effects. In a self-sustaining cycle, IL-8 increases expression of its own mRNA in adipocytes, leading to persistent inflammation and macrophage infiltration [5]. In support of this relationship, we recently observed that IL-8 was increased in nascent MetS compared to controls and also positively correlated with TLR4 [52].

Once activated and embedded in tissue, macrophages induce inflammation via their own secreted mediators, which can lead to adverse cardiovascular events and increased insulin resistance. IL-6 is secreted by M1 macrophages which in turn increases CRP, leading to increased risk of cardiovascular events. While IL-6 and CRP is increased in MetS with ASCVD [36], it's also increased in MetS without ASCVD, suggesting that inflammation is causal in the disease process and that IL-6 plays an important role [17,66]. Additionally, IL-6 is associated with increased insulin resistance in adipocytes and hepatocytes [69,70]. IL-6, along with TNF-α, act to increase insulin resistance via activation of the MAPK and protein kinase C pathways as well as degradation of insulin receptor substrate (IRS)-1 [71]. Though increased levels of TNF-α correspond with increasing adiposity [72] and heightened TNF-α has been observed in other MetS studies [6,73], TNF-α was not significantly increased compared to controls in nascent MetS and was not significantly correlated with HOMA-IR, which casts doubt on its pathogenic role in MetS [52].

IL-1β is another major cytokine secreted by macrophages. In our study on nascent MetS, we observed elevations in IL-1β, but without a significant relationship to HOMA-IR, HDL, or TG [17]. Interestingly, a recent study of metabolic syndrome in obese school children showed increased levels of IL-1β, TNF-α, and IL-6, but there was no significant difference between levels in obese children with MetS compared to obese children without MetS [74]. These findings suggest that increases in inflammatory markers may be driven by adipose tissue more than circulating monocyte activity. Future studies of adults where BMI of controls is matched to a MetS group would be useful in parsing out the role of the monocyte in the subclinical inflammation inherent to the syndrome.

MetS is also associated with a state of increased oxidative stress leading to ASCVD and IR [6,52]. In a study of 56 MetS patients, 99 patients with 1–2 cardiovascular risk factors, and 28 healthy controls, mononuclear cell NADPH oxidase activity was increased in the MetS group and correlated with increased insulin ($p < 0.05$). Furthermore, oxidized (ox) LDL and nitrotyrosine, additional markers of oxidative stress, were also elevated in the MetS group. Though the MetS patients were not studied in a nascent state, they nonetheless had increased markers of oxidative stress compared to the group with cardiovascular risk factors [75]. The oxidative stress induced by monocytes needs to be further parsed out from that of the lymphocyte, but this study provides more evidence that monocytes are directly inducing oxidative damage. In support of this, Jialal et al.'s 2012 study of 43 patients with nascent MetS vs 33 controls showed increased release of superoxide from monocytes with increased oxLDL and nitrotyrosine. They also showed increase in monocyte NADPH oxidase activity evidenced by increase in p22phox and p47 phox and a decrease in a critical antioxidant defense nuclear factor erythroid 2-related factor 2 (Nrf-2) [76]. Additionally, Shim et, al observed decreased glutamate in the nascent MetS population, which inversely correlated with endotoxin and IL-6 [20]. This decrease may have been a result of increased gamma-Aminobutyric acid (GABA) production or glutamate being used as an alternate source of energy in the TCA cycle, however, the relationship with endotoxin and IL-6 may also indicate increased need for glutathione in response to monocyte-induced oxidative stress. The role of monocytes is MetS is often shrouded by similar activity performed concurrently by adipose tissue.

Endoplasmic reticulum stress along with activation of unfolding protein response has been associated with inflammatory disorders such as MetS, T2DM, and ASCVD [77]. For instance, in a study done by Sage

et al., mRNA of markers of endoplasmic reticulum stress response such as spliced X-box binding protein-1, glucose-related protein 78, and CCAAT-enhancer binding protein, C/EBP protein were significantly increased in leukocytes of patients with MetS compared to controls. Elevation in these endoplasmic reticulum stress response markers was found to correlate with impaired glucose tolerance. In fact, the endoplasmic reticulum stress response could be reproduced by incubating isolated healthy leukocytes in media that contained 15 mmol/1 glucose with insulin. Postprandial hyperglycemia with glucose-induced endoplasmic reticulum (ER) stress may play a significant role in inducing proinflammatory gene expression. In light of this, ER stress must be considered as a significant factor in the pathogenesis of MetS and may help explain the increased monocyte inflammatory response in particular [78].

5. Role of PMNs in MetS

Despite their key role in mediating inflammation, neutrophils have received little attention in regard to MetS. Researchers have found that MetS is associated with alterations in hematopoietic progenitors. As neutrophils predominate during early stages of inflammation, they lead to a significant cascade of events such as tissue infiltration by macrophages. In a study that induced MetS in rats after 6 to 12 weeks of a high fructose diet, significant neutrophil infiltration into intra-abdominal tissue was observed compared to control groups. Neutrophils are thought to be primed, leading to changes in surface receptors on adipose tissue in the early stages of MetS, which leads to subsequent infiltration of adipocyte tissue. These priming events include nicotinamide adenine dinucleotide phosphate (NADPH) oxidase phosphorylation, G protein reorganization, and Phospholipase A2 activation. Facilitation of adipocyte tissue infiltration is mediated by other events such as interaction between CD11b receptor on neutrophils and ICAM on adipocytes. Ultimately, neutrophils may promote the clinical manifestations of MetS by increasing blood pressure and promoting insulin resistance [79]. Insulin resistance is mediated by neutrophil elastase through IRS-1 degradation and inhibition of insulin-stimulated AKT phosphorylation in hepatocytes and adipocytes [80]. Hyperglycemia has even been shown to reduce apoptosis of neutrophils [81]. Increased leptin levels in MetS are also thought to enhance reactive oxidative species production by neutrophils [79].

As these significant biochemical and immunologic effects of neutrophils in mediating inflammation have been theorized, multiple studies have demonstrated the increased presence of neutrophils in MetS. For instance, Kaur et al. illustrated significantly elevated WBC counts in patients with MetS compared to controls after adjustment for age, sex, BMI, and waist circumference ($P = 0.01$). More importantly, they showed that monocyte and lymphocyte counts did not differ significantly between patients with MetS and controls. This illustrated that increased neutrophil counts significantly contributed to these increased WBC counts. There was also a significant positive correlation between neutrophil counts with HOMA-IR ($r = 0.29$, $p = 0.004$) and hsCRP ($r = 0.35$, $p = 0.0004$). Total WBC counts correlated positively with HOMA-IR and hsCRP ($p = 0.03$, $p = 0.0014$). Additionally, there was also a positive correlation between PMNs and Nitrotyrosine, a marker of oxidative stress. A significant positive association was seen between overall WBC count and Nitrotyrosine ($r = 0.32$, $p = 0.06$) [82].

As the role of the neutrophil in MetS has become better appreciated, the Neutrophil to Lymphocyte ratio, NLR, has also emerged as a potential biomarker for grading the severity of MetS. Buyukkaya et al. divided patients with MetS into 3 groups: 3 criteria of MetS satisfied (group 1), 4 criteria of MetS satisfied (group 2), and 5 criteria of MetS satisfied (group 3). Patients with MetS had a significantly higher NLR compared to the controls. Interestingly, group 3 patients had a higher NLR compared to patients who met group 1 and group 2 criteria ($p = 0.008$ and $p = 0.078$ respectively). Overall, there is a direct association between NLR and the severity of MetS ($r = 0.586$, $P < 0.01$). The NLR also correlated with mediators of inflammation such as hs-CRP ($r = 0.388$, $p < 0.001$), suggesting that NLR can be used to grade inflammatory levels in MetS [83]. In another study conducted in Asian Indians with MetS, subjects with five metabolic abnormalities were found to have the highest NLR. Moreover, NLR decreased linearly with decreasing numbers of metabolic abnormalities in these patients with MetS ($P < 0.0001$) [84]. Similar to its predictive role in grading severity of MetS, NLR has also demonstrated its utility as a prognostic marker for different grades of glucose tolerance and insulin resistance among patients with impaired glucose tolerance and T2DM [85]. A significant positive correlation was found between NLR and glycated hemoglobin ($r = 0.411$, $P < 0.001$), fasting plasma glucose ($r = 0.378$, $P < 0.001$), and HOMA-IR ($r = 0.233$, $P < 0.001$). Of note, a high NLR has even been associated with atherosclerotic events and is of prognostic importance in ASCVD. Admission NLR has been shown to be an important predictor of in-hospital and 6 month mortality in patients suffering from acute coronary syndrome [86]. While the NLR has demonstrated its utility as a predictive marker in the spectrum of diseases ranging from MetS to atherosclerotic events some studies have failed to confirm its utility and much further research is needed in exploring the utility of NLR in studies excluding confounders.

The significance of neutrophils extends beyond isolated MetS. It has been shown to be associated with the many concomitant diseases that can presage, accompany, or follow MetS. For instance, the NLR has emerged as a tool that can identify MetS in patients with chronic obstructive pulmonary disease (COPD). Chronic systemic inflammatory syndrome has emerged as the etiology responsible for mediating the inflammation common to COPD and frequently accompanies diseases such as MetS and chronic heart failure. COPD and MetS are both regarded as diseases that are mediated through the same pathophysiological mechanism of bronchial and systemic inflammation. Yasar et al. explored the utility of the NLR in predicting MetS in patients with COPD, and 45% of patients with COPD were found to have MetS. Moreover, NLR values were significantly higher in stable COPD patients with MetS compared to stable COPD patients without MetS ($p < 0.001$). NLR in patients with both stable COPD and MetS correlated negatively with forced expiratory volume in one minute (FEV1) (R = -0.043, $p < 0.0002$) and positively with severity of dyspnea ($R = 0.0631$, $p < 0.001$). An NLR cutoff score of 2.56 mg/L emerged as a differentiator between patients with stable COPD who did and did not meet criteria for MetS [87]. NLR has also illustrated its utility in predicting onset of colorectal adenomatous polyps in patients with MetS. Because of its highly inflammatory nature, MetS has been linked to colorectal adenoma. In a study done Kim et al., patients with MetS were found to have significantly higher prevalence of colorectal adenoma ($P = 0.032$). They also found that a NLR ratio equal to or > 2.0 was an independent factor that significantly increased risk of colorectal adenoma in patients with MetS. Moreover, the NLR was found to be higher in MetS patients with tubular adenoma, villous adenoma, and tubulovillous adenoma compared to those with non-neoplastic polyps [88]. NLR could serve as a valuable tool that can monitor progression of an colorectal adenoma to carcinoma in patients with MetS and ultimately differentiate between neoplastic polyps versus non-neoplastic polyps.

6. Metabolomics and inflammation in MetS

Multiple investigations have established a connection between inflammation and changes in metabolites including amines, amino acids, and lipids in the setting of MetS. Recent studies have further elucidated the role of these metabolites in the development, screening, and treatment of MetS as well as their contribution to the chronic, low-grade inflammatory state in MetS [17]. Lent-Schochet et al. found that increased levels of biogenic amines such as choline, L-carnitine, and trimethylamine-N-oxide were associated with inflammatory pathways and increased the risk of metabolic dysfunction [17]. Literature has also

Table 2
Notable biomarkers of metabolic syndrome.

Biomarker	Function	Status in MetS
Adiponectin	Promotes fatty acid oxidation and insulin sensitization.	May have a protective role. Decreased in patients with MetS.
Leptin	Induces satiety and facilitates energy expenditure. Improves insulin sensitivity in liver and regulates beta cell function. Increases cytokine production and T cell proliferation.	Increased independent of adiposity in MetS. Correlated positively with pro-inflammatory amino acids and lipids such as L-Carnitine, Isoleucine, and Phosphatidylcholine 34:2.
PAI-1	An inhibitor of fibrinolysis synthesized in adipocytes and stromal vascular cells	PA1-1 that is circulating and secreted by SAT is increased in MetS. Increased levels are found when adipocytes are stimulated by TNF-α, which is involved in MetS inflammatory pathways
CRP	Promotes release of proinflammatory cytokines in the inflammatory response.	Independent predictor of T2DM and atherosclerotic events in MetS.
Fibrinogen	Mediates the final step of the coagulation cascade. Plays a significant role in inflammation, atherogenesis, and thrombogenesis. Ligand for ICAM-1.	Higher levels in correlation with increased features of MetS. Correlates negatively with insulin sensitivity.
SAA	Acute phase protein predominantly released by liver in response to pro-inflammatory cytokines.	Increased extrahepatic synthesis seen in patients with MetS. Increased secretion of SAA by adipocytes in obese individuals.
NLR	Neutrophils mediate early stages of inflammation in MetS and involved in pathogenesis of insulin resistance and generation of ROS.	Neutrophil counts predominantly responsible for increased WBC count in patients with MetS. Increased value correlates with higher severity of MetS. Higher values associated with diseases linked to MetS such as COPD and colorectal adenoma.
IL-1	Major cytokine secreted by macrophages that mediates inflammation, cell proliferation, cell differentiation, and cell apoptosis	Elevated in patients with MetS, but without significant relationship to HOMA-IR, HDL, or triglycerides.
IL-6	Secreted by macrophages and increases production of CRP.	Increased in both MetS patients with and without ASCVD. Associated with increased insulin resistance in adipocytes and hepatocytes.

linked branched chain amino acids including isoleucine, leucine, and valine with prominent inflammatory markers and cardiometabolic features of MetS. Reddy et al. observed that increased levels of isoleucine and tyrosine and decreased levels of lysine and methionine appear to be early biomarkers of nascent MetS and significant contributors to the pro-inflammatory burden of MetS. Low levels of lysine, in particular, were associated with increased inflammation and elevated blood glucose. Thus, increased dietary lysine may promote anti-inflammatory effects [19]. In a recent investigation, Ramakrishnan et al. explored the role of the lipidome in nascent MetS and showed that phosphatidylcholine 34:2, PC (34:2) was significantly increased in nascent MetS and correlated positively with certain inflammatory parameters. Thus, PC (34:2) is also emerging as a potential early biomarker in MetS that promotes inflammatory processes [18]. In a recent report centered on exploratory metabolomics in MetS, Shim et al. discovered significantly increased levels of GABA ($p < 0.0001$) and d-pyroglutamic acid (PGA) ($p = 0.004$) in MetS patients compared to controls with direct correlation to inflammatory biomarkers. This review also found that *N*-acetyl-d-tryptophan (NAT) decreased by 90% in MetS patients compared to controls ($p < 0.001$) and was inversely correlated with inflammatory biomarkers [20]. More extensive analysis of these particular metabolites will improve our understanding of the pro-inflammatory state of MetS as well as its pathogenesis and potential treatments.

7. Conclusion

As the incidence of MetS continues to rise globally little is still understood in regard to its pathogenesis and treatment. Despite this dearth of information, multiple studies have identified MetS as a condition driven by inflammation. More specifically, a variety of biomarkers/biomediators, and cell types have emerged as significant mediators of this inflammation. It is critical to explore and characterize the major players and pathways of the inflammatory cascade in MetS to make significant strides in elucidating this disease. In this review we present cogent data on the role of adipose tissye and phagocytes as cococonspirators in fueling a pro-inflammatory phenotype allowing us to support our thesis that Met S is an Inflammatory state. In Table 2 we have summarized what we believe the most relevant biomarkers.

Whilst we review a wide repertoire of biomarkers, most do not fulfil the scrutiny to advance beyond the research laboratory based on poor standardization, calibration, and precision. Thus, in addition to the lipid profile and plasma glucose (HBA1C), we submit that the complete blood count including the NLR, hsCRP and fibrinogen have the greatest clinical utility to inform health care providers about MetS and its complications.

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Conflict of interests

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