CHAPTER TWO

# New markers in metabolic syndrome

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## Abstract

Metabolic syndrome (MetS) is increasing globally and is clinically significant due to its association with cardiovascular disease, type 2 diabetes and cancer. Although the pathogenesis of MetS has not been clearly elucidated, insulin resistance and chronic low-grade inflammation derived from central obesity are the most widely accepted as underlying pathophysiology. Accordingly, insulin resistance indices, adipokines and various inflammatory markers have been suggested as reliable biomarkers for MetS. Others, such as uric acid, alkaline phosphatase, γ-glutamyl transferase, are also known to positively correlate with MetS and could be diagnostically useful. In this review, we provide a comprehensive overview of MetS biomarkers and the development of a systematic approach to laboratory analysis.

## 1. Introduction

Metabolic syndrome (MetS), also known as syndrome X, insulin resistance syndrome, and Reaven syndrome, is a cluster of clinical and metabolic abnormalities, including abdominal obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia. MetS is defined slightly differently by various organizations. Three popular definitions used in the literature and clinical settings are shown (Table 1). The clinical importance of MetS has emerged since it was first described. As the prevalence of obesity increases globally, MetS also increases, leading to increased risk of cardiovascular disease (CVD) and premature mortality. According to the US Centers for Disease Control and Prevention (CDC), more than one in three adults have MetS [1]. Most people with MetS are asymptomatic, but they have a 10-year risk of a first coronary event of 16% to 18% according to the Framingham Risk Score [2]. MetS increases the risk of CVD by 5 fold and of type 2 diabetes mellitus (T2DM) by 2 fold [3]. In addition to CVD and T2DM, patients with MetS are more susceptible than others to diseases such as non-alcoholic fatty liver disease, polycystic ovary syndrome, sleep disturbances, and cancer [4,5].

Although the exact pathophysiology of MetS remains unclear, emerging evidence indicates that insulin resistance and chronic low-grade inflammation induced by excess adipose tissue play a main role in its development and progression [6]. Some research suggests that the systemic oxidative stress caused by central obesity is also involved in the pathophysiology of MetS [7–9].

Biomarkers can be a useful aid in diagnosing many pathological conditions that have no obvious clinical signs or anatomical abnormalities. This chapter provides an overview of biomarkers for MetS to offer a systematic approach to laboratory findings for the disease.

**Table 1** Definitions of metabolic syndrome.

| | NCEP ATP III | IDF | WHO |
|---|---|---|---|
| Criteria | Any 3 of the 5 criteria | Obesity + any 2 criteria | Impaired fasting glucose + any 2 criteria |
| (1) Obesity | WC:<br>≥102 cm (M)<br>≥88 cm (F) | WC:<br>≥94 cm (M)<br>≥80 cm (F) | Waist/hip ratio:<br>>0.90 (M) >0.85 (F)<br>or BMI > 30 kg/m$^2$ |
| (2) Serum fasting glucose | Fasting glucose:<br>≥100 mg/dL | Fasting glucose:<br>≥100 mg/dL<br>Or<br>Previously diagnosed T2DM | Fasting glucose:<br>≥110 mg/dL |
| (3) Serum triglycerides | TG:<br>≥150 mg/dL<br>Or<br>Rx | TG:<br>≥150 mg/dL<br>Or<br>Rx | TG:<br>≥150 mg/dL |
| (4) Serum HDL cholesterol | HDL:<br><40 mg/dL (M)<br><50 mg/dL (F)<br>Or<br>Rx | HDL:<br><40 mg/dL (M)<br><50 mg/dL (F)<br>Or<br>Rx | HDL:<br><35 mg/dL (M)<br><39 mg/dL (F)<br>Or<br>Rx |
| (5) Hypertension | SBP:<br>>130 mmHg<br>DBP:<br>>85 mmHg<br>Or<br>Rx | SBP:<br>>130 mmHg<br>DBP:<br>>85 mmHg<br>Or<br>Rx | SBP:<br>≥140<br>DBP:<br>≥90 mmHg |
| (6) Other criteria | | | Microalbuminuria |

NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel III; IDF, International Diabetes Federation; WHO, World Health Organization; WC, waist circumference; M, men; F, women; TG, triglyceride; T2DM, type 2 diabetes mellitus; HDL, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; Rx, remedy.

## 2. Epidemiology

The exact prevalence of MetS worldwide is not known because it differs depending on the diagnostic criteria used and geographic and sociodemographic factors. However, epidemiologic studies in various countries have similarly shown that the incidence and prevalence of MetS have

increased in recent years. The incidence of MetS tends to parallel the incidence of T2DM and obesity [10]. The CDC has reported that about 30.2 million (12.2%) adults have T2DM, and the prevalence of MetS is about three times higher than T2DM [1]. Because MetS prevalence is 3-fold that of T2DM, the global prevalence of MetS can be estimated to be about a quarter of the world population [10]. According to National Health and Nutrition Examination Survey data from the United States and using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria, 35% of adults and 50% of those older than 60 years have MetS [11]. Using the International Diabetes Federation (IDF) criteria, the prevalence of MetS in Europe has been estimated to be 41% in males and 38% in females [12]. A report from Middle Eastern epidemiological data using the ATP III criteria found MetS prevalence to be 20.7–37.2% in males and 32.1–42.7% in females [13]. In China, the prevalence of MetS was estimated to be 15.4% in 2017 [14].

## 3. Pathogenesis

The pathogenesis of MetS has not been elucidated, but several mechanisms have been hypothesized. The most plausible hypothesis for MetS pathophysiology is insulin resistance (aided by fatty-acid excess) as a consequence of inappropriate lipolysis [8]. Visceral fat accumulation has been identified as a key factor in initiation of MetS through insulin resistance and chronic low-grade inflammation. In 1988, Reaven introduced that insulin resistance is the underlying cause of MetS [15]. Since then, many studies have shown that hyperinsulinemia is associated with development of MetS, even after adjusting for baseline obesity, fat distribution, and other confounding factors [16,17]. Insulin, which is secreted from islet of Langerhans β-cells, binds to insulin receptors (IRs) in the liver, skeletal muscle, adipose tissue, and endothelial cells. The IRs, heterotetrametric transmembrane glycoproteins composed of α and β subunits [18], are autophosphorylated when insulin binds to it, recruiting and phosphorylating insulin receptor substrate-1 (IRS-1). Phosphorylated IRS activates the phosphatidylinositol-3-kinase (PI3K)/Akt (also known as the protein kinase B, PKB) pathway through several stages of signaling. Under physiological conditions, the activated PI3K/Akt pathway plays a significant role in the insulin signaling cascade by translocating glucose transporter 4 (GLUT4) to the cell membrane. The activated Akt pathway ultimately induces glycogen, lipid, and protein synthesis and inhibits gluconeogenesis in hepatocytes

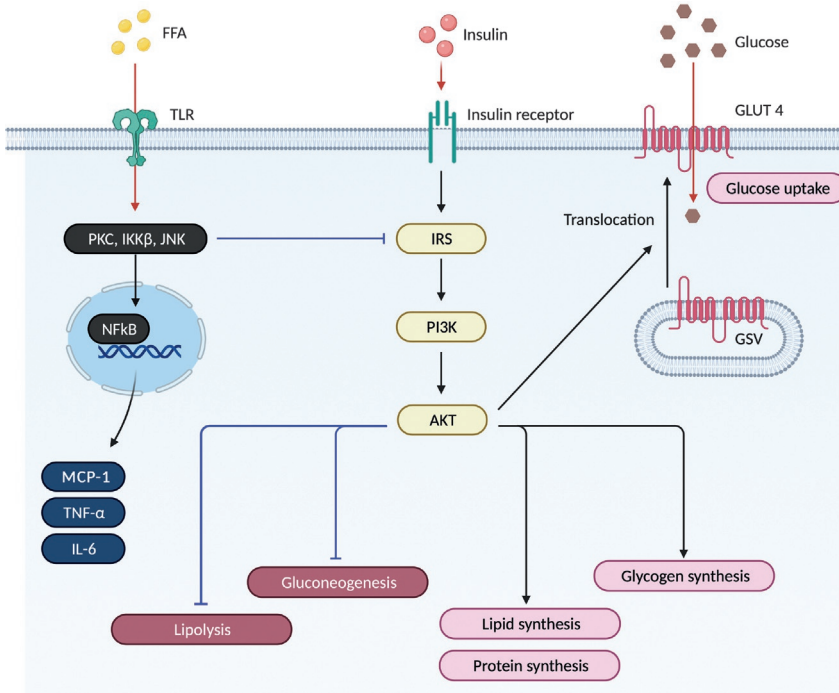


**Fig. 1** Insulin signaling pathway and the interactions of free-fatty acids. A black arrow is promotion or activation downstream, a red arrow is movement of substances, and a blue line represents inhibition. GLUT4, glucose transporter 4; GSV, glucose transporter 4 storage vesicle; IKKβ, Ik kinase; IL-6, interleukin-6; IRS, insulin receptor substrate; JNK, c-Jun N-terminal kinase; MCP-1, macrophage chemotactic protein 1; NF-κB, nuclear factor-kappa B; PI3K, phosphatidylinositol-3-kinase; PKB, protein kinase B; PKC, protein kinase C; TLRs, toll-like receptors; TNF-α, tumor necrosis-alpha. This image was created using BioRender (http://biorender.com/).

and lipolysis in adipocytes [19,20]. Elevated lipid accumulation in skeletal muscle seems to reduce tyrosine phosphorylation, inhibiting the subsequent activation of PI3K. In addition, glucose uptake is promoted by activation of translocation of the GLUT4 storage vesicle to the cell membrane via the PI3K/Akt pathway. Reduced Akt activation driven by acyl-CoA derivatives can contribute to insulin resistance by reducing the translocation of GLUT4 and glycogen synthesis [8] (Fig. 1).

An accumulation of visceral fat leads to the release of non-esterified free-fatty acids from adipose tissue [21]. The elevated levels of free-fatty acids impair the insulin-mediated inhibition of lipolysis, causing more free-fatty acids to be released [21]. Free-fatty acids also inhibit insulin-dependent

glucose uptake in skeletal muscle and increase the production of glucose and triglycerides in the liver, producing insulin resistance [22]. Activated toll-like receptors (TLRs) mediated by elevated free-fatty acids induce the downstream activation of protein kinase C (PKC), Ik kinase (IKKβ), and c-Jun N-terminal kinase (JNK), which produces insulin resistance by inhibiting IRS [19]. Nuclear factor-kappa B (NF-κB) is also activated through those pathways, inducing pro-inflammatory status through transcription of macrophage chemotactic protein 1 (MCP-1), interleukin-6 (IL-6), tumor necrosis-α (TNF-α), and cell adhesion molecules.

Increased visceral adipose tissue, mediated by environmental and genetic factors, plays a key role in development of MetS. Adipose tissue from obese individuals undergoes structural and cellular remodeling, such as adipocyte hyperplasia and hypertrophy [23]. An expanding adipocyte has impaired angiogenesis that results in development of local hypoxia. That phenomenon triggers cellular stress, cell necrosis, infiltration of macrophages, and chronic inflammation, which together lead to adipose tissue dysfunction [23]. Infiltrated macrophages in adipose tissue secrete inflammatory cytokines such as IL-6, TNF-α, and pro-thrombotic mediator plasminogen activator inhibitor-1 (PAI-1) [24]. Also, abrupt accumulation of visceral adipose tissue promotes lipolysis, which leads to an increase in the plasma level of free-fatty acids and a decrease in adiponectin secretion. The elevated free fatty acids induce insulin resistance in the liver and skeletal muscle by inhibiting glycogen synthesis and glucose uptake, which induces gluconeogenesis. Increased plasma glucose levels induce hyperinsulinemia, which contributes to endothelial dysfunction and insulin resistance. In the liver, inflammatory cytokines and plasma free fatty acids increase the production of glucose and triglycerides and the secretion of C-reactive protein (CRP), and very-low-density lipoprotein (VLDL). Lipid and lipoprotein abnormalities decrease the level of high-density lipoprotein (HDL) cholesterol and increase the level of low-density lipoprotein (LDL) cholesterol, resulting in dyslipidemia (Fig. 2).

Inflammation is another important hypothesis for understanding the pathophysiology of MetS. Inflammatory cytokines, such as IL-6 and TNF-α, secreted from adipocytes, play a significant role in aggravating insulin resistance and endothelial dysfunction, resulting in hypertension, atherosclerosis, and chronic inflammation. Inflammatory cytokines and reactive oxidative species (ROS) secreted by macrophages can raise blood pressure by triggering vascular endothelial dysfunction [25]. Several epidemiologic studies have demonstrated that IL-6 and TNF-α were

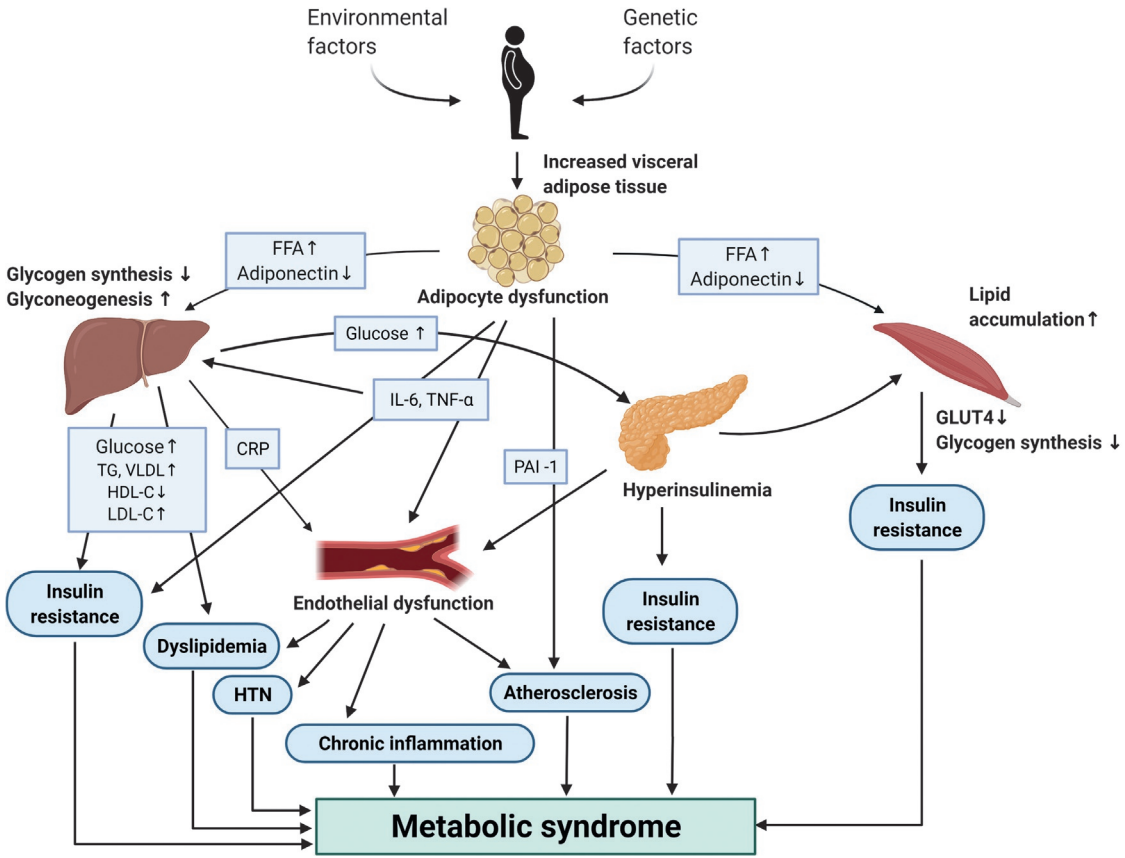


**Fig. 2** Pathophysiology of metabolic syndrome. CRP, C-reactive protein; FFA, free fatty acid; GLUT4, glucose transporter 4; HDL-C, high-density lipoprotein cholesterol; HTN, hypertension; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides; TNF- α, tumor necrosis factor-α; VLDL, very-low-density lipoprotein. This image was created using BioRender (http://biorender.com/).

elevated in patients with diabetes mellitus (DM), hypertension, atherosclerosis, and cardiovascular events [8].

MetS has been linked to many risk factors and numerous postulated pathophysiologic mechanisms, including insulin resistance, low-grade inflammation, and oxidative stress. Central obesity seems to link all those mechanisms together.

## 4. Insulin resistance biomarkers

Even though insulin resistance is one of the main factors known to potentiate the MetS pathway, no measurement of insulin resistance is included in the diagnostic criteria for MetS [26]. The gold standard measurement for assessing insulin resistance is the hyperinsulinemic-euglycemic clamp, but it has several limitations in terms of accessibility, reproducibility, and cost [27,28]. Therefore, many studies have tried to find alternative indicators of insulin resistance. The Homeostasis Model Assessment of IR (HOMA-IR), triglyceride to high density lipoprotein-cholesterol ratio (TG/HDL-C ratio), and triglycerides and glucose index (TyG index) are commonly used as alternative markers of insulin resistance.

### 4.1 Homeostasis model assessment of insulin resistance (HOMA-IR)

The HOMA-IR has been used widely as an indirect method for quantifying insulin resistance and pancreatic β-cell function. It was first developed in 1985 by Matthews et al. and is calculated using a timely assessment of fasting glucose and insulin concentration [29]. The HOMA-IR is defined as [fasting glucose (mmol/L) × fasting insulin (μmol/L)/22.5] or [fasting glucose (mg/dL) × fasting insulin (μmol/L)/405]. Several studies based on different geographical populations have been conducted to define cut-off values for the HOMA-IR [30–33] and they vary greatly according to the age, sex, ethnicity, and metabolic conditions of the populations studied [34]. Gayoso-Diz et al. found that its cut-off values were lower in diabetic individuals than in non-diabetic individuals (1.60 vs. 2.06 for MetS in Spanish male adults). Those cut-off levels are lower than reported in a study of healthy Italians, who had a value of 2.77 [35], in a non-diabetic Spanish population, which had a value of 3.8 [36], and in an Iranian population-based study using pooled data from males and females, which found a cut-off value of 1.77 [37]. In a systematic review of MetS studies in children and adolescents, the HOMA-IR cut-off point for avoiding MetS risk ranged from 2.30

to 3.59, and the diagnostic odds ratio ranged from 4.39 to 37.76 [38]. Although the threshold for HOMA-IR levels that define MetS depend on factors such as age, sex, ethnicity, and clinical conditions, most studies have found a higher prevalence of MetS in individuals with elevated HOMA-IR [32,34,35,37]. Therefore, HOMA-IR is a robust surrogate method for assessing MetS in clinical settings.

## 4.2 Triglyceride to high density lipoprotein-cholesterol ratio (TG/HDL-C ratio)

Both low HDL cholesterol and hypertriglyceridemia are components of MetS criteria. Hypertriglyceridemia, a component of atherogenic dyslipidemia, leads to a decrease in HDL cholesterol and an increase in LDL cholesterol, which is associated with a high risk of myocardial infarction [39]. On the contrary, HDL cholesterol has a protective effect against atherosclerosis by antagonizing oxidation, thrombosis, and inflammation and delivering excess cholesterol to the liver through reverse cholesterol transport [40]. Because the TG/HDL ratio correlates better with atherosclerotic lipid changes than individual lipid levels, it could be an effective tool in screening for MetS [41]. Previous studies have identified the TG/HDL ratio as a reliable marker of insulin resistance in various study populations [29,42]. A cut-off value of 3.0 mg/dL is commonly used for insulin resistance in overweight individuals [43].

The usefulness of the TG/HDL-C ratio for diagnosing MetS has been demonstrated in many previous studies. Krawczyk et al. showed that the TG/HDL-C ratio is a good surrogate for predicting MetS in obese children [29]. In that study, the TG/HDL-C ratio showed the largest area under the curve (AUC) for predicting MetS among all the other insulin resistance indicators tested. Shin et al. also found that the TG/HDL-C ratio was positively and independently associated with MetS in healthy Korean adults [44]. Furthermore, the TG/HDL ratio was a better marker than other lipid ratios, such as LDL-C/HDL-C and total cholesterol/HDL-C, for identifying MetS in an Iranian population [45]. On the other hand, some studies have found that although this ratio is a reliable marker for insulin resistance, its usefulness varies by sex and ethnicity [46–48]. For example, some studies showed that TG/HDL-C was not as useful a marker for predicting insulin resistance in African Americans as it was in Whites [48,49]. This suggests that different cut-off points for the TG/HDL ratio should be applied according to sex and ethnicity. Nevertheless, this ratio is a useful indicator of insulin resistance, MetS, and CVD in various populations. Even though waist

circumference (WC) is a component of MetS, it has been reported that only 6% of primary care physicians in Canada measure WC [50]. Because TG and HDL-C are measured routinely, allowing the TG/HDL-C ratio to be easily calculated, this ratio can be used widely in the clinical setting.

## 4.3 Triglycerides and glucose index (TyG index)

Because insulin testing is expensive and unavailable in most laboratories in undeveloped countries, an insulin-free surrogate for evaluating insulin resistance has been sought and developed. Recently, the TyG index, which uses triglycerides and fasting glucose levels, has been recommended as a useful marker for insulin resistance. The TyG index is determined using the following formula: ln [fasting triglyceride (mg/dL) × fasting glucose level (mg/dL)/2]. Simental-Mendia et al. compared the TyG index and HOMA-IR for assessing insulin resistance in apparently healthy adults and found that the TyG index could be a useful surrogate when diagnosing insulin resistance [51]. The insulin-resistance cut-off points for the TyG index varied depending on the study population, ranging from 4.43 to 4.78 [52]. Navarro-González et al. demonstrated that the TyG index is also more useful than fasting plasma glucose or triglyceride levels alone for the early detection of individuals at risk for T2DM [53]. Biomarkers of insulin resistance are also potential markers for MetS because insulin resistance is a main mechanism in MetS pathophysiology.

Li et al. showed that the TyG index correlated with MetS in middle-aged and elderly Chinese after adjusting for potential confounding factors such as age, sex, smoking status, daily drinking, and history of hypertension, DM, and previous stroke [54]. The adjusted odds ratios (95% CIs) of the TyG index used to predict MetS were 6.42 (95% CI, 4.61–8.93) in middle-aged and elderly Chinese. In addition, TyG values increased significantly as the number of MetS components increased in both sexes. Moon et al. analyzed the TyG index cut-off value for MetS in adolescents and the TyG index showed high accuracy in predicting MetS in both American and Korean adolescents, with an overall AUC above 0.85 [55].

The TyG index is less costly than other insulin-based markers and is easily accessible in the clinical setting, which are advantages for epidemiological studies. Although further studies are required to standardize and evaluate the capacity of the TyG index to diagnose MetS, it is an attractive indicator for MetS.

## 5. Cytokines and inflammation biomarkers

MetS is a pro-inflammatory and pro-thrombotic state, with central obesity playing a major role in its pathophysiology [56,57]. Expanded adipose tissue mass results in an increase in pro-inflammatory cytokines, such as IL-1,6, TNF-α, and the systemic biomarker CRP. Adipose tissue–derived macrophages appear to function as a main source of pro-inflammatory cytokines both locally and in the systemic circulation. Adipose tissue macrophages are classified into two main types, M1 (classically activated macrophages) and M2 (alternatively activated macrophages) [58]. M1 macrophages are induced by pro-inflammatory factors and secrete inflammatory cytokines, including IL-6, IL-1β, inducible NOS, and TNF-α [24].

### 5.1 Interleukin 6 (IL-6)

IL-6 is a pro-inflammatory cytokine produced by almost every nucleated cell in the body. It is often secreted by M1 macrophages and T cells to stimulate an immune response against infection and tissue injury [59]. Adipocyte dysfunction, which often accompanies MetS, is associated with an increased M1 macrophage population in adipose tissue. In MetS, IL-6 and other pro-inflammatory cytokines act through several cell-signaling pathways, such as mTOR and protein kinase C (PKC), leading to insulin resistance. In mice fed a high-fat diet, increased IL-6 induced hepatic insulin resistance by upregulating the suppressor of cytokine signaling 3, a protein that binds and inhibits the IR [60]. IL-6 is also involved in vascular dysfunction and atherosclerosis through endothelial cell damage.

Previous studies have demonstrated that increased IL-6 levels are associated with MetS and each of its components. Chedraui et al. reported that increased IL-6 was associated with central obesity, low HDL-C, and hypertriglyceridemia in postmenopausal women [61]. Increased IL-6 was found in Chinese adults with MetS independently of central obesity [62]. In a mouse model, insulin signaling was impaired after the administration of IL-6, resulting in hyperglycemia and insulin resistance [63]. Similarly, patients with MetS showed significantly higher serum IL-6 and TNF-α than the control group, suggesting that inflammation plays a key role in the pathogenesis of MetS [64]. On the contrary, Wannamethee et al. found that IL-6 was associated with central obesity and HDL-C, but they found no relationship to insulin resistance or other MetS components such as blood glucose,

triglycerides, or blood pressure in older males [65]. Overall, although the association between IL-6 and MetS is somewhat controversial, IL-6 has potential to be a biomarker for MetS.

## 5.2 Tumor necrosis factor alpha (TNF-α)

TNF-α is a pro-inflammatory cytokine that has various effects in the response to injury and infection, angiogenesis, apoptosis, and other physiological processes [66]. It was first observed in some cancer patients who survived bacterial infection and showed the surprising result of tumor regression [66]. TNF-α is expressed in adipose tissue, more in visceral than subcutaneous fat, and is derived from infiltrating macrophages [67]. Dysregulated adipocytes, which are often present in individuals with MetS, tend to secrete a high level of TNF-α and other pro-inflammatory adipokines. Increased TNF-α aberrantly activate the mTOR and PKC signaling pathway, leading to insulin resistance [59]. Several studies have shown that TNF-α induces the impairment of insulin signaling in hepatocytes and adipose tissue [68,69]. In obese rodents, the targeted deletion of TNF-α and its receptors improved insulin sensitivity and glucose tolerance [70]. Additionally, high levels of TNF-α and other pro-inflammatory cytokines were associated with insulin resistance and hypertriglyceridemia in middle-aged adults with MetS [71]. That study proposed that inflammatory markers such as TNF-α and IL-6 could be helpful in early monitoring and intervention for MetS and its comorbidities.

## 5.3 C-reactive protein (CRP)

CRP is an inflammatory protein produced primarily in liver hepatocytes but also found in other tissues such as macrophages, endothelial cells, adipocytes, and muscle cells [72]. CRP triggers the classical complement pathway of innate immunity after binding to polysaccharides on microorganisms [73]. Transcription of the CRP gene is induced by increased levels of inflammatory cytokines, especially IL-6 [74]. TNF-α also induces CRP secretion in the liver in a dose-dependent manner [75]. Conversely, increased CRP levels in atheroma induce IL-6 and TNF-α production by macrophages [76]. Since IL-6 and TNF-α are associated with adipocyte dysregulation in MetS, CRP is also involved in obesity-mediated inflammation. In this regard, CRP is increasingly used in cardiovascular risk assessment [77,78]. Increased CRP levels have also been shown to correlate with a high risk of DM and multiple components of MetS, including obesity,

insulin resistance, dyslipidemia, and high blood pressure [79,80]. Recent studies have suggested that high CRP levels contribute to the pathogenesis of MetS by damaging insulin signaling [81,82]. Xu et al. reported that recombinant CRP induces the phosphorylation of JNK and IRS-1 at the Ser306 site through a spleen tyrosine kinase and RhoA-activation signaling pathway, resulting in endothelial insulin resistance and dysfunction [82]. This mechanism is reported to impair insulin-stimulated glucose uptake, GLUT4 translocation, and glycogen synthesis mediated by the IRS-1/PI3K/Akt/glycogen synthase kinase 3 pathway [81]. Moreover, CRP induces endothelial dysfunction, which is well-known to be associated with each component of MetS [83]. CRP impairs endothelial vasoreactivity and decreases endothelial nitric oxide synthase 3 activity, leading to high blood pressure [84].

Studies have reported that patients with MetS showed higher CRP levels than controls [85–87]. Fröhlich et al. showed a positive correlation between CRP and MetS components, including triglycerides ($r=0.29$), glucose ($r=0.11$), and body mass index (BMI) ($r=0.32$) (all $P<0.0001$) [86]. In that study, CRP levels increased significantly with the number of MetS features. Furthermore, Ridker et al. proposed to add high-sensitivity CRP levels as a clinical criterion for MetS [88].

Although it is unclear whether the elevated CRP found in MetS patients is a causative factor, emerging laboratory and clinical evidence suggests that CRP is a good biomarker for MetS. Also, the addition of CRP to the present definition of MetS could be helpful in the early detection of patients with a high risk of future CVD and DM.

## 5.4 Complete blood count: White blood cell, platelets, hemoglobin, mean platelet volume

A complete blood count (CBC) is an inexpensive test routinely performed in clinical settings to evaluate overall health and detect a wide range of disorders, including infection, inflammation, anemia, and leukemia. The CBC test includes several components: red blood cells (RBCs), white blood cells (WBCs), hemoglobin (Hb), platelets, etc. Due to the accessibility and cost of the CBC, many investigators have worked to determine whether it can be used as a biomarker for MetS. As a result, numerous studies have shown that hematological parameters tested in the CBC do correlate with MetS and its components [89–91].

It is not surprising that the WBC count is associated with MetS, because WBCs themselves are a marker for inflammation. Neutrophils are known to

be involved in inducing obesity-related chronic inflammation and insulin resistance, mainly through elastase production [92]. Also, macrophages that secrete pro-inflammatory cytokines are one type of WBC that has been shown to be significantly activated in adipose tissue [93]. Interestingly, not only WBCs, but also other hematological parameters such as platelets [91], RBCs [89], Hb [94], and mean platelet volume (MPV) [95] all showed similar patterns. For example, Jesri et al. investigated the association between MetS and platelet and WBC counts [91]. Both platelet and WBC levels increased significantly according to the number of MetS components after adjusting for age, sex, ethnicity, total cholesterol, and LDL-cholesterol. Platelets are known to play a significant role in inflammation by inducing the expression of cyclooxygenase-2 and prostanoids, which aggravate atherothrombosis and other components of MetS [96,97]. Li et al. assessed the association between hematogram components and MetS and found that WBC and Hb were related to MetS in an elderly population [98]. The exact mechanism is still unclear, but the role of insulin in stimulating erythropoiesis could be a plausible hypothesis for that association [98]. The association between MPV and MetS has been controversial. Zhao et al. and Park et al. showed an inverse association between MPV and MetS in females [95,99], whereas Aypak et al. demonstrated the opposite result in pubertal girls [100]. This discrepancy could be caused by several factors, including sex, ethnicity, smoking habits, alcohol drinking, and physical activity. Despite the controversial results, MPV still has potential as a biomarker for MetS.

## 6. Adipocytokines

Traditionally, adipocytes have been considered as an inert energy storage depot or heat insulator. However, adipose tissue is now known to play a key role in the pathophysiology of insulin resistance and MetS by secreting adipokines such as adiponectin, leptin, and resistin [101]. Adipokines are involved in the regulation of appetite, inflammatory and immune functions, cardiovascular homeostasis and reproduction, and glucose and lipid metabolism [102].

### 6.1 Leptin

Leptin is an adipocyte that binds to the hypothalamic leptin receptor. Because leptin is secreted mainly by mature adipocytes, its level in the body is proportional to the amount of body fat [103]. Leptin concentrations also

correlate with insulin, insulin resistance, and glucose levels, especially in females [103,104]. Its plasma levels are 5–15 ng/mL in lean individuals, and can reach up to 50 ng/mL in obese individuals [105]. Leptin is also secreted by various tissues other than adipocytes, including the placenta, stomach, vascular smooth muscle cells, skeletal muscle, and liver. Several studies have found leptin receptors on a variety of tissues, such as cardiomyocytes, endothelial cells, myometrium, smooth muscle cells, and cerebral and coronary vessels [106]. Therefore, this hormone has many functions other than being a satiety factor. Under normal physiology, the increased expression of leptin mediated by insulin stimulates the expression of an anorexigenic peptide, which suppresses appetite and weight gain [107]. Leptin also influences the vascular structure by promoting hypertension, atherosclerosis, and angiogenesis [106].

In mice fed a high fat diet, long-term administration of leptin increased AMPK-mediated lipid oxidation and lipolysis in skeletal muscle. Obese individuals showed high leptin levels, though leptin transport was low, providing a mechanism for leptin resistance [108]. In mice fed a high fat diet, serum leptin increased, but the transport of leptin through the blood-brain barrier declined, leading to leptin resistance in peripheral organs, including the liver and skeletal muscle.

Many previous studies have demonstrated that leptin is a useful biomarker for MetS in different populations. Regardless of which demographic was studied, high leptin levels were found to be associated with MetS. Nappo et al. found that a high leptin concentration is associated with MetS in European children, even after adjusting for BMI [109]. Similarly, leptin level was positively correlated with abdominal obesity and the number of MetS components in postmenopausal females [110]. Leyva et al. also reported that hyperleptinemia was strongly correlated with the principal components of MetS, that included central adiposity, blood pressure, fasting triglycerides, and fasting glucose and insulin in healthy males [111]. On the contrary, Martins et al. reported a positive association between leptin and obesity and insulin resistance, but it was only weakly correlated with other components of MetS [112]. Although there is some dissenting research, these observations suggest that leptin can be considered as an effective biomarker for MetS.

## 6.2 Adiponectin

Adiponectin is another adipocytokine produced by adipose tissue and macrophages [113]. Adiponectin plasma levels are 3–30 μg/mL in humans, and

it is present in the bloodstream in different forms, such as a low molecular weight trimer, middle molecular weight hexamer, and high molecular weight complex [114]. The high molecular weight isoform is more biologically active than the others and plays a key role in insulin sensitization and protection against diabetes [106]. Adiponectin promotes insulin sensitization through an AMPK-mediated increase in muscle glucose transport and the reduction of hepatic gluconeogenesis [104]. Adiponectin also stimulates fatty acid oxidation in liver and skeletal muscle through the phosphorylation of AMPK, which stimulates acetyl CoA carboxylase [115]. Furthermore, adiponectin expression attenuates elevation in insulin, TNF-α, and glucocorticoid levels, all factors implicated in the pathogenesis of insulin resistance, subclinical inflammation, endothelial dysfunction, and the development of MetS [116]. Yamauchi et al. reported that knockout mice without AdipoR1/R2, receptors of adiponectin, showed insulin resistance that was reversed by the administration of adiponectin [115]. Several studies demonstrated an inverse relation between adiponectin concentration and MetS criteria [117–120]. For example, increased adiponectin was significantly associated with a lower incidence of T2DM in a Japanese population [121]. Additionally, hypoadiponectinemia correlated negatively with serum triglycerides ($r = -0.33$) and the atherogenic index [(total cholesterol − HDL-C)/HDL-C] ($r = 0.39$), and that correlation became stronger after adjusting for BMI or body fat mass [120]. Iwashima et al. demonstrated that low adiponectin was observed in hypertensive patients after adjusting for obesity, insulin resistance, and T2DM [119]. Increased procollagen type I carboxy-terminal propeptide (PICP) accelerated collagen deposition, resulting in an acceleration of the arterial stiffening process, a phenomenon closely associated with the development of hypertension and MetS [122,123]. In a cross-sectional study of 188 hypertensive patients without T2DM, increased adiponectin was associated with decreased PICP [124].

Several cross-sectional studies have investigated the association between adiponectin and different MetS features in various populations. Patients with MetS had lower adiponectin than individuals without MetS, and each component of MetS was also associated with a decreased adiponectin [125]. In an Asian population older than 40 years, lower adiponectin was associated with high WC and increased triglycerides, CRP, fasting glucose, and insulin. Furthermore, individuals with more circulating adiponectin had higher HDL-cholesterol [126]. Because hypoadiponectinemia occurs in patients with MetS, measurement of adiponectin can be helpful in detecting patients with MetS.

## 6.3 Adiponectin/leptin ratio

Chronic obesity is accompanied by an increase in leptin levels and a decrease in adiponectin levels [127]. Therefore, the adiponectin/leptin ratio has been proposed as a biomarker for adipose tissue dysfunction [128]. This ratio correlated negatively with BMI [129] and was strongly associated with insulin resistance indices such as HOMA-IR and the quantitative insulin sensitivity check index in several cohort studies [129,130]. The adiponectin/leptin ratio showed a stronger correlation with insulin resistance than adiponectin or leptin alone in patients with T2DM [131]. This ratio was also negatively associated with MetS [7,129] and decreased depending on the number of MetS components [128]. Falahi et al. suggested that the ratio of adiponectin and leptin is a better biomarker than adiponectin or leptin alone for diagnosing MetS [132]. However, sex-specific association between the adiponectin/leptin ratio and MetS should be considered in clinical practice. Females showed a weaker association between MetS and this ratio because they had higher levels of adiponectin than males. Frühbeck et al. reported that a low adiponectin/leptin ratio was associated with elevated levels of inflammatory markers [7]. Therefore, adipose tissue dysfunction, characterized as a low adiponectin/leptin ratio, could express a hallmark of obesity and MetS through elevated pro-inflammatory factors that are potential mediators in its pathogenesis [7]. Although further studies are required to set a proper cut-off value for predicting cardiometabolic risk, one study suggested the following values for the adiponectin/leptin ratio (with adiponectin concentration in μg/mL and leptin levels in ng/mL): normal (more than 1.0), moderate risk (0.5–1.0), and severe risk (less than 0.5) [127]. These cut-off points should be applied in a fasting state.

## 6.4 Pro-thrombotic mediator plasminogen activator inhibitor-1 (PAI-1)

PAI-1 is one of the most widely studied biomarkers of the fibrinolysis system. Fibrinolysis degrades fibrin, maintains vascular patency, and participates in tissue remodeling by breaking down extracellular matrix and controlling cell adhesion and migration [133]. Although PAI-1 is secreted by endothelial cells, adipocytes, vascular smooth muscle cells, platelets, and hepatocytes under physiologic conditions, it is also induced by many pro-inflammatory and pro-oxidant factors under pathologic conditions [134]. Consequently, increased levels of PAI-1 affect inflammatory signaling, adiposity, and insulin resistance [135]. Elevated PAI-1 levels result in impaired fibrinolysis, which is directly linked to vascular injury in

individuals with MetS or T2DM [136]. Several studies found that elevated levels of PAI-1 are associated with CVD risk and components of MetS, including central obesity and insulin resistance [137,138]. Since the association between PAI-1 and MetS was first demonstrated in 1986 [133], many studies have been conducted to explain the underlying mechanism [133,139,140]. These studies showed that elevated PAI-1 levels are not associated with inflammation or dyslipidemia but rather with central obesity and the insulin resistant state [133,139]. Increased plasma PAI-1 seems to originate primarily from adipocytes in response to chronically increased insulin, transforming growth factor β, and TNF-α levels [141]. Notably, PAI-1 levels positively correlate with visceral fat but not subcutaneous fat [142,143]. Ectopic fat accumulation in the liver also correlates with strong PAI-1 expression [144]. These findings suggest that a fat distribution phenotype such as central obesity, which is a MetS component, contributes to PAI-1 levels. Also, an *in vitro* study showed that PAI-1 interferes with the insulin signaling pathway and inhibits insulin-induced Akt phosphorylation, leading to insulin resistance [145].

## 7. Chemistry

### 7.1 Uric acid

Uric acid, the final product of purine degradation, is synthesized in the liver, intestines, and other tissues, including vascular endothelium, kidneys, and muscles [146]. Uric acid has extracellular antioxidant activity as a scavenger of ROS and peroxynitrite [147]. Despite its protective capacity, elevated uric acid levels are commonly associated with a high risk of CVD and premature mortality as uric acid has pro-inflammatory and pro-oxidant intracellular activity. Recent studies have shown that increased uric acid levels are related to obesity, T2DM, hypertension, endothelial dysfunction, and MetS [148]. These conditions are all thought to be mediated by systemic inflammation and oxidative stress [149,150]. Under ischemic conditions or tissue damage, uric acid oxidizes lipids, resulting in inflammation that impairs reverse cholesterol transport [151]. Chronic low-grade inflammation and oxidative stress in excessive adipose tissue contribute to an imbalance in the production of adipocyte-specific hormones and cytokines, resulting in the insulin resistance and cardiovascular risk associated with obesity [9,152,153]. Experimental studies have shown that uric acid accelerates triglyceride accumulation in cultured liver cells and in the livers of rats through intracellular and mitochondrial oxidative stress [154–156].

Abnormal triglyceride accumulation in the liver is associated with insulin resistance and non-alcoholic fatty liver disease, which is a hepatic feature of MetS.

Several studies have examined the association between hyperuricemia and MetS and its components [157–160]. Feig et al. reported that asymptomatic hyperuricemia is associated with the development of hypertension [161]. In an animal study, the administration of a uricase inhibitor, an enzyme that breaks down uric acid, induced mild hypertension in rats [162]. Watanabe et al. proposed that chronic hyperuricemia induces microvascular and inflammatory changes in the kidney and eventually enhances sensitivity to the effects of salt [163]. That study suggested that hyperuricemia helps initiate hypertension and that microvascular alterations in the kidney maintain the hypertensive state. Other mechanisms, including endothelial dysfunction that stimulates endothelin and activates the renal and intracellular renin angiotensin system, have been suggested to correlate with hyperuricemia-mediated hypertension [164–166]. Hyperuricemia is also one of the best independent predictors of DM and commonly precedes the development of both insulin resistance and T2DM. A meta-analysis of prospective cohort studies [167] and a recent critical review [168] concluded that serum uric acid is a strong and independent risk factor for DM in middle-aged and older people. A positive correlation between MetS and uric acid has been identified in several epidemiological studies [148,157,169]. Moreover, uric acid concentration increased relative to the number of MetS components and predicted the risk of MetS [170,171]. Given the close association between hyperuricemia and MetS that has been reported in several populations considering the age group, sex, and race, uric acid is a reliable biomarker for MetS.

## 7.2 Alkaline phosphatase

Alkaline phosphatase (ALP) is an enzyme that catalyzes the hydrolysis of monophosphate esters in alkaline pH [172]. It is mainly present in the bone and liver, and plays an integral role in metabolism within the skeletal and hepatobiliary systems [173,174]. In this regard, serum ALP has long been regarded as a useful biomarker for hepatobiliary and bone disorders. ALP is also present in other tissues, including the intestine, kidney, placenta, and leukocytes [175]. Interestingly, recent studies found that elevated serum ALP activity is positively associated with inflammation and cardiometabolic diseases, including hypertension, T2DM, dyslipidemia, and

MetS [176–179]. Kim et al. demonstrated that the prevalence of MetS significantly increased with serum ALP quartile, with the OR for MetS in the highest quartile being 1.32 in males and 1.99 in females after adjusting for age, aspartate transaminase, alanine transaminase, γ-glutamyl transferase (GGT), smoking, alcohol intake, regular exercise, and socioeconomic factors [178]. Also, an elevated ALP level was a significant predictor of MetS in middle-aged people [180]. The mechanism underlying the association between ALP level and MetS is still uncertain, though low-grade inflammation and visceral obesity seem to be involved. ALP activity increases in parallel with lipid accumulation during adipogenesis in human preadipocytes [181]. Kim et al. showed that serum ALP levels are positively associated with body fat mass and visceral fat mass [180]. Additionally, increased ALP was positively associated with CRP, which is the most widely used biomarker of inflammation [182]. Obesity-mediated oxidative stress, which promotes inflammation pathways, augments ALP activity in vascular, bone, and intestinal epithelial cells [183].

## 7.3 γ-Glutamyl transferase (GGT)

GGT is an enzyme that is present in many organs, with the highest level found in the liver. It has been used as a biomarker for hepatobiliary disease and alcohol abuse [184]. However, mounting evidence suggests that GGT plays an important role beyond liver disease. GGT is involved in common pathophysiological processes, such as oxidative stress and lipid peroxidation, that are strongly associated with the development of insulin resistance and MetS [185,186]. GGT plays a significant role in glutathione metabolism, which is the principal thiol antioxidant in humans. This enzyme promotes intracellular glutathione re-synthesis by enhancing the availability of cysteine to defend against oxidant stress [187]. On the other hand, GGT contributes to pro-oxidant activity, particularly in the presence of iron or copper [184]. Elevated GGT levels impair the membranes of RBCs, resulting in the release of toxic transition metals that can initiate pro-oxidant reactions [188]. Elevated levels of pro-oxidation can cause cell, tissue, and DNA damage and the generation of ROS or nitric oxide [189]. Those factors all contribute to the association between GGT and many chronic diseases, including CVD, T2DM, dyslipidemia, and MetS [184,190,191]. Douglas et al. found that high GGT levels were associated with higher MetS prevalence, and increased serum GGT levels also predicted the onset of MetS,

incident CVD, and mortality in Framingham study participants [192]. That study suggested GGT as a marker of MetS and cardiovascular risk. Several other studies showed similar results and suggested optimal cut-off values for GGT as a MetS marker [193]. Yousefzadeh et al. proposed a cut-off value of 16.5 U/L for GGT to discriminate MetS, with sensitivity and specificity of 78.4% and 78.4, respectively [193]. A Chinese study suggested different cut-off values by sex, 31.5 U/L for males (sensitivity 74% and specificity 62%) and 19.5 U/L for females (sensitivity 76% and specificity 70%) [194]. Although further studies are needed to set optimal cut-off values for GGT, accumulating evidence suggests that GGT is a potential biomarker for MetS.

## 7.4 Calcium

Calcium is a universal divalent cation involved in blood coagulation, muscle contraction, skeletal mineralization, and nerve excitability. Serum calcium homeostasis is regulated within a narrow range and is under tight hormonal control, including by calcitonin and parathyroid hormone, that can be influenced by factors such as diet, daily activity, and vitamin D levels [195]. Emerging epidemiological data indicate that a high level of serum calcium is associated with an increased risk for T2DM, abdominal obesity, hypertension, dyslipidemia, and CVD, as well as MetS [195–200]. Intracellular calcium could play a crucial role in the regulation of insulin sensitivity and lipid metabolism [201,202] Moreover, an increase in serum calcium concentration has been shown to be related to deteriorated lipid profiles [203,204]. It is also known that higher levels of intracellular free calcium, a secondary messenger system, correlate with greater catecholamine secretion and vasoconstrictor tone and elevated blood pressure [205,206]. On the contrary, dietary calcium intake is associated with a protective effect of MetS. A recent meta-analysis of eight cross-sectional and two prospective cohort studies found a reduced risk of MetS in the group with the highest levels of dietary calcium intake (RR: 0.89; 95% CI, 0.80–0.99; $I^2 = 75.3\%$) [207]. The dietary calcium intake was more strongly associated with a lower risk of MetS among less heterogeneous females (RR: 0.74, 95% CI, 0.66–0.83; $I^2 = 0.0\%$) than among males (RR: 1.06, 95% CI, 0.82–1.37; $I^2 = 72.6\%$) in a dose-response manner [207]. Therefore, further prospective research is warranted to elucidate any correlations between serum calcium levels, dietary calcium intake, and the risk of MetS.

## 8. Oxidative stress

When antioxidant defenses decrease or oxidation mechanisms increase, uncontrolled oxidation of cellular targets induces accumulation of ROS, leading to a state of 'oxidative stress' that is detrimental to the cells [208]. Oxidative stress plays critical roles in the pathogenesis of cardiometabolic diseases such as obesity, T2D, atherosclerosis, hypertension, as well as MetS [8,209–212]. Prolonged oxidative stress is one of main risk factor to increase CVD risk in patients with T2D and MetS. Hyperglycemia and inflammation increase ROS production leading to oxidative condition with over-activation of NADPH oxidase [213]. Accumulation of plasma free-fatty acids also increase ROS production in endothelial and vascular smooth muscle cells [214]. In an in vitro study, cultured adipocytes with increased levels of fatty acids exhibited increased oxidative stress through the NADPH pathway [9]. This process decreases the bioavailability of nitric oxide in the vascular wall, which can contribute to cardiovascular complications [215]. Furthermore, adipose tissue exposed to oxidative stress demonstrates a systemic inflammatory state, eventually contributing to obesity-associated CVD risk [216].

The association between severity of oxidative stress and number of MetS components has been suggested in previous studies [9,217–219]. Sánchez-Rodriguez et al. showed that individuals with more MetS components had greater risk of exacerbation of oxidative stress [217]. Another study conducted in India reported that several oxidative stress markers, such as neopterin and oxidized LDL (OxLDL) were significantly higher among individuals with MetS [220]. On the contrary, patients with MetS showed decreased antioxidant enzymes, including superoxide dismutase activity, catalase, and glutathione peroxidase [209]. Therefore, oxidative stress could be considered as candidate diagnostic tools for MetS.

### 8.1 Oxidized LDL (OxLDL)

OxLDL, a product of lipid oxidation, is considered as a marker of oxidative stress [134]. OxLDL is a potent inducer of foam cells, which produce the hallmark atherosclerosis-fatty streaks, and systemic inflammation alongside propagation of atherosclerosis [221–224]. OxLDL can react as a signaling compounds for pathways of cellular antioxidants in low concentration. However, when the antioxidant capacity of cells is impaired, as often is seen in MetS, OxLDL contributes to an oxidative cascade leading to cell damage

and apoptosis [225]. Antioxidant cytokines that include adiponectin are downregulated in MetS, leading to activation of an oxidative cascade of OxLDL [225]. This extensive cell damage and apoptosis can contribute to vascular dysfunction, and dysfunctional OxLDL can contribute to dyslipidemia, one of the components of MetS. Also, previous studies have shown that elevated level of OxLDL is associated positively with insulin resistance, MetS and its components in adults [226]. In addition to its association with the components of MetS, OxLDL levels are significantly elevated in MetS patients [220,227,228]. Rao et al. suggested that OxLDL is the best predictor of MetS among various inflammatory and oxidative stress markers [220]. Additionally, a longitudinal study conducted for 20 years showed a significant positive relationship between OxLDL levels and incidence of MetS after 15-year and 20-year follow-ups [222]. The study also reported association of increased OxLDL levels with central obesity, hyperglycemia, and hypertriglyceridemia, which are components of MetS [222]. These results suggest that OxLDL not only serves as a useful biomarker for MetS assessment, but also involves in the pathogenesis of MetS.

## 9. Conclusion

The prevalence of MetS has increased rapidly worldwide and the importance of detecting and preventing this syndrome is becoming increasingly clear. This review provides a comprehensive overview of MetS and the biomarkers currently in use or under development for the diagnosis of MetS. Because MetS is a cluster of clinical and metabolic abnormalities, including central obesity, insulin resistance, hypertension, dyslipidemia, and glucose intolerance, various markers related to those components have been suggested as biomarkers for MetS as a whole. Based on the pathogenesis of MetS, adipokines and inflammatory markers such as cytokines are important diagnostic markers for it. Those markers directly and indirectly produce insulin resistance, which is the most widely accepted mechanism for the development of MetS. Alternative insulin resistance indices such as the HOMA-IR, TG/HDL ratio, and TyG index can also be used as biomarkers for MetS. Other biomarkers, such as uric acid, ALP, GGT, and calcium, are known to correlate with MetS and could also be useful additional biomarkers for MetS. Those markers are cost-effective, and tests for them are already routinely performed in clinical practice, making them more practical markers than adipokines or cytokines. However, large,

well-characterized population studies are required to validate each biomarker because some of them have shown different correlations depending on age, sex, and ethnicity. Therefore, the use of a combination of biomarkers could improve sensitivity and specificity in detecting and predicting MetS as early as possible.

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