Chapter 6

Biomarkers in Metabolic Syndrome

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Abstract

Nowadays, biomarkers are useful in the early detection and risk stratification of metabolic syndrome (MetS) patients. Studies confirmed the implication of adipokines, neuropeptides, inflammatory cytokines, prothrombotic factors, and others in MetS pathogenesis. Leptin:adiponectin ratio is useful in predicting insulin resistance and MetS severity; leptin is correlated with obesity and waist size and adiponectin is inversely related with MetS components. Ghrelin is inversely correlated with MetS components, and studies confirmed its role in MetS prediction. Regarding the pro-inflammatory cytokines, studies confirmed that interleukin (IL)-6 and tumor necrosis factor (TNF)-alpha are positively correlated with hypertriglyceridemia, hypertension, fasting glucose levels, insulin resistance, and in postmenopausal women with central obesity. Oxidized low-density lipoprotein (LDL) levels could be implicated in insulin resistance. Recent studies also confirmed that novel biomarkers such as pentraxin-3 are positively correlated with MetS severity and the presence of vascular lesions, and it could bring new data on the MetS mechanism. Within this chapter, we review data on the contribution of biomarkers as well as on the stratification of MetS patients, discussing their key contribution for creating a risk assessment algorithm.

Keywords: metabolic syndrome, biomarkers, cytokines, obesity, insulin resistance, leptin, adiponectin, ghrelin, pentraxin-3, paraoxonase, interleukins

1. Introduction

Metabolic syndrome (MetS) is a cluster of cardiovascular risk factors with a reported prevalence of 20–25% in general population [1] and also with an increased two-fold risk to develop

cardiovascular disease [2]. Recent studies have shown that, being involved in MetS pathogenesis, some adipokines, neuropeptides, inflammatory cytokines, prothrombotic factors, and others could be used in diagnosing and monitoring these patients.

Various studies confirmed that the leptin:adiponectin ratio (LAR) could have a superior predictive power in determining insulin resistance and MetS severity than the use of leptin or adiponectin alone [3]. Leptin is positively correlated with obesity and waist size [4–8]. Adiponectin has important physiological functions in maintaining metabolic balance and is inversely related with MetS components independently of body mass index (BMI) [7, 9].

Ghrelin is inversely correlated with MetS components, and studies confirmed its role in MetS prediction. Also, a positive correlation of ghrelin levels with hypertension, insulin resistance, and obesity has been found [10–16].

Regarding the pro-inflammatory cytokines, studies confirmed that interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) are positively correlated with hypertriglyceridemia, hypertension, fasting glucose levels, insulin resistance, and in postmenopausal women with central obesity [17, 18, 19–25]. Oxidized low-density lipoprotein (LDL) levels have been found to be correlated with insulin resistance, hyperinsulinemia, impaired glycemic control, and excessive adipose tissue and could predict the occurrence of MetS [26–28].

Recent studies also confirmed that novel biomarkers such as pentraxin-3 are positively correlated with MetS severity and the presence of vascular lesions, and it could bring new data on the MetS mechanism. Also, pentraxin-3 (PTX3) was found to be correlated with low high-density lipoprotein (HDL) cholesterol levels and high triglycerides [29–31].

Paraoxonase-1 (PON-1) was inversely correlated with the presence of MetS, more precisely with central obesity, hypertriglyceridemia, and hypertension [32–35]. Interleukin-10 (IL-10) is an anti-inflammatory cytokine, and decreased levels of IL-10 are associated with insulin resistance and the presence of MetS [36–39].

2. Leptin, adiponectin, and leptin:adiponectin ratio

2.1. Leptin

Leptin is a hormone produced mainly by white adipose tissue, but also by non-adipose ones (placenta, stomach, mammary gland, and immune system) [40, 41]. Its regulation is achieved through various factors dependable on the metabolic status (**Figure 1**). Thus, the implications of leptin in pathogenic mechanisms comprise energy homeostasis, obesity syndromes, metabolic dysfunctionalities, neuroendocrine function, and bone metabolism. The pathogenic pathways of leptin follow similar targets through different mechanisms [40]. Leptin binds to its functional receptor and activates several transduction pathways, such as Janus kinase (JAK)/signal transducers and activators of transcription (determines autophosphorylation of JAK1 and JAK2 with STAT3 activation), mitogen-activated protein kinase (activates this MAPK pathway in central and peripheral tissues), phosphatidylinositol-4,5-bisphosphate

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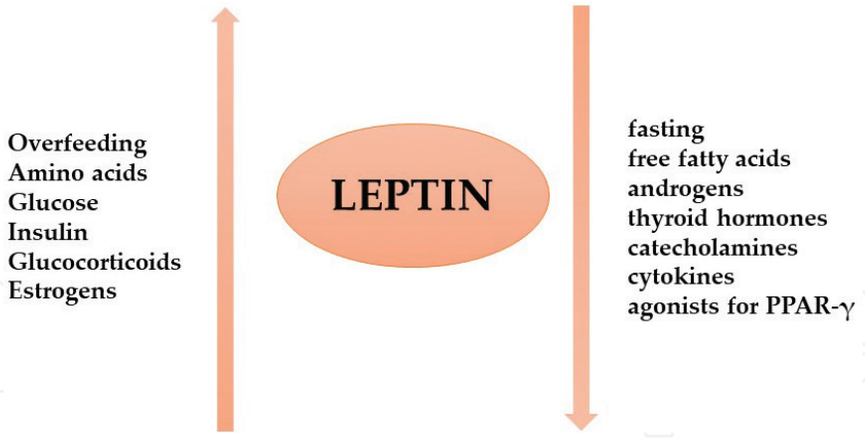

Figure 1. Factors that regulate leptin plasmatic levels.

3-kinase/protein kinase B (leptin activates directly PI3K in peripheral tissue), and AMP-activated protein kinase [42, 43].

Since its discovery, many studies have focused on the role of leptin in the evaluation of cardiovascular risk. High levels of leptin lead to a global and/or selective leptin resistance. MetS is a condition that favors leptin resistance through systemic inflammation, insulin resistance, hyperlipidemia, hypertension, atherosclerosis, and obesity [44]. Leptin levels correlate mainly with obesity and waist circumference, as it has been confirmed in numerous studies, the aspects of which are detailed in **Table 1** [4–8].

2.2. Adiponectin

Adiponectin is a protein hormone produced exclusively by adipocytes. Its high-molecular weight form is proved to have the most intense metabolic activity. Circulating levels of adiponectin are higher in females than in males due to the stimulating activity of testosterone on adiponectin secretion [45]. It plays an important role in metabolic balance, and its lower levels are correlated with an increased cardiac, vascular, and metabolic risk.

Study	Year	Subjects	Leptin and MetS
García-Jiménez et al.	2014	204	Leptin is strongly correlated with BMI; plasma leptin concentration is proportional to the degree of central obesity causing leptin resistance
Yoshinaga et al.	2008	321	Leptin was the most sensitive marker for predicting MetS in elementary school children
Lee et al.	2012	153	Elevated leptin in MetS women in postmenopausal
Gannage-Yared et al.	2006	153	Leptin was strongly correlated with waist size in Lebanese population
Yun et al.	2010	9995	Serum leptin levels increased as the components of MetS, thus reduction of leptin levels may be protective

Table 1. Leptin correlations with metabolic syndrome.

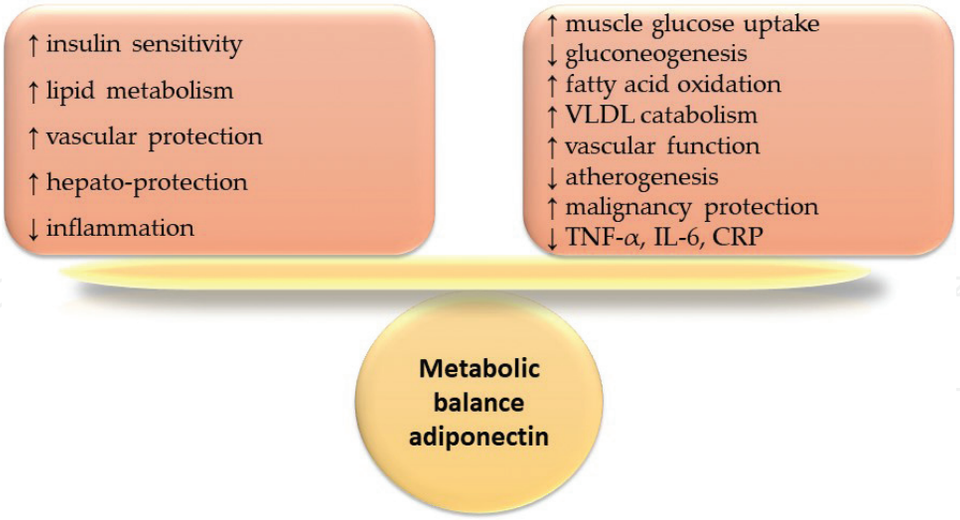

Figure 2. Metabolic balance mediated by adiponectin.

In normal subjects, adiponectin has important physiological functions in maintaining the metabolic balance (**Figure 2**); therefore, in patients with MetS, adiponectin levels are decreased [43]. Numerous studies have demonstrated its positive effect on metabolic protection, mainly based on its potentially inhibitory activity on the atherogenic process [46]. Recent studies have shown that adiponectin is inversely correlated with MetS components and that it has benefic effects on metabolic disorders [47]. Hypoadiponectinemia induced by visceral obesity determines vascular changes and insulin resistance. Likewise, two clinical studies conducted by Gannage-Yared et al. and by Santaneimi et al. have demonstrated the correlation of adiponectin with MetS independent of BMI [7, 9].

2.3. Leptin:adiponectin ratio

Various studies recommend using the leptin:adiponectin ratio (LAR) due to its increased predictive power, despite determining leptin and/or adiponectin alone. Recent data suggest the fact that leptin and adiponectin are two molecules that possess antagonistic effects. In addition, the study by Thorand et al. has been suggested that leptin and adiponectin interact with each other in order to modulate the risk of diabetes [3]. Therefore, Finucane et al. have demonstrated that LAR is a useful marker of insulin resistance in non-diabetic adults [48]. Lopez-Jaramillo et al. have emphasized the use of LAR in the evaluation of insulin resistance, and Kotani et al. have confirmed the predictive value of LAR in Japanese patients with MetS; other studies have also shown the correlation between LAR with all five MetS components [49–51].

3. Ghrelin

3.1. Generalities

Ghrelin is a peptide hormone produced in the gastrointestinal tract, and it has an important role in regulating the use of energy in human organism. Ghrelin undergoes posttranslational changes resulting in two circulating forms: unacylated ghrelin (UAG) and acylated ghrelin (AG) [51].

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This hormone acts directly on hypothalamus and indirectly by increasing the expression of orexigenic peptides such as neuropeptide Y, Agouti-related protein, proopiomelanocortin, and corticotropin-releasing hormone [52].

In addition to its effect on hunger, ghrelin has important effects on glucose homeostasis, energy homeostasis, heart, muscular atrophy, bone metabolism, and tumors [53]. Recent studies emphasize that AG excess is correlated with insulin resistance and metabolic alterations; thereby, the AG/UAG ratio could play a role in the development of MetS [54].

3.2. Ghrelin and metabolic syndrome

Ghrelin is inversely associated with MetS components, and progressively lower ghrelin levels are being correlated with its severity. Ukkola O et al. emphasized the correlation of low ghrelin levels in obese patients with metabolic syndrome [55]. Also, the positive correlation of ghrelin levels with hypertension, insulin resistance, and obesity has been confirmed by numerous studies. McLaughlin et al. have concluded that ghrelin correlates with MetS mainly based on obesity as well as they identified lower ghrelin levels in patients with MetS and obesity than in non-obese MetS patients [10]. Likewise, many studies confirm the relation between MetS and ghrelin [11–16].

4. Interleukin-6

4.1. Interleukin-6 and inflammation response

IL-6 is a human cytokine that plays important roles in acute and chronic inflammation, immune cell development, and the pathogenesis of autoimmune disease. It is known that the increased activity of IL-6 gene is associated with an elevated risk of developing diabetes mellitus [56]. Likewise, IL-6 is linked with all the components of the inner immunity and yields a pro-inflammatory effects explained by different pathways **(Figure 3)**. Nevertheless,

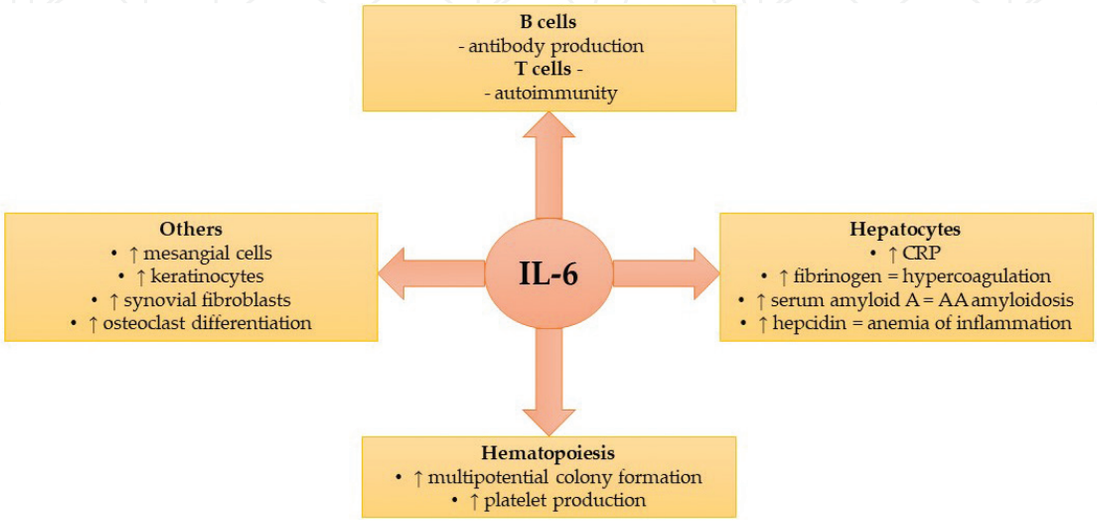

Figure 3. Inflammation pathways that involve IL-6.

studies confirmed that IL-6 also controls processes involved in the resolution of inflammation, emphasizing its anti-inflammatory function [57].

4.2. Interleukin-6 in metabolic syndrome

Studies confirmed that IL-6 is correlated with all five of MetS components. The main explanation relies on the fact that the dysfunctional adipose tissue induces macrophagic proliferation with increased IL-6 production [58]. Weiss et al. have found that IL-6 is associated with hypertriglyceridemia, fasting plasma glucose, and hypertension [59]. The same results are confirmed by Sarbijani et al. [17]. They also reported that increasing levels of IL-6 are correlated with MetS severity [17, 59]. Also, Chedraui et al. found increased levels of IL-6 in women with abdominal obesity, lower levels of HDL-C, and hypertriglyceridemia [18]. Another study demonstrated that high IL-6 levels within hepatocytes in a state of chronic inflammation could be a determining cause of MetS development [60].

5. Tumoral necrosis factor-alpha

5.1. Tumoral necrosis factor-alpha in human metabolism

TNF-α is an inflammatory cytokine mainly produced by macrophage cells, but also by other type of inflammatory cells. Among its many roles, TNF-α is an acute inflammatory response protein, which increases C-reactive protein levels and also determines insulin resistance by interacting with insulin receptor [18]. TNF-α plays important roles in regulating lipid metabolism **(Figure 4),** cholesterol metabolism, and adipokine synthesis [61].

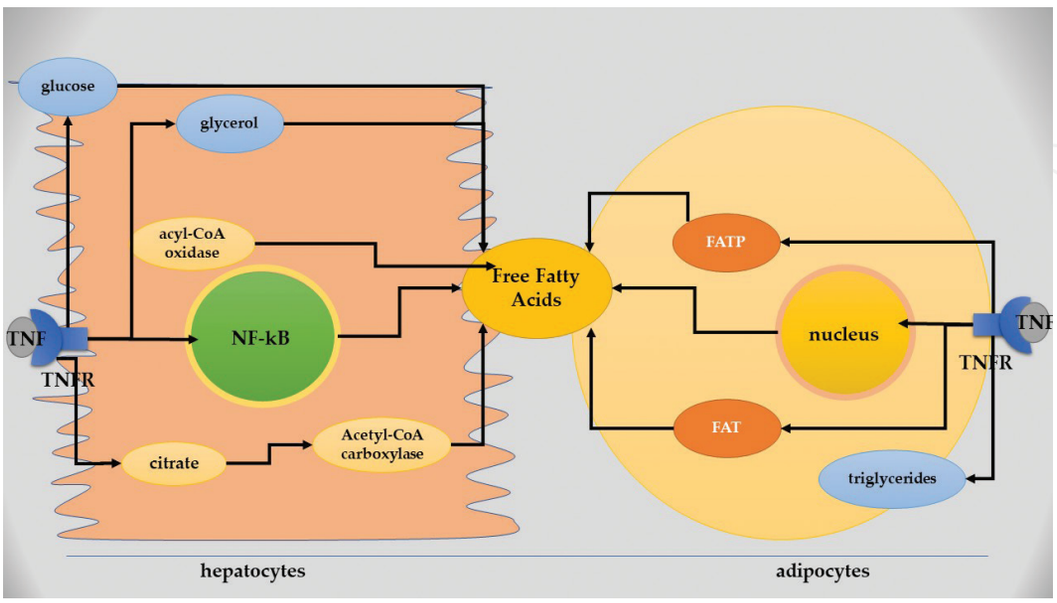

Figure 4. Effects of TNF-α production of free fatty acids in hepatocytes and adipocytes.

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5.2. Tumoral necrosis factor-alpha and metabolic syndrome

TNF-α can be produced by inflammatory cells from the dysfunctional adipose tissue, similar to IL-6. TNF-α is involved in numerous MetS pathways and alterations, in insulin resistance through similar mechanism of mTOR and protein C kinase activation and systemic inflammation [62]. As many studies have shown, TNF-α is being associated with all MetS components.

In the study by Moon et al. on obese adolescents, it was confirmed that TNF-α had higher levels in obese patients, even higher in male subjects, also, TNF-α positively correlated with BMI and waist circumference. Initially, TNF-α correlated positively with triglyceride levels and diastolic blood pressure, and inversely with HDL cholesterol, but after adjustment for BMI and waist circumference, only the association with triglyceride levels persisted [19].

In the meta-analysis of Sookoian et al. conducted on 16 homogeneous studies, it has been shown that obesity, systolic blood pressure, and serum insulin levels positively correlate with TNF-α -308A gene (genetic polymorphism that influences the plasmatic level of cytokine) variant and determine a 23% increased risk to develop MetS [20].

Obesity induces a systemic inflammatory status that determines dysfunctions of the macrophages and adipocytes and inappropriate cytokine production [21]. As a result, higher levels of TNF-α determine insulin resistance through various mechanisms and promote disease progression in patients with MetS **(Figure 5).** Studies emphasize that insulin resistance caused by TNF-α is based on abnormal insulin signaling, overexpression of tissular and plasmatic levels of TNF-α in subjects with insulin resistance, and administration of TNF-α determines and TNF-α neutralization improves insulin resistance [22–25]. Therefore, TNF-α is involved in MetS pathogenesis and progression and could be used in determining patients with MetS.

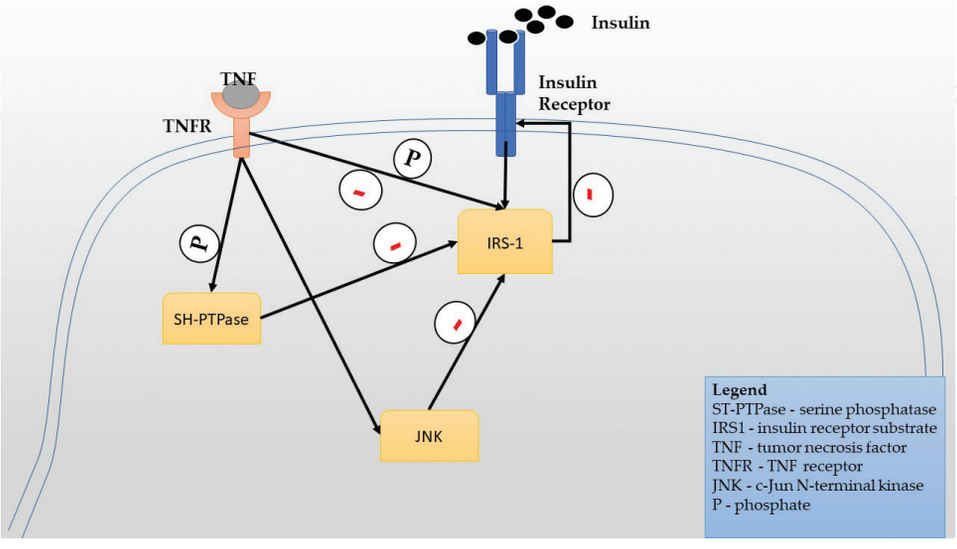

Figure 5. TNF-α and insulin resistance.

6. Oxidized low-density lipoproteins

6.1. Pathogenesis of oxidized LDL

In human organism, LDL particles undergo a series of oxidation processes, resulting in reactive oxygen species (ROS) and oxidized LDL (Ox-LDL) particles. These products create negative electric charges that will cause macrophagic stimulation and inflammation.

During LDL oxidation process, a series of products are generated: fatty acid oxidation products, lipid-derived products, protein oxidation products **(Figure 5)** [63].

Lara-Guzman et al. have shown that THP-1 human macrophage exposure to Ox-LDL caused a series of changes, such as an increased intake of Ox-LDL, overexpression of its receptors, and ROS production. Likewise, in the same study, it has been demonstrated that Ox-LDL determines the synthesis of isoprostanes as oxidation markers and of prostaglandines and prostaglandine metabolites as inflammation markers. Therefore, this study emphasizes that Ox-LDL links oxidative stress with inflammation via macrophages, resulting in systemic and local consequences [64]. Besides that, Schwarz et al. demonstrated that Ox-LDL increases Jun activation domain-binding protein-1 and stimulates inflammatory signaling in macrophages [65].

6.2. Oxidized LDL and endothelial dysfunction

Atherosclerosis represents one of the main alterations caused by MetS, and endothelial dysfunction is the earliest event within it. As mentioned earlier, Ox-LDL triggers inflammation and oxidation process that determines macrophagic activation and ROS production with cytotoxic effect on vascular endothelium [66].

Ox-LDL interacts with lectin-type oxidized LDL receptor 1 (LOX-1) from the surface of endothelial cells and determines their activation [67]. Withal, Ox-LDL causes endothelial

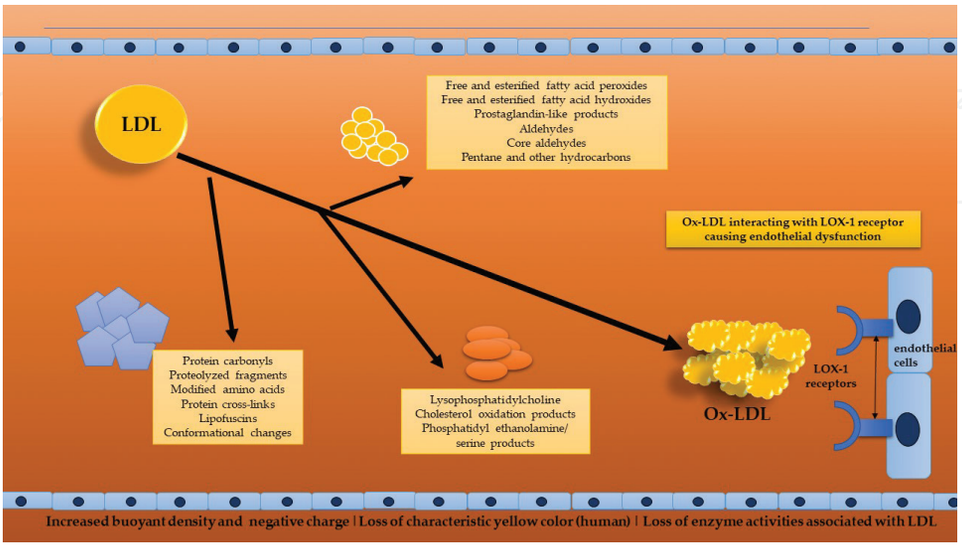

Figure 6. LDL oxidation products.

dysfunction by increasing endothelial adhesivity, by recruiting inflammatory cells into the endothelial wall, and by reducing nitric oxide production **(Figure 6)** [68, 69].

6.3. Oxidized LDL and metabolic syndrome

Various studies have shown that Ox-LDL levels are associated with MetS. Holvoet et al. demonstrated that patients with MetS had higher Ox-LDL values. They also reported that hyperinsulinemia and impaired glycemic control were associated with increased Ox-LDL levels, independent from lipid levels. The same research found that elevated Ox-LDL levels could predict the development of MetS in future [26].

Hurtado-Roca et al. in a study conducted on 3987 subjects demonstrated that Ox-LDL levels are positively correlated with MetS and its components even after adjustments for central obesity and insulin resistance. The strongest association was with triglyceride levels [27]. Another study conducted on overweighted/obese children showed that Ox-LDL positively correlated with BMI, percent body fat, waist circumference, percent trunk fat, abdominal visceral fat, abdominal subcutaneous fat (all p-values <0.0001), and with insulin resistance [28].

7. Pentraxin-3

7.1. The role of pentraxins in human organism

Pentraxins are a cluster of seric proteins with similar structures and calcium-dependent ligands that play important roles in body protection and in inflammatory mediation. The main mechanism is based on complement activation and interaction with Fc receptors [70].

PTX3 is being produced by immune cells as a response to bacterial substances, endotoxins, IL-1, and TNF-alpha. PTX3 is an acute phase protein with very low serum levels. PTX3 levels rise rapidly as a response to diverse inflammation stimuli. Therefore, PTX3 is considered to be a marker of local and general inflammatory and immune response [71–73].

7.2. Pentraxin-3 and metabolic syndrome

Recently, it has been shown that increased PTX3 levels are associated with MetS development and progression. In a study conducted on adolescent subjects with obesity, Kardas et al. have shown that subjects with obesity and MetS had higher values of PTX3 than the subjects without MetS. They also observed that low HDL cholesterol and high triglyceride levels were associated with increased PTX3 levels [29]. Also, Zanetti et al. demonstrated that PTX3 was higher in patients with MetS and subclinical atherosclerosis and that PTX3 was independently correlated with low HDL cholesterol levels [30]. Furthermore, a recent study found that PTX3 correlates with the severity of MetS, more precisely, after multivariate analysis PTX3 correlation persisted for glucose level ($\beta = 0.23$, $p < 0.001$), waist circumference ($\beta = 0.37$, $p < 0.001$), and HDL cholesterol ($\beta = -0.31$, $p < 001$) [31]. In conclusion, PTX3 could be a valuable biomarker in the prediction of MetS, but further studies should be conducted.

8. Paraoxonase

8.1. Paraoxonase-1

PON-1 is an enzyme produced mostly by the liver that protects against lipid oxidation and exogenous toxics. PON-1 extends the lag phase of the oxidation process and reduces the aldehyde concentration, resulting in protective effects on LDL and HDL molecules [74]. Aharoni et al. in a murinic study demonstrated that PON-1 interacts with macrophages scavenger receptor class B type I, thus inhibiting IL-6 and TNF-α production and promoting PON-1 anti-inflammatory effects [75].

The anti-inflammatory role of PON-1 is mainly validated by its anti-atherogenic effect [32]. Likewise, in the study of Ikhlef et al., it has been found that PON-1 could regulate cholesterol homeostasis by stimulating cholesterol efflux via HDL and by potentiating inverse cholesterol transport [33]. On the contrary, in subjects with diabetes, it is assumed that PON-1 becomes malfunctional by excessive glycation, thus it lowers its protective effects and potentiates the atherosclerotic lesion [34].

8.2. Paraoxonase 1 and metabolic syndrome

PON-1 has scientifically confirmed to be connected with MetS. A cross-sectional study conducted on 354 Caucasian subjects with MetS has shown that PON-1 activity was significantly lower among patients who met all five MetS criteria ($p < 0.05$). The same study revealed that lower levels of HDL cholesterol and ApoA1 decrease the PON-1 activity [35]. A like, in a study conducted on 2404 subjects with MetS criteria, it has been demonstrated that PON-1 activity followed a downward trend with increasing MetS components and increasing lipid peroxides [76]. In conclusion, it is assumed that PON-1 through its antioxidant and anti-inflammatory effects could have important roles in lowering of the progression of MetS.

9. Interleukin-10

9.1. Interleukin-10 and metabolic syndrome

IL-10 is a potent anti-inflammatory cytokine that modulates the immune response in order to prevent excessive activation and auto-damage [36]. Based on its properties, IL-10 plays important roles in modulating insulin resistance and atherosclerotic development and, in a cross-sectional study conducted on children and young adolescents, it has been found that plasmatic IL-10 levels were lower in overweight/obese children, and they concluded that IL-10 could be a marker of metabolic risk [37]. On the contrary, Esposito et al. found that IL-10 levels were lower in obese compared with normal weight women, but were lower in both groups that had MetS criteria [38]. Likewise, van Exel et al. found reduced plasmatic levels of IL-10 in patients with MetS and diabetes mellitus [39].

9.2. Interleukin-10 and adiponectin

MetS is characterized by low levels of both adiponectin and IL-10, and recent studies have been evaluating if there is any link between the two molecules. In a study conducted on 117 men, it has been found that IL-10 levels significantly correlated with adiponectin levels especially in patients with MetS, but the correlation was stronger in MetS patients who presented abdominal obesity [77]. Also, Wolf et al. demonstrated that adiponectin modulates human monocytes and macrophages in producing anti-inflammatory cytokines such as IL-10 and IL-1RA [78].

10. Conclusions

The combined use of biomarkers of MetS could increase the rate of an early diagnosis and could prevent the complications of this disease. Associated usage of these biomarkers would increase their predictive value. However, to be able to create a diagnosis algorithm, their cutoff value for the presence of MetS and the causes that would yield false results should be determined. Last but not least, the usefulness of these biomarkers could be extended into guiding pharmacological and non-pharmacological therapeutic interventions. Also, treatment efficiency could be monitored by determining these biomarkers dynamically.

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