Chapter 6

Gender-Associated Biomarkers in Metabolic Syndrome

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Abstract

Metabolic syndrome (MetS) is a cluster of risk factors for atherosclerosis, including abdominal obesity, hypertension, insulin resistance, dyslipidemia with high triglycerides, and low high-density lipoprotein cholesterol. Affected patients have a significantly increased risk of developing cardiovascular disorders (CVD), that are the leading cause of death in the Western countries. Several epidemiological studies have investigated the evolution of CVD hypothesizing the presence of a gender difference in the pathogenetic and progression determinants detectable in men and women. In this chapter, we will examine new gender-associated bioindicators of possible diagnostic or prognostic value in the MetS. Moreover, we will provide an overview on current knowledge on sex-associated cardiovascular determinants with the aim to improve CVD diagnostic and prognostic clinical courses and to develop new and gender-biased prevention strategies.

Keywords: metabolic syndrome, biomarkers, gender differences

1. Introduction

This chapter is aimed to detect gender-associated biomarkers in metabolic syndrome (MS), a clustering of several risk factors associated with significant cardiovascular morbidity and mortality. Cardiovascular diseases (CVD) are the first cause of death in the world according to the World Health Organization. Over 17 million people died from CVD in 2015 and the economic burden of CVD each year is estimated at 396 billion dollars in the US, with similar perspective in Europe, and is expected to rise above 1 trillion dollars in 2030 [5]. Several epidemiological studies, the Framingham in particular, have investigated into the evolution of CVD hypothesizing the presence of a gender difference in the pathogenetic and progression

determinants detectable in men and women [36]. Metabolic syndrome contributes considerably to cardiovascular mortality, particularly among women [33].

Here, we will examine new gender-associated bioindicators of possible diagnostic or prognostic value in the MS. Moreover, we will provide an overview on current knowledge on sex-associated cardiovascular determinants with the aim to improve CVD diagnostic and prognostic clinical courses and to develop new and gender-biased prevention strategies.

2. Metabolic syndrome

In 1977, Haller used the term "metabolic syndrome" (MS) to describe the association between hypertension, dyslipidemia, obesity, and disturbed glucose metabolism [29]. In particular, he demonstrated how the presence of multiple of these factors increased the risk of developing cardiovascular disease [29]. Some years later, Phillips suggested that the combination of risk factors not only predisposed to heart disease, but was also related with an increased risk for obesity. This cluster of risk factors included glucose intolerance, hyperinsulinemia, and a high level of triglycerides, glucose, cholesterol, and insulin [73]. MS is due to the increase in body mass index (BMI) as result of an increase in caloric intake, increase in obesity percentage, and increased sedentary life habits [96]. As said before, this clinical entity has a cluster of risk factors such as hypertension, central obesity, increased triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), increased blood glucose, and insulin resistance [11, 44]. The prevalence of the MS worldwide is estimated to be between 10 and 84%, highlighting a certain correlation with developed countries, but it also depends on various factors such as socioeconomic status, lifestyle, BMI, and region studied [38, 96]. Moreover, a higher rate was found in urban compared with rural populations [76, 114].

A study by Khosravi-Boroujeni and coworker showed that the prevalence of MS has changed from 2001 to 2013 [41]. They also mentioned that incidence of diabetes has also been increasing over the years. Data from the International Diabetes Federation (IDF) suggested that 25% of worldwide adult population suffer from the syndrome with 5% in those exhibiting normal weight, 22% being overweight, and 60% being obese [52, 114]. This has been attributed to aging, life style changes, population growth, obesity, and decline in physical activity. Central obesity was labeled as a critical component of the MS. The prevalence of the hypertriglyceridemia also declined, due to use of the statins, healthy eating with cutting back on fat [41].

3. Biomarker

3.1. Definition and characteristics

To predict cardiovascular risk, numerous biomarkers have been developed. Some of them are used in medicine to facilitate diagnosis, assess risk, direct therapy, and determine efficacy of treatment. The FDA-NIH Biomarker Working Group in the Biomarkers, Endpoints, and other

Tools (BEST) Resource (https://www.ncbi.nlm.nih.gov/books/NBK326791/) define a biomarker as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention." A clinically useful biomarker must be able to meet one of the following criteria: (i) show specificity and sensitivity for a certain disease (diagnostic); (ii) have prognostic value; and (iii) correlate with disease activity. Some of them are simple traditional biomarkers based on lipid profile and risk factors [74, 81, 93].

In the INTERHEART study, 9 major risk factors could explain 90% of the population-attributable risk in men and 94% in women of 52 countries. These factors are abdominal obesity, elevated lipids, hypertension, diabetes, smoking, psychosocial factors, consumption of fruits/vegetables, consumption of alcohol, and regular physical activity [110]. However, the importance of these factors varies significantly from one country to another and some of these factors act as predisposing and not causal factors, like obesity and diet [111]. The prevalence of risk factors can change in different directions around the world, often because of socioeconomic and political cues.

Hypertension, central obesity, increased triglycerides, decreased high-density lipoprotein cholesterol (HDL-C), increased blood glucose and insulin resistance are collectively defined as risk factors for cardiovascular disease triggered by metabolic syndrome [11, 44, 62] (**Table 1**). In the last few years, in addition to the clinical factors, new factors in the pathogenesis of MS have also been taken into consideration. These factors can be classified on the basis of their function (e.g., marker of exposition, markers of effects, etc.) or in their biochemical or biologic properties (e.g., proteins metabolites, hormones, cytokines, etc.) [92].

Ample evidence favors a key role for mitochondrial injury, oxidative stress, and apoptosis in MS [7]. Moreover, recent findings depicted an essential role for autophagy, a cellular process of degrading long-lived, injured proteins and organelles, in the pathogenesis of MS [65, 108, 114]. Indeed, dysregulated autophagy is present in multiple metabolic anomalies including obesity, insulin resistance, diabetes mellitus, and dyslipidemia [42, 47, 61, 112, 113].

Recent studies implicated that inflammation, especially chronic low-grade inflammation, might play an even greater role in the development of MS [56]. One possible mechanism is that the growth of adipose tissue and infiltration of immune cells lead to the increase of

Components	International Diabetes Federation
Obesity-waist circumference (cm)	≥35 cm for women or ≥ 40 cm for men
Hypertension-blood pressure (mmHg)	130/85 mm Hg
Dyslipidemia-reduced HDL (mg/dL)	<40 mg/dL in men or < 50 mg/dL in women
Dyslipidemia-elevated triglycerides (mg/dL)	≥150 mg/dL
Glucose-fasting blood glucose (mg/dL)	≥100 mg/dL

HDL: high-density lipoprotein.

Table 1. Current criteria for the diagnosis of the metabolic syndrome.

proinflammatory adipokines such as tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), and interleukin-6 (IL-6) [37, 59, 104, 105], which cause increased insulin resistance from insulin-sensitive tissues by decreasing insulin signaling [34].

We will present the current state of knowledge for modifiable biomarkers that can be used to predict MS events in the general population.

3.2. Elevated systolic blood pressure

Elevated systolic blood pressure (SBP) is one of the leading risk factors for global mortality and for CVDs. In 2015, the prevalence of raised blood pressure was around 20% in females aged 18 and over 24% in males [100]. Studies have reported conflicting results on the association between increments in SBP and CVDs with differences between sexes [2]. An analysis carried out in 2013 found that every 10 mm Hg increment in SBP was associated with a 15% increased risk of coronary heart disease and a 25% increased risk of stroke in both men and women, indicating a similar impact of hypertension on cardiovascular outcomes in both sexes [71]. In contrast, a recent study on US population indicates that women experienced a 10% greater risk in CVDs per 10 mm Hg increment in SBP than men [103].

3.3. Dyslipidemia

Higher total cholesterol (TC) is estimated to account for over 2.6 million deaths (4.5% of total) worldwide every year [100]. The prevalence of elevated TC is similar in men and women [100] and studies addressing the possible sex-/gender-specific effects of TC on CVD risk have reported inconsistent results [72]. The cholesterol associated with high-density lipoproteins (HDL-C) has long been considered a useful biomarker of CVD and MS risk. In population studies, HDL-C is inversely related to the risk of myocardial infarction and death [57]. Low HDL was initially suggested to be more predictive of coronary risk in women compared to men [82]; however, analyses indicated that the association between HDL cholesterol levels and fatal coronary heart disease did not vary significantly by sex [22]. The first systematic meta-analysis evaluating the impact of TC on CVD risk in women compared with men [72] found that for every 1-mmol/L increment in TC, the risk of coronary heart diseases increased by 20% in women and by 24% in men, indicating essentially a similar TC-related risk of coronary heart diseases in both sexes.

3.4. Triglycerides

Plasma triglycerides (TG) are product in the intestine and in the liver. As elevated TG are often associated with reduced levels of the negative cardiovascular risk biomarker HDL-C, the causal role of elevated plasma TG in CVD has been debated over the last 50 years. Fortunately, different types of genetic and epidemiological evidence have recently strengthened the causality relationship between TG and CVD and promoted TG lowering as a fundamental factor for CVD prevention. The question is important considering the high prevalence of TG levels: 47% of the US population at over 1.7 mmol/L based on the 2011 NHANES survey [10].

Initially, it was thought that TG level was a stronger risk biomarker in women than in men. Some years later, in a meta-analysis of 29 Western prospective studies with 262,525 subjects, a significant association of TG with cardiovascular events was found, which was attenuated by adjusting for HDL-C but remained significant [81, 88].

3.5. Body fat, excess body weight, and obesity

Excess body weight is another major risk factor for CVDs and MS; moreover, excess body weight is currently one of the greatest public health issues worldwide [99]. According to the WHO, over 650 million adults were estimated to be obese worldwide in 2016 and prevalence has almost tripled since 1975 confirming that excess body weight has reached epidemic proportions globally. The association between BMI and coronary heart diseases has been shown to be the same between men and women in several studies [23, 66, 78]. The increased BMI has the same deleterious effects on the risk of MS onset in women and men [11, 62]. However, there are numerous differences between men and women regarding body fat, excess body weight, and obesity that could be due to either direct activation by sex steroids or by sex steroid-independent mechanisms.

3.6. Dysglycemia

Dysglycemia is a global term referring to either impaired fasting glucose or impaired glucose tolerance. However, the two conditions are physiologically distinct. Impaired fasting glucose results from inadequate basal insulin secretion or sensitivity in the liver, whereas impaired glucose tolerance is a consequence of insufficient insulin response or sensitivity to a carbohydrate load in not only the liver but also skeletal muscle. Impaired glucose tolerance is more common in women than in men (except at older ages), whereas impaired fasting glucose is more often seen in men than in women. The reasons for this pattern are unknown, but sex differences in muscle mass, visceral adiposity, altered susceptibility to free fatty acid-induced peripheral insulin resistance, and other factors may play a role [77]. Because impaired glucose tolerance is not included in most current MS definitions, it is possible that, compared with their men counterparts, dysglycemic women are underdiagnosed with the syndrome [77].

3.7. High-sensitivity C-reactive protein

High-sensitivity C-reactive protein (hs-CRP) is a sensitive marker of inflammation. Some findings have indicated that there is an association between CRP, development of atherosclerotic disease [83, 84], and components of the metabolic syndrome [25, 49]. Indeed, many studies have shown a direct association between high concentrations of CRP and insulin resistance or components of MS [17, 27, 39, 53, 87].

While elevated TGs do not exert an inflammatory stimulus per se, endothelial damage may occur, also because of the occurrence of intravascular TGs hydrolysis via the activity of lipoprotein lipase either at the endothelial surface or within the arterial intima. This process leads

to a release of free fatty acids and monoacylglycerols which generate local inflammation and high levels of CRP [69, 86].

3.8. Mitochondria functions and its role in MS

Mitochondrial dysfunction is an early pathophysiological event in the development of insulin resistance and obesity [15]. The origin of mitochondrial dysfunction may relate to a variety of processes ranging from inflammation to epigenetic inheritance [48, 94]. Mitochondria are crucial, multifunctional organelles, which actively regulate cellular homeostasis. The main function of mitochondria is the energy production as adenosine triphosphate (ATP) via citric cycle (tricarboxylic acid cycle and Krebs cycle). Other cell functions include ionic homeostasis, production and regulation of reactive oxygen species (ROS), lipid and carbohydrate utilization, pH regulation, steroid hormone synthesis, calcium homeostasis, thermogenesis, and cell death [70, 85, 98]. An intricate homeostatic system regulates and maintains optimal mitochondrial function in healthy cells, the failure of which is seen in obesity, asthma, and metabolic syndrome [6].

Mitochondria are known to adapt physically to nutrient availability [26, 79]. The study's Durigon and coworker demonstrates that changes in nutrient availability and utilization remodel the nucleoprotein complexes in mitochondria and thereby indicates how nutrients can modulate gene expression and energy production in the organelle. It is clear that genetic defects in metabolic factors linked to mitochondrial nucleoprotein complexes, or their regulators, can produce a pseudostarvation state, owing to an inability to utilize an available nutrient [21].

Several cardiovascular risk factors such as type 2 diabetes mellitus, hypertension, atrial fibrillation, peripheral artery disease, obesity, MS, dyslipidemia, habit of smoking, and pollution are associated with an increased production of ROS [75].

The most common cause of obesity, caloric excess, and high fat consumption, leads to nutritional overload, excess electron flux, increased oxidative stress, accumulation of partially oxidized substrates, and, eventually, damage [45, 102]. As mentioned above, mitochondria are the primary intracellular site of oxygen consumption and the major source of reactive oxygen species (ROS), most of them originating from the mitochondrial respiratory chain. These highly reactive molecules, radicals, and nonradicals have the ability to capture electrons from molecules they come in contact with, including proteins and nucleic acids, leading in consequence to cell damage. A fine equilibrium between ROS production and ROS removal determines the physiological versus pathological function of ROS. In fact, an excessive amount of ROS induces oxidative stress and promotes cell death under hypoxic conditions. Conversely, at physiological levels, ROS function as "redox messengers" in intracellular signaling [18, 98]. ROS can be removed by antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase [18]. An efficient antioxidant system is also necessary to cope with reactive nitric species (RNS) generated by the reaction between O_2^- and nitric oxide (NO) [4]. Similar to ROS, excessive accumulation of RNS leads to irreversible damage to biomolecules [1].

The mitochondrial dysfunction leads to activation of stress pathways that reduce cellular sensitivity to insulin, limiting nutrient influx, and preventing further damage. Chronically, this manifests as reduced mitochondrial metabolism, insulin resistance in organs, such as liver and skeletal muscle, with consequent hyperinsulinemia and diversion of nutrients to storage as adipose tissue [63]. In addition, mitochondrial dysfunction, with rising intracellular oxygen and oxidative stress, interferes with NO synthesis and leads to oxonitrative stress in epithelial and vascular endothelial cells. This pattern underlies the metabolic syndrome with obesity, diabetes, dyslipidemia, and hypertension as the phenotypic components. MS is thought to be related to inflammatory processes and oxidative stress that are linked to underlying adipocyte cellular dysfunction [3, 20].

3.9. Autophagy in MS

Autophagy (or self-eating) is a conserved process aimed at maintaining of cellular and tissue homeostasis under normal as well as stress conditions, including nutrient starvation, changes in metabolism, energy and oxygen status. Autophagy is a degradation mechanism for nonessential or damaged cytoplasmic components, including damaged organelles, toxic protein aggregates, and intracellular pathogens [64]. It is an evolutionarily conserved process, in which cells engulf a portion of the cytoplasm and damaged organelles (such as mitochondria, peroxisomes, and endoplasmic reticulum) into double-membraned vesicles which later fuse with lysosomes for the degradation of enclosed materials [14, 32, 50]. Degradation byproducts, such as amino acids, can then be re-used for the building of new macromolecules or for meeting metabolic demands [43, 109]. Autophagy serves as an indispensable process for cellular homeostasis involved in immunity, inflammation, and metabolism [16]. Either excessive or defective autophagy may be associated with human metabolic diseases [91], indicating the unique role of autophagy in the regulation of metabolic homeostasis [114]. Besides the main function of energy production, mitochondria are also able to turn on and tune autophagy by ROS production and oxidation of mitochondrial lipids. Excessive accumulation of ROS leads to impairment of mitochondria structure and function, which in turn triggers a selective process of mitochondria self-removal called mitophagy. As already mentioned, mitophagy is an autophagic response that allows elimination of defective mitochondria and accelerates the mitochondrial turnover, thus preserving the pool of healthy organelles [80]. It has been proposed that upon nutrient deprivation, mitochondria protect themselves from degradation by promoting fusion and inhibiting fission events. It is only after long-term starvation that mitochondria undergo fragmentation and are eventually removed by mitophagy [79]. A reciprocal regulatory mechanism exists between autophagy and key metabolic elements such as glucose and lipids [54, 55, 80]. For example, lipotoxicity in metabolic anomalies impairs lysosomal function and autophagy, further exacerbating lipid accumulation and ultimately cell injury [95]. Autophagy plays a pivotal role in the maintenance of the body's metabolism. Clinical and experimental evidences have depicted a link between autophagy and metabolic risk factors such as obesity, dyslipidemia, alcoholism, insulin resistance, hypertension, diabetes mellitus, sepsis, and inflammation [16, 51, 58, 90, 101, 114]. The bioengineered autophagy

models also show a key role of autophagy in systemic metabolic regulation. Specifically, they highlight how not only changes in autophagy affect metabolic homeostasis but also the metabolic stress affects the state of autophagy. Indeed, autophagy is suppressed in genetic or diet-induced models of obesity in various tissues, including liver, skeletal muscle, and cardiac muscle [12, 13, 31, 35, 54, 55, 106, 107]. Recent data show that elevated circulating insulin, an autophagy-inhibitory hormone, is believed to be responsible for changes in autophagy genes [89]. A more in-depth understanding of the role of autophagy in metabolic diseases should yield potential therapeutic strategies for better management of metabolic syndrome.

4. Metabolic syndrome and gender differences

Individuals with MS are four to five times more likely to develop diabetes and about twice as likely to develop CVDs than those without the syndrome [60, 77]. Recently, a meta-analysis of data from five cohorts with a total of 18,353 participants suggested that MS is associated with similar elevations in CVD risk in women and men [77]. It is unclear whether MS confers additional risk beyond its individual components. Comparative data from two U.S. National Health and Nutrition Surveys (NHANES III (1988–1994) and NHANES (1999-2006)) show a striking rise in prevalence of MS, with the relative increase larger in women (22.8%) than in men (11.2%) [68]. In NHANES III, the prevalence of specific risk factor clusters responsible for the MS diagnosis differed between the sexes, at least in the cluster under age 65 [46]. Abdominal obesity was a dominant feature in females with MS, whereas risk factor combinations were more heterogenous in their male counterparts. Sex affects not only the clinical expression but also the pathophysiology of MS. A recent review [77] demonstrates that sex differences in dysglycemia, body fat, adipocyte biology, and the hormonal control of body weight may have a role in cardiometabolic aftermath of women and men with the MS. Moreover, the estrogen decline, that occurs postmenopausally, may have also implications for cardiometabolic sequela in MS women [77].

The sex difference in the distribution of body fat is well known. Specifically, there is an adipose tissue accrual in the upper body (trunk and abdomen) and lower body (hips and thighs) more prominent in men and women, respectively. Visceral adipose tissue in the abdomen is a stronger correlate than subcutaneous adipose tissue of metabolic disturbances and cardiovascular risk. The amount of visceral adipose tissue, as well as the ratio of visceral adipose tissue to total body fat, is lower in premenopausal women than in men. These findings imply that BMI and waist circumference, commonly used in epidemiologic settings, are less accurate indicators of visceral obesity in women and may thus underestimate the impact of visceral adipose tissue on cardiometabolic risk in this group [60].

Sex influences adipocyte size in certain anatomic locations. For example, in men, omental adipocytes (a type of intraperitoneal visceral adipose tissue) and abdominal subcutaneous adipocytes are approximately equal in diameter, and show only minimal size increases with increasing BMI. In contrast, in women, omental adipocytes are 20–30% smaller than abdominal subcutaneous adipocytes, and show larger size increases as BMI increases. Thus,

sex differences in adipocyte size may affect the cardiometabolic risk associated with MS in women and men [60].

Sex differences in hormonal control of body weight may also contribute to the clinical expression and sequelae of MS. The hormones insulin, leptin, and estrogen may interact to play a role in weight control via "adiposity signals" to the brain. In particular, insulin is secreted from pancreatic beta cells in response to rising glucose levels. Leptin, which has the effect of inhibiting food intake, suppressing insulin secretion, and increasing lipolysis, is released from adipose tissue in direct proportion to fat mass [19, 30]. Leptin expression is greater in subcutaneous than in visceral adipocytes, whereas insulin is a better marker of visceral than subcutaneous fat [19]. Given the aforementioned sex differences in visceral vs. subcutaneous fat, it seems likely that hormonal control of body weight varies in women and men. Sex differences in adipose tissue are not limited to white adipose depots, as females have more brown adipose tissue and an enhanced capacity to beige their adipose tissue [24].

The mass changes that occur in adipose tissue gene expression in response to diet-induced obesity are different between males and females, demonstrating significant differences in how obesity affects adipose tissue [28].

The estrogen family and its two respective receptors, ERα and ERβ, have been widely suggested to be protective against obesity, type 2 diabetes, and cardiovascular disease [67]. Accumulating data also suggest that estrogen affects adipocyte biology, as well as glucose and lipid metabolism. Estrogens have significant effects on insulin and leptin sensitivity and on the body's response to changes in glucose levels [19, 67]. At menopause, a time of fluctuating and ultimately falling estrogen levels, an increase in visceral adiposity occurs, along with atherogenic lipid changes characteristic of MS [60].

Estrogens can exert significant effects on one important cellular component as mitochondria. Differences in mitochondrial number and function have been suggested to underlie the differences in life span between the sexes [97] and may also be responsible for some of the differences in response to the early life nutritional environment. Females have increased mitochondrial number in skeletal muscle, adipose tissue, and heart [8, 9, 40].

5. Conclusions

Progressive obesity, insulin resistance, abnormal cholesterol, or triglyceride levels that lead to metabolic syndrome are emerging problems. Many strategies have been recently proposed to minimize health-related consequences of metabolic syndrome. Sex seems to be the one element that plays a key role not only in the clinical expression but also in the pathophysiology of MS. The endogenous causes of the sex differences observed in many diseases are largely unknown, and the situation in CVD research is not much different. Much remains to be learned about mechanisms for these sex differences. Gaining this knowledge would allow us to therapeutically target the relevant protective pathways. Sex differences in the clinical expression and physiology of metabolic syndrome may be important in refining predictions of cardiovascular risk.

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