Gender Differences and Cardiometabolic Risk

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Metabolic syndrome (Mets) is a clinical condition characterized by a cluster of major risk factors for cardiovascular disease (CVD) and type 2 diabetes: proatherogenic dyslipidemia, elevated blood pressure, dysglycemia, and abdominal obesity. Each risk factor has an independent effect, but, when aggregated, they become synergistic, doubling the risk of developing cardiovascular diseases and causing a 1.5-fold increase in all-cause mortality.

metabolic syndrome gender cardiovascular disease

1. Introduction

Metabolic syndrome (MetS) is a complex disorder with a high socioeconomic cost that is generally thought to be a consequence of social and environmental changes related to urbanized living conditions, high-caloric food intake, and sedentary lifestyle [1]. It is considered a worldwide epidemic. MetS is defined by a cluster of causally interconnected metabolic and cardiovascular risk factors (CVRF) such as atherogenic dyslipidemia, arterial hypertension, dysregulated glucose homeostasis, and abdominal obesity. Several MetS definitions, differing in their focus and their diagnostic threshold values, have been proposed by different international organizations, such as the World Health Organization (WHO) [2], the European Group for the study of Insulin Resistance (EGIR) [3], the National Cholesterol Education Programme Adult Treatment Panel III (NCEP ATP III) [4], the American Association of Clinical Endocrinologists (AACE) [5], the International Diabetes Federation (IDF) [6], and the American Heart Association/National Heart, Lung, and Blood Institute [7] (**Table 1**).

Table 1. Criteria for the diagnosis of metabolic syndrome.

	World Health Organization [2]	European Group for the Study of Insulin Resistance [3]	National Cholesterol Education Programme Adult Treatment Panel III [4]	American Association of Clinical Endocrinologists [5]	International Diabetes Federation [6]	American Heart Association/National Heart, Lung, and Blood Institute [7]
Criteria	Insulin resistance + ≥2 other components	Insulin resistance + ≥2 other components	≥3 components	No specified number of factors for diagnosis, left to clinical judgment	Increased waist circumference ≥2 other components	≥3 components

	World Health Organization [2]	European Group for the Study of Insulin Resistance [3]	National Cholesterol Education Programme Adult Treatment Panel III [4]	American Association of Clinical Endocrinologists [5]	International Diabetes Federation [6]	American Heart Association/National Heart, Lung, and Blood Institute [7]
Dysglycemia	Impaired glucose regulation or diabetes	Impaired fasting glucose or impaired glucose tolerance (diabetes excluded)	Blood glucose ≥ 110 mg/dL (6.1 mmol/L) or previously diagnosed diabetes	Impaired glucose tolerance (but not diabetes)	Fasting plasma glucose >100 mg/dL (5.6 mmol/L) or previously diagnosed diabetes	Fasting plasma glucose >100 mg/dL (5.6 mmol/L) or on drug treatment for elevated glucose
Raised plasma triglycerides	≥150 mg/dL (1.69 mmol/L)	≥150 mg/dL (1.69 mmol/L)	≥150 mg/dL (1.69 mmol/L)	≥150 mg/dL (1.69 mmol/L)	≥150 mg/dL (1.69 mmol/L) or on triglycerides treatment	≥150 mg/dL (1.69 mmol/L) or on triglycerides treatment
Low HDL cholesterol	<35 mg/dL (0.90 mmol/L) in men and <39 mg/dL (1.01 mmol/L) in women	<39 mg/dL (1.01 mmol/L) in men and women	<40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women	<40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women
Increased blood pressure	≥160/90 mmHg	≥140/90 mmHg or on antihypertensive medications	≥130/85 mmHg or on antihypertensive medications	≥130/85 mm Hg	≥130/85 mmHg or on antihypertensive medications	≥130/85 mmHg or on antihypertensive medications
Central obesity	Waist to hip ratio >0.9 in men and >0.85 in women and/or body mass index >30 kg/m^2	Waist circumference ≥94 cm in men and ≥80 cm in women	Waist circumference ≥102 cm in men and ≥88 cm in women	Body mass index ≥25 kg/m^2	Waist circumference > ethnicity-specific thresholds	Waist circumference ≥102 cm in men and ≥88 cm in women
Other	Microalbuminuria					

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2. Gender Differences in Metabolic Syndrome Components

2.1. Proatehrogenic Dyslipidemia

Atherogenic dyslipidemia has a direct correlation with CVD. It is a clinical condition characterized by elevated levels of serum triglycerides and small dense low-density lipoprotein (sdLDL) and by low levels of high-density lipoprotein (HDL) cholesterol. Additional features are elevated levels of triglyceride-rich very low-density lipoproteins (VLDL) and apolipoprotein B (ApoB), as well as reduced levels of small HDL [8][9].

It is well-known that premenopausal women exhibit a better lipid profile compared with men, as shown by lower levels of total cholesterol (TC), LDL, and triglycerides along with higher HDL concentrations, which have been partly linked to the specific action of estrogens [10][11]. Indeed, women commonly show better regulation, transport, and removal of VLDL from vessels than their male counterparts [8][9]. On the other hand, several trials have reported a shift toward an unhealthy atherogenic lipid profile in postmenopausal women, who have the tendency to reach higher levels of TC, LDL cholesterol, triglycerides, and lipoprotein(a), and who tend to have lower HDL levels compared with premenopausal women [11]. These menopause-linked changes in the lipid profile are proatherogenic (increased plasma concentration of TC, LDL, and triglycerides) and procoagulatory (higher levels of lipoprotein(a)), and are strongly connected to the increase of visceral fat mass classically associated with menopause-induced modifications [9].

Abdominal fat accumulation, particularly visceral fat (VF) mass, contributes to worsening the dyslipidemic and hypertensive profile detected in women with impaired glucose tolerance [12]. VF accumulation is generally accompanied by insulin resistance (IR), increased release of free fatty acid by adipose tissue, and secretion of ApoB containing particles by the liver, leading to hyperlipidemia. This cascade ultimately results in a preponderance of sdLDL particles and a reduction in antiatherogenic HDL. A similar pattern emerges with menopause, when LDL composition shifts from a low prevalence of sdLDL particles in premenopausal women to one as high as 30%-49% after menopause. These lipid changes are indicative of increased cardiovascular risk and contribute to the number of women meeting the diagnosis of MetS. Thus, monitoring and controlling waist circumference, a marker of abdominal obesity and VF accumulation, represents a key strategy to counteract the clinical consequences of MetS, especially in postmenopausal women [12].

2.2. Arterial Hypertension

Gender differences in the pathophysiology of arterial hypertension seem to be multifactorial and are still not entirely understood [13]. Some of the current hypotheses include differences in sympathetic activation and arterial stiffness, with a specific role of sex hormones [14].

The overactivation of the sympathetic nervous system is not only important in the early stages of the development of hypertension, but it is also associated with several comorbidities commonly associated with hypertension [15]. Importantly, autonomic dysfunction seems to play a more prominent role in female than in male hypertension [16]. Moreover, the age-related increase in sympathetic traffic is higher in women than in men, and it is independent of body mass index and menopausal status [17][18].

Androgens and estrogens regulate blood pressure (BP) through the renin-angiotensin system (RAS). RAS is stimulated by androgens, resulting in an increase in BP [19], whereas ovarian hormones have the opposite effect, reducing plasma renin and angiotensin-converting enzyme (ACE) activity [20]. Sex hormones' effects on the reabsorption of renal sodium and on the vascular resistance could also explain the differences in BP control between men and women [21]. Estrogens seem to maintain normal endothelial function by stimulating the

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production of nitric oxide (NO), inducing structural and functional beneficial effects on the arterial wall that, in turn, reduce vascular stiffness [20]; moreover, they modulate the effects of the sympathetic nervous system [22][23].

Moreover, arterial hypertension is a powerful risk factor for incident heart failure (HF) [24]. According to the Framingham Heart Study, the hazard ratio for developing HF in hypertensive compared with normotensive subjects was about two-fold in men and three-fold in women [25]. Arterial hypertension has the highest population attributable risk (PAR) of all factors: 39% for males and 59% for females.

2.3. Dysglycemia

Abnormal glucose homeostasis is commonly diagnosed by establishing the presence of impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT); these two pathological conditions are not interchangeable and represent metabolically distinct abnormalities characterized by different pathophysiological pathways.

The prevalence of IGT and IFG is different between the sexes. The analyses of the study groups of “Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe/Asia” highlighted that IFG is 1.5–3 times more prevalent in men than in women in nearly all age groups, and is 7–8 times more prevalent in older age groups (50–70 years). On the other hand, IGT prevalence is higher in women, with the exception of those over the age of 60 and 80 years in Asian and European populations, respectively [26].

The significant gender differences observed in diabetic patients exist due to different pathophysiological processes in men and women. Differences in body composition, fat deposition, mass and activity of brown adipose tissue, and expression of some fat-related biomarkers clearly contribute to the sex-dimorphic diabetes risk. Moreover, predisposition, development, and clinical presentation of diabetes are affected by genetic effects, epigenetic mechanisms, health behavior, nutritional factors, sedentary lifestyle, and stress in different ways in males and females [27][28]. It is well-known that the onset of T2DM in premenopausal women nullifies the cardiovascular protection due to sexual hormones, as evidenced by the reduced endothelium-dependent vasodilatation reserve, which is still higher than that induced in men [29]. In addition, hyperglycemia reduces the production of NO mediated by estrogens [30].

2.4. Obesity and Adiposity

Although obesity is undoubtedly influenced by diet, exercise, and genetics, its pathophysiology extends beyond these factors, and an important role is played by the sympathetic nervous system. In fact, it makes a major contribution to the integrated regulation of food intake, involving satiety signals and energy expenditure. The overactivity of the sympathetic nervous system is not only a hallmark of obesity, but it may also take part in the development of metabolic disturbance and cardiovascular complications in obese subjects [31][32].

Sex differences in adipose tissue distribution are well-supported by many findings in the literature and are associated with whole-body metabolic health [33]. Premenopausal women tend to accrue more fat in the gluteus–femoral area (lower-body, “ginoid” or “pear” phenotype), predominantly due to a superficial increase in size, and

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3. Impact of Gender on Cardiometabolic Risk in NAFLD

NAFLD is a metabolic disease that is diagnosed when the accumulation of hepatic triglycerides is >5.5% in absence of or with moderate alcohol consumption (i.e., daily intake less than 20 g (2.5 units) in women and less than 30 g (3.75 units) in men) [38]. NAFLD is closely linked with IR and, bidirectionally, with the MetS, of which it may be both a cause and a consequence.

Gender and reproductive status modulate the risk of developing NAFLD [39]. Below the age of 50 years, the incidence of NAFLD is higher in the male as compared to the female gender due to the protective effect of estrogens, which wanes after menopause. Accordingly, after the fifth decade of life, postmenopausal women have a similar or even higher prevalence of NAFLD compared to men of the same age. Moreover, women with polycystic ovary syndrome (PCOS) or a history of gestational diabetes mellitus (GDM) have a risk similar to or even higher than that of men.

4. Gender Differences in Biochemical Markers of Cardiometabolic Risk

MetS is characterized by increased concentrations of pro-inflammatory cytokines (Interleukin-6, Tumor Necrosis Factor-β), markers of pro-oxidant status (oxidized LDL, uric acid), prothrombotic factors (Plasminogen Activator Inhibitor-1), and leptin, and by decreased concentrations of anti-inflammatory cytokines (Interleukin-10), ghrelin, adiponectin, and antioxidant factors (paraoxonase-1) [40].

Interleukin-6 (IL-6) is considered to be one of the cytokines at the top of the inflammatory cascade. Despite some controversial findings, the main body of literature suggests that, compared to men, women have higher IL-6 reactivity to mental and/or physical acute stressors [41][42] and pharmacological inflammatory stimulation [43]. Several reports have described IL-6 as a biomarker in CHD, highlighting a potential point of relevance for IL-6 mediated pathways. A large cohort prospective study showed that long-term IL-6 levels are highly associated with CHD, with the CHD risk increasing continuously with increasing levels of circulating IL-6 concentrations [44]. Another study confirmed a risk association of IL-6 with CHD, including a possible role of IL-6 in mediating the associations of circulating inflammatory markers with the risk of CHD in men [45]. However, no strong evidence of an association between IL-6 and incident CHD was found in older British women after controlling for established CHD risk factors [46]. Further studies need to address whether this could reflect a gender difference.

OxS is a condition that occurs when the rate of reactive oxygen species (ROS) formation exceeds the rate of the antioxidant defense system. Gender is a possible factor associated with differences in OxS levels and antioxidant enzyme expression, likely related to estrogen antioxidant properties [47]. Accordingly, much data has suggested greater antioxidant potential in females over males, as men appear more susceptible to OxS [47]. In particular, OxS biomarkers are generally found to be higher in men when compared to premenopausal women. However, postmenopausal women show higher levels of OxS biomarkers than men in general populations, as well as in coronary and peripheral artery disease cohorts [48][49].

Uric acid (UA) is a commonly used laboratory biomarker, and hyperuricemia is more associated with MetS in females than in males [50]. UA has been primarily identified as a powerful antioxidant; therefore, UA elevation in CVD may represent a compensatory mechanism in response to pro-oxidative and pro-inflammatory status. UA concentration is physiologically lower in women than in men due to the role of steroids in UA regulation, also called "uricosuric effect", and to the possible urate-depressing effect of estrogens in women. However, emerging findings show that UA is more related with CVD in women than in men [51].

Plasminogen activator inhibitor-1 (PAI-1) is a critical regulator of the fibrinolytic system. PAI-1 levels are lower in females than in males, likely due to differences in genetics, environmental factors, and/or sex hormones [52][53]. Circulating levels are elevated in patients with CHD and may play an important role in the development of atherothrombosis [54]. In large epidemiological studies, elevated plasma PAI-1 levels have been identified as a predictor of myocardial infarction. No study has assessed the presence of a gender difference in the PAI-1-CVD link. H

Leptin has an important role in the long-term regulation of body weight. It has also been proposed as an independent risk factor for CVD and as an important link between obesity and cardiovascular risk [55]. Plasma leptin levels are higher in women than in men due to the higher proportion of adipose tissue and increased production rate of leptin per unit mass of adipose tissue. A significant association between leptin level and stroke has been demonstrated in women, but not in men, after adjustment for age, smoking, body mass index, waist circumference, and hypertension [56].

Adiponectin is an adipocyte-derived hormone with anti-atherogenic, antidiabetic, and anti-inflammatory properties. Women have higher levels of adiponectin than men; in addition, postmenopausal women have significantly higher levels of plasma adiponectin than premenopausal women. Clinical studies have implicated hypoadiponectinemia in the pathogenesis of T2DM, coronary artery disease (CAD), and left ventricular hypertrophy. The data in the Framingham Offspring Study indicate that low adiponectin is a significant independent CHD risk factor only in men [57].

Similarly to adiponectin, resistin is another cytokine produced mainly by adipose tissue. Alterations to resistin's secretion process (increased levels in plasma or expression in metabolic and gonadal tissues) have been observed in some metabolic pathologies (e.g., obesity). Specifically, resistin has been reported to be higher in patients with MetS, and it has been shown to be proportional to increased fat mass, possibly being directly linked to insulin

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resistance. Thus, it functions as a pro-inflammatory molecule in the presence of obesity and represents a candidate hormone that can potentially link obesity to diabetes [58][59].

5. Women-Specific Risk Factors for Cardiometabolic Disease

Pregnancy is a contributor to weight gain and MetS. Normal pregnancy is associated with a shift of coagulation and fibrinolytic systems towards hypercoagulability. Although these changes are aimed at minimizing the risk of blood loss during delivery, they increase the risk of thrombosis three-fold to four-fold. Nulliparous women have lower CVD prevalence compared with parous women (18.0% vs. 30.2%) [60].

GDM significantly increases the risk for subsequent glucose intolerance and T2DM (from 2.6% to over 70%) [61][62], as well as for MetS. In fact, MetS is more prevalent in women with a history of GDM compared with healthy controls [63]. The risk is primarily due to increased abdominal obesity.

Pre-eclampsia is defined as a systolic blood pressure of at least 140 mmHg and/or a diastolic blood pressure of at least 90 mmHg on at least two occasions. Proteinuria is present after the 20th week of gestation in women known to be normotensive before pregnancy. Increased pre-pregnancy BMI is a risk factor for pre-eclampsia [64]. Pre-eclampsia increases the risk for subsequent hypertension [65] and diabetes [66][67] in perimenopausal years. The association of both pre-eclampsia and GDM with diabetes and hypertension may arise from common pathogenic pathways. Both conditions are associated with insulin resistance [68][69] and with the presence of endothelial dysfunction and markers of chronic vascular inflammation [70][71].

PCOS has many characteristics similar to those of the MetS. Women with PCOS show a prevalence of metabolic syndrome of approximately 40% [72]. PCOS and MetS share the same components: central obesity and proatherogenic dyslipidemia. Hypertension, increased fasting glucose levels, and impaired glucose tolerance are also commonly present in PCOS [73].

The menopause transition (MT) represents a vulnerable time for women, and its incidental hormonal changes have been associated with unfavorable changes in several indicators of metabolic health, such as negative alterations in the lipid profile, increased susceptibility to weight gain, accumulation of abdominal adiposity, and increased blood glucose [74][75][76]. Therefore, in women, the incidence of MetS and cardiovascular disease increases after menopause, regardless of chronological aging [77][78].

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