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ORIGINAL ARTICLE

Metabolic Syndrome: Does it Differ Between Women and Men?

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Abstract Cardiovascular disease represents a massive healthcare burden worldwide. Gender differences in the pathophysiology, presentation and prognosis of cardiovascular disease have been described in the literature. Metabolic syndrome, characterized by a cluster of metabolic abnormalities is associated with increased risk for type 2 diabetes mellitus and atherosclerotic cardiovascular disease. With the global obesity epidemic, the prevalence of metabolic syndrome is rising rapidly in the developed as well as developing world. However, there is considerable variation in the prevalence based on geography, age, sex and, definition used for diagnosis. Data on gender related differences in metabolic syndrome is relatively scarce. Here, we aim to review the gender differences in epidemiology and pathophysiology of metabolic syndrome as well as its individual components. Knowledge of gender differences in metabolic syndrome can help design gender specific preventative and therapeutic strategies that will have a positive impact on overall population health.

Keywords Metabolic syndrome · Gender differences · Sex differences · Cardiovascular disease · Hypertension · Dyslipidemia · Insulin resistance · Obesity · Pathophysiology of metabolic syndrome · Role of hormones in metabolic syndrome

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Introduction

Metabolic syndrome (MetS), characterized by a cluster of metabolic abnormalities including hypertension, central obesity, insulin resistance and atherogenic dyslipidemia, is a well-known risk factor for type 2 diabetes mellitus (DM) and atherosclerotic cardiovascular disease (CVD) [1]. With increase in obesity and sedentary lifestyles globally, the prevalence of MetS has reached epidemic proportions [2]. Significant variations in prevalence of MetS exist based on geography, age, sex and, definition used for diagnosis [2]. These variations can be explained by differences in genetic and environmental factors such as dietary patterns, activity and stress levels, socioeconomic status and education. While sex related differences in CVD have been elucidated in the past [3], it is not clear if presentation of MetS differs between men and women. Here, we aim to review the sex differences in epidemiology and pathophysiology of MetS with emphasis on individual components of MetS.

Metabolic Syndrome – Definitions

MetS, also referred to as 'Insulin resistance syndrome' [4], 'syndrome X' [5], 'hypertriglyceridemic waist' [6] and 'the deadly quartet' [7] represents a cluster of metabolic abnormalities that heighten CVD risk [8]. The first diagnostic criteria, proposed by the Type 2 diabetes consultation group of the World Health Organization, included insulin resistance (impaired fasting glucose [IGF] impaired glucose tolerance [IGT] or type2 DM) in addition to two other metabolic abnormalities such as, obesity (based on waist-hip ratio or body mass index), hyperlipidemia (hypertriglyceridemia, low LDL cholesterol), hypertension or microalbuminuria [9]. Since then, this definition has undergone several iterations to

improve sensitivity and ease of use (Table 1). The National Cholesterol Treatment Adult Treatment Panel III (NCEP-ATP) proposed a more clinically suited definition in 2001; requiring presence of 3 of the 5 following criteria for diagnosis: i) abdominal obesity (waist circumference >102 cm in men and >88 cm in women), ii) dyslipidemia (low HDL, elevated triglyceride levels), iii) hypertension and iv) insulin resistance (IFG, IGT or DM) [10]. The International Diabetes Federation proposed a revision in 2004, defining different obesity thresholds for different ethnic groups based on population estimates and mandating presence of obesity for diagnosis [11]. NCEP-ATP further modified their definition in 2005 to lower waist circumference thresholds and fasting blood glucose level [12]. The most updated version of the definition, issued in 2009 has been designed collaboratively by global expert groups and is similar to the modified NCEP-ATP definition with national or regional cut offs for waist circumference [13]. MetS, diagnosed based on any of the above definitions, continues to be associated with a higher CVD risk [14].

Epidemiology of Metabolic Syndrome – Sex Differences

Prevalence of MetS varies widely across populations. Various factors including age, sex, race, socioeconomic status and education levels influence the prevalence of MetS (Fig. 1). There is significant sex disparity in the pathogenesis, clinical definition and prevalence of MetS as well. Thus, while individuals from both sexes may have a diagnosis of MetS, the criteria met for diagnosis may be different. Degree of sex disparity also follows regional and ethnic variations, reflecting the interplay between environmental and host factors in pathogenesis.

MetS is known to affect a third of the population in the United States based on various studies [15, 16] and a quarter of the population in Europe [2]. Age-adjusted prevalence of MetS in NHANES has been reported to increase from 29.2 to 34.2 % between the 1988–94 and 1999–2006, with a greater relative increase in prevalence in women compared to men (22.8 vs. 11.2 %) [17]. While Mexican Americans continue to remain the highest risk group, prevalence of MetS in non-Hispanic whites and a non-Hispanic blacks has gone up significantly, most prominently in younger women [17]. Miller et al. estimate the prevalence of MetS in adolescents in the US is 10.1 %, higher in boys as compared to girls (13.0 vs. 6.4 %, $P<0.05$) [18], but with increasing age MetS becomes more prevalent in women. Loucks et al. in a study based on the third NHANES participants, found that low income and education levels are associated with significantly higher prevalence of MetS in women as compared to men. Women from lower educational backgrounds have a significantly higher prevalence of all components of MetS compared to men with similar levels of education [19]. Similar patterns of MetS have been identified in the Caribbean islands, with women having a higher waist circumference, lower HDL cholesterol compared to men [20]. High parity and psychosocial stressors; such as poverty, unemployment, single parenting; are more frequent in women from lower socioeconomic classes, predisposing to poor lifestyle choices leading to development of metabolic abnormalities.

On the contrary, epidemiological studies from Far East Asia report a higher prevalence of MetS in men. Ishii et al. have reported a MetS prevalence rate of 28.9 % in women and 43.6 % in men in a prospective cohort study in Japan [21]. Similarly, in the Macau health survey prevalence of MetS in men was twice as high as in women [22]. Studies done in Korea also showed an increased prevalence of MetS in men. However, studies from China indicate a higher prevalence of MetS in women, both rural and urban, than in men [23, 24].

Middle Eastern countries also have a sex disparity in prevalence of MetS similar to the United States with a reported prevalence of 32.1 to 42.7 % in women and 20.7–37.2 % in men [25, 26]. Interestingly, studies reported from the European Union showed a lower prevalence of MetS with little sex disparity. Men were found to have only a slightly higher prevalence in reports from France and Greece, with significant differences based on the definitions used for the diagnosis of MetS [27–29].

Based on the above data, there is a significant sex disparity in the epidemiology of MetS (Table 2). Geographic variation appears to influence this disparity, implying the effect of local environmental and cultural factors in its pathogenesis.

Components of MetS – Sex Differences

Hypertension

Hypertension is a leading precursor of CVD and is the most frequent component of MetS in men. Prevalence of hypertension, like MetS, varies based on age, race, sex and geography. Studies assessing variability in the incidence of hypertension between women and men have found that men demonstrate a steep increase in blood pressure during and after adolescence while women demonstrate a steep rise in blood pressure in the postmenopausal period [30]. In a study assessing sex related differences in CVD risk factors in the NHANES 1999–2004 population, women were noted to have higher mean systolic pressures and lower mean diastolic pressures as compared to men. It is of note that systolic blood pressure is a better predictor of CVD risk [31]. Further, 82 % of hypertensive women were postmenopausal, and hypertension was associated with a significantly higher prevalence of other CVD risk factors such as low HDL, elevated total cholesterol

Table 1 Diagnostic criteria for metabolic syndrome

Clinical measure	WHO 1998 [7]	EGIR 1999 [68]	ATP III 2001 [8]	IDF 2005 [9]	AHA/NHLBI 2005 [10]
Criteria	Insulin Resistance + any other 2	Insulin Resistance + any other 2	Any 3 of 5	Increased WC (population specific) + any other 2	Any 3 of 5
Insulin resistance	IGT/ IFG/ IR	Plasma insulin> 75th percentile	–	–	–
Blood glucose	IFG/ IGT/ T2DM	IFG/ IGT (Excludes Type 2 diabetes)	≥110 mg/gL (Includes Type 2 diabetes)	≥100 mg/gL	≥100 mg/gL (Includes Type 2 diabetes)
Dyslipidemia	TG≥150 mg/dL HDL-C Men <35 mg/dL Women<39 mg/dL	TG≥150 mg/dL HDL-C <39 mg/dL in men and women	TG≥150 mg/dL HDL-C Men<40 mg/dL Women<50 mg/dL	TG≥150 mg/dL or on TG treatment HDL-C Men<40 mg/dL Women<50 mg/dL Or HDL treatment	TG≥150 mgl/L or on TG treatment HDL-C Men<40 mg/dL Women<50 mg/dL Or HDL treatment
Blood pressure	≥140/90 mm Hg	≥140/90 mm Hg or on treatment	≥130/85 mm Hg or on treatment	≥130/85 mm Hg or on treatment	≥130/85 mm Hg or on treatment
Obesity	Wasit:Hip (W:H) ratio Men >0.9; Women >0.85 and /or BMI >30 kg/m^2	WC Men≥94 cm; Women≥80 cm	WC Men≥102 cm Women≥88 cm	WC≥94 cm	WC Men≥102 cm Women≥88 cm
Other	Microalbuminuria				

WHO World Health Organization, *EGIR* European Group for Study of Insulin Resistance, *ATP* Adult Treatment Panel, *IDF* International Type 2 diabetes Federation, *IGT* Impaired glucose tolerance, *IFG* Impaired fasting glucose, *IR* Insulin resistance, *T2DM* Type 2 Type 2 diabetes mellitus, *TG* Triglycerides, *BMI* Body mass index, *HDL-C* High density lipoprotein cholesterol, *WC* Waist circumference

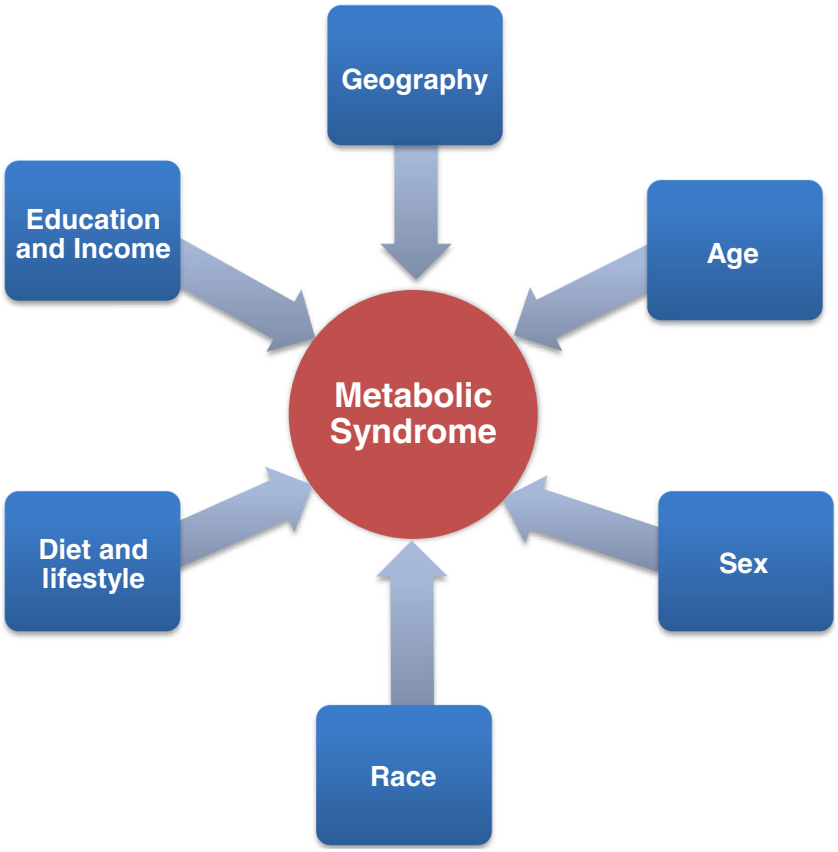

Fig. 1 Factors influencing the prevalence of metabolic syndrome

and central obesity in women than in men. While the prevalence of uncontrolled blood pressure was similar in men and women during treatment, women had greater improvements in systolic blood pressure as compared to men [31]. Trajectory of arterial blood pressure with age is dissimilar between men and women due to biological differences in endocrine parameters, adipose tissue morphology and distribution, and arterial stiffness [32]. Studies report anatomic differences in the vasculature and heart between men and women; women have stiffer hearts and arteries. During the reproductive years, this effect is thought to be tempered by sex hormones. In the post-menopausal period, there is a steep increase in the incidence of systolic hypertension in women [33].

Sex hormones, especially estrogen, play a role in regulation of the renin angiotensin system and exert neuromodulatory functions that can affect sympathetic activity. Estrogen increases synthesis of angiotensinogen and expression of angiotensin type 2 receptor while decreasing synthesis of renin, angiotensin converting enzyme, and decreasing the expression of angiotensin type 1 receptor. Actions of angiotensin II mediated by angiotensin receptor 1 are associated with hypertension while those mediated by angiotensin receptor 2 are associated with a paradoxical drop in blood pressure [34]. A sympathoexcitatory effect of progesterone and sympathoinhibitory effect of estrogen have also been described. Animal studies demonstrate a protective effect of female hormones against the development of arterial hypertension [32]. The sex hormone mediated effects are attenuated with aging, which explains the rise in hypertension in postmenopausal women.

A difference in prevalence of hypertension between women and men is very heavily influenced by age. Young women are at a lower risk for developing hypertension but the overall prevalence of MetS is rising rapidly in this population. The overall effect of these differences on composite CVD risk profile is, however, not known.

Insulin Resistance

Insulin resistance, measured as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or overt Type 2 diabetes is an integral component of MetS. IFG is a state of relative basal insulin deficiency while IGT indicates a state of peripheral insulin resistance. Several epidemiologic studies indicate that prevalence of IGT is universally higher than IFG and sex related variations in prevalence also exist [35–37]. Results from the analyses of the DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) and DECODA (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Asia) groups, that included 13 European and 10 Asian studies, indicate that the prevalence

Table 2 Prevalence of MetS based on geography, sex and definition

Geography	Investigators/ Year of publication	Study population (n)	Prevalence of MetS (%)	Prevalence in men (%)	Prevalence in women (%)	Defining criteria
North America						
US	Beltran-Sanchez et al. 2013 [74]	2034	22.9	23.69	21.80	Harmonized criteria [11]
US	Hari et al. 2012 [73]	6770	33.1	29.23	36.56	NCEP-ATP III
Canada	Riediger et al. 2011 [75]	1800	19.1	20.5	17.8	NCEP-ATP III
US (Hispanics)	Heiss et al. 2014 [76]	16319	33.7	34	36	Harmonized criteria
US	Scuteri et al. 2005 [77]	5888	35.1	32.1	37.4	NCEP-ATP III
US	Ford et al. 2010 [78]	3461	34.3	36.1	32.4	NCEP-ATP III
Asia						
Korea	Yang et al. 2014 [79]	14888	28.4	26.6	21.3	ATP III
Thailand	Podang et al. 2013 [80]	2544	16.6	18.2	10.3	ATP III
China	XI et al. 2013 [24]	7488	21.3	20.9	21.7	ATP III
Rural China	Yu et al. 2014 [23]	11,496	39 %	45.6	31.4	M - ATP III [10]
Macau	Sobko et al. 2014 [22]	1592		10.5	3.7	IDF [9]
South India	Deepa et al. 2007 [81]	2350	18.3	17.1	19.4	ATP III
India	Deedwania et al. 2014 [82]	6198		33.3	40.1	Harmonized criteria
Africa and Middle East						
Morocco	El Brini et al. 2014 [83]	820	35.73	18.56	40.12	Harmonized criteria
UAE	Malik et al. 2008 [84]	4097	41.8	37.1	44.3	IDF
Saudi Arabia	Al-Daghri et al. 2014 [85]	9164		47.2	40.3	ATP III
Europe						
France	Vernay et al. 2013 [86]	1856	14.1	14.4	13.7	ATP III
Greece	Athyros et al. 2005 [27]	4153	23.6	24.2	22.8	ATP III
Italy	Maggi et al. 2006 [87]	5632		25.9	55.2	ATP III

US United States, *UAE* United Arab Emirates, *ATP III* Adult Treatment Panel III, *M-ATP III* Modified Adult Treatment Panel Criteria, *IDF* International Diabetes Federation

of IFG is higher in men compared to women, typically 1.5–3 times and can be up to 7–8 times higher in men between 50 and 70 years of age [37]. In contrast, prevalence of IGT is higher in women except in Asian women over 60 years of age and European women over 80 years of age [37].

Metabolic regulation varies considerably in men and women owing to differences in muscle mass, adiposity and hormones. Sex related differences in lipolysis, glucose metabolism and insulin action are very well described [38]. In summary, women have higher percentage body fat (mostly deposited in the lower body), lower lean mass, more subcutaneous adipose tissue (abdominal and gluteofemoral locations) and higher insulin sensitivity, whereas men have more visceral fat stores in the abdomen or upper body, have higher lean mass and are less sensitive to the action of insulin [38]. Studies on sex differences in insulin resistance support this explanation, Aldhoon-Hainerova et al. studied insulin resistance in 1518 Czech adolescents and discovered that obese adolescent boys are at a higher risk for insulin resistance and impaired fasting glucose when compared with obese adolescent girls [39]. Both IFG and IGT have a similar risk for progression to Type 2 diabetes, but IGT, and not IFG, is associated with higher risk for CVD and all-cause mortality [37]. Some studies also report that IGT correlates with a higher CVD risk in women, but not men [40].

In summary, sex differences in insulin resistance influence CVD risk and progression to overt Type 2 diabetes.

Dyslipidemia

Dyslipidemia is widely recognized as an important risk factor with large randomized trials demonstrating significant benefit of lipid modifying therapy in the management of CVD. Significant sex differences in the pathogenesis, diagnosis and management of dyslipidemia have been reported. In the MESA study, women had significantly higher levels of total and HDL cholesterol, and similar levels of LDL and triglycerides as men [41]. This sex-based difference in lipid patterns has been reported by other prospective epidemiological studies. In addition to serum total cholesterol concentration, sex differences in lipid fractions and lipoprotein levels have also been identified, which play a crucial role in cholesterol

metabolism and in the pathogenesis of CVD [42]. Studies have revealed that small LDL, small HDL and large VLDL are the lipid fractions that increase CVD risk. Large HDL has been shown to have athero-protective properties. Analysis of lipid fractions in large epidemiological studies showed that women have higher levels of large HDL, higher large HDL to total HDL ratio and less small HDL compared to men. In the STRRIDE (Studies of a targeted risk reduction intervention through defined exercise) study, large HDL composed 65 % of total HDL in women, while it was only 45 % in men [42]. This difference in lipid fractions was strongly evident in LDL fractions as well, with men having a higher fraction of small dense LDL, which has been implicated as a major CVD risk factor. Among women, those with CVD have a higher fraction of small LDL compared to those without CVD. Men also have larger VLDL particles compared to women. These observations suggest that men tend to have a more pathogenic lipid fraction pattern than women, which leads to an increased risk of CVD in men compared to women, even with comparable serum total lipid concentrations [42].

Various mechanisms have been proposed to explain the differences in lipid profile patterns between men and women. These include differences in hepatic lipase and lipoprotein lipase activity and the effect of hormones. Lipoprotein lipase mediates triglyceride uptake by the adipose tissue. Women have higher lipoprotein lipase activity per unit of adipose tissue when compared to men, which leads to more favorable cholesterol metabolism. The effect of hormones on lipid metabolism is more complex. An interesting finding was that differences in HDL fractions and particle size between men and women emerge at puberty, with variations in lipoprotein concentrations through the menstrual cycle. In the post-menopausal period, women have an increase in total and small dense LDL cholesterol levels [43]. Hormone replacement therapy alters cholesterol metabolism in the post-menopausal period. In epidemiological studies, women on hormone replacement therapy had an increase in triglycerides, total cholesterol, HDL and large HDL cholesterol along with a reduction in total LDL, small LDL and lipoprotein lipase activity [43]. Though these changes in lipid profiles with hormone replacement therapy appear encouraging, they have not translated into clinical benefit with large trials showing an increase in CVD risk with hormone replacement therapy.

In summary, there are significant sex differences in lipid profiles and lipid fractions between men and women. Epidemiological differences in lipid fractions play an important role in determining CVD risk. Variations in lipid metabolism and effect of hormones appear to be major contributors for these differences in lipid patterns. For a given lipid profile, women are at a lower CVD risk compared to men and this has to be considered prior to initiating lipid lowering therapy. LDL cholesterol is a good CVD risk predictor in men, whereas levels of non-HDL cholesterol are better predictors in women.

Obesity

Obesity and overweight are well-recognized CVD risk factors and component of MetS. Sex differences in the epidemiology and pathophysiology of obesity exist. In a worldwide global survey of 183 countries, Ng et al. reported a prevalence of being overweight to be 38 % in women and 36.9 % in men [44]. Interestingly, there were significant geographic variations in sex disparities in obesity patterns. Women had a higher prevalence of overweight and obesity in developing countries, whereas more men were obese in developed countries [44]. Waist circumference has been shown to be better marker of CVD risk compared to BMI. In a recent study using the NHANES database, Beydoun et al. have reported an increase in waist circumference by 4.8 cm in women and 4.2 cm in men over a 10 year period, paralleled by an increase in BMI [45]. In a recent ecological analysis of data from 192 countries, Garawi et al. reported a higher prevalence of obesity in women with a mean sex difference of 6 % [46]. Various genetic, hormonal, environmental and social factors have been implicated in contributing to sex differences in obesity patterns. Patterns of food consumption and physical activity play an important role in initiating and sustaining this sex difference. Females are known to have a sharp decline in physical activity patterns at adolescence as compared to men, and this disparity continues into adulthood. The ‘feminine’ expectation of a sedentary and physically inactive lifestyle across various cultures also plays a role in perpetuating disparity in weight patterns. This has led to the concept of ‘sex inequality’ influenced by cultural patterns. Differences in body fat distribution have also been attributed to alter CVD risk [47]. Visceral adipose tissue, more common in men, is anatomically and metabolically different from subcutaneous adipose tissue, more frequent in women. Visceral adipose tissue is metabolically active, produces adipokines and inflammatory mediators, and is associated with insulin resistance and higher CVD risk. Adipokine production is a function of adipocyte morphology, which demonstrates sex related differences. Adipose tissue in women exhibits hyperplasia, while in men it exhibits hypertrophy; increase in cell size is associated with greater pro-inflammatory adipokine production [48]. In addition to environmental and social factors, hormonal influence on weight patterns has been explored. A fall in estrogen levels following menopause has been associated with increased visceral obesity and CVD risk [49]. Though estrogen therapy has shown promise in reversing the metabolic effects of visceral obesity in animal models, clinical studies have failed to demonstrate any benefit of estrogen supplementation on CVD risk; there may even be more harm related to estrogen supplementation. This has led

to identification of estrogen receptor subsets, selective modification of which may be a potential therapeutic target [49].

Significant sex disparities in weight patterns exist worldwide with women having a higher prevalence of obesity. Lifestyle patterns influenced by cultural factors are major contributors to this difference, supplemented by genetic and hormonal influences.

Influence of Hormones on Sex Disparity of MetS

The association between sex steroids and MetS has been described in several studies [50–53]. Hormones that have been studied include, testosterone, estradiol and dehydroepiandrosterone (DHEA). While the gonadal organs, ovaries in women and testis in men produce estrogen and testosterone respectively; DHEA is produced by the adrenal glands in both sexes. Estrogen is also produced by peripheral aromatization of testosterone in men and postmenopausal women. These hormones are bound to proteins such as sex hormone binding globulin in circulation, which regulates the free hormone level. Effects of estrogen at the cellular and organ levels are mediated by the alpha and beta estrogen receptors and modulate feeding behavior, glucose utilization, insulin production and visceral fat deposition [48]. Metabolic effects of testosterone include inhibition of lipid uptake, inhibition of lipoprotein lipase activity, increase in lean mass and decrease in visceral adipose tissue mass [54].

Aging is associated with a decrease in sex hormone and SHBG levels leading hormonal imbalance; a relative increase in testosterone and decrease in estrogen levels in women and vice versa in men. Central obesity causes endocrine disturbances through various mechanisms that include increased sensitivity of the hypothalamic pituitary axis, increase in cortisol, decrease in sex specific steroids and increase in adrenal androgens in women [55]. Change in the hormonal milieu has been associated with development of MetS, largely mediated by insulin resistance [55, 56].

Association between MetS and hormones demonstrates sex dimorphism. Laaksonen et al. report a significant increase in the prevalence of MetS and Type 2 diabetes in men with hypoandrogenism [57]. Testosterone deficiency has been associated with insulin resistance, central obesity and hypertriglyceridemia in middle-aged men in several other studies [58]. Brand et al. in a meta-analysis of 52 studies that included 7839 women and 22,043 men describe a sex dependent association between testosterone and MetS [50]. MetS was reported to be associated with higher testosterone levels in women and lower testosterone levels in men [50]. In a meta-analysis by Ding et al., women with testosterone levels in the highest quartile were found to have a three-fold increase in the risk for development of Type 2 diabetes [59]. Higher estrogen levels have been associated with an increased risk of Type 2 diabetes in men and postmenopausal women [59, 60]. Men and women with low circulating levels of sex hormone binding globulin have been shown to have a higher risk of MetS and Type 2 diabetes [50, 56, 59]. Apart from regulating the free hormone levels, sex hormone binding globulin is postulated to have other biologic modulatory effects [61]. While sex hormone biding globulin is an independent risk factor for MetS, it is not clearly understood if this effect is mediated by an increase free hormone levels [62] or inherent modulatory properties of this molecule [61]. Low levels of sex hormone binding globulin have also been associated with development of hypertension and this is postulated to be due to the direct effects of sex hormone binding globulin on endothelial cells [63].

While the underlying pathophysiology of MetS involves a complex interaction of various biologic and sex hormone related factors, the sex related differences are not entirely hormone driven. This is evidenced by lack of benefit of hormone replacement therapy in the lowering the risk for MetS or CVD, in large studies in women such as the Women's Health Initiative study [64].

Relationship with Polycystic Ovarian Syndrome

Polycystic ovarian syndrome (PCOS) is a state of hormonal imbalance characterized by androgen excess, primarily mediated by hyperinsulinemia and insulin resistance [65]. Prevalence of MetS in women with PCOS has been reported to be 2-fold higher than in the general population. Women with PCOS were found to have significantly lower sex hormone binding globulin levels and higher free testosterone levels [66]. Hillman et al. studied the prevalence of MetS in 519 women with PCOS compared with age and race matched controls from the NHANES dataset. African American women with polycystic ovarian syndrome were at highest risk for MetS [67]. Components of MetS seen with a higher frequency in women with PCOS include impaired glucose tolerance, low HDL-C levels and high body mass index [68].

Clinical Implication of Sex Differences

The association between MetS and increased risk of incident Type 2 diabetes as well as CVD is clear [69, 70]. Whether MetS is an independent risk factor for CVD, or represents a summative risk of each of its component is under considerable debate. The nature of the definition of MetS allows for several permutations and combinations of components to come together to establish a diagnosis. Based on the data presented above, it is evident the presentation of MetS is different in men and women. However, whether these sex related differences in metabolic profiles are associated with a differential risk for

Type 2 diabetes, CVD and overall mortality, is not clearly known [71]. While there are studies that support the notion of differential risk based on the combination of MetS components [72], to our knowledge, only a very few sex specific analyses of CVD and mortality risk in patients with MetS have been described [71, 73]. Future studies from large community-based investigations should help better understand this concept of differential risk in MetS, as it is an important consideration when designing risk reduction strategies. For instance, dyslipidemia related differences between men and women suggest that statin treatment guidelines and risk calculators may need to be better formulated to treat differential risk. Obesity thresholds and management options may need to be tailored to sex since the distribution or fat as well as pattern of weight/fat loss differs between men and women [48]. Acknowledgement of sex related differences in MetS is essential in order to employ sex specific preventive and therapeutic strategies to reduce CVD and DM risk as well as improve overall population health.

Conclusion

The prevalence of MetS is reaching epidemic proportions worldwide and is influenced by various genetic, environmental and cultural factors. The overall prevalence of MetS rising steeply in countries going through an economic transition from underdeveloped to developing status. Socioeconomic empowerment increases buying power leading to a shift in the dietary patterns, increased dependence on mechanization and sedentary lifestyles. A significant sex disparity is obvious with women having a seemingly higher risk of having MetS, but men having a higher CV risk due to differences in prevalence of individual components included in defining MetS. Overeating, decreased physical activity, cultural expectations, educational and economic status contribute to sex and geographic disparities in MetS, in addition to hormonal and genetic factors, representing interplay between 'nature' and 'nurture'. Clinicians need to be made aware of differential risk of MetS imposed by sex in risk stratification and use of preventive strategies in the management of these patients.

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