Gender Aspects of the Role of the Metabolic Syndrome as a Risk Factor for Cardiovascular Disease

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ABSTRACT

Background: The interaction of the risk factors of abdominal obesity, disturbed glucose homeostasis, dyslipidemia, and hypertension is believed to represent a distinct entity, termed *the metabolic syndrome* (MetS), that leads to a greater increase in cardiovascular risk than does the sum of its components.

Objective: We reviewed currently available information regarding gender differences in the role of the MetS as a risk factor for cardiovascular disease (CVD).

Methods: Using the search terms *women*, *men*, *sex*, *gender*, *sex differences*, and *gender differences* in combination with *the metabolic syndrome*, we conducted a systematic review of the available literature on sex differences in the MetS. The National Institutes of Health, PubMed, and MEDLINE databases were searched retrospectively from 2007 to 1987. Reference lists of identified articles were also used as a source, and articles were not restricted to the English language.

Results: In recent years, the MetS has been more prevalent in men than in women but has risen particularly in young women, where it is mainly driven by obesity. Diagnostic criteria for the MetS vary for the cutoff points and definition of its components in a gender-specific manner. Based on the definition of impaired glucose homeostasis and pathologic abdominal circumference or waist/hip ratio, more or fewer women are included. Glucose and lipid metabolism are directly modulated by estrogen and testosterone, with a lack of estrogen or a relative increase in testosterone inducing insulin resistance and a proatherogenic lipid profile. Hypertension is a strong risk factor in both sexes, but the prevalence of hypertension increases more rapidly in aging women than in men. Menopause and polycystic ovary syndrome contribute to the development of MetS by the direct effects of sex hormones. Some components of the MetS (eg, diabetes and hypertension) carry a greater risk for CVD in women.

Conclusions: Future gender-related clinical and research activities should focus on the identification of sex- and gender-specific criteria for risk management in patients with the MetS. We propose small, focused, mechanistic studies on sex-specific surrogate end points and sex-specific studies in animal models for diabetes and aging. (*Gend Med*. 2007;4[Suppl B]:S162–S177) Copyright © 2007 Excerpta Medica, Inc.

Key words: metabolic syndrome, menopause, cardiovascular disease, gender differences.

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INTRODUCTION

The metabolic syndrome (MetS) was identified as a diagnostic entity in the 1980s, with the realization that obesity, disturbance of glucose metabolism, dyslipidemia, and hypertension formed an important cluster of cardiovascular risk factors. The combination of these risk factors is believed to represent a distinct entity that leads to a greater increase in cardiovascular risk than does the sum of its components.[1,2] We reviewed currently available information regarding gender differences in the role of the MetS as a risk factor for cardiovascular disease (CVD).

METHODS

We conducted a systematic review of the available literature on sex differences in the MetS. Using the search terms *women*, *men*, *sex*, *gender*, *sex differences*, and *gender differences* in combination with *the metabolic syndrome*, the National Institutes of Health, PubMed, and MEDLINE databases were searched retrospectively from 2007 to 1987. Articles were not restricted to the English language, and reference lists of identified articles were also used as a source.

IDENTIFICATION AND PREVALENCE OF THE METABOLIC SYNDROME

Several definitions of the MetS are currently available. They all include the risk factors of obesity, disturbance of glucose metabolism, dyslipidemia, and hypertension, but assign different weights to the individual risk factors, set different cutoff values, and differ in the feasibility of measuring the required parameters (**Table**).[3–8] The World Health Organization (WHO) definition is the only one to include impaired glucose tolerance (IGT) as a criterion for the MetS.[4] A number of women will be identified only by this criterion, because isolated IGT as a marker of prediabetes is relatively more prevalent in women than in men.[9–11] In contrast, the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III) definition relies on fasting glucose concentration, and determination of insulin resistance levels is not required.[5] Therefore, the NCEP/ATP III definition is more practicable than the WHO criteria for large-scale screening purposes. In both definitions, the presence of type 2 diabetes mellitus (DM) does not exclude the MetS. In Mexican Americans, the NCEP/ATP III criteria seem well suited for identifying individuals with MetS or with increased risk of diabetes.[12,13] In Germany, the NCEP/ATP III definitions are generally used to classify patients, thereby excluding women with IGT, who would receive the diagnosis of MetS using the WHO criteria. The European Group for the Study of Insulin Resistance (EGIR) compared their definition of the prevalence of the MetS with the WHO's definition in different European populations.[14] Classification according to the WHO definition led to a 50% higher estimation of prevalence in 3 different age groups (<40, 40–55, and >55 years) in nondiabetic patients (women: WHO [4%, 13%, and 26%, respectively] vs EGIR [3%, 7%, and 17%, respectively]; men: WHO [14%, 23%, and 41%, respectively] vs EGIR [10%, 9%, and 22%, respectively]), and to a higher prevalence in men than in women (**Figure 1**).[7] This can mainly be explained by the different cutoff values for central obesity for women and men in the WHO and EGIR criteria. Diagnosis of the MetS using the American College of Endocrinology criteria depends on clinical judgment based on risk factors and may therefore be less reproducible. The criteria of the International Diabetes Federation also rely mainly on clinical judgment.

A highly age-dependent prevalence of the MetS has been a consistent finding worldwide.[15] In recent years, MetS has increased in prevalence and now affects ~30% of the adult population in the United States. An age-adjusted greater increase in the prevalence of the MetS in women than in men was observed in the United States. Women aged <40 years had a 76% relative increase of prevalence of the disease compared with a nonsignificant increase of 5% in men in this age group (**Figure 2**).[7] This was mainly due to the consistent rise in obesity in women, which presently affects 2 million more women than men in the United States.[16]

Table. Definitions of the metabolic syndrome from the European Group for the Study of Insulin Resistance (EGIR),[3] the World Health Organization (WHO),[4] the National Cholesterol Education Program/ Adult Treatment Panel III (NCEP/ATP III),[5] and the American College of Endocrinology (ACE),[6] as adapted.[7]

EGIR	WHO	NCEP/ATP III	ACE
Insulin resistance hyperinsulinemia	Diabetes or IFG or IGT or insulin resistance		
Plus ≥2 of the criteria below	Plus ≥2 of the criteria below	≥3 of the criteria below	No defined number is specified
Central obesity waist ≥80 cm for females or ≥94 cm for males	Obesity BMI >30 kg/m^2 or WHR >0.85 for females or >0.9 for males	Central obesity waist ≥88 cm for females or ≥102 cm for males	Overweight/obesity BMI ≥25 kg/m^2
HDL-C <1.0 mmol/L (<40 mg/dL) or TG >2.0 mmol/L (>180 mg/dL)	HDL-C <1.0 mmol/L (<40 mg/dL) for females or <0.9 mmol/L (<35 mg/dL) for males; TG ≥1.7 mmol/L (≥194 mg/dL)	HDL-C <1.3 mmol/L (<50 mg/dL) for females or <1.0 mmol/L (<40 mg/dL) for males; TG ≥1.7 mmol/L (≥194 mg/dL)	HDL-C <1.29 mmol/L <50 mg/dL) for females or <1.04 mmol/L (<40 mg/dL) for males; TG ≥1.69 mmol/L (≥193 mg/dL)
Hypertension ≥140/ 90 mm Hg and/or medication	Hypertension ≥140/ 90 mm Hg	Hypertension ≥135/ 85 mm Hg or medication	Hypertension ≥130/ 85 mm Hg
Fasting plasma glucose ≥6.1 mmol/L (≥110 mg/dL)		Fasting plasma glucose ≥6.1 mmol/L (≥110 mg/dL)	Fasting plasma glucose 6.1–6.99 mmol/L (110–125 mg/dL)
	Microalbuminuria >20 µg/min or albumin/creatinine ratio ≥30 mg/g		Family history of type 2 DM, CVD, PCOS; sedentary lifestyle; advancing age; ethnic groups with high risk for type 2 DM or CVD

IFG = impaired fasting glucose; IGT = impaired glucose tolerance; BMI = body mass index; WHR = waist-to-hip ratio; HDL-C = high-density lipoprotein cholesterol; TG = triglycerides; DM = diabetes mellitus; CVD = cardiovascular disease; PCOS = polycystic ovary syndrome.

In Europe, a continuing increase has also been observed in the prevalence of the MetS. European studies still indicate lower prevalences of MetS than do US studies, and lower prevalences in women than in men.[14,17,18] In a recent study in France, a prevalence of the MetS of 10.1% and 6.2% was reported in men and women (mean age, 47.4 and 48.5 years), respectively.[17] In Hungary, the general prevalence of the MetS was 11.5% (14.9% in men and 8.6% in women).[18] One study compared prevalence rates in the United States and Europe, choosing San Antonio, Texas (patients from the San Antonio Heart study) and Spain (patients from a Spanish insulin resistance study). In men, the MetS was less prevalent in Spain than in Texas (20.8% vs 28.9%). Surprisingly, in women the MetS was more prevalent in Spain (30.9% vs 27.1%). The most prevalent component of the MetS in Spanish women was waist/hip ratio (66.4% vs 40.2% in Texas), and in Spanish men it was high blood pressure (48.1% vs 33.9% in Texas).[19]

CONTRIBUTION OF OBESITY IN WOMEN AND MEN

Lipid accumulates differently in women's bodies than in men's. Peripheral adiposity with gluteal fat accumulation characterizes premenopausal

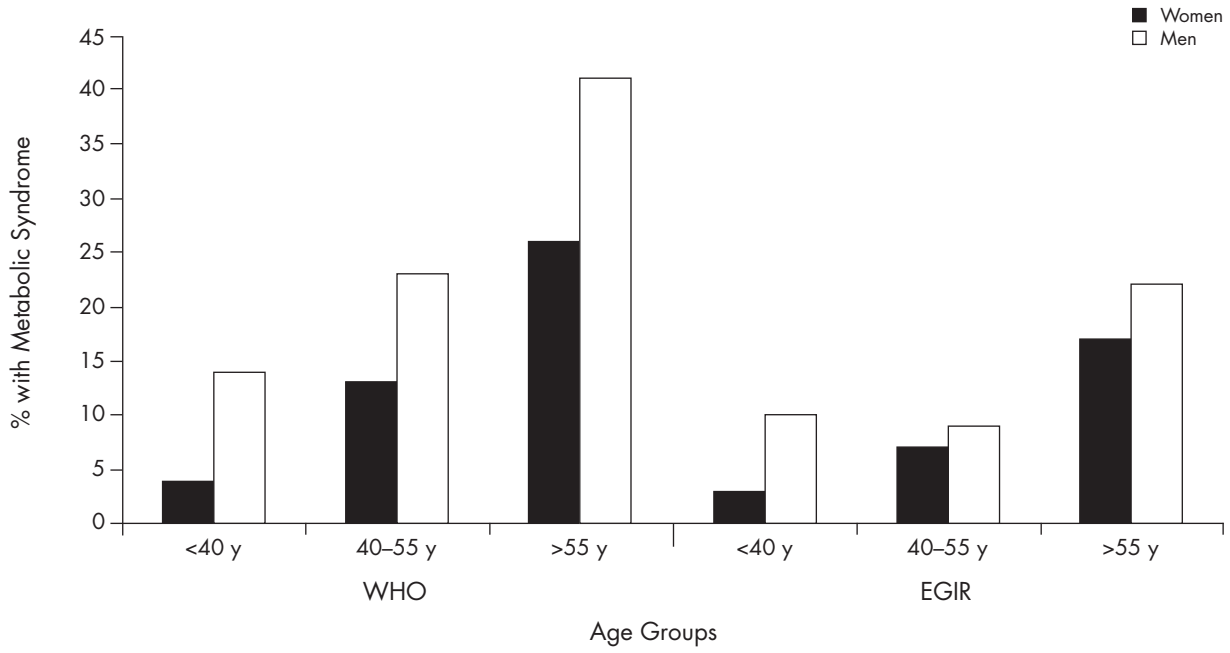

Figure 1. Prevalence of the metabolic syndrome according to World Health Organization (WHO) and European Group for the Study of Insulin Resistance (EGIR) classifications of women and men. Adapted with permission.[7]

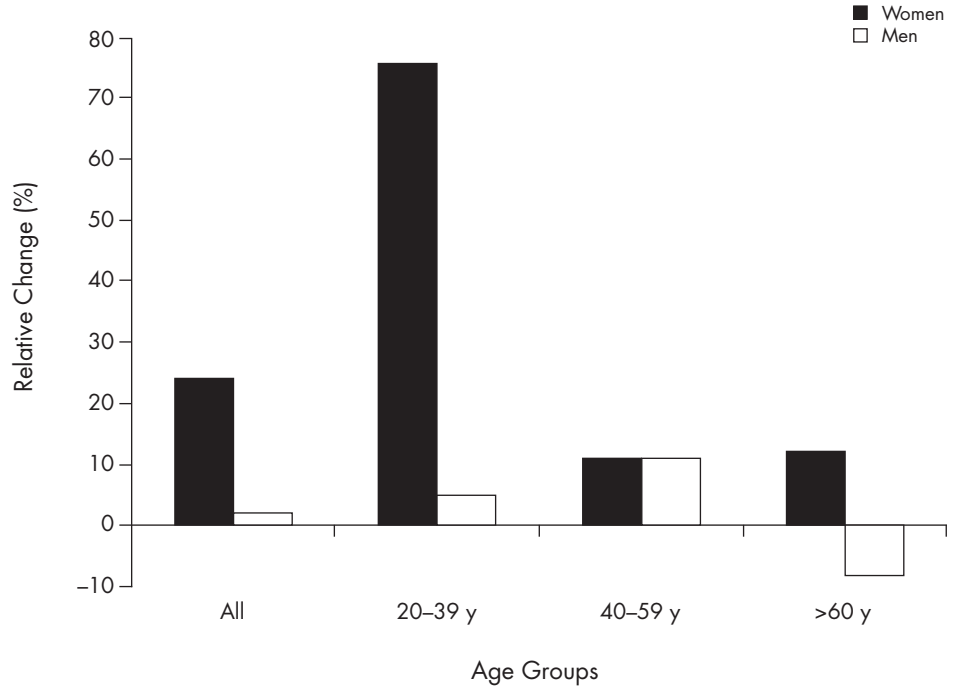

Figure 2. Relative change (%) in age-adjusted and age-dependent prevalence of the metabolic syndrome in US population of women and men. Adapted with permission.[7]

women.[20] However, in the perimenopause, women frequently become obese and the body fat distribution develops a more male pattern, which is termed *android obesity*.[21,22] The changes are closely related to the hormonal state: a decrease in ovarian hormones, a decrease in thyroid function, an increase in androgens, and a decrease in leptin concentration.[23,24] A tendency toward an increase in central obesity is also observed in males in advanced age and in both sexes after gonadectomy.[25]

The shift from peripheral to visceral obesity has a number of negative consequences. First, visceral fat is an important source of free fatty acids and inflammatory mediators (eg, tumor necrosis factor-α, interleukins, and adipokines), which are directly delivered to the liver via the portal vein. Both free fatty acids and inflammatory mediators affect hepatic glucose and fat metabolism and contribute to the development of hepatic insulin resistance.[26,27] Visceral adipocytes differ from peripheral adipocytes in their lipolytic activity and their response to insulin, adrenergic and angiotensin stimulation, and sex hormones. Estrogens decrease noradrenalin-stimulated lipolysis in women by upregulating the number of α-2 adrenergic antilipolytic receptors in adipose tissue.[28] Higher rates of lipolysis in men, which contribute to unfavorable plasma lipid profiles, are regulated by α- or β-adrenergic receptors, creating a link between sympathetic stimulation and cardiovascular risk.[26,29]

In addition to inflammatory mediators, fat produces various bioactive substances that modulate lipid, glucose, and hormone metabolism. Leptin is secreted from adipose tissue, mainly from subcutaneous fat and less from omental fat,[30] and inhibits food intake by central control mechanisms. Leptin concentrations are higher in women than in men.[31] It has been speculated that low leptin secretion from omental fat contributes to the development of visceral obesity in men.[30,32] Adiponectin is an adipose tissue-derived plasma protein with antiatherogenic and insulin-sensitizing activities. Hypoadiponectinemia is closely related to the clinical phenotype of the MetS.[33] Physiologically, women appear to have higher adiponectin concentrations than do men.[33,34] In the Pittsburgh Epidemiology of Diabetes Complications Study, adiponectin concentrations were elevated in women with type 1 DM compared with their male counterparts, and adiponectin concentrations inversely predicted the incidence of coronary artery disease (CAD).[34] No clear association of adiponectin with coronary heart disease (CHD) or mortality was found in the Rancho Bernardo Study.[35] Thus, use of adiponectin in cardiovascular risk prediction and in sex-specific predictions for CVD risk seems premature at present.

Fat tissue is not only a source of cytokines, but also interferes with hormone metabolism. White fat is the major source of estrogens in elderly women and men, because testosterone is converted there to estradiol in women and men. The conversion is related to adipocyte functions. Obese male subjects exhibit reduced plasma testosterone concentrations and altered cortisol secretion and growth hormone concentrations.[36] Thus, adipocyte dysfunction in visceral obesity may participate in the development and progression of hormonal disturbances and the MetS.

Along with lack of physical activity and consumption of too many calories, a number of genetic variables play a role in the development of obesity. Some genetic polymorphisms act in a sex-specific manner. For example, mutations in the peroxisome proliferator–activated receptor (*PPAR)* genes affect obesity differently in women and men. Two polymorphisms in the *PPAR γ-2* gene are associated with severe overweight in women only.[37] Inherited factors can play different roles in women and men.

The partially sex-dependent differences between subcutaneous and abdominal fat may provide one explanation of why android obesity is linked to increased cardiovascular mortality.[36] The reduced tendency to accumulate fat at intra-abdominal sites may be one of the primary metabolic differences underlying the reduced risk of CVD, the MetS, and diabetes in women.[20,38,39]

In both sexes, obesity is associated with an increased risk for CAD and heart failure. In young women, obesity was a significant predic-

tor of increased myocardial oxygen consumption and decreased myocardial efficiency.[40] The study was limited to women, because the authors argued that obesity was a more severe risk factor for heart failure in women than in men. Because overweight is frequently associated with increased incidences of left ventricular hypertrophy, diabetes, hypertension, and dyslipidemia, it is still not known whether it represents an independent risk factor. A recently published study in a large French cohort suggests that overweight is a cardiovascular risk determinant mainly because of its frequent association with hypertension.[41]

HYPERLIPIDEMIA AND DYSLIPIDEMIA

Circulating lipids are different, are differently regulated, and have different significance in women and men. Concentrations of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and plasma triglycerides (TG) are lower, and high-density lipoprotein cholesterol (HDL-C) concentration is higher, in premenopausal women compared with men, partially due to the effects of estrogen.[20] Women normally have greater activity in lipoprotein transport and removal of very-low-density lipoprotein cholesterol (VLDL-C) from the plasma than do men. Thus, an equivalent impairment in lipoprotein turnover induced by obesity or diabetes leads to a greater rise in plasma lipoproteins in women.[42] The elevation in TC concentration in postmenopausal women is mainly due to LDL-C, because menopause leads to a decrease in HDL-C concentration.[43] In addition, the increase in visceral fat after menopause drives increased synthesis of VLDL-C, leading to elevated triacylglycerol concentrations in the fasting state. An increase in lipoprotein (a) [Lp(a)] can contribute to the procoagulatory effects of menopause.[44,45] Together, these menopause-induced lipid changes are proatherogenic and procoagulatory. The available epidemiologic data indicate that elevated TG and Lp(a) concentrations are more important cardiovascular risk factors in women than in men. In men, TC and LDL-C are the most significant risk factors.[46,47] Plasma TG concentration is also one of the most important risk factors for the development of diabetes in women; it is less important in men.[9]

HYPERTENSION

Premenopausal women have a lower tendency to develop hypertension than do age-matched men. However, in advanced age, the increase in the rate of hypertension is steeper in women than in men, leading to a prevalence of hypertension of 69% in men and 72% in women at age 65 to 75 years.[48] The increased incidence of hypertension postmenopause may be mainly due to the activation of the renin–angiotensin system (RAS) and to the development of obesity.

The RAS is regulated differently in men and women, with endogenous estrogen suppressing the prohypertensive angiotensin receptor type 1 and stimulating the protective angiotensin receptor type 2 (AT2) and angiotensinogen synthesis.[49] Activation of the RAS may play a role in the postmenopausal increase in hypertension in women.[50] The RAS and sex hormones also influence pressure natriuresis, renal hemodynamics, and tubular response to salt.[51–53] This partially explains why women exhibit low salt sensitivity in their blood pressure regulation before menopause and become increasingly salt-sensitive after menopause.[52]

The Framingham Heart Study and the Nurses' Health Study clearly showed that obesity is associated with hypertension, and that android obesity, in particular, is an independent risk factor for the development of hypertension.[52] Obesity and hyperinsulinemia induce hypertension by an increase in intraabdominal pressure, glomerular and tubular effects, and direct vasoconstricting actions of insulin.[54] In centrally obese hypertensive women, accumulation of visceral abdominal fat is accelerated by menopause and is associated with higher blood pressure levels and insulin resistance.[55]

Genetic variables modify the hypertensive phenotype in a sex-dependent manner. Sex differences have been found for the association of hypertension with polymorphisms in a coactivator of PPAR-γ (*PGC1*) and the AT2 receptor.[56–58]

Once established, hypertension carries a relatively greater risk in women compared with men.[59] The age-dependent risk associated with hypertension and hyperlipidemia has been determined in the Framingham and the Prospective Cardiovascular Munster (PROCAM) study cohorts and has been used to calculate risk assessment scores. Only in the new European System for Cardiac Operative Risk Evaluation (EuroSCORE) study have numbers for women and men been determined in a comparative manner.[60] The beneficial effects of antihypertensive therapy were found to be comparable in women and men.

GLUCOSE METABOLISM

Disturbances in glucose metabolism exhibit some relatively unknown sex and gender differences. In recent epidemiologic studies (European Prospective Investigation into Cancer and Nutrition [EPIC]; H.G. Joost, PhD, oral communication, October 2005) diabetes seems to have become more common in women than in men in Germany. In the Cooperative Health Research in the Region of Augsburg (KORA) study, the prevalence of overt diabetes was comparable in women and men, but elevated fasting blood glucose concentrations were found more frequently in nondiabetic men, whereas IGT was found more frequently in nondiabetic women.[9] A total of 8.7% of the KORA population had known and 8.2% had previously unknown diabetes, 16.4% had IGT, and 7.2% had elevated fasting glucose (EFG) concentration. IGT affected 17.0% of men and 15.7% of women, and EFG affected 9.9% of men and 4.4% of women. Thus, in men, IGT occurred approximately twice as frequently as EFG, whereas in women, it was 3.5-fold as frequent. Therefore, 50% of women compared with 34% of men with newly diagnosed diabetes had disturbed glucose tolerance, which could only be detected by 2-hour glucose measurements. This agrees with data from the Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study[61] and from investigations from other parts of the world, such as the Mauritius study and the Risk Factor in IGT for Atherosclerosis and Diabetes (RIAD) cohort, demonstrating that the prevalence of diabetes and impaired glucose homeostasis defined by isolated postload hyperglycemia is higher in women than in men, but the prevalence of diabetes and EFG is higher in men.[11,62–65] Also in agreement with these findings are the results of the Rancho Bernardo Study in elderly patients, in which the diagnosis of diabetes solely based on post-challenge hyperglycemia was made more frequently in women than in men.[66] Isolated post-challenge hyperglycemia was the only predictor of diabetes in 72% of women compared with 48% of men. The diagnosis would have been missed if only the criterion of impaired fasting glucose had been used.

Pathologic post-challenge glucose concentrations mainly reflect insulin secretion disturbances, whereas EFG is more closely related to primary insulin resistance.[11,66] Thus, a different pathophysiology of diabetes development in women and men could contribute to the different prevalences in EFG and IGT. Diabetes and impaired glucose homeostasis have been linked to X chromosome loci,[67] but the relative contribution of these loci to the clinical syndrome remains unknown.

Insulin resistance is associated with greater relative cardiovascular risk in women compared with men (**Figure 3**).[68] Isolated post-challenge hyperglycemia is an independent predictor of cardiovascular events in older women, but not in older men.[69] Many studies have reported a relatively greater increase in cardiovascular risk with the occurrence of diabetes in women than in men.[69–72] Whereas diabetic women have a 3- to 6-fold increased risk of myocardial infarction (MI), diabetic men have a 2- to 4-fold increased risk.[70] The Framingham Heart Study, the Chicago Heart Association Detection Project in Industry, and the Minnesota Heart Survey all found that diabetic patients had a greater risk of developing heart failure after MI and confirmed the higher relative increase in early and late mortality in women compared with men when diabetes developed.[68] A relatively greater increase in the diabetes-associated risk of MI in women

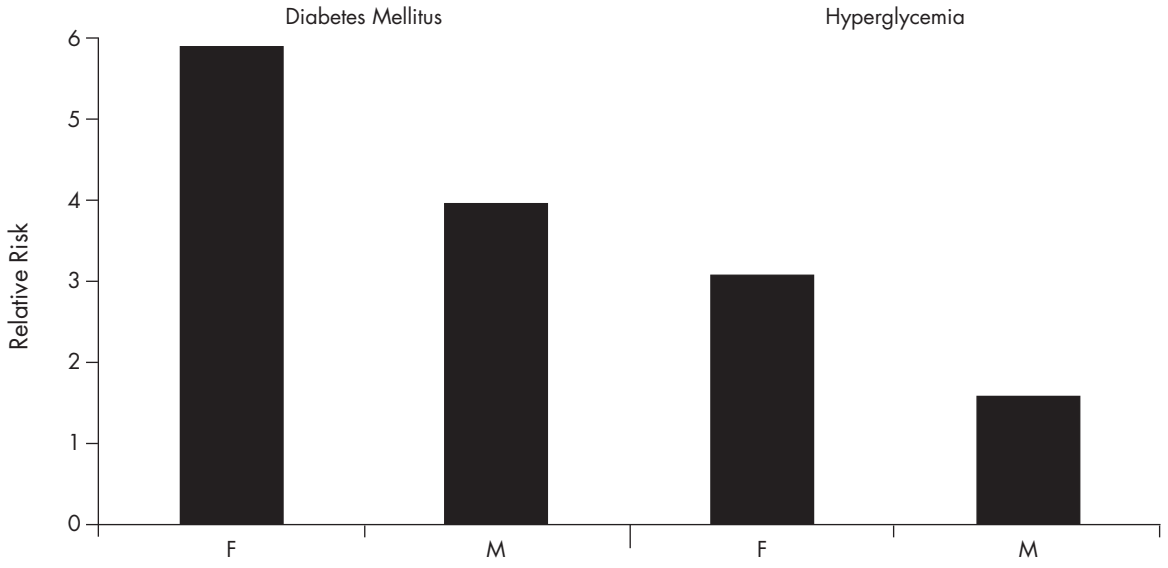

Figure 3. Cardiovascular risk associated with diabetes mellitus and hyperglycemia in females (F) and males (M).[68]

compared with men was also found in the Swedish Monitoring Trends and Determinants on Cardiovascular Diseases (MONICA) project, which attributed 17% of infarctions in women and 11% of infarctions in men to diabetes and described a higher relative increase in mortality from MI with diabetes in women (7-fold) compared with men (4-fold).[70] This more-severe effect of diabetes may be related to differences in the fibrinolytic system and endothelial function. Diabetes and insulin resistance reduce the physiologically higher fibrinolytic potential in women,[73] and also nullify sex differences in nitric oxide availability and endothelial function.[74] Long-term data have been obtained in the Rancho Bernardo cohort, which reported a 14-year, sex-specific effect of noninsulin dependent diabetes on cardiovascular outcome.[71] The relative hazard of diabetic versus nondiabetic patients was 1.8 in men and 3.3 in women after multivariate adjustment for other risk factors.[72] A meta-analysis of 37 prospective cohort studies including 447,064 diabetic patients confirmed that the increase in risk for fatal CAD from diabetes was greater among women (3.5-fold) than among men (2.06-fold).[75]

EFFECT OF SEX HORMONES ON THE METABOLIC SYNDROME AND ITS COMPONENTS

Disturbances of sex hormones (eg, polycystic ovary syndrome [PCOS]) represent a risk factor for diabetes and CVD, and PCOS affects 4% to 6% of women of reproductive age.[76] Women with PCOS have elevated rates of obesity, central adiposity, insulin resistance, IGT, DM, hypercholesterolemia, hypertension, and atherosclerosis. Insulin resistance is found in ~50% of young women with PCOS. Insulin excess modifies sex hormone-binding globulin (SHBG) in the liver, favors androgen synthesis in the ovarian thecal cells, and leads to hyperandrogenic states (**Figure 4**).[77] Therefore, obesity-related hyperinsulinemia plays a key role in the development of the MetS in women with PCOS.[78,79] Hyperandrogenism favors the development of insulin resistance and android obesity in women with PCOS. The relationship of plasma insulin to sex hormones in a small sample of black adults suggested that hyperinsulinemia cosegregates with increased androgenicity in females, creating a genetic link between the syndromes.[63]

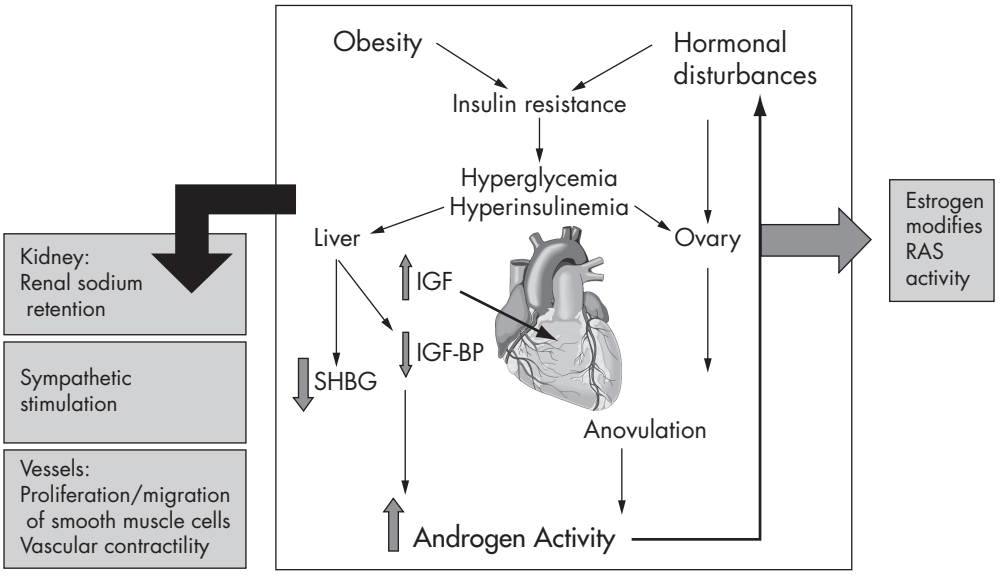

Figure 4. Interaction between obesity, insulin resistance, and sex hormones, and effects on heart and vasculature. IGF = insulin-like growth factor; BP = blood pressure; SHBG = sex hormone-binding globulin; RAS = renin–angiotensin system.

Alterations in sex hormones in the menopause also lead to metabolic alterations. Whereas the decline in ovarian function leads to a reduction in estrogen production, androgen synthesis by the adrenal cortex is less affected. The resulting higher ratios of estrone to estradiol and of androgens to estrogens may be partially responsible for menopause-related metabolic changes.[8,80] Menopause is associated with an increase in all single components of the MetS (ie, with the development of android obesity, hypertension, unfavorable changes in the lipid profile, and hyperinsulinemia).[24]

Complications of pregnancy (eg, gestational diabetes and preeclampsia) share similarities with the MetS in the activation of inflammatory cytokines and the RAS.[81,82] Both conditions are powerful predictors for the development of diabetes and CVD later in life.

Testosterone also has direct effects on components of the MetS. Its effects on lipid metabolism directly counteract those of estrogen,[42] and testosterone negatively influences renal function, establishing a predisposition to hypertension.[83–85] In elderly men, SHBG was found to correlate inversely with the MetS.[86] However, low SHBG concentration, which leads to high free androgen concentration, and low testosterone concentration were both correlated with abnormal glucose tolerance and cardiovascular risk factors. Low and high testosterone concentrations in men have been associated with CVD risk[87]; however, large-scale intervention studies to clarify these issues are lacking.

SEX DIFFERENCES IN CARDIOVASCULAR RISK ASSOCIATED WITH THE METABOLIC SYNDROME

It was assumed that using the MetS leads to additional power in predicting cardiovascular events that exceeds the sum of the combination of the risk factors involved. Accordingly, in a large community-based sample of Swedish middle-aged men in Uppsala County, the presence of the MetS increased the risk for total and cardiovascular mortality by 40% to 60% when the established risk factors for CVD were taken into account.[88–90]

However, other recent studies have claimed that the NCEP/ATP criteria for the MetS are inferior to established predictive models for CAD, particularly if diabetic patients are excluded.[10,91] This also agrees with data from the Copenhagen City Heart Study, which showed that it is possible to fit a simple linear model for the effect of changed numbers of metabolic risk factors to the risk of CAD.[92] The introduction of the MetS was not found to be necessary to improve risk prediction. In a prospective study of 5128 men aged 40 to 59 years with no history of CVD (ie, CHD or stroke) or type 2 DM, drawn from general practices in 24 British towns and followed for 20 years, the presence of the MetS was a significant predictor of CVD and type 2 DM but a stronger predictor of type 2 DM than of CHD. The MetS did not predict CHD as well as did the Framingham risk score, but it served well as a simple clinical tool for identifying high-risk individuals predisposed to CVD or diabetes.[93] Although the MetS includes the major risk factors, they are defined dichotomously and therefore cannot predict CVD as accurately as a risk model based on continuous variables.[10]

These uncertainties regarding the diagnostic power of the MetS, and the fact that in early studies on cardiovascular risk associated with the MetS, outcomes were not specified according to gender and were first assessed in men or male-dominated cohorts,[94,95] make it difficult to assess sex differences in the predictive value of the MetS. A recent study found that the MetS worsens the prognosis of women with CAD,[96] with an ~5-fold increase in risk. In women with CVD, the predictive value of the MetS was higher than the homeostasis model assessment index for insulin resistance alone. In women without CAD, developing the MetS had only a weak impact on the prognosis of cardiovascular events. It has been speculated that the increased risk due to the MetS in women with preexisting CAD might be caused by associated inflammatory processes, promoting destabilization of preexisting atherosclerotic plaques. Thus, the value of the MetS for cardiovascular risk assessment requires further appraisal.

CLINICAL AND RESEARCH IMPLICATIONS

Some of the findings described previously have direct clinical implications. Risk factors for diabetes should be considered in a gender-specific manner, with more weight on elevated TG concentration in women and on waist circumference in men. Physicians should recognize that incident diabetes probably carries a stronger cardiovascular risk in women than in men, even though there are not yet enough data to install gender-specific criteria for the diagnosis of prediabetes. Patients with disturbed glucose homeostasis should be critically evaluated to determine whether other risk factors are present, and if so, diagnostic tests for myocardial ischemia should be performed, with the recognition that pharmacologic stress testing and imaging procedures are particularly useful in women.[7,97] In Europe, we need to develop specific aspects in our guidelines to cover cardiovascular risk management in women, as has been accomplished in the United States.[98]

Clinical long-term follow-up studies in women with suspected CAD are needed to assess the effects of sex hormone disturbances. In addition, we need more gender-specific pathophysiologic analysis in small focused studies with mechanistic and surrogate end points, such as exercise tolerance, endothelial function, intima media thickness, or coagulatory factors. Clinical and pathophysiologic studies should also assess the response to hormone therapy in women and men. The outcome after cardiovascular interventions in dependence on hormone status should also be studied. Epidemiologic studies should be conducted to clearly define threshold values or gender-specific relative risk in women and men. In part, gender differences can be identified in animal models, and mechanistic studies in animal models can contribute to an understanding of the sex-specific role of diabetes and its interaction with cardiovascular function. Models of MI and pressure overload in diabetic animals with consideration of both sexes in different age groups may contribute to such an understanding. The role of estrogens and androgens can be identified in deletion and substitu-

tion studies, and genetic models can help to identify the hormone receptors involved.[7]

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