Cardiac Health in Women With Metabolic Syndrome: Clinical Aspects and Pathophysiology

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Although the classical cardiovascular risk factors (e.g., smoking and hypertension) are becoming more effectively managed, a continuous increase of the so-called “cardiometabolic risk” is noted. Starting from this century, the nomenclature “metabolic syndrome” has become more popular to identify a cluster of disorders including obesity, dyslipidemia, hypertension, and insulin resistance. It is a primary risk factor for diabetes and cardiovascular disease in both genders. Interestingly, the metabolic diseases display a distinct gender disparity with an apparent “female advantage” in the premenopausal women compared with age-matched men. However, women usually lose such “sex protection” following menopause or affliction of metabolic syndrome especially insulin resistance. A controversy exists in the medical literature concerning whether metabolic syndrome is a real syndrome or simply a cluster of risk factors. Several scenarios are speculated to contribute to the gender dimorphism in the cardiovascular sequelae in patients with metabolic syndrome including sex hormones, intrinsic organ function, and the risk factor profile (e.g., hypertension, dyslipidemia, obesity, sedentary lifestyle, and atherogenic diet). With the alarming rise of obesity prevalence, heart problems in metabolic syndrome continue to rise with a distinct gender dimorphism. Although female hearts seem to better tolerate the stress insults compared with the male counterparts, the female sex hormones such as estrogen can interact with certain risk factors to precipitate myopathic changes in the hearts. This synthetic review of recent literature suggests a role of gender disparity in myopathic factors and risk attributable to each metabolic component in the different prevalence of metabolic syndrome.

METABOLIC SYNDROME, HEART DISEASES, AND GENDER DISPARITY

Clinical and experimental evidence has demonstrated that risk factors for cardiovascular disease often cluster together, most notably overweight/obesity, diabetes mellitus, dyslipidemia, and hypertension (1). Over the past several decades, the intensive clinical management to fight against cardiovascular diseases has resulted in a dramatic reduction in cardiovascular mortality. However, many patients still fail to achieve adequate and satisfactory clinical management of cardiovascular risk factors. In addition, the growing prevalence of obesity (~66% of Americans are overweight or obese) and type 2 diabetes mellitus threatens to undermine the improvement in the management of cardiovascular diseases (2).

Even modest excess body weight gain may lead to a significant increase in the risk of cardiovascular mortality. The increased incidence of obesity may also predispose the onset of other key cardiovascular risk factors such as hypertension, dyslipidemia, insulin resistance, and type 2 diabetes (2). This cluster of risk factors has been collectively known as cardiometabolic syndrome or metabolic syndrome after the beginning of this century. In essence, unlike diabetes, metabolic syndrome is not a specific disease but rather a cluster of factors predisposing to the development of cardiovascular diseases. Since its appearance in the medical vernacular two decades ago, the cardiovascular sequelae of metabolic syndrome have been widely recognized. Recent criteria consider metabolic syndrome as a cluster of symptoms including large waist size (central obesity), hypertension, hyperglycemia, dyslipidemia, and insulin resistance, all commonly associated with the increased prevalence of obesity and type 2 diabetes mellitus (3). Moreover, metabolic syndrome may lead to deteriorated cardiac geometry and function independent of any macrovascular and microvascular diseases (4,5). Myocardial contractile dysfunction especially diastolic dysfunction is the most prominent cardiac defect associated with metabolic syndrome especially obesity and type 2 diabetes characterized by reduced ventricular compliance and myocardial relaxation (4–6). Systolic and diastolic dysfunctions are usually manifested as prolonged ventricular contraction and relaxation duration, reduced velocity...
of ventricular contraction and relaxation, and depressed myocardial compliance (4,7–9). Several mechanisms are known to contribute to the myocardial dysfunction including reduced energy production due to decrease in mitochondrial respiration and pyruvate dehydrogenase activity, oxidative stress, defective cardiac contractile, and intracellular Ca\(^{2+}\) regulatory proteins such as myosin, titin, sarco(endo)plasmic reticulum Ca\(^{2+}\)-ATPase, phospholamban, and Na\(^+\)-Ca\(^{2+}\) exchanger (10). The high prevalence of cardiac problem in patients with metabolic syndrome warrants a more stringent clinical management. Up-to-date, the two primary approaches to optimally control risk factors associated with metabolic syndrome are lifestyle modification and medication. Pharmacologic therapies currently available for the cardiovascular treatment of metabolic syndrome include angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, digoxin, diuretics, \(\beta\)-blockers, and Ca\(^{2+}\) channel blockers (11,12). The insulin-sensitizing agents such as thiazolidinediones and peroxisome proliferators–activated receptors subtypes \(\alpha/\gamma\) agonists are recommended over insulin secretagogues to reconcile hyperinsulinemia and insulin resistance (12). Lipid/cholesterol-lowering drugs, fibric acid derivatives, endocannabinoid receptor antagonists and several agents that modulate the activity of glucagon-like peptide-1 are the newer medications with the potential to improve several cardiovascular risk factors significantly for long-term management (13). Although a wide variety of pharmacological targets and agents have been discovered, the clinical management of cardiovascular risk associated with metabolic syndrome is still dismal. Typically, the first recommended step for the management of metabolic syndrome is lifestyle modifications such as smoking cessation, weight loss, aerobic exercise, and improved diet, all of which may improve insulin resistance and retard progression to type 2 diabetes mellitus (14). Nonetheless, success obtained via lifestyle modification may be limited and difficult to sustain. It has been commonly accepted that specific dietary changes may only be appropriate for certain aspects of metabolic syndrome (15). For example, reduction in the intake of saturated fat intake, sodium and high-glycemic-index carbohydrate may help to lessen the risk of insulin resistance, hypertension, and hypertriglyceridemia, respectively.

Metabolic syndrome afflicts both men and women of all races and increases the risk of heart disease in both genders, although it seems to elicit a greater impact in women. In the recent Atherosclerosis Risk in Communities Study including 2,932 black and 9,777 white men and women aged 45–64 years without diabetes at baseline, difference in the prevalence of metabolic syndrome was identified, namely 40% of black women, 30% of white women, 28% of black men, and 35% of white men. More interestingly, no correlation between socioeconomic status and metabolic syndrome was detected in male (black or white) participants, although black and white women with low-to-medium socioeconomic status were more likely to have metabolic syndrome compared with those with high socioeconomic status (16). A better understanding of the gender difference should help to offer insights for reducing the prevalence of metabolic syndrome and its disease sequelae. For example, it has been demonstrated that women display a stronger positive association between waist circumference and insulin resistance than in men (17), making waist circumference (>88 cm) alone is nearly as good as metabolic syndrome in predicting insulin resistance in women. Without metabolic syndrome, women display a significantly lower risk of heart disease before menopause but only lose this “female advantage” following menopause. It is speculated that the interaction between female sex hormones such as estrogen and certain risk factors for metabolic syndrome be responsible for such “gender bias” in the disease sequelae. With the increased life expectancy, an average woman will spend one-third to one-half of her life in an “estrogen-free” status. Thus, one critical issue most postmenopausal diabetic women have to face is the impact of estrogen replacement therapy on the prevalence of metabolic syndrome. Estrogen replacement therapy has been shown to reduce the incidence of type 2 diabetes and improve glycemic control, although the results seem to vary depending on patient’s individual variance, the route and dose of estrogen administration (5,18,19). Although it is still controversial with regards to the benefit-risk ratio of coronary heart disease for estrogen replacement therapy, benefit has been implicated largely for younger postmenopausal diabetic women (19). It is advised that cardioprotective treatment adjuncts (such as statins or low-dose aspirin) should be included for postmenopausal diabetic women with proven heart disease risk. Nonetheless, these cardioprotective agents are not typically recommended for the sole purpose of cardiovascular disease prevention. This review discusses the gender difference in a wide range of contributing/confounding factors for cardiac sequelae of metabolic syndrome and the role of estrogen in the regulation of glucose and insulin metabolism, neurohormonal and myogenic factors involved in the onset and progression of metabolic syndrome. It should be mentioned that “other” factors such as the male sex hormone testosterone (20), age (21,22), and race (16,23) may also participate in the manifestation of gender dimorphism of metabolic syndrome and its cardiac complications, which will not be discussed due to space limitation.

**GENDER DISPARITY IN CARDIAC PROPERTY AND METABOLIC SYNDROME**

Global cardiovascular risk is the probability of affliction of a coronary event or stroke deriving from risk factors including metabolic factors (total cholesterol, high-density lipoprotein cholesterol (HDL-c), blood glucose), hemodynamic factors (blood pressure), and lifestyle factors (exercise, smoking), all modifiable beyond those nonmodifiable ones such as age and gender. For decades, women’s health has been viewed in a “bikini” style, focusing mainly on breast and reproductive system. This rather misleading health care tactics essentially assumes equal propensity to diseases...
and drugs between genders. Although women are equally afflicted by cardiovascular diseases, cancer, diabetes, and respiratory diseases compared with men, the gender disparity in the onset and progression of diseases, clinical manifestation, and management has prompted the discipline of gender-specific medicine (24). Compared to men, women are usually better protected from cardiovascular diseases (25–28). However, such “female advantage” usually vanishes following menopause, and is presumably related to the reduced levels of female sex hormones especially estrogen (28–30). Following menopause, estrogen deficiency may adversely affect the metabolic profile including glucose and lipid metabolism, leading to an abrupt increase in the incidence of cardiovascular morbidity and mortality in postmenopausal women. In a retrospective search focusing on metabolic syndrome using the National Institutes of Health, PubMed, and MEDLINE databases between 1987 and 2007, men are found to possess higher metabolic syndrome prevalence than women. Interestingly, data revealed a recent rapid rise in women particularly young women largely driven by obesity (31). An ample of data has suggested that interaction among metabolic factors, neurovascular regulation, myocardial and electromechanical property plays a role in the gender disparity in cardiovascular disease (25,26). Although women seem to present less severe clinical symptom upon heart attack compared with men (32), the prognosis is usually worse in women recovering from a heart attack. Approximately 40% of women die within a year of their first heart attack compared with 25% in men. The risk of having a second heart attack within 6 years of the first one is doubled in women (32). Therefore, gender awareness becomes an issue not only for gender advantage but also for potential “female gender bias.” In fact, females of all ages have been underrepresented in clinical research historically. The long-lasting female underrepresentation in clinical studies has generated in the “gender blindness” in the understanding, diagnosis, and treatment of disease between men and women (33). Reasons for this female gender exclusion are multifactorial and may possibly be related to regulations prohibiting the participation of females of childbearing potential during the early phase of clinical trials for drug approval purpose. As a result, medicine is mostly “male-biased” because most available knowledge on health care and illness is from men. In addition, the gender role ideology negatively influences treatment and health outcomes. All these factors have prompted the “gender inequality” which is overlooked as a determinant for health care and disease management (34). Therefore, contemporary awareness, knowledge, and perceptions with regards to gender issue in metabolic syndrome and its cardiovascular sequelae are pertinent to the better management of women health.

It has been recognized for a long time the gender differences in the clinical manifestation, diagnosis, and treatment outcomes of cardiac disease (5,35). Despite the “female advantage” in cardiovascular disease prevalence, the total number of cardiovascular mortality since mid-1980s has been higher for women than for men. For example, more women (52%) than men (42%) with myocardial infarction had sudden cardiac death before arriving at hospital (35). Although issues may argue that women tend to have more nonspecific prodromal symptoms rather than chest pain to mask the diagnosis of cardiac origin, difference in the intrinsic myocardial geometry and function has been considered a key factor in the gender difference of heart disease prevalence independent of any other neurohormonal and metabolic determinants (25,28,36–39). To better understand the gender disparity in cardiac seque­lae of metabolic syndrome, it is crucial to understand the gender disparity in heart physiology and pathophysiology. Because of the apparent difference in body size, women usually possess less left ventricular mass, thinner wall thickness, and lower chamber volume even after adjusting for body surface area (40). Nonetheless, the ventricular pressure and ventricular ejection fraction (EF) are much higher in women than men (41), possibly due to a reduced end systolic volume in women (41). The higher EF may explain the higher frequency of heart failure with normal EF in women than in men (42). Not surprisingly, women with low normal EF display severe contractile dysfunction and require a more aggressive treatment algorithm compared with men with similar levels of EF. Several individual components of the metabolic syndrome cascade including hypertension, obesity, and insulin resistance along with aging and ischemia have been identified to be among major risk factors for heart failure with normal EF (42). For example, hypertension is more frequent in women than men, which may contribute to left ventricular and arterial stiffening in a gender-specific manner (42). In addition, a gender dimorphism also exists for myocardial function with regards to duration and maximal velocity of contraction and relaxation (36–38,43–45), which are essential determinants for cardiac rhythm and contractility. Moreover, gender difference in cardiac electrical property also affects the clinical consequence of metabolic syndrome. The mean rate adjusted Q-T interval, a valuable index influenced by metabolic syndrome–triggered subclinical atherosclerosis, is significantly longer in women than in men. Interestingly, metabolic syndrome was associated with significantly prolonged Q-T interval in men but not in women, following adjustment for other risk factors (46). Q-T measurement usually provides additive diagnostic and prognostic information for cardiovascular risk screening. It was speculated that the gender difference in ventricular repolarization and Q-T interval may be responsible for this apparent dissociation of metabolic dysfunction and Q-T prolongation in females (46). Taken together, these differences in the intrinsic myocardial structure and function may contribute to the gender disparity in cardiac morbidity and mortality independent of any other confounding factors. Other than the intrinsic myocardial properties, the sex hormones including estrogen and androgen also regulate cardiac electromechanical function and play a role in the gender difference in
myocardial function (47–49). For example, estrogen is known to elicit beneficial effects on myocardial function, lipoprotein profile, redox state, and peripheral vascular tone (49–51). Estrogen is also capable of altering a number of genes involved in myocardial metabolism such as lipoprotein lipase, prostaglandin D2 synthase, and peroxisome proliferator–activated receptor γ co-activator 1 α (52). Nevertheless, recent clinical trials such as the Women’s Health Initiative found an increased cardiovascular incidents in women on hormone replacement therapy (53–56), suggesting that it may be premature to recommend hormonal (estrogen) replacement therapy to women with known cardiovascular diseases or risks. The role of estrogen and estrogen replacement therapy with regards to aspects of metabolic syndrome will be discussed in more detail in the later section of this review.

GENDER, INSULIN SENSITIVITY, GLUCOSE AND LIPID HOMEOSTASIS

The diagnostic criteria for metabolic syndrome display a gender-specific manner in terms of the cutoff points among components of metabolic syndrome (31). Based on the definition of impaired insulin sensitivity, glucose homeostasis and pathologic waist circumference or waist/hip ratio, more or fewer women will be included. In a recent study on the rate of metabolic dysfunction in late adolescence or early adulthood using the World Health Organization and International Diabetes Federation criteria, gender differences in both continuous and dichotomous metabolic variables were tested. Different criteria between genders identified that undiagnosed metabolic dysfunction was high for low levels of HDL-c (24%), impaired fasting glucose (9%), and hypertriglyceridemia (9%). Males were found more obese, hypertensive, and hypertriglyceridemic than females. However, all cases of impaired glucose tolerance were female participants, suggesting a higher incidence in insulin resistance in females (57). However in a study using the Göttingen minipigs, female minipigs were found more obese and insulin resistant and possessed a more atherogenic plasma profile than males. The female minipigs had a larger abdominal circumference and higher concentrations of C-peptide, insulin, triglyceride, total cholesterol, HDL-c, and leptin associated with a lower concentration of free fatty acids and lower HDL-c/total cholesterol ratio. Male minipigs had higher concentrations of testosterone and estradiol which may protect them from obesity and metabolic disturbances (58). These data support a gender dimorphism in glucose and lipid metabolism, both of which are directly modulated by estrogen and testosterone (31). These data suggest that unique gender differences in insulin sensitivity, glucose and lipid metabolism, which should be considered in the design of metabolic syndrome intervention strategies in men and women.

An ample of evidence has speculated a link between gender and insulin/glucose/lipid homeostasis. Although men possess unfavorable body fat distribution and higher vulnerability to cardiovascular events, it was the female gender which ties into a poor glycemic control and insulin homeostasis (59). A Turkish study revealed that women likely to develop abnormal glucose metabolism followed by cardiovascular disease whereas men tend to develop cardiovascular disease after the onset of metabolic syndrome (60). Obese especially abdominally obese women with normal glucose metabolism are prone to metabolic syndrome and diabetes. However, abdominally obese men are prone to metabolic syndrome and cardiovascular complications independent of concurrence of diabetes (60). It is worth mentioning that waist circumference shows the best association with metabolic syndrome, whereas body fat mass correlates more accurately with a high coronary heart disease risk (61). Given that BMI displays a weaker relationship with the prevalence of metabolic syndrome and cardiovascular consequence, it was recommended that the body fat mass may be used as a complementary measure to identify coronary risk (61). Therefore, the body fat mass especially the rate of visceral fat accumulation according to the individual’s gender and ethnic background may directly predict the cardiac risk. For example, visceral fat accumulation is more prominent in white men, African-American women, and Asian Indian and Japanese men and women, which may explain the variation in the cardiac risk between genders or races (62).

Experimental evidence suggested that female rats are better protected from hyperglycemic and insulin resistance–induced insult unless they are ovariectomized, consistent with the observation that estrogen alleviates diabetic complications in males (63,64). Estrogen is known to maintain normal adipose tissue biology, liver fatty acid metabolism, and suppression of hepatic glucose production. In addition, estrogen promotes pancreatic β-cell function, cell survival, and insulin secretion (63). Although a number of mechanisms have been postulated for the gender disparity in the onset of metabolic syndrome–associated cardiovascular sequelae, interaction between the polyl enzyme aldose reductase and estrogen seems to play a key role (65). Glucose is converted to sorbitol by aldose reductase via oxidation of nicotinamide adenine dinucleotide phosphate before the oxidation of sorbitol by sorbitol dehydrogenase at the expense of NAD+ (66). Increased NADH/NAD+ ratio leads to inhibition of glyceraldehyde-3-phosphate dehydrogenase and accumulation of triose phosphate, which promotes the formation of advanced glycation end products, diacylglycerol, and protein kinase C activation, all of which triggers for complications associated with metabolic syndrome (67). Estrogen may upregulate aldose reductase mRNA expression (68). However, diabetes-induced changes in polyl metabolism may be reversed by castration, suggesting a role of androgen in polyl glucose metabolism (69). Furthermore, estrogen may promote nitric oxide (NO) release whereas the later inhibits the polyl pathway (70). However, limited information is available with regards to the role of aldose reductase in obesity and other components of metabolic syndrome. Therefore, it may be premature to credit sex dimorphism in the prevalence of metabolic syndrome to glucose metabolism and its
interaction with the sex hormones (71). Secondary phenotypic traits of men and women (e.g., body fat composition, BMI, regional fat distribution) as well as the associated insulin and lipid metabolism may also participate in such sex dimorphism of metabolic syndrome. Insulin was reported to increase significantly with aging in females whereas it drops in males. Androgen is believed to affect the postinsulin receptor signaling and interrupt insulin sensitivity in men. The fact that androgen levels rise significantly with aging in female, especially following menopause, helps to interpret the compromised insulin sensitivity in postmenopausal women (72).

Interplay of lipid metabolism with gene, gender, and environmental factor has been shown to modulate disease susceptibility. In the Framingham Heart Study, complex interactions were identified between a promoter polymorphism at the apolipoprotein A1 gene, gender, and dietary polyunsaturated fatty acid intake which modulate plasma concentrations of HDL-c. In particular, a gender-dependent association has been demonstrated between the lipid metabolism polymorphisms at the PLIN locus and obesity risk, supporting the notion that gender-specific differences in morbidity and mortality may be mediated in part by genetic factors associated with lipid metabolism (73). In another study involving overweight and obese middle-aged men and women, representative lipogenic and lipolytic genes from major lipid metabolism pathways, as well as representative lipogenic and lipolytic transcription factors were examined in skeletal muscle biopsies. The results revealed increased lipoprotein lipase, peroxisome proliferator–activated receptor γ co-activator 1 α, carnitine palmitoyltransferase-1 β, diacylglycerol acyltransferase-1, and acid ceramidase mRNA in women, but not men, following endurance exercise (74). These new pieces of data should assist to elucidate the complex interaction between gender and lipid metabolism in metabolic syndrome. As a result, the optimal personalized recommendation may be made to manage metabolic syndrome with a focus on dyslipidemic disorders.

NEUROVASCULAR REGULATION OF METABOLIC SYNDROME IN HEARTS
Alterations in several neurovascular signaling cascades have been demonstrated to play a role in the cardiovascular sequelae of metabolic syndrome including the renin–angiotensin system and NO (75–77). Moreover, the cross-talks between insulin and angiotensin II or NO signaling systems directly influence insulin sensitivity and thus provide the rationale for clinical drug therapy targeting glucose metabolism and prevention of metabolic syndrome components (78). For example, angiotensin II is capable of acting on JAK-2/IRS1-IRS2/PI3-kinase, JNK, and ERK to elicit serine phosphorylation to inhibit insulin signaling. Binding of angiotensin II to the AT1 receptor may directly suppress insulin-stimulated NO release via an ERK- and JNK-dependent mechanism to activate nicotinamide adenine dinucleotide phosphate oxidase and reactive oxygen species accumulation (78). It is thus rational to improve insulin sensitivity and reduce the incidence of diabetes via inhibition of the renin–angiotensin system and/or upregulation of NO signaling. This alternative approach has received some intense attention recently for the management of metabolic syndrome, although the gender aspect is relatively vague.

Angiotensin II
Angiotensin II is usually elevated in patients with metabolic syndrome leading to heart dysfunction (79–81). Angiotensin II inhibits K⁺ currents and prolongs action potential duration in cardiomyocytes (82). This is supported by augmented K⁺ currents following angiotensin-converting enzyme inhibition or AT1 receptor blockade (83). Interestingly, such angiotensin II inhibition-elicited effect on cardiac K⁺ currents vanishes in the “estrogen-intact” females (83), suggesting a role of estrogen in gender-associated difference in cardiac response to angiotensin II. In a recent study examining the association between angiotensin-converting enzyme 2 gene A/G single-nucleotide polymorphism and hypertension in Chinese patients with metabolic syndrome, female patients with metabolic syndrome who carry the GG genotype were found to possess a significantly higher diastolic blood pressure compared with other genotypes, suggesting the key role of the female gender in the ACE2 A/G polymorphism-associated hypertension in patients with metabolic syndrome (84).

NO
A gender difference in NO cascade has been documented. Both endothelial nitric oxide synthase and neuronal nitric oxide synthase are tightly regulated by estrogen (85). The higher NO bioavailability offered by estrogen is likely responsible for the beneficial cardiovascular effect of the female gender (86,87). One of the key downstream signaling molecules of NO is the serine/threonine protein kinase Akt with a key role in cardiac survival and function (88). Female myocardium possesses a higher Akt activity, which may contribute to the gender difference in myocardial function (43,89). Both estrogen and phytoestrogen facilitate Akt phosphorylation (Ser473) in cardiomyocytes (89). Observation from our group suggested chronic Akt activation at the site of Ser473 by diabetes and female gender, although there was no additive effect between the two (43). Activation of Akt and its upstream signal molecule phosphatidylinositol-3 kinase is essential to cardiac function and morphology (88–90). Although Thr308 phosphorylation of Akt directly facilitates glucose uptake, Akt phosphorylation at Ser473 seems to compromise insulin sensitivity, through phosphorylation of a threonine residue on insulin receptor β-subunit (91,92). Therefore, “hyperactivation” of Akt (Ser473) resulted from a higher NO levels in females may interrupt insulin signaling in cardiomyocytes (93). To the contrary, estrogen may preserve the integrity of ischemic myocardium following infarction by recruiting the bone marrow–derived endothelial progenitor cells for neovascularization. This mobilization and incorporation process is mediated via an endothelial nitric oxide synthase–mediated upregulation of matrix metalloproteinase-9 in bone marrow (94). It is worth mentioning that
the precise biological and social factors responsible for the gender disparity in stem cell and progenitor cell differentiation remain to the explored.

**GENDER, ADIPOKINES, INFLAMMATION, AND METABOLIC SYNDROME**

Metabolic syndrome is more common in men than in women, although women especially young women display a steeper increase in the disease prevalence during the last decade (95). Several hormones and cytokines have been associated with the increased prevalence of metabolic syndrome in both young premenopausal and elderly postmenopausal women (31,96). A gender difference in fat accumulation has been identified with premenopausal women more frequently exhibit peripheral obesity with subcutaneous fat accumulation. However, men and postmenopausal women are more prone to central or android obesity, which is more tightly associated with increased cardiovascular mortality and development of type 2 diabetes (95). Clinical data indicated that metabolic syndrome occurs in 40% of postmenopausal women and is largely determined by overweight status and central obesity. The increase in central adiposity and visceral adipocytes in men and postmenopausal women (96) prompts to a role of cytokines and inflammation in the gender disparity of metabolic syndrome. Visceral adipocytes, the major source of circulating cytokines, differ from peripheral adipocytes in their lipolytic activity and their response to insulin, adrenergic and angiotensin stimulation and sex hormones (95). Visceral fat is directly delivered to the liver via portal vein to promote the development of fatty liver and insulin resistance specifically via cytokines and low-degrade inflammation (97).

**Leptin**

Leptin, a cytokine to reduce appetite and enhance energy expenditure, acts on the hypothalamic centers to regulate body fat and weight. Mice deficient in leptin due to a genetic mutation (ob/ob, now known as lep/lep) are obese and infertile. A sex dimorphism in circulating leptin levels exists with women displaying higher leptin levels. Estrogen replacement therapy was reported to result some conflicting data, including unchanged, increased or decreased leptin levels. It was speculated that postmenopausal hypoestrogenism may mask the leptin-induced changes in body composition such as body weight, BMI, and fat mass, the effect of which may be prevented or even reversed by estrogen replacement (98). Gender difference in circulating leptin levels is expected to contribute to the phenotype of cardiac contractile function given the effect of leptin on sympathetic nerve activity, glucose use, and insulin sensitivity (99,100). Elevated leptin level has been demonstrated to correlate with insulin resistance, obesity, and diabetes, independent of total adiposity. Elevated circulating leptin levels is usually followed by tissue leptin resistance, which are independent risk factors for cardiovascular diseases (99). Estrogen replacement therapy may generally decrease abdominal fat in normal postmenopausal women, although the efficacy of transdermal estrogen is more preferable compared to oral therapy (96). In women with metabolic syndrome, oral estrogen therapy was found to increase leptin and the leptin/adiponectin ratio, whereas the transdermal estrogen therapy showed no effect. In addition, estrogen replacement therapy alleviates insulin resistance in postmenopausal women, although mixed data have been seen (96). Oral estrogen therapy was found to worsen parameters of insulin resistance, whereas transdermal therapy had minimal effects in postmenopausal women.

**Adiponectin**

Adiponectin is a unique adipocyte hormone among adipocyte-derived hormones in that its circulating concentrations are inversely proportional to visceral adiposity (101). Low adiponectin levels usually predict the increased propensity of metabolic syndrome and other cardiovascular diseases. Not surprisingly, a great deal of effort has been generated to explore the application of adiponectin as a potential therapeutic agent and/or target for metabolic syndrome. Plasma adiponectin levels display an age- and gender dependence. Adiponectin production is inhibited by several hormones including testosterone, prolactin, glucocorticoids, and growth hormone, and by inflammation and oxidative stress in adipose tissue (101–103). Levels of adiponectin are also negatively correlated with leptin, insulin resistance and total cholesterol, and positively correlated with HDL-c (102,103). Women possess higher adiponectin levels compared with men of equal body mass. Interestingly, although adiponectin level displays a negative correlation with testosterone, it exhibits little relationship with the levels of estrogen (101,103). Serum adiponectin levels have been found to be lower postmenopausal women (104). Unlike leptin, direct impact of adiponectin on myocardial electromechanical properties is still incomplete, although studies from our lab and other have demonstrated the beneficial effect of adiponectin on myocardial function in obesity (105) and ischemia-reperfusion injury (106).

**Inflammation and resistin**

Visceral adipose tissue and its adipose tissue resident macrophages are capable of producing abundant proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6. These cytokines changes trigger insulin resistance and play a major role in the development of metabolic syndrome (107). The low-grade inflammation associated with obesity has been considered a major roadblock for the prevention and treatment of obesity despite the newly discovered hormones such as leptin. Up-to-date, several proinflammatory markers including paraoxonase, interferon regulatory factor-1, toll-like receptors, CXCR4, and SOD1 have been considered as possible targets for obesity intervention (107). Although a number of attempts were made trying to elucidate the gender aspects of inflammation, the results have been inconsistent. A gender difference was postulated in both the immunoinflammatory factors and the frequency of pro/anti-inflammatory gene variants (108). Direct evidence has clearly depicted the interaction between proinflammatory markers and sex hormones such as
Estrogen possesses pleiotropic actions including its anti-inflammatory effects. Interactions between estrogen or 17β-estradiol and the proinflammatory mediators, nuclear factor kappa-B or C-reactive peptide, have been identified. 17β-estradiol may activate nuclear factor kappa-B via nongenomic pathways and induce expression of the protective proteins such as heat shock proteins. Alternatively, genomic 17β-estradiol can also inhibit nuclear factor kappa-B (96,109). Both oral and transdermal estrogen therapy reduce essential inflammation markers with the exception of C-reactive peptide and matrix metalloproteinase-9 (96), suggesting a beneficial role of estrogen in alleviating the risk of metabolic syndrome. Resistin, another key inflammatory adipokine, displays a modest association with inflammation. The link between resistin and metabolic syndrome is still somewhat controversial. Some suggest that increased serum resistin levels are associated with obesity, visceral fat, insulin resistance, type 2 diabetes, and inflammation, whereas others failed to observe such correlations (110). Resistin polymorphism was found unrelated to BMI, fasting glucose, insulin resistance, metabolic syndrome, or adipokines (111) whereas plasma resistin levels has also been reported elevated in the presence of metabolic syndrome and cardiovascular risk (112). No difference was found in basal resistin levels between genders neither did estrogen deficiency due to menopause affect serum resistin levels (113). Interestingly, plasma resistin levels were reported to be highly positively correlated with triglycerides, waist circumference, waist/hip ratio, systolic blood pressure, and ApoAI/ApoB ratio, whereas they were inversely correlated with high density lipoprotein and ApoAI levels. More importantly, this finding was female-gender specific (110).

**ESTROGEN REPLACEMENT THERAPY: PROS AND CONS FOR METABOLIC SYNDROME**

Menopause contributes to the development of metabolic syndrome through direct impact of sex hormones (31). Estrogen replacement therapy controls menopausal symptoms, reduces the incidence of osteoporotic fracture, and improves lipoprotein profiles in postmenopausal women. Estrogen is known to alter a wide spectrum of genes involved in metabolism such as lipoprotein lipase, prostaglandin D2 synthase, and peroxisome proliferator-activated receptor γ co-activator 1 α. The beneficial effect of estrogen can also be testified by increased insulin resistance prevalence and a proatherogenic lipid profile with loss of estrogen and/or a relative rise in testosterone (52). Although estrogen replacement may benefit cardiac contractile function, blood lipid profile, vascular resistance, and oxidative stress (50,51), several clinical trials (e.g., Heart and Estrogen/progestin Replacement Study, Women’s Ischemia Syndrome Evaluation and Women’s Health Initiative) have reported some rather unpredicted findings regarding benefit vs. risk of estrogen replacement on heart function (53,114,115). Data from these clinical trials favor that estrogen replacement therapy does not provide sufficient cardiovascular benefit in women with heart diseases or risks. However, it needs to be pointed out that many participants are elderly with pre-existing cardiovascular conditions. Considering the “pros and cons” with regards to the controversies on estrogen replacement therapy, it is generally recommended that women should not consider estrogen replacement unless obvious benefit can be identified. Considering the impact of estrogen replacement therapy on the prevalence of metabolic syndrome, reduced incidence of type 2 diabetes was reported in otherwise healthy postmenopausal women who received estrogen (116). This correlation between estrogen and metabolic syndrome suggests that estrogen deficiency or menopause represents a fundamental corner stone in the onset and development of metabolic syndrome. Thus, despite the controversies of estrogen replacement therapy for postmenopausal women due to a higher cardiovascular risk (55,114,115), younger postmenopausal women with metabolic syndrome should be benefited from estrogen replacement therapy.

**CONCLUSION**

The gender difference in the prevalence of heart disease in patients with metabolic syndrome may be underscored by a number of factors including intrinsic electromechanical properties, myocardial structure, neurovascular factors, adipokine and inflammatory status. Female sex hormones such as estrogen are undoubtedly essential to the “on and off switch” of some of these factors during the progression of metabolic syndrome. Nevertheless, the male sex hormone androgen and testosterone should not be underestimated given their roles in the regulation of cardiovascular function. In fact, ovary becomes an important source for androgen production in postmenopausal women (117). Today, clinical management against metabolic syndrome is usually not tailored to the gender specificity. Given the complexity of metabolic syndrome, scrutinized investigations on the etiology, pathogenesis, clinical presentation, and management of metabolic syndrome are instrumental for the better awareness of women health. The recent advances in study design, methodologies, and the promise of evolving technologies should foster a better understanding of the biology governing the gender difference in metabolic syndrome. Future gender-related clinics and research should focus on the identification of gender-specific criteria for prevention, diagnostics, and therapy of metabolic syndrome.

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