REVIEW ARTICLE

Women and the metabolic syndrome: an overview of its peculiarities

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Objective: **The peculiarities of the Metabolic Syndrome in women regarding frequency, pathophysiology, manifestations and therapy will be analyzed. Recommendations will be given for prevention of metabolic syndrome and possible reduction of risks factors for cardiovascular disease.**

Methods: **A review of pertinent studies serves as the basis for the analysis and recommendations of therapeutic strategies in women with metabolic syndrome.**

Results: **Metabolic syndrome, a conglomerate of obesity, hypertension, hyperglycemia, low high density cholesterol and elevated triglycerides can be found frequently in women, especially with polycystic ovaries or in the post-menopausal period. Insulin resistance and its metabolic consequences can lead to an increased risk of cardiovascular disease. There are interventions that can reduce insulin resistance and the other components which may lessen this risk in women with the metabolic syndrome.**

Conclusion: **This article summarizes the peculiarities of the metabolic syndrome in women, especially with polycystic ovaries or at postmenopause. Evidence-based medicine is reviewed and used together with the recommendations for therapy and for the prevention of cardiovascular disease in women with this condition.**

Key words: Women with metabolic syndrome, Cardiovascular disease in women, Risk factors in metabolic syndrome, Insulin resistance.

Metabolic syndrome (MS) encompasses several factors characterized by insulin resistance. It is very common in women and is emerging as a health epidemic, parallel to the obesity epidemic (1). It is associated with a higher risk of cardiovascular disease (CVD) in women, especially after menopause. CVD is the most common reported cause of death in women in Puerto Rico (2) and in the United States (3). In both sexes, CVD prevalence increases with age, but appears later in life in women than in men, with approximately a ten-year lag. One in three adult females in the United States develops CVD and the number of related deaths has exceeded those of males since 1984. There are well-recognized risk factors associated to CVD, both in women as in males, namely, smoking, high blood pressure (HBP), family history, obesity, diabetes, inactivity, low levels of high density lipoprotein cholesterol (HDL-C), elevated triglyceride levels (TG) and high levels of low density lipoprotein cholesterol (LDL-C). The diagnosis of MS requires three out of the following five criteria: abdominal obesity, elevated TG, decreased high density lipoproteins, elevated blood pressure and elevated levels of plasma glucose. The aim of this article is to review the peculiarities of MS in women and their possible impact in CVD. The definition, prevalence, pathophysiology and its management in women will be discussed.

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Definition

The National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults [Adult Treatment Panel III (ATP III)](4) included in its 2001 guidelines hypertension, obesity, hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) as risk factors associated with coronary artery disease. The ATP III was the first report to detail the metabolic syndrome (MS). MS encompasses several of the risk factors included in the ATP III report. ATP III's definition of MS includes having three (3) out of the following five (5) criteria: abdominal obesity, hypertension, elevated fasting plasma glucose (FPG), elevated triglycerides (TG) and low HDL-C levels. MS is characterized by insulin resistance (IR). In order for a woman to meet the ATP III criteria for MS, she must have 3 out of 5 of the following criteria: waist circumference greater than thirty-five (>35) inches (88 centimeters), blood pressure levels greater than 130/85 mm Hg, FPG greater than

110 mg/dl, TG greater than 150 mg/dl and HDL-C less than 50 mg/dl. The ATP III criteria will be used in this article.

The World Health Organization (WHO) has published a slightly different definition of MS (5). It places a central role in insulin resistance. Accordingly, MS encompasses type 2 diabetes or impaired fasting glucose plus two other of the following factors: hypertension (systolic pressure greater than (>) 140 or diastolic pressure greater (>) than 90 mmHg; Body Mass Index (BMI) greater than 30; elevated urinary albumin excretion rate; hypertriglyceridemia or low HDL-C (normal values are similar to the ATP III criteria).

Prevalence of metabolic syndrome in women

According to the data from the Third National Health and Nutrition Examination Survey (NHANES III), based on 8814 participants and using the same definition criteria for Metabolic Syndrome (MS) as the ATP III, the age-adjusted prevalence for adults is approximately twenty-four percent (23.7%) in the United States (US) (6). MS increases with age and affects 42% of the population 60 to 69 years of age. It varies between different ethnic groups, there is a 57% higher prevalence among women of African American descent and 26% higher among Mexican American women. The prevalence of women with MS was reported as almost twenty-three percent (22.9%) in whites and almost twenty-one percent (20.9%) among blacks in the same study. MS is strongly associated to CAD in both sexes, but it is strongly associated with CVD risk in middle-age women (7).

A telephone survey conducted in 2004 by the Centers for Disease Control and Prevention (CDC) in 195,005 adults living in the U.S. revealed that 23 million women are obese. The number of persons classified with obesity and overweight has steadily increased in the US throughout the years. Many of these women carry most of their weight around the waistline, a feature of MS.

In a small retrospective study conducted in Puerto Rico in women with PCOS. Rabelo, et al. (8) identified MS in 44% of sampled women. Obesity and low HDL-C levels were the most common MS criteria found in this group. In another study conducted in 200 employees of the University of Puerto Rico, of which 121 were women, Gómez, et al. (9) found a 33% age-adjusted prevalence according to ATP III criteria. Hypertension and waist circumference greater than 35 inches were the most common abnormalities. Haddock (10) studied the prevalence of MS in a cohort of 400 post-menopausal women in the Puerto Rican metropolitan area and found a 35.2% prevalence of MS among this group. Hyperglycemia and obesity were the most common criteria of MS in this group.

Pathophysiology of the metabolic syndrome

MS is characterized by insulin resistance (IR), the core defect. IR favors the production of inflammatory cytokines by adipocytes. It is associated with changes in lipoprotein quality and quantity, such as increased free fatty acids, increased TG production by hepatocytes, production of smaller denser LDL-C particles and decreased HDL-C levels. IR causes lipolysis with an increase in circulating free fatty acids, and a concomitant elevation of blood triglycerides. Insulin resistance may also lead to hyperglycemia due to increased hepatic glucose production and decreased glucose uptake by muscle tissue. IR contributes to sodium and water retention, resulting in hypertension, and increases the pro-coagulatory state. Thus, IR favors cardiovascular disease.

Obesity and the metabolic syndrome in women

The Department of Health and Human Services of the United States has reported an alarming trend in the prevalence of overweight and obesity in this country. The Behavioral Risk Factor Surveillance System (BRFSS) stated in its report that obesity prevalence in American adults over 18 years of age increased across all racial groups and sexes (11). According to data up to year 2000, older women are more likely to be heavier than younger women and the prevalence of obesity among women aged 50 years and older was more than 20% in 36 states. The age adjusted prevalence of obesity in women, according to the NHANES survey 2001-2004, is 26% in the fifth decade and 34% in the sixth decade (12). Obesity may contribute to insulin resistance. Since obesity is common in women and more common as women age, MS is also more prevalent in older women.

Obesity may be linked to MS, especially if excess body weight is associated to fat deposited around the waistline. This excess of visceral fat cells produces a series of products which are markers of inflammation and endothelial dysfunction. Adipocytes produce substances such as angiotensinogen, interleukin-6, tumor necrosis factor alpha, C reactive protein, leptin, plasminogen activator factor 1 and adipokines. All of these substances, except for adipokines, are associated with insulin resistance. Visceral fat is associated to insulin resistance (13). Insulin resistance provokes an alteration of lipid metabolism that results in elevated levels of very high density lipoproteins (VLDL), decreased levels of high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) cholesterol particles of a smaller size. Small LDL-C particles are more prone to oxidation and are atherogenic. Insulin resistance, with its sodium and water retaining properties, also contributes to hypertension.

In a cross-sectional study conducted in 1998-1999 of 200 female Puerto Ricans living in Connecticut, it was found that obesity was prevalent (14). A reported 40% obesity was found in these low-income women with a mean age of 29 years old. Obesity was associated with physical inactivity, smoking and less acculturation.

Hyperglycemia and the metabolic syndrome

MS is a high-risk predictor of future diabetes. In the San Antonio Heart Study, the incidence of new-onset diabetes was double in persons with MS than in those without the ATP III criteria of MS at baseline (15). Visceral fat, fat deposits around the waistline, is more resistant to insulin. This leads to hepatic glucose over-production and hyperglycemia. Obesity is also associated to the development of hyperglycemia. Data from the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA) showed a linkage between MS and new-onset diabetes. In this large study of hypertensive patients with three or more risks factors of CVD, nearly 32% had MS. Among this sub-group, there was a three fold risk of developing diabetes (16).

Dyslipidemia and the metabolic syndrome

Women with MS may present elevated triglyceride levels and/or low HDL-C levels. There are gender differences in the lipoprotein pattern, women having higher levels of HDL-C than men by approximately 10 mg/dl. Levels of LDL-C are lower in women than men (17). Hormone levels influence lipoprotein levels and vary throughout the lifespan. Post-menopausal women tend to have higher post-prandial elevation of triglycerides, lower HDL-C and higher LDL-C. The lipoprotein abnormalities present in MS constitute an atherogenic dyslipidemia. This dyslipidemia is common in postmenopausal or estrogen deficient women.

Insulin resistance, coronary artery disease and the metabolic syndrome

Insulin resistance is a core component of MS. Although the ATP III recognizes the importance of insulin resistance in MS, it is the WHO that places IR as indispensable. The metabolic consequences of IR, such as hyperglycemia, hypertension, hypertriglyceridemia and lowering of HDL-C, act as compounding factors which may increase the risk of CVD. IR is a pro-coagulant state which predisposes to the formation of thrombi and endothelial dysfunction, thus favoring strokes, peripherovascular disease and myocardial infarctions.

A study conducted in the United States, Women's Ischemia Syndrome Evaluation (WISE), collected data pertaining to the diagnosis, prevalence and progression of CAD in women (18). Data reported from this study points towards the different presentation of CAD in women, concluding that the standard approach of symptomatic chest pain leading to stress testing, coronary angiography and correction of obstructive lesions may not be appropriate for all women. In one study, WISE investigators found that MS is a powerful predictor of future coronary events when there is pre-existing coronary disease, while not in women without angiographic obstructive lesions (19). In another report of the WISE study, investigators reported that obesity alone did not predict CAD while MS, regardless of obesity, could predict CAD (20).

Polycystic ovarian syndrome and the metabolic syndrome

Polycystic ovarian syndrome (PCOS) is the most common endocrinopathy of young women. It affects 5%-10% of women in reproductive age. It was first described in 1935 by Stein and Leventhal and is characterized by chronic anovulation with menstrual dysfunction, infertility, hirsutism, obesity and hyperandrogenism. Several metabolic derangements may be associated to PCOS such as significant increases in insulin levels (hyperinsulinemia) and hepatic insulin resistance.

Hyperinsulinemia stimulates the ovaries to produce testosterone and decreases the levels of sex-hormone binding globulin, causing chronic anovulation, irregular menstrual periods and hirsutism. Up to one third of women with PCOS may have impaired glucose tolerance and 2-10% have Type 2 diabetes mellitus. Insulin resistance provokes an alteration of lipid metabolism manifesting itself with elevated levels of very high density lipoproteins (VLDL), decreased levels of high density lipoproteins (HDL-C) and low density lipoproteins (LDL-C) cholesterol particles with a smaller size. Small LDL-C particles are more prone to oxidation and are atherogenic. VLDL carries triglycerides in blood. Elevation of VLDL is equal to high levels of TG or hypertriglyceridemia. Hypertriglyceridemia, low HDL-C cholesterol levels and highly atherogenic small LDL-C cholesterol particles ensue. Hypertriglyceridemia, low HDL-C cholesterol levels and highly atherogenic small LDL-C cholesterol particles comprise the diabetic dyslipidemia. Insulin resistance, with its sodium and water retaining properties, also contributes to hypertension. Obesity may contribute to the insulin resistance. Women with PCOS and insulin resistance may show hyperglycemia, obesity, hypertension and diabetic dyslipidemia.

PCOS and MS share many components: insulin resistance, dyslipidemia, hemodynamic changes, and

elevated markers of inflammation. Both conditions predispose to coronary artery disease. Patients with PCOS should be evaluated for MS. Thus, women with PCOS are candidates for early CVD screening. Women with PCOS and MS should be treated to reduce insulin resistance and the risk of coronary artery disease (CAD). Lifestyle changes that increase insulin sensitivity should be encouraged, such as an increase in physical activity, weight reduction and caloric restriction. Insulin sensitizers such as metformin and the thiazolidinediones have proven beneficial in reducing insulin resistance, inducing ovulation and reducing the risk of developing diabetes. In the Diabetes Prevention Program (DPP), metformin prevented the appearance of diabetes mellitus in a group of people with an impaired tolerance by 31% (21). Sixty-eight percent (68%) of the subjects participating in the DPP were women, the mean age was 51 years of age and the mean body mass index (BMI) was 34 (obese). Metformin has also been shown to induce ovulation in many patients with PCOS. In the DREAM Study, rosiglitazone, a thiazolidinedione, prevented the appearance of diabetes in people with an impaired glucose tolerance and an impaired fasting glucose by 62% (22). The use of oral contraceptive pills (OCP) in women with PCOS may reduce hyperandrogenism and associated hirsutism. OCP's with a high estrogen content and prothrombotic potential should be avoided in patients with PCOS and MS.

Menopause and the metabolic syndrome

Although the effects of aging are difficult to separate from the effects of menopause, there is no doubt that CVD increases after menopause. Post-menopause is associated with a 60% increased risk of MS (23). After menopause, there is loss of fat deposition around the gluteus promoted by estrogen and fat tends to accumulate around the waist. High levels of abdominal fat are associated with insulin resistance and diabetic dyslipidemia. Abdominal adiposity favors the production of cytokines and an excess in cardiovascular risk. Abnormal levels of lipoproteins are a strong risk factor for CVD in men and women, particularly elevated levels of LDL-C, elevated levels of TG and decreased levels of HDL-C. Estrogens affect the metabolism of lipoproteins favoring a production of TG, increasing the levels of HDL-C and lowering LDL-C. Higher levels of HDL-C may confer protection from CVD during the reproductive years. When estrogen levels decrease with menopause, LDL-C and TG levels increase and HDL-C levels are lower. The increased risk of CVD seen in women after menopause may be due to alterations in these lipoproteins. In post-menopausal women, there is a decrease in HDL-C and an increase in LDL-C (24). HDL-C levels are strong predictors of atherosclerosis in women according to the Framingham Study (25). Whereas elevated LDL-C is the most important risk factor for CVD in men; in women, lowered HDL-C levels and higher TG after menopause are more important. Menopause tends to be associated to less lean body mass and physical inactivity. Both of the latter may predispose to an increased risk of CVD. It is not clear whether menopause increases the risk of CVD in all women or only on those with MS.

Therapy of the metabolic syndrome

Treatment should be focused on lifestyle modifications, aiming at reducing obesity and insulin resistance (26). Individual components of the metabolic syndrome should be addressed and treated accordingly.

Obesity and weight circumference: Most women with MS are overweight. Lifestyle modifications with emphasis on weight loss and an increase in physical activity should be stressed. A moderate weight loss of 7-10% has been associated to metabolic improvements in hyperglycemia, prevention of diabetes in people at risk with impaired fasting glucose and impaired glucose tolerance and a drop in blood pressure.

Physical activity: Advised physical activity for weight loss is 30 minutes of moderate exercise every day. Exercise promotes weight reduction, increases good cholesterol (HDL-C) and reduces insulin resistance.

Insulin Resistance: The use of medications to treat insulin resistance is controversial, but in the DPP, the use of metformin prevented the appearance of diabetes mellitus in a group of people with an impaired tolerance by 31%. In the DREAM study, the use of rosiglitazone was shown to prevent the appearance of diabetes in people with impaired glucose tolerance and an impaired fasting glucose by 62%.

Hyperglycemia: In women with impaired fasting glucose, lifestyle modification changes should be advised and steps taken trying to prevent the development of diabetes. A woman with diabetes should be managed accordingly, with dietary measures and medications as needed.

Hypertension: A woman with hypertension should be advised on lifestyle modifications, weight loss, exercise and diet. If blood pressure continues above the desirable target levels, then antihypertensive medications should be added.

Lipid abnormalities: Strategies to decrease triglycerides, increase HDL-C and lower LDL-C include weight loss, increased physical activity and limited intake of fats, carbohydrates and alcoholic beverages. If lipid levels continue out of targets after these measures, lipid lowering

medications should be added. ATP III panel recommends to first lower LDL-C to target levels, followed by an increase in HDL-C and lowering of triglycerides. Trials with statins for lowering LDL-C in women have shown a beneficial effect in reducing mortality and cardiovascular events. A 24% relative risk reduction was shown in the Heart Protection Study (27).

Smoking: Smoking cessation should be advised in every woman, especially those with other major coronary risks factors.

Conclusions

Metabolic syndrome, a conglomerate of central obesity**,** hypertension, hyperglycemia, low high density cholesterol and elevated triglycerides, can be frequently found in women, especially those with polycystic ovaries or in the postmenopausal period. Associated insulin resistance and its metabolic consequences can lead to an increased risk in cardiovascular disease. There are interventions that can reduce insulin resistance. Addressing the individual components of MS with lifestyle modification and medications may reduce the risk of cardiovascular disease in women with metabolic syndrome.

Resumen

Se analizarán las peculiaridades del Síndrome Metabólico en mujeres en cuanto a frecuencia, pato fisiología, manifestaciones y terapia. Se darán recomendaciones para la prevención del Síndrome metabólico y posible reducción de riesgo de enfermedad cardiovascular. Un repaso de estudios pertinentes sirve de base para el análisis y recomendaciones de estrategias terapéuticas en mujeres con síndrome metabólico. El Síndrome Metabólico, un conglomerado de obesidad, hipertensión, hiperglucemia, niveles bajos de colesterol de baja densidad y elevación de triglicéridos se encuentra con frecuencia en mujeres, especialmente aquellas con ovarios poliquísticos o en el periodo post-menopáusico. La resistencia a la insulina y sus consecuencias metabólicas pueden llevar a un aumento en riesgo de enfermedad cardiovascular. Existen intervenciones que pueden reducir la resistencia a insulina y otros componentes del síndrome metabólico con una posible reducción de este riesgo en mujeres con síndrome metabólico. Este artículo resume las peculiaridades del síndrome metabólico en mujeres con ovarios poliquísticos o en el periodo post-menopáusico. Se revisa y utiliza la medicina basada en evidencia para hacer recomendaciones de terapia y prevención de enfermedad cardiovascular en mujeres con el síndrome metabólico.

References

1. Steinbaum, S. The Metabolic Syndrome: An Emerging Health Epidemic in Women. Progr Cardiovasc Dis 2004;464;321-336.
2. Prevalence of Heart Disease United States. MMWR 2007;56: 113-118.
3. American Heart Association Heart and Stroke Statistical update Available from: URL: http://www.americanheart.org.
4. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on the Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001;285:2486-2497.
5. World Health Organization definition, diagnosis and classification of diabetes mellitus and its complications. 1999 Report of a WHO consultation.
6. Ford ES, Giles WH, Dietz WH. Prevalence of the Metabolic Syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287;356-359.
7. Ford ES, Giles WH, Dietz WH. Prevalence of the Metabolic Syndrome among US adults: findings from the Third National Health and Nutrition Examination Survey. JAMA 2002;287;356-359.
8. Rabelo M, Ramírez M. Association between the Polycystic Ovarian Syndrome and the Metabolic Syndrome in Puerto Rico. P R Health Sci J; 2005;24:203-206.
9. Gomez M, Ramírez M, et al. Prevalence of the Metabolic Syndrome among a Determined Puerto Rican Population. P R Health Sci J 2005;25:111-116.
10. Haddock L, Pérez C, et al. Prevalence of the Metabolic Syndrome in a Female population 50 years and older in San Juan, Puerto Rico, 2002-2003. Diabetes 2004;53(Suppl 2):A243:994.
11. Zablotsky D, Mack K. Changes in Obesity Prevalence among Women aged 50 Years and Older: results from the Behavioral Risk Factor Surveillance System: 1990-2000 Res Aging 2004;26;1314-1330.
12. Heart Disease and stroke statistics Unpublished data Available from: URL: http://www.americanheart.org.
13. Sanchez-Torres R, Delgado-Osorio H. The Metabolic Syndrome and its Cardiovascular Manifestations. Bol Asoc Med PR 2005;97:271-280.
14. Fitzgerald N, Himmelgreen GD, et al. Acculturation, socioeconomic status, obesity and lifestyle factors among low-income Puerto Rican Women in Connecticut, U.S., 1998-1999. Rev Panam Sal Pub 2006;19:306-313.
15. Lorenzo C, Okoloise M, et al. The metabolic syndrome as predictor of type 2 diabetes: the San Antonio Heart Study. Diabetes Care 2003;26;3153-3159.
16. Gupta, A. New-Onset Diabetes New Analysis of the Blood Pressure Lowering Arm of ASCOT (ASCOT-BPLA) European Society of Cardiology 2006 World Congress.
17. Bittner V. Perspectives on Dyslipidemia and Coronary Heart Disease in Women. J Amer Coll Cardiol 2005;l46:1628-1635.
18. Quyyumi A. Women and Ischemic Heart Disease Pathophysiologic Implications from the Women's Ischemia Syndrome Evaluation (WISE): Study and future Research Steps. J Am Coll Cardiol 2004;l47:(Suppl S);66-71.
19. Marroquin O, Kip K, et al. Metabolic Syndrome modifies the cardiovascular risk associated with angiographic coronary artery disease in women. Circulation 2004;109;714-721.
20. Kipp K, Marroquin O. Clinical importance of obesity versus the metabolic syndrome in cardiovascular risk in women, a report from the Women's Ischemia Syndrome Evaluation (WISE) Study. Circulation 2004;109:706-713.
21. Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin NEJM 2002;346:393-403.

22. The DREAM Trial investigators Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomized controlled trial. Lancet 2006;368:1096-1105.
23. Carr M. The Emergence of the Metabolic Syndrome with Menopause. JCEM 2003;88:2404-2411.
24. Knoop, Robert H. Risk Factors for Coronary Artery Disease in Women. Am J Cardiol 2002;89:28E-34E.
25. Gordon DJ, Probstfield JL, Garrison RJ, et al. High Density lipoprotein cholesterol and cardiovascular disease, Four Prospective American Studies. Circulation 1989;79;8-26.
26. Garber AJ. The Metabolic Syndrome. Med Clin N Am 2004;88: 837-846.
27. Collins R, Armitage J, et al. MRC/BHF Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet 2003;361:2005-2016.