Managing metabolic syndrome in women

Abstract: Cardiovascular disease (CVD) death rates in women in the United States are rising. This is attributed to the obesity epidemic and its contribution to cardiometabolic risk. Various gender-related factors and strategies must be considered to effectively manage metabolic syndrome in women and improve outcomes.

By Kelly Bosak, PhD, APRN

Approximately half of all deaths from cardiovascular disease (CVD) occur in women.[1,2] In 2007, one woman died of CVD every minute, more than women who died of cancer, chronic respiratory disease, Alzheimer disease, and accidents combined.[3]

The adverse trends in CVD risk factors among women are cause for concern. CVD death rates in U.S. women ages 35 to 54 years old are increasing, and are attributed to the obesity epidemic.[4] The average body weight of women is increasing, with nearly two out of three women in the United States over age 20 in the overweight or obese category.[3] Overweight or obesity is associated with metabolic syndrome and increased overall risk for diabetes, CVD, and stroke (see *Pathogenesis of obesity-related type 2 diabetes mellitus*).[5] Healthcare providers must consider many factors when managing metabolic syndrome in women to decrease CVD risk (see *Case study*).

The National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines use the term, "metabolic syndrome" to indicate increased cardiometabolic risk, and define it as abnormalities of at least three of the following five biomarkers: elevated BP, increased fasting plasma glucose, elevated triglycerides, increased waist circumference, and low high-density lipoprotein (HDL) cholesterol.[6] The Framingham Offspring Study indicated that of these biomarkers, the combination of elevated BP, abdominal obesity, and hyperglycemia has the greatest risk for CVD and mortality.[7] Further, a marked increase was found in the prevalence of biomarkers of cardiometabolic risk in women, independent of other factors that occurred during the transition to menopause.[8]

Clinical guidelines

The Guidelines for the Prevention of Cardiovascular Disease in Women challenged the conventional thinking that women should be treated the same as men. As more women participated in large clinical trials, the science suggested that many of the recommendations to prevent CVD are similar for women and men, but with some exceptions. Women are typically older and have more comorbidities than men when they seek care for CVD. Healthcare providers must consider gender differences when deciding the degree of relative and absolute potential benefits and risks of preventive interventions.[9]

Healthcare providers must also consider that the recently updated Guidelines for the Prevention of Cardiovascular Disease in Women are not entirely based on a review of clinical trial data. One major change from the previous guidelines is that effectiveness (benefits and risks observed in clinical practice) of preventive interventions was strongly considered and recommendations were not limited to evidence that showed efficacy (benefits observed

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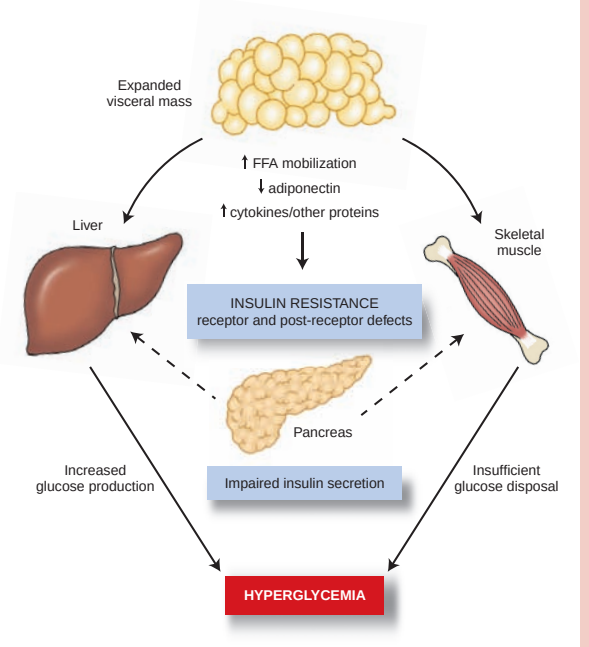
Pathogenesis of obesity-related type 2 diabetes mellitus

Increased visceral fat mass in upper body obesity, especially seen in patients with metabolic syndrome, causes a release of several factors that contribute to tissue insulin resistance. There is an increase in circulating free fatty acids (FFAs), cytokines, and proteins that inhibit insulin action. There is also a decrease in factors that enhance insulin signaling, such as adiponectin. These changes block insulin action in the liver and skeletal muscle at the insulin receptors resulting in the failure of insulin to suppress hepatic glucose production and to facilitate glucose uptake in the muscles, thus resulting in hyperglycemia.



Source: Rubin, R., Strayer, D. (Eds). Rubin's Pathology: Clinicopathologic Foundations of Medicine. 5th ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2008; 982.

in clinical research).[9] Therefore, the current update of these guidelines is labeled "effectiveness-based," rather than "evidence-based."

Risk stratification in women

The Third Report of the NCEP ATP, developed under the direction of the National Heart, Lung, and Blood Institute (NHLBI), is intended for healthcare providers to guide the management of lipid and lipoprotein abnormalities, including dyslipidemia associated with metabolic syndrome. These guidelines are a somewhat complex and extensively referenced report based on epidemiology studies, large randomized clinical trials, and independent research. Healthcare providers must keep in mind that population-level data are the foundation for these guidelines when making recommendations to individual patients.

Risk stratification is an important part of developing a treatment plan to manage patients with metabolic syndrome. The guidelines specify criteria for categorizing patients into two risk groups to guide treatment: multiple (two or more) CVD risk factors other than low-density lipoprotein (LDL) cholesterol and zero or one risk factor. Additionally, three subcategories of risk are defined for those with multiple (two or more) risk factors based on the Framingham Risk Score (FRS), including 10-year risk for CVD events: greater than 20%, 10% to 20%, and less than 10%. The 10-year risk for CVD depends on the FRS risk factors including age, gender, serum total cholesterol, and smoking status, in addition to some metabolic syndrome components such as HDL cholesterol and systolic blood pressure. It is recommended that the FRS be assessed in all higher-risk patients with metabolic syndrome. Research indicates that the FRS is a better predictor of CVD than metabolic syndrome diagnostic criteria alone. Further, metabolic syndrome criteria did not significantly improve the risk prediction achieved by the FRS in two large clinical trials: the San Antonio Heart Study and the Atherosclerosis Risk in Communities study.[10,11]

The FRS has been criticized as underestimating women's risk.[12] Women rarely fall into the high-risk category using this tool, despite the fact that since 1984, cardiovascular disease has been the number one killer of women.[2] One reason for this is that women generally develop heart disease 10 to 15 years later than men. Another reason is that the risk calculator includes HDL, LDL, and total cholesterol levels, but not triglycerides. A high triglyceride level seems to confer a higher risk of dying from heart disease in women than in men.[13,14]

The FRS also underestimates risk in patients with cardiometabolic risk factors. Not all of these risk factors are included in the risk score calculation.[12] Until recently, few women qualified for aggressive CVD prevention based on their Framingham 10-year risk calculation. The Framingham equation has now been revised to predict 10- and 30-year risk for all CVD events, including coronary heart disease (CHD), stroke, heart failure, and claudication.[15-17] The newly revised Framingham equation appears to be more beneficial for use with women.

The Reynolds Risk Score is another risk stratification tool based on information collected from more than 24,000 women for more than a decade. When used on study participants, the Reynolds Risk Score did as well as the FRS for women at high and low risk.[18] The tool was more accurate than the FRS in women with moderate

risk. This model reclassified almost half of the women into high- and low-risk groups. The new assignments predicted almost exactly the actual outcomes for these women over the next 10 years.[19] Analysis of high-sensitivity C-reactive protein (hsCRP), an inflammatory marker, is required for use in the Reynolds Risk Score. Currently, there is a few data to support the association between a reduction in hsCRP (considered an emerging biomarker) and improved clinical outcomes.[20] Other risk scores are available that may be clinically useful if based on a population and on end points relevant to a particular patient.[21,22]

Metabolic syndrome biomarkers

One of the main biomarkers is elevated fasting plasma glucose resulting from insulin resistance. The currently accepted definition for elevated fasting glucose for both women and men is greater than or equal to 100 mg/dL. Physical activity is one of the most effective strategies to reduce elevated glucose levels associated with metabolic syndrome. Activity not only lowers serum glucose levels, but increases insulin sensitivity, so less is needed to transport glucose into cells. A review of five large longitudinal studies involving more than 240,600 participants demonstrated that brisk walking for at least 150 minutes per week reduced the risk of elevated fasting glucose and diabetes by 30%.[23]

Hypertension is another marker of cardiometabolic risk defined as systolic BP greater than or equal to 140 mm Hg and/or diastolic BP greater than or equal to 90 mm Hg, taking antihypertensive medication or having been told at least twice by a healthcare provider that one has high BP.[6] Those with the highest rates of hypertension are more likely to be middle-aged or older, less educated, overweight or obese, and physically inactive, and are also more likely to have other cardiometabolic risk factors.[23] After 65 years of age, a higher percentage of women than men have hypertension, a gap that will likely increase with aging of the female population.[3]

Dyslipidemia also marks cardiometabolic risk, and is characterized by low HDL

Case study

Ms. S is a 38-year-old Hispanic female with a history of hypertension and dyslipidemia, and a body mass index (BMI) in the overweight category. She reports a sedentary lifestyle with no regular physical activity. She does not smoke. She denies alcohol or illicit drug use. Her mother and father are alive and have no history of premature coronary heart disease. Her NP referred her to a cardiology lipid specialist for persistent dyslipidemia (high triglycerides greater than 300 mg/dL and low HDL cholesterol less than 40 mg/dL), and she had been prescribed atorvastatin 20 mg daily in the past.

Ms. S returns to the primary care clinic for ongoing follow-up after consultation with the lipid specialist. At this visit, her physical exam reveals BP 123/78 mm Hg, HR 84, height 5 ft 5 in., weight 179 lb (BMI 29.8). The NP notes that the lipid specialist discontinued atorvastatin, and Ms. S has been taking fenofibrate 145 mg daily and omega-3 fatty acids (fish oil) 4 g daily for the past 3 months. Her fasting lipid profile completed 2 days ago reveals total cholesterol 189 mg/dL; triglycerides 240 mg/dL; HDL cholesterol 40 mg/dL; LDL cholesterol 98 mg/dL; and fasting serum glucose was 96 mg/dL.

Upon further discussion, Ms. S reports that she is tolerating the medication changes without difficulty and is taking them every day as prescribed. She adds that she is now following a low-saturated fat, low-cholesterol diet as recommended. She has been reducing carbohydrates by limiting her intake of bread, rice, pasta, cereal, and potatoes. She has discovered many low-fat snack products, and has added these to her diet. She reports that she occasionally climbs two flights of stairs to her office. Ms. S was advised to begin a regular physical activity program with at least moderate physical activity on most days of the week. Ms. S was not able to start exercising due to increased demands on her time and energy. As the NP, what is your priority at this visit?

A. Restart atorvastatin at 10 mg daily

B. Add extended-release niacin 1,000 mg daily

C. Initiate healthy lifestyle changes, including daily physical activity and a low refined carbohydrate diet

D. None of the above

Answers A and B are not the best option at this time. Restarting the HMG-CoA reductase inhibitor (statin) or adding extended-release niacin as an adjunct to statin therapy is a good option when LDL cholesterol is above goal. Due to Ms. S's elevated triglycerides and protective HDL cholesterol below the goal of 50 mg/dL or higher for females, the best answer is C.

Ms. S has two risk factors for CHD, so based on the FRS, her non-HDL cholesterol is currently at goal of 130 mg/dL. Thus, with no established CHD or CHD equivalents, a statin is not the priority at this time. Lipid specialists may further assess CHD risk marked by emerging risk factors, such as high-sensitivity C-reactive protein (hsCRP) and homocysteine, if clinically indicated. Based on the provider's judgment, the test results for emerging risk factors may affect the selection of lipid-lowering medications. It is important to note that patients with lipid abnormalities may replace fat in the diet with refined carbohydrates found in many low-fat foods, especially snack products. Intake of refined carbohydrates contributes to elevated triglycerides.

One of the greatest contributions to Ms. S's ongoing dyslipidemia appears to be her sedentary lifestyle with no regular physical activity. Lifestyle changes, such as beginning a regular physical activity program, are difficult for most adults to initiate and maintain long-term. The NP must be prepared to help the patient achieve the recommended health behaviors.

cholesterol, high triglycerides, and relatively normal LDL cholesterol levels.[6] Metabolic syndrome is generally not associated with markedly elevated LDL cholesterol, although the LDL particles are often smaller, denser, and, therefore, more atherogenic.[24] Low HDL cholesterol is defined as less than 50 mg/dL in women (less than 40 mg/dL in men), and is recognized as an important indicator of insulin resistance and CVD risk.[6] Conversely, high HDL cholesterol levels convey decreased CVD risk.

Elevated serum triglycerides are considered an independent CVD risk factor and are associated with insulin resistance, glucose intolerance, and a prothrombotic state. Triglycerides are classified by the NCEP into four categories: normal less than 150 mg/dL, borderline high 150 to 199 mg/dL, high 200 to 499 mg/dL, and very high 500 mg/dL or greater. Physical inactivity contributes to hypertriglyceridemia. A high-carbohydrate diet, specifically refined carbohydrates, also contributes to elevated triglycerides. Often unrecognized sources of refined carbohydrates in the diet include low-fat or fat-free foods and snack products. In a previous study, substitution of carbohydrate for saturated fatty acids in the diet decreased HDL cholesterol and increased triglycerides.[25]

Increased waist circumference, also referred to as abdominal obesity or visceral adiposity, is characteristic of metabolic syndrome. A waist circumference greater than 35 in. (greater than 88 cm) in women and greater than 40 in. (greater than 102 cm) in men are biomarkers of metabolic syndrome.[6] Some women of non-Asian origin with marginally increased waist circumference (31 to 35 in. [80 to 88 cm]) may have a strong genetic contribution to insulin resistance, and will benefit from cardiometabolic risk reduction.[26] In susceptible individuals, physical inactivity leads to an accumulation of adipose tissue in the abdomen, and is associated with insulin resistance.[27] Abdominal obesity is also an independent risk factor for ischemic stroke in all racial and ethnic groups.[28] Waist circumference can be reduced through physical activity and overall weight reduction, and is critical to decreasing cardiometabolic risk.

Therapeutic lifestyle changes

The NCEP identifies health behaviors termed, "Therapeutic Lifestyle Changes" as first-line therapy to reduce cardiometabolic risk. Any patient at high risk or moderately high risk, who has lifestyle-related risk factors, including abdominal obesity, physical inactivity, elevated triglycerides, and/or low HDL cholesterol, is a candidate for therapeutic lifestyle changes regardless of LDL level.[6] Considering the high-risk category of patients with cardiometabolic risk factors, including elevated hsCRP, it is advisable that most of these patients be treated to an LDL less than 100 mg/dL and some with very high risk to even more aggressive level of LDL less than 70 mg/dL.[29]

Nurse practitioners (NP) routinely recommend health behavior changes for patients. The NCEP guidelines recommend 30 minutes or more of moderate- or greater-intensity physical activity on most, if not all, days of the week to reduce cardiometabolic risk. To achieve weight loss, the guidelines recommend increasing physical activity to 60 minutes most days of the week.[6] Healthcare providers must remember that few respondents (only one-third) in a study examining awareness of current U.S. physical activity guidelines had direct knowledge of the recommended amount of physical activity (that is, frequency and duration).[30]

Physical activity of low, moderate, and high intensity levels can be beneficial for reducing cardiometabolic risk. Growing evidence underscores the adversity of inactivity. A sedentary lifestyle has typically been overlooked as having a direct contribution to cardiometabolic risk. Sitting for long periods of time leads to changes in cellular regulation of skeletal muscle and alterations in lipoprotein lipase activity (a protein important in controlling plasma triglyceride catabolism, HDL cholesterol, and other cardiometabolic risk factors).[31]

The benefits of low-intensity physical activity throughout the day (vacuuming, gardening, climbing stairs), also referred to as lifestyle activity, have largely been underestimated in terms of reducing cardiometabolic risk. The resultant nonexercise activity thermogenesis (NEAT) or energy expended in low-intensity physical activity increases resting metabolic rate and, over time, imparts greater benefits than episodic exercise activity alone.[32] The cumulative effects of NEAT conducted every hour throughout the day produced reductions in triglycerides that were greater over time than episodic sessions of moderate-intensity exercise.[31] Low-intensity physical activity may also be more acceptable to women as they age, as it is advantageous in terms of accessibility, tolerance, and cost, and is associated with fewer activity-related injuries.[33]

Adherence

Adherence to physical activity recommendations is a demanding behavior and is often difficult for many women with cardiometabolic risk. Maintenance over time is necessary to achieve the best outcomes. The level of scientific evidence incorporated in most guidelines, however, is much more robust than the research available for practical implementation and maintenance of lifestyle behaviors, such as physical activity.[3] New and effective strategies are needed to improve adherence and long-term maintenance of physical activity, and other health behaviors.

There are currently no universal strategies found to be effective for initiating and maintaining physical activity. Healthcare providers must be aware of the current state of the science of behavior change strategies for use in clinical practice. It is important for healthcare providers to remember that research over the years documents that simply educating patients about physical activity or other healthy lifestyle behaviors is not adequate to change behavior.[35] Effective strategies focus on the process of behavior change, and not just informing patients about the health consequences of a behavior, such as inactivity. Strategies recommended by healthcare providers for health behavior change include setting realistic goals, as well as self-monitoring, feedback, and reinforcement. Healthcare providers must also recognize that the science continues to advance, and it is critical to remain informed of innovative strategies in health behavior change. Areas with promise for the future include gene-environment interactions; environmental influences that reinforce or undermine individual behavior changes technological devices (for example, mobile phones) designed specifically for a target population; application of real-time functional magnetic resonance imaging of the brain to improve understanding of the basic mechanisms of behavior as well as patterns of brain activation supporting adherence.

Managing cardiometabolic risk in women requires consideration of the patient's socioeconomic status as well as racial and ethnic diversity. Over the past two decades, the prevalence of hypertension in adults has increased, and was particularly high among Black women at 44%.[36] CVD rates in the United States are significantly higher for Black females (286.1 per 100,000) compared with their White counterparts (205.7 per 100,000).[20] This parallels a substantially lower rate of awareness of heart disease and stroke among Black versus White women.[3,20,37,38] In addition, the rate of diabetes is more than double in Hispanic women compared with non-Hispanic White women (12.7% versus 6.45%, respectively).[3] Outcomes may be improved by delivering healthcare in a culturally sensitive manner, which involves applying the guidelines broadly to match the diversity of women.[39]

Cost-effectiveness

The expert panel that developed the updated guidelines for the prevention of CVD in women emphasized the need for more cost-effective analyses based on gender. Gender-specific analyses for both efficacy and adverse effects of preventive interventions must be reported to inform future gender-specific guideline updates.[20] There is also growing discussion about individualized guidelines based on individual risk status, and this strategy has promise for improving adherence as well as quality, while reducing cost.

Cost-effectiveness of interventions to reduce cardiometabolic risk is different for women compared to men. Regardless of gender, lifestyle approaches to reduce cardiometabolic risk are emphasized, as health behavior changes are generally the most cost-effective strategies currently available. Based on cost-effectiveness analyses and modeling techniques, medications for antihypertensive and smoking cessation appear cost-effective for women.[34] Weight management approaches, such as gastric bypass surgery, appear effective for weight loss, but add costs.[39] NP

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