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# Considerations for Managing the Metabolic Syndrome in Women

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### Keywords

Metabolic syndrome; gender-related considerations; prevention; adherence; cost effectiveness

## Case Study

The patient is a 38 year old Hispanic female with a history of hypertension, dyslipidemia, and 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 and illicit drug use. Her mother and father are alive and well. She was referred to a Cardiology lipid specialist by her primary provider for persistent dyslipidemia (high triglycerides >300 mg/dL and low HDL cholesterol <30 mg/dL), despite Lipitor 20 mg daily for 3 months.

The patient returns to the primary care clinic for ongoing follow-up after consultation with the lipid specialist six months ago. At this visit, physical exam reveals blood pressure 123/78 mm Hg, heart rate 84, height 5′5″, weight 179 pounds (BMI 29.8 kg/m$^2$). The primary provider notes that the Lipitor was discontinued by the lipid specialist, and the patient has been taking fenofibrate 140 mg daily and Omega-3 Fatty Acids (Fish Oil) 4 grams daily for the past 3 months. Fasting lipid profile completed two days prior to today's visit reveals: total Cholesterol 170 mg/dL, triglycerides 240 mg/dL, HDL cholesterol 40 mg/dL, LDL cholesterol 90 mg/dL, and fasting serum glucose 101 mg/dL.

Upon further discussion, the patient reports that she is tolerating the medication changes without difficulty, and is taking the medications every day as prescribed. She adds that she is now following a low saturated fat, and low cholesterol diet as recommended. She has been reducing the carbohydrates in her diet, limiting her intake of bread, rice, pasta, cereal, potatoes, etc. 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 at work to her office. Due to increased demands on her time and energy, she has not started a regular physical activity program as recommended, involving at least moderate physical activity on most days of the week. As the primary provider, what is your priority at this visit?

**A.** Restart Lipitor 20 mg QD

**B.** Add niacin extended release (Niaspan) 1,000 QD

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**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 statin or adding niacin in extended release form as an adjunct to statin therapy is a good option when LDL cholesterol remains above goal. In view of the continued elevation in Triglycerides, and low protective HDL cholesterol below the goal of 50 mg/dL or greater in a female, the best answer is C. Based on the Framingham Risk Score (FRS), the non-HDL cholesterol is currently at goal of 130 mg/dL for this woman with two risk factors for CHD. Thus, with no established CHD or CHD equivalents, a statin is not the priority at this time. It is likely that the lipid specialist checked some of the emerging risk factors for CHD, such as hsCRP and homocysteine to further risk stratify this patient for coronary heart disease. Based on provider judgment, the results of testing 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. The greatest contribution to ongoing dyslipidemia in this Hispanic female appears to be a sedentary lifestyle and no regular physical activity. Lifestyle changes, such as a regular physical activity program are difficult for most adults to achieve long-term. In this article you will find some background information and strategies for use in the clinic setting to assist patients in maintaining a physical activity program to reduce cardiometabolic risk.

## Background

Approximately half of all deaths from cardiovascular disease (CVD) occur in women.[1,2] In 2007, CVD caused approximately one death per minute among women in the United States (US), more women's lives than were claimed by cancer, chronic respiratory disease, Alzheimer disease, and accidents combined.[3] It wasn't until 1999 that the American Heart Association (AHA) first published clinical recommendations for cardiovascular disease (CVD) prevention that were specific to women.

The adverse trends in CVD risk factors among women are cause for concern for healthcare providers. Cardiovascular disease death rates in US women 35 to 54 years of age now actually appear to be increasing, likely a result of the effects of the obesity epidemic[4] and the contribution to cardiometabolic disease risk. The average body weight of women is also increasing, with nearly two of every three US women over the age of 20 years now in the overweight or obese category.[3] The increasing prevalence of overweight or obesity is associated with the metabolic syndrome and increased overall risk of diabetes, cardiovascular disease, and stroke.[5] Healthcare providers must take into consideration a number of factors when managing the metabolic syndrome in women to improve cardiovascular disease risk reduction in this population.

The term metabolic syndrome is used by the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines to indicate increased cardiometabolic risk, and is defined as abnormalities of at least three of the following five biomarkers:

elevated blood pressure, increased fasting plasma glucose, elevated triglycerides, increased waist circumference, and low HDL cholesterol.[6] Among these biomarkers, the combination of elevated blood pressure, abdominal obesity and hyperglycemia were found to have the greatest risk for CVD (HR, 2.36; 95% CI, 1.5 to 3.61), and mortality (HR, 3.09; 95% CI, 1.93 to 4.94) in the Framingham Offspring Study.[7] Further, a marked increase was found in the prevalence of biomarkers of cardiometabolic risk in women, independent of other factors as hormonal changes occurred during the perimenopausal transition.[8]

## Clinical Guidelines

The Guidelines for the Prevention of Cardiovascular Disease in Women challenged the conventional wisdom that women should be treated the same as men. As more women participated in large clinical trials, the evolving science suggested that many of the recommendations to prevent CVD are similar for women and men, with some exceptions. Women are typically older and have more comorbidities than men when they experience CVD. This point to the need for healthcare providers to develop an appreciation for gender differences in the degree of relative and absolute potential benefits and risks of preventive interventions.[9]

Providers must also take into consideration that the recently updated Guidelines for the Prevention of Cardiovascular Disease in Women are not entirely based on review of the literature. One major change from the previous guidelines to the current update is that effectiveness (benefits and risks observed in clinical practice) of preventive interventions was strongly considered and recommendations were not limited to evidence that shows efficacy (benefits observed 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 the metabolic syndrome. These guidelines are a somewhat complex and extensively referenced report based on epidemiology studies, large randomized clinical trials, and independent research. Providers must keep in mind that population level data is 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 the metabolic syndrome. The guidelines specify criteria for categorizing patients into risk groups to guide treatment. The two risk groups include: multiple (two or more) CVD risk factors other than 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-based risk calculator or Framingham Risk Score (FRS), including 10-year risk for CVD events: >20%, 10–20%, and <10%. The 10-year risk for CVD depends on the risk factors of the FRS including age, gender, serum total or LDL cholesterol and smoking status, in addition to some of the metabolic syndrome components. It is recommended that the FRS be assessed in all higher risk patients with the metabolic syndrome. Research

indicated that the FRS was a better predictor of CVD than the metabolic syndrome diagnostic criteria alone. Further, the metabolic syndrome criteria did not significantly improve the risk prediction achieved by the FRS in two large clinical trials, the San Antonio Heart Study[10] and the Atherosclerosis Risk in Communities (ARIC)[11] study.

A major criticism of the FRS is that it underestimates risk in women.[12] Women rarely fall into the high-risk category despite the fact that heart disease is the number one killer of women.[2] One reason 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. This clustering of heart disease risk factors are not all included in the risk score calculation.[12] Until recently, few women qualified for aggressive CVD prevention based on their Framingham 10-year risk calculation. Now the Framingham equation has been derived to predict 10-year and 30-year risk for all CVD events, including coronary heart disease, stroke, heart failure, and claudication.[15,16,17] The newly derived 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 Framingham Risk Score for women at high and low risk.[18] For those with moderate risk, this tool was most accurate. This model reclassified almost half of women into high-risk and low-risk groups. The new assignments, done by computer, corresponded almost perfectly to what actually happened to 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. There is little data at the current time, however, 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 the patient in question.[21,22]

## Metabolic Syndrome Biomarkers

The metabolic syndrome biomarkers are improved by regular physical activity. 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 to100 mg/dL. Physical activity is one of the most effective strategies to reduce elevated glucose levels associated with the 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 blood pressure greater than or equal to 130 mmHg and/or diastolic blood pressure greater than or equal to

85 mmHg, taking antihypertensive medication or having been told at least twice by a healthcare provider that one has high blood pressure.[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 cholesterol, high triglycerides, and relatively normal LDL cholesterol levels.[6] The 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 <50 mg/dL in women (<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 <150 mg/dL, borderline high 150–199 mg/dL, high 200–499 mg/dL and very high ≥500 mg/dL. 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 the metabolic syndrome. A waist circumference ≥88 cm or >35 inches in women (≥102 cm or >40 inches in men) is a metabolic syndrome biomarker. Some women of non-Asian origin with marginally increased waist circumference (e.g., 80–88 cm or 31–35 inches) 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 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] Providers must remember that approximately one third of respondents in a study examining awareness of current US physical activity guidelines had direct knowledge of the recommended “dose” of physical activity (i.e., 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 non-exercise activity thermogenesis (NEAT) or energy expended in low intensity physical activity increases resting metabolic rate, and over time, imparts greater benefits that 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 to maintain. Adherence 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. A recent study indicates that the strategies for initiation and maintenance of health behaviors, like physical activity require new and innovative approaches.[34]

There are currently no universal strategies found to be effective for initiating and maintaining physical activity. Providers must remain aware of the current state of the science of behavior change strategies for use in clinical practice. It is important for 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

providers for health behavior change include setting realistic goals, as well as self-monitoring, feedback and reinforcement.

Providers must also recognize that the science continues to advance, and it is critical to remain informed of new developments in health behavior change. Areas with promise for the future include gene-environment interactions; environmental influences that reinforce or undermine individual behavior changes; virtual social networks; technological devices (e.g., mobile phones) designed specifically for a target population; application of real-time functional magnetic resonance imaging (fMRI) of the brain to improve understanding of the basic mechanisms of behavior as well as patterns of brain activation; and metacognition or an individual's awareness of the ability to control their health behaviors.

Managing cardiometabolic risk in women includes 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 increased, and was particularly high among black women at 44%.[36] Cardiovascular disease rates in the US 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, while avoiding disparity of care.[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 dialogue 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. Decision analysis methods now being applied for analyzing complex, dynamic and multilevel data show cost-effectiveness for weight loss in younger and middle-aged obese women.[39]

## Conclusion

The metabolic syndrome and cardiometabolic risk are complex issues, and approaches to management differ according to gender. Multiple factors must be considered to achieve the

best outcomes. Cardiometabolic risk in women can be improved by focusing on gender-specific trends, use of risk stratification tools developed specifically for women, and individualizing guidelines to match patient characteristics. This approach has the potential to improve adherence and quality of care, while reducing cost. Research is ongoing in this area and multiple new approaches appear to hold promise for future health behavior change interventions that can be translated to the clinical setting. More gender-specific data is needed to reach conclusions about cost-effectiveness, and to document the utility of individualized gender-based interventions. Providers must take multiple factors into consideration when developing, implementing and monitoring treatment plans for physical activity in women to reduce cardiometabolic risk and improve outcomes.

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