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Evaluation of metabolic syndrome and male sexual dysfunction

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Abstract

Cardiovascular disease and erectile dysfunction are commonly encountered disorders in men of advancing age that share a common pathophysiologic pathway with endothelial dysfunction. Metabolic syndrome and its various components play pivotal roles in the development of both cardiovascular disease and erectile dysfunction. The evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known underlying cardiovascular disease, can include exercise stress testing, determining the coronary artery calcium score, and measuring carotid intima-media thickness. Knowledge of potential underlying increased cardiometabolic risks can alert the clinician toward appropriate risk stratification and evaluation to minimize future coronary events. ■ *Heart Metab*. 2015;66:32-36

Keywords: cardiometabolic risk; erectile dysfunction; male sexual dysfunction; metabolic syndrome

Cardiovascular disease (CVD) is a leading cause of death in men worldwide. Erectile dysfunction (ED) is a common disorder in men as they age that often leads them to engage in medical care in the absence of underlying and unknown cardiovascular disease or risk equivalents. Several risk factors overlap for the development of both CVD and ED including advancing age, smoking, metabolic syndrome (MetS), sedentary lifestyle, abdominal obesity, visceral adiposity, insulin resistance, hypertension, hyperlipidemia, and type 2 diabetes mellitus.[1-5]

Research over the last decade has discovered common pathophysiologic links between CVD and ED including endothelial dysfunction,[6] patterns of systemic inflammation,[7] and low serum total testosterone.[8] A population-based, longitudinal study of ED and future risk of CVD determined that when accounting for common cardiovascular risk factors, ED is associated with a 45% to 80% increased risk of coronary artery disease (CAD).[9-11]

The Princeton III Consensus Recommendations,[12] which serve as an evidence-based guideline for the management of CVD and ED, have created a platform upon which clinicians can risk stratify men to establish the presence of vasculogenic ED and the volume of subclinical atherosclerotic burden. Novel criteria have emerged in understanding the relationship between MetS and ED relative to the prediction

Abbreviations

CAD: coronary artery disease; **CIMT:** carotid intima-media thickness; **CVD:** cardiovascular disease; **ED:** erectile dysfunction; **EST:** exercise stress testing; **HDL:** high-density lipoprotein; **MetS:** metabolic syndrome; **NO:** nitric oxide

of CVD events that may not be discovered by the traditional Framingham Risk Score risk stratification.

The metabolic syndrome

MetS is commonly defined by a cluster of overlapping factors including dyslipidemia (eg, elevated triglycerides and apolipoprotein B [apoB]–containing lipoproteins, low levels of high-density lipoprotein [HDL] cholesterol), hypertension, and deregulated glucose homeostasis) that directly increase the risk of coronary heart disease and other forms of cardiovascular atherosclerotic disease. In addition to the many clinical implications of MetS, there are still no universally accepted pathogenic mechanism(s) or consensus diagnostic criteria. The most current definition of MetS incorporates the International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definitions and requires a patient to have any three of the following five conditions[13]: (i) waist circumference >40 inches in men and >35 inches in women; (ii) triglycerides >150 mg/dL; (iii) HDL <40 mg/dL; (iv) blood pressure >135/85 mm Hg; and (v) fasting glucose >100 mg/dL.

ED has been causally linked to multiple aspects of the MetS including overall CVD risk, type 2 diabetes mellitus, hypertension, and visceral adiposity.[14-19] Several interrelated mechanisms have been proposed to explain the observed relationship between the MetS and ED. The most commonly suggested mechanism is a low serum testosterone level, which has been shown to be associated with both moderate and severe degrees of ED via diminished nitric oxide (NO) synthesis.[20] Increasing α-adrenergic activity has been linked to several established aspects of the MetS and could explain the link between the MetS and ED.[21]

Cardiovascular evaluation of erectile dysfunction

Evaluation of subclinical CVD in men at low to intermediate risk via noninvasive testing for underlying cardiovascular disease provides a useful strategy in identifying CAD in men with ED, MetS, and type 2 diabetes mellitus.[22,23] ED and CVD, specifically CAD, have the common denominator of endothelial dysfunction. Several studies have determined that ED may precede a clinically significant CAD event by a period estimated between 2 and 5 years and at an average of 3 years.[24,25] Reported symptoms of ED also have the ability to predict the likelihood of an acute coronary syndrome as well as increased mortality, suggesting the rupture of an asymptomatic coronary plaque. *Figure 1* provides an algorithm for the evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known cardiovascular disease recommended for the primary care physician.[26]

Exercise stress testing

A prospective trial of 65 men with physical ED and no symptoms of CAD were screened for CVD via exercise stress testing (EST) and multidetector computed tomography, which aims to detect subclinical plaque formation that may be at risk of rupture and that does

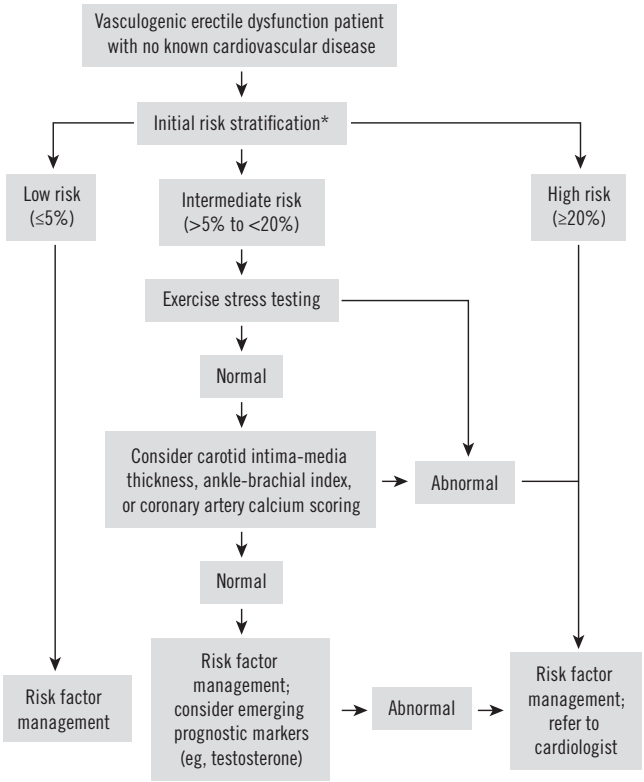

Fig. 1 *Evaluation and management of cardiovascular risk in men with vasculogenic erectile dysfunction, but no known cardiovascular disease recommended for the primary care physician. *Based on the Framingham Risk Score.*
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not have a significant luminal stenosis to negatively influence the EST.[27] In three men, the exercise electrocardiogram was borderline abnormal and in 62 men it was normal. CT calcium was present in 53 men (score range 5 to 1671) and noncalcified plaque was present in seven men. Thus, the estimated window of 2 to 5 years between ED and a clinically significant CAD event offers an opportunity for aggressive risk factor reduction, and should, thus, be a routine component in any cardiovascular risk calculator.

Carotid intima-media thickness

Carotid intima-media thickness (CIMT) has been proposed as a possible measurement of determination of risk for ED. The American College of Cardiology Foundation (ACCF)/AHA,[22] and, more emphatically, the Society for Heart Attack Prevention and Eradication Task Force,[28] support assessment during evaluation of patients at intermediate risk for underlying CVD. One trial found that 50% of 136 asymptomatic subjects (mean age, 57±11 years) with no history of vascular events and a Framingham Risk Score less than 10% had CIMT ≥75th percentile.[29] The challenge with interpreting this data is the assumed extrapolation to ED as a risk factor for CVD. Another study of 32 men with MetS compared with 29 healthy controls yielded a higher prevalence and severity of ED in men with MetS, as scores on the International Index of Erectile Dysfunction (IIEF-5) correlated inversely with CIMT.[30]

Coronary artery calcium scoring

Coronary artery calcium (CAC) scoring has been validated prospectively in several trials as a predictor of CVD. A recent review of four major trials concluded that CAC is the strongest marker for clinical risk prediction and is the most likely to positively predict future clinical cardiovascular outcomes.[31] CAC scores are considered more accurately predictive of CVD outcomes compared with CIMT measurements and have been shown to be independently predictive of mortality in men less than 45 years of age and in the elderly via a cohort study of over 44 000 subjects.[32] One trial, which consisted of EST and CAC scoring in 20 men aged 39 to 69 years with ED and no cardiac symptoms or known underlying CVD, yielded CAC scores of >50 in 11 men, all of whom were found to have angiographic evidence of CAD on coronary CT angiography, nine of whom had normal ESTs.[33] The authors concluded that ED is a bona fide predictor of subclinical, non–flow-limiting CAD that was not detectable via EST, and that CAC coupled with coronary CT angiography may help detect subclinical CAD in men with normal ESTs.

Testosterone and the metabolic syndrome

Increasing evidence supports the notion that testosterone supplementation can have a positive effect in men with MetS and ED. The Princeton III Consensus Recommendations from 2012 posit that testosterone levels should be measured in all men with physical ED.[12] This statement is in contrast with the American College of Physicians guideline from 2009 that neither recommend for or against hormonal testing and/or treatment in men with ED.[34] The TIMES2 study (Testosterone replacement In hypogonadal Men with Either metabolic Syndrome or type 2 diabetes), a large randomized trial, demonstrated that 6 to 12 months of transdermal testosterone replacement therapy significantly improved insulin resistance and glycemic control in hypogonadal men with diabetes.[35] A meta-analysis of five randomized controlled trials determined that men who received testosterone replacement therapy for an average of 58 weeks demonstrated significant benefit in the reduction of fasting serum glucose, insulin, and triglyceride levels as well as waist circumference.[36] It was noted, however, that testosterone replacement therapy, in this meta-analysis, was not found to have an appreciable improvement in HDL, blood pressure, or body mass index.

Conclusion

Growing evidence supports the relationship between MetS and ED. Additional research will further investigate biomarkers relative to visceral adiposity, testosterone, dyslipidemia, and other inflammatory and endocrine factors that place men at increased risk of a hopefully reversible metabolic disease. Clinicians in both primary and specialty care require the inquisitiveness to investigate each male patient's risks and offer appropriate evidence-based risk stratification. We recommend the following metabolic investigation in men with ED, in conjunction with the 2013 atherosclerotic cardiovascular disease (ASCVD) Risk Esti-

mator[37] (in conjunction with the AHA and AAC) to determine 10-year and lifetime ASCVD risk (myocardial infarction and cardiovascular accident) for men aged 40 to 59 years:

- Abdominal waist circumference.
- Blood pressure and heart rate.
- Fasting serum insulin and glucose levels.
- Baseline renal function (serum blood urea nitrogen and creatinine).
- Fasting serum lipid profile.
- Morning serum total testosterone level.
- Serum high-sensitivity C-reactive protein.
- Serum 25-hydroxyvitamin D.

Men's health specialists are uniquely poised to educate their male patients on both cardiometabolic risk factors as well as lifestyle strategies to reduce risk. Engaging men to understand the link between MetS and ED can serve as a powerful motivating factor in promoting such changes. ■

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