The Metabolic Investigation of Erectile Dysfunction: Cardiometabolic Risk Stratification

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15.1 Introduction

Erectile dysfunction (ED), defined as the inability to maintain and achieve an erection sufficient for satisfactory intercourse, has a high prevalence and incidence worldwide [1]. A systematic review of epidemiologic evidence undertaken in 2002 showed a clear increase in prevalence in with advancing age, with rates for men younger than 40 years ranging from approximately from 2 to 9 %, compared with 18–86 % for those older than 80 years [2]. Although not life threatening, it may be a precursor or marker of more serious conditions, particularly coronary artery disease (CAD). Inman et al. [3] have shown when ED occurs in younger men, it is associated with a marked increase in the risk of future cardiac events and that overall ED may be associated with an approximately 80 % higher risk of subsequent CAD.

Sexual function is a complex, multifactorial process. The development of ED is attributable to both psychogenic factors and physiologic alterations in neural, vascular, hormonal, and metabolic perturbations, all mediated through endothelial and smooth muscle dysfunction. While this cascade of metabolic parameters can lead to early endothelial dysfunction and eventually, late cardiovascular events, this chapter will focus on the metabolic investigation of erectile dysfunction. Specifically, we will illustrate from our practice a clinical case and the value of the metabolic workup of the ED patient and the evolving concept of "cardiometabolic risk."

Cardiometabolic risk entails the risk of developing any of the following: type 2 diabetes (T2DM), cardiovascular disease (CVD), or metabolic syndrome (Met S). The assessment of cardiometabolic risk uses traditional risk factors such as smoking,

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high LDL-C cholesterol, hypertension, and elevated serum glucose as well as emerging risk factors closely related to abdominal obesity, especially intra-abdominal or visceral obesity. The relationship between traditional cardiovascular risk factors (hypercholesterolemia, hypertension, and smoking) and the occurrence of cardiovascular events is well understood. Our increasing understanding of the pathophysiology of cardiovascular disease is now defining value of a range of new cardiovascular risk factors. Risk stratification requires measurement tools of CVD risk that must be valid in the general male population, and measurement tests or biomarkers that help predict cardiac risk [4]. ED should become part of this CVD risk assessment.

Traditional models of cardiovascular risk such as Framingham Risk Score (FRS) are weighted toward age, and 80 % of men age 40–59 will have a low 10-year risk [5]. Incorporating some assessment of lifetime risk has been proposed as an added step to evaluate cardiovascular risk in this young middle-aged population noted by Inman with ED to be at particularly elevated CVS risk [3].

New data have emerged to justify a new version, though controversial, to better target lipid management therapies for the reduction of cardiovascular events in the adult population [6]. New guidelines have attempted to address the shortcomings of older risk models. ED guidelines such as Princeton III [7] have attempted to utilize evidence-based evaluation to further stratify men for cardiovascular (CVS) risk following the utilization of keen history taking and traditional risk models to establish the presence of predominantly vasculogenic ED and the volume of subclinical atherosclerotic burden which are markers for subsequent CVS events of MI and CVA in men [8]. These guidelines are an attempt to elaborate the following questions:

- Is a history of ED a harbinger for future cardiovascular risk? Is it best described as a risk marker or risk factor for future CVS events, and just what is the difference?
- Are there cost-effective, sensitive, and specific metabolic tests that might indicate increased cardiovascular risk?
- Will these tests delineate treatment based on identification of obstructive coronary artery disease (CAD) and atherosclerotic burden and thereby lower future CVS risk and improve erectile function?

15.2 The Metabolic Syndrome: A Cluster of Findings Increasing Risk of Type 2 DM and CVD (Its Relationship to ED)

Metabolic syndrome (Met S) is a complex disorder with high socioeconomic cost that is considered a worldwide epidemic. Met S is defined by a cluster of interconnected factors that directly increase the risk of coronary heart disease (CHD), other forms of cardiovascular atherosclerotic diseases (CVD), and type 2 DM. Its main components are dyslipidemia (elevated triglycerides and apolipoprotein B (apoB)-containing lipoproteins, and low high-density lipoproteins (HDL), hypertension, and

deregulated glucose homeostasis, while abdominal obesity and insulin resistance (IR) have gained increasing attention as the core manifestations of the syndrome [9]. Recently, other abnormalities such as chronic proinflammatory and prothrombotic states, nonalcoholic fatty liver disease, and sleep apnea have been added to the entity of to the syndrome, making its definition even more complex. Besides the many components and clinical implications of Met S, there is still universally accepted pathogenic mechanism or clearly defined diagnostic criteria. Furthermore, there is still debate as to whether this entity represents a specific syndrome or is a surrogate of combined risk factors that put the individual at particular risk [10].

The most current definition 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 [11]:

- Elevated waist circumference (ethnicity specific values, e.g., European males >94 cm [40 in.] and females >80 cm)
- Triglycerides 1.7 mmol/l or greater 150 mg/dL
- HDL-chol below 1.03 mmol/l [<40 mg/dL]
- BP >135/85 mmHg
- Fasting glucose >5.6 mmol/l [>100 mg/dL]

ED has been linked to multiple selected aspects of the metabolic syndrome, including type 2 diabetes mellitus [12, 13], increased fasting blood glucose [14, 15], arteriosclerotic disease manifestations [16–18], hypertension [13, 14, 19, 20], and obesity [13–15], and to the metabolic syndrome as defined by different health organizations [14, 15, 20, 21]. Moreover, Bal et al. [15] noted that the risk of ED increased in line with the number of factors of the Met S exhibited by a patient. Several interrelated mechanisms may explain the observed relationship between the Met S and ED. One obvious mechanism could be a low testosterone level, which has been shown to be associated with moderate and severe [22], possibly via a mechanism of diminished NO synthesis [23]. This hypothesis was supported by a report that testosterone treatment increases cavernosal expression of NO synthase mRNA in rats [24]. In this way, hypogonadism as a manifestation of the Met S could result in a diminished NO synthesis and subsequent ED. Another mechanism is peripheral arterial insufficiency due to an atherosclerotic disease. The presence of arterial vasculogenic ED is associated with ischemic heart disease in men >40 years old in several studies [25]. Furthermore, men with ED are twice as likely to have sustained a myocardial infarction compared with men without ED, and the risk becomes more pronounced with increasing age [26]. Increasing alpha adrenergic activity has been linked to several established aspects of the Met S and is an attractive potential mechanism that could explain the link between the Met S and ED. Evidence supporting this mechanism has come from a study demonstrating that patients with nonorganic ED have significantly higher sympathetic activity than those without ($p < 0.05$) [27]. This mechanism has been supported by studies that have concluded that treatment with alpha-receptor antagonists, doxazosin [28],

and alfuzosin [29, 30] may improve sexual function including ED. This mechanism is also attractive because it explains the link between ED and LUTS, which was confirmed by the Multinational Survey of the Aging Male (MSAM7) study [31]. This study included more than 14,000 men, aged 50–80 years, representative of the population of six European countries and the USA [32]. A fourth mechanism explaining the link between the Met S and ED involves increased activation of the Rho/Rhokinase pathway, acting downstream of norepinephrine and endothelin1 receptors. Diabetes and hypertension have been linked to increased activity in this pathway [28]. Increased activity in Rho/Rho-kinase pathway results in the inhibition of smooth muscle and subsequent smooth muscle contraction [33]. Although this mechanism has not been specifically demonstrated in erectile tissue, it adds to the body of evidence suggesting that ED is also an expression of the Met S and could arise via this mechanism [34].

There are several hypotheses concerning the mechanism linking the metabolic syndrome and male hypogonadism. Obesity, especially visceral obesity, is an established aspect of the metabolic syndrome. The activity of aromatase, an adipose enzyme that is involved in the irreversible conversion of testosterone into estradiol [35], is higher in men who are obese, and, consequently, they tend to have a decreased testosterone level and increased estradiol level [35, 36]. Thus, the metabolic syndrome provides an endocrine mechanism to explain the development of hypogonadotropic hypogonadism, as it is believed that the effect of estradiol on gonadotropin suppression is more potent than that of testosterone [37]. The findings of Zumoff and colleagues [38], who treated six obese men with oral testolactone (an aromatase inhibitor), support this conclusion. After 6 weeks, men treated with testolactone had higher levels of testosterone and LH and decreased levels of estrogen compared with their baseline levels [38].

The hypothalamic–pituitary–adrenal (HPA) axis provides yet another mechanism that could explain the link between the metabolic syndrome and hypogonadism. The HPA axis has been shown to be overactive in subjects suffering from the metabolic syndrome [39], and it is well established that cortisol inhibits the reproductive axis at several levels including secretion of GnRH and LH and also at the level of the testes themselves [40]. This emerging link between the metabolic syndrome and male hypogonadism via increased aromatase activity, hypogonadotropic hypogonadism, and increased activity of the HPA axis seems to suggest that male hypogonadism is also a urological aspect of the metabolic syndrome.

15.3 Novel Biomarkers (Metabolic and Imaging) to Clarify CVS Risk in the ED Patient

By definition, cardiac biomarkers are measurement tests that help predict cardiac risk [41]. They include traditional measurements of cardiovascular risk: the lipid panel, blood sugar, and blood pressure. They can include anthropomorphic measurements such as waist circumference (WC), body mass index (BMI), and other measures of visceral obesity. They can include imaging studies such as coronary

artery calcification (CAC) as measured by electron-beam computed tomography or computed tomography or carotid intima–media thickness (CIMT) or carotid plaque. They can be surrogate measures of endothelial function such as peripheral arterial tonometry or serum asymmetric dimethylarginine (ADMA). They can be surrogate measures of arterial inflammation: highly sensitive C-reactive protein (hsCRP), TNF-alpha, adipokines, or Interleukin-6 (IL-6). They can measure insulin resistance and include fasting serum insulin, HOMA-IR, fasting glucose, or glycosylated A1C (HgBA1c). Lastly, they might include the measurement of the extremely atherogenic level of small, dense LDL particles (LDL-P), or Apolipoprotein B (apo-B) as measured by nuclear magnetic resonance.

Therefore, a range of important novel risk factors or biomarkers for cardiovascular disease are associated with the Met S, although not yet included within its definition. Most have yet to be validated for efficacy and cost-effective screening in both the asymptomatic and symptomatic ED patient. These include the above-noted chronic, low-grade inflammation, and disturbances in the secretion of bioactive substances from adipocytes ("adipokines") [42, 43], hsCRP, apo B, and vitamin D levels.

The cardiovascular risk factors associated with the metabolic syndrome, whether included within its diagnostic criteria or not, contribute to the progression of atherosclerotic cardiometabolic disease. Current diagnostic and therapeutic approaches do not adequately address these factors, and further clarification of the utility of these biomarkers in the ED patient is required.

We examine a few nontraditional markers and evaluate the quality of the evidence for their value as potential markers for cardiometabolic disease and thereby, in the ED patient. These have been graded according to the recommendations of the Centre for Evidence-Based Medicine: (http://www.cebm.net/levels_of_evidence.asp) [44]. Levels of evidence have been determined by consensus of the author following review of the present literature.

15.3.1 Waist Circumference (Intra-abdominal Adiposity) (IAA) in Men with ED: Level of Evidence = 1a

Intra-abdominal adiposity (IAA) drives the progression of multiple risk factors directly, through the secretion of excess free fatty acids and inflammatory adipokines and decreased secretion of adiponectin. The important contributions of IAA to dyslipidemia and insulin resistance provide an indirect, though clinically important, link to the genesis and progression of atherosclerosis and cardiovascular disease [45–47]. Presence of excess IAA is an important determinant of cardiometabolic risk. IAA is associated with insulin resistance, hyperglycemia, dyslipidemia, hypertension, and prothrombotic/proinflammatory states. Excess IAA typically is accompanied by elevated levels of C-reactive protein and free fatty acids (FFAs), as well as decreased levels of adiponectin. Abdominal obesity has been shown to be associated with the inflammation cascade, with adipose tissue expressing a number of inflammatory cytokines. Inflammation is now believed to play a role in the development of

atherosclerosis and type 2 DM. Elevated levels of CRP are considered to be predictive of cardiovascular disease and insulin resistance [47, 48].

These components help to explain why excess abdominal adiposity is considered to be a great threat to cardiovascular and metabolic health. Abdominal obesity is associated with multiple cardiometabolic risk factors, including dyslipidemia [49], elevated blood glucose [50], and inflammation [41] – all factors leading to the development of CVD and DM in male ED patients. DM is, after age, the greatest risk factor for ED [2]. Patients with DM were three times more likely to develop ED than those who did not have DM [13, 51]. The prevalence for ED in these patients was as high as 75 % [52–54]. The Cologne Male Survey noted a fourfold increase in ED in men with DM as compared to the general population [55]. In the Health Professionals Follow-up Study, which involved greater than 30,000 subjects, Bacon et al. [56] found duration of DM strongly associated with incidence of ED. Rhoden et al. [57] found higher glycosylated hemoglobin levels in patients with DM to be significantly associated with more severe ED ($p < 0.05$). The risk of ED in men with DM is also significantly associated with other diabetic complications such as diabetic neuropathy ($p < 0.05$) [58].

Adipocytes generate inflammatory cytokines, and patients with obesity and T2DM tend to have a higher inflammatory profile. Inflammatory markers, such as IL-6 [59, 60], TNF-apha [59], or hsCRP [41], are elevated and have been associated with impaired endothelial function, cardiovascular events, and ED [60, 61].

15.3.2 Testosterone Levels and Cardiometabolic Risk: Level of Evidence = 2a

Hypogonadism is a common condition in men – especially older men – that can affect both health status and quality of life. Mulligan et al. [62] examined the prevalence rates and odds ratios for selected comorbidities associated with low testosterone levels in 2,162 primary care patients. They observed that the odds ratios of having low levels (hypogonadism is both the presence of low levels and clinical signs and symptoms) were increased in the presence of certain risk factors. The odds ratios for the presence of hypogonadism (the odds of having hyopogonadism if one has this risk factor versus not having the risk factor) being of 2.38 for obesity, 2.09 for diabetes, 1.84 for hypertension, and 1.47 for hyperlipidemia [62].

Research to date strongly and consistently shows testosterone replacement therapy (TT), at least over the short term (up to ~3 years), has positive effects on body composition – decreasing fat mass and increasing muscle mass – which in turn can reduce the risk for Met S and type 2 DM [63]. Evidence is moderately consistent for TT improving bone mineral density. Research to date also is strong showing TT has positive effects on various aspects of sexual function, though the specific effects differ from study to study. Most studies to date showed that TT increased sexual awareness and arousal, erectile function, and the frequency of spontaneous erections but was less consistent in enhancing actual sexual behavior and performance [64]. It is beyond the scope of this chapter to address the conflicting issues regarding

testosterone and CVS events and mortality. One can simply say that studies thus far both positive and negative are cross-sectional and thereby, inconclusive. Yet, the authors feel it is vital to screen all men with ED for testosterone deficiency and thereby perhaps gain a sense of a man's overall health and stress. This is especially true in those men with a history of inadequate response to prior PDE5 inhibitors [65].

15.3.3 CAC Potential Role in ED Management: Level of Evidence = 1b

Coronary artery calcium (CAC) scores are better than carotid intima–media thickness (CIMT) as shown in a cohort of 44,052 asymptomatic patients referred for cardiovascular risk stratification. All-cause mortality rates (MRs) were calculated after stratifying by age groups and CAC score [66]. Another aim was to determine if coronary artery calcium (CAC) scoring is independently predictive of mortality in young adults and in the elderly population and if a young person with high CAC has a higher mortality risk than an older person with less CAC. Indeed, the value of CAC for predicting mortality extends to both elderly patients and those less than 45 years old. Elderly persons with no CAC have a lower MR than younger persons with high CAC [66].

In another MESA subanalysis, Detrano et al. [67] collected data on risk factors and performed coronary calcium scoring in an ethnically diverse population without cardiovascular disease at entry who were followed for a median of 3.8 years. They found that the adjusted risk of a CVD event was increased by a factor of 7.73 among participants with a CAC score of 101–300 compared to those individuals with no coronary calcium [67]. This risk increased to 9.67 among those with CAC scores exceeding 300 [67]. They noted that CAC scores are a strong predictor of incident CHD and provides predictive value beyond the standard Framingham risk data, regardless of race or ethnicity.

Thus, we propose the use of CAC scoring in men deemed at intermediate risk of CAD with ED according to the Framingham Risk Stratification or patients with low lifetime risk but one that might fall out of the present grading criteria [8]. The absence of CAC is conclusive of minimal to no risk of ASCVD in the following 10 years. The presence of CAC may help guide the clinician regarding appropriate primary prevention therapy and certainly is one of the strongest discriminatory tests for the intermediate-risk patient in CVD risk stratification.

15.3.4 The Role for Peripheral Arterial Tonometry (PAT) Assessment and Asymmetric Dimethylarginine (ADMA) as Markers of Endothelial Cell Function in Men with ED: Level of Evidence = 2a

Because endothelial dysfunction is considered the first step toward the generation of atherosclerotic plaque [68] and can be found in patients with cardiovascular risk factors [69, 70], the use of flow-mediated vasodilation (FMD) has long had a role

in the evaluation of the pathology of erectile dysfunction. Indeed, Kaiser et al. [71] studied 30 men with ED and no other clinical cardiovascular disease and compared them with 27 age-matched controls without ED. The ED group had penile vascular disease present on Doppler ultrasound testing (mean peak systolic flow of 28 cm/s ± 3), an IIEF-5 score of 12.9 vs. 22.3 ($p = 0.000001$) with a cutoff value for ED <21. While no significant differences were noted in fasting lipids, glucose, homocysteine, and CAC scores in the two groups, there was a significant difference in brachial artery flow-mediated vasodilation studies thereby illustrating the idea that ED appears to occur before the development of overt structural or functional systemic vascular disease and that abnormalities in the penile cavernosal nitric oxide/cyclic GMP vasodilator system may result in ED as an early clinical manifestation of vascular disease [72].

This led to the theory that endothelial dysfunction is believed to be the common initiator of ED and other atherosclerotic diseases. The importance of this study cannot be understated. Men with ED but no other clinical cardiovascular disease were found to have reduced flow-mediated vasodilation in the brachial artery in response to sublingual nitroglycerine, indicating endothelial dysfunction and abnormal smooth muscle relaxation. Evidence is accumulating that endothelial dysfunction is an early functional change thought to precede ASCVD changes in the cerebrovascular, coronary, and peripheral circulations [72].

Obesity is associated with increased activation of the rennin–angiotensin system, which in turn, leads to vasoconstriction and impaired endothelial function [73]. DM is associated with higher levels of asymmetric dimethylarginine (ADMA) [74]. ADMA is an endogenous analogue of L-arginine that competitively inhibits nitric oxide synthase (NOS) [75]. Elevated plasma ADMA levels signify impaired endothelial cell function [74, 75] and predict cardiovascular events [76–80]. A strong link of ADMA to CAD and ED has been reported [81].

Endothelial dysfunction is characterized by a reduction in endogenous nitric oxide activity that may be attributed to an elevation in ADMA levels [82]. Thus, it may be speculated that the elevation of endogenous ADMA may be associated with the systemic manifestations of endothelial dysfunction in patients with cardiovascular risk factors and ED [83].

15.3.5 Vitamin D and Cardiovascular Health: Level of Evidence = 2b

Vitamin D is known to have a well-defined role in bone and calcium metabolism, but it has also been implicated as a factor in cardiovascular health. Vitamin D deficiency as defined by the American Endocrine Society as less than 20 ng/ml affects nearly fifty percent of the world's population [84]. It has been observed that the incidence of cardiovascular disease increases with increasing distance from the equator, and correlation with vitamin D deficiency has been proposed as a mechanism [85]. Both the Framingham Offspring Study and the Health Professionals Follow-up Study showed an approximately doubled risk for cardiovascular events in vitamin

D-deficient subjects [84, 86]. Analysis of retrospectively collected data from 27,686 patients in the Intermountain Heart Collaborative Study Group (IHC) demonstrated that vitamin D levels were highly associated with coronary artery disease and myocardial infarction [87]. In the Multi-Ethnic Study of Atherosclerosis, lower 25(OH) D concentration was associated with an increased risk for incident coronary artery calcification, a measure of coronary atherosclerosis [88].

Study of the effects of the vitamin D receptor (VDR) has revealed potential mechanisms for the effects of vitamin D on vascular health. Vitamin D receptors are present in all of the key mediators of atherosclerosis including endothelial cells, vascular smooth muscle cells, and immune cells [89]. Vascular cell growth, migration, and differentiation along with immune response modulation and cytokine expression are tied to the activation of the VDR. Vitamin D is also directly involved in the systemic inflammatory response contributing to atherosclerosis [90]. Although interventional studies have not yet shown benefits of vitamin D supplementation in risk reduction, it is clearly evolving as an important marker of risk.

Most importantly, the use of these novel biomarkers and surrogates begs the question whether these markers or risk factors validate an organic cause for ED and whether modification of these markers/risk factors can improve both ED and lessen overall ASCVD risk? The honest answer is that we do not have clarification of this at present. There remains a disconnect between imaging surrogates and outcomes.

From the above evidence and our experience, we propose the following metabolic investigation of men with ED, including anthropomorphic and vital sign measurements:

- 2013 ASCVD AHA/ACC Risk Estimator to determine 10-year and lifetime ASCVD risk (MI and CVA) for men ages 40–59 years old [91].
- Waist circumference measured at the umbilicus.
- Blood pressure/heart rate.
- Fasting insulin and glucose levels.
- Baseline renal function (BUN/creatinine).
- Fasting lipid profile.
- Morning total testosterone level.
- Hs CRP.
- Vitamin D3 (OH).
- If there is any doubt with the use of the 2013 ASCVD Risk Estimator, then CT calcium scoring may clarify risk and treatment options.

When we examine the use of biomarkers, we must distinguish between screening to define a population at risk that we are not currently treating and reducing surrogate endpoints (e.g., MI, acute coronary syndrome, stroke). These questions, together with the issue posed by Thompson [92]. “Could erectile dysfunction serve as a surrogate measure of treatment efficacy in preventive interventions for cardiac disease?” can only be answered by further studies of cardiovascular disease prevention strategies in men with largely vasculogenic ED. Men with ED with or without CVS risk factors should be considered an “intermediate”-risk group for future cardiovascular

Table 15.1 Key points/potential pitfalls: what to avoid

1. Guidelines should never replace clinical judgment. They should aid and inform decision-making
2. Avoid layering tests. Testing should be ordered when specific information is required to aid in risk stratification and clinic decision-making
3. Lab testing should be interpreted in the appropriate context – checking morning samples of testosterone, repeating testosterone levels to confirm borderline results, checking two values of hsCRP, not screening during an acute illness. Results taken out of context can be misleading
4. Do not underestimate the value of lifestyle modification as an intervention. Estimation of risk can drive changes in behavior and promote health and wellness (over the usual paradigm of disease and treatment)

events. It is this group of men, particularly under the age of 60 years, who may benefit from utilization of some of these surrogate markers of cardiometabolic risk in a cost-effective manner to stratify them for subsequent aggressive treatment of preventative cardiovascular risk factors. These men, many of whom may be missed by the traditional Framingham risk criteria, may find the risk elaborated with prudent use of these biomarkers or imaging studies. Only further studies of men with vasculogenic ED and preventative measures will provide evidence as to which of the surrogate markers are impactful and efficacious in the delineation of such risk.

Conclusion

The metabolic investigation of erectile dysfunction involves primarily the investigation of metabolic sequela of visceral adiposity leading to type 2 DM or CVD. This is known as cardiometabolic risk. Older models of cardiovascular risk assessment (FRS) have generally underestimated risk in younger and middle-aged populations. The authors of the new risk models make adjustments for this and introduce the idea of balancing 10-year risk with lifetime risk to aid in decision-making in younger adults. Whether it is lifetime risk or ED that is used to enhance 10-year risk assessment, the concept is the same: to discern those who have started down the path of inflammation, endothelial dysfunction, and vulnerable plaque formation and thereby intervene somewhere upstream from the first ASCVD event. Lifetime risk may be something abstract to most patients, and current evidence does not support its use to guide pharmacotherapy. The value is to motivate therapeutic lifestyle changes. ED is something tangible. It affects mental health and quality of life. Young and middle-aged male patients with ED are likely to make changes that will have an immediate impact on both their CVS risk and overall sexual function (Table 15.1).

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