Review Article

Erectile dysfunction, metabolic syndrome, and cardiovascular risks: facts and controversies

Edward Sanchez[1], Alexander W. Pastuszak[1,2], Mohit Khera[1]

[1]Scott Department of Urology, [2]Center for Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: AW Pastuszak, M Khera; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: E Sanchez, AW Pastuszak; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Mohit Khera, MD, MBA, MPH. 7200 Cambridge St., Houston, TX 77030, USA. Email: mkhera@bcm.edu.

Abstract: Erectile dysfunction (ED) is the most common male sexual dysfunction, and shares many risk factors with systemic conditions including cardiovascular disease (CVD) and the metabolic syndrome (MetS). ED is considered to be an independent risk factor for CVD and can be a harbinger of future cardiovascular events. Given this relationship, each encounter for ED should be viewed by healthcare providers as an opportunity to screen for CVD and other comorbid conditions, including the MetS, that can significantly affect a man's overall health. While universally accepted screening guidelines are lacking, expert panels do recommend an approach to risk stratification in men with ED. In this review, we discuss the current state of understanding of the relationship between ED, the MetS, and CV risk, and how this impacts the approach to the patient presenting with ED.

Keywords: Hypogonadism; testosterone; hormone replacement; prostate cancer; prostatectomy; radiation therapy

Submitted Apr 08, 2016. Accepted for publication Aug 25, 2016.
doi: 10.21037/tau.2016.10.01
View this article at: http://dx.doi.org/10.21037/tau.2016.10.01

Introduction

Erectile dysfunction (ED) is the most frequently treated sexual dysfunction in men worldwide, and is defined as the recurrent or consistent inability to obtain and/or maintain an erection sufficient for satisfactory sexual performance (1). ED is seen in 15% of men 40–50 years old, 45% of men in their 60s, and 70% of men over 70 (2,3). Over the past decade, an association between ED and cardiovascular disease (CVD) has been identified. While causality remains difficult to establish, ED may be an indicator of systemic disease, with both ED and CVD stemming from a common etiology. A better understanding of this association is warranted in order to properly counsel, screen, and treat patients presenting with ED.

Shared risk factors

Several studies have demonstrated that common CVD risk factors are also risk factors for ED, including age, hypertension, diabetes, insulin resistance, smoking, increased body mass index (BMI), cholesterol, and decreased levels of high-density lipoprotein (HDL) cholesterol (4). In a large, prospective study, Fung *et al.* assessed seven classic CVD risk factors in male subjects and subsequently evaluated these men for ED 25 years later. Mean age, BMI, cholesterol, and triglycerides were all significantly associated with an increased risk of ED (5). A review of the Massachusetts Male Aging Study (MMAS) revealed that, after adjusting for age, a higher probability of ED correlated with a history of prior heart disease, hypertension, and diabetes (6). A follow-up study revealed that cigarette smoking almost doubled the likelihood of moderate or complete ED (7).

In obese men with a sedentary lifestyle, a significantly higher incidence of ED is observed than in normal men (8). Obesity also increases the risk of ED as a function of BMI. A multivariate analysis performed in a cohort study of 22,086 American men found that, compared to men

with BMI <25 kg/m^2, those with a BMI of 25–26.9 kg/m^2 had a 19% increased risk of developing ED, while those with BMI 27–29.9 kg/m^2 had a 33% increased risk of developing ED (9).

The link between ED and another known CVD risk factor, diabetes mellitus, is also strong. Males with both type 1 and type 2 diabetes are at increased risk of ED when compared with non-diabetic men (10). The prevalence of ED in diabetic males ranges from 35–90% (11). Kalter-Leibovici *et al.* observed severe ED in nearly one third of men with diabetes and noted that ED worsened in severity with both advancing age and diabetes duration (12).

Links to CVD

A study of 300 men with angiographically documented coronary artery disease (CAD) found that 49% suffered from ED. The study, by Montorsi *et al.*, utilized the validated International Index of Erectile Function (IIEF) to assess ED severity in study subjects (13). A prospective study by Vlachopoulos *et al.* examined the incidence of asymptomatic CAD in patients with non-psychogenic, non-hormonal, vasculogenic ED. Ultimately, 19% of subjects were found to have angiographically-documented, but clinically asymptomatic CAD (14). Both studies found that ED symptoms preceded CAD by a significant time period. In the Vlachopoulos study, onset of symptomatic ED occurred 25 months prior to the discovery of silent CAD (14). Montorsi's subjects experienced ED symptoms an average of 39 months prior to the onset of CAD symptoms (13). Studies such as these support the conclusion that patients with ED may be suffering from a more significant, systemic process, and that ED may be a useful predictor of CVD.

The risk of all CV events, myocardial infarction, cerebrovascular events, and all-cause mortality were elevated in men with ED in several meta-analyses (15,16). These studies support the hypothesis that ED is a silent marker for CVD. Ponholzer *et al.* calculated the 10-year risk of developing CVD in men with ED using the Framingham Risk Score (FRS), and reported that men with moderate to severe ED had a 43% and 65% increased relative risk for developing coronary heart disease or stroke, respectively (17). One study evaluated ED's role in disease prediction beyond the FRS. In 2010, Araujo *et al.* further evaluated data from the MMAS and found that ED was indeed associated with a higher incidence of CAD, but that it did not predict who would develop future CAD better than established risk factors and the FRS (18). Contrary to this, the Princeton III Consensus Conference suggested that ED itself is an independent marker of increased risk for CVD, CAD, stroke, and all-cause mortality. This consensus panel considered a man with organic ED to be at increased CVD risk until further evaluation suggested otherwise and provided guidance on CV risk screening and stratification (19).

A common pathophysiology for ED and CVD

To better understand the link between ED and CVD, an understanding of the physiology of erection is useful. Erection results from coordinated communication of hormonal, neural, and vascular systems as well as psychological inputs. Sensory input from receptors in the skin, glans, urethra, and corporat cavernosa travel via the dorsal nerve of the penis, and later the pudendal nerve, to S2–S4 nerve roots. Interaction with the thalamus and sensory cortex leads to parasympathetic activation and release of nitric oxide (NO) from the cavernous nerves and endothelial cells. NO activates guanylyl cyclase, which catalyzes the formation of cyclic guanosine monophosphate (cGMP). Protein kinase G is activated by cGMP and leads to phosphorylation of potassium and calcium channels, cellular hyperpolarization, reduced intracellular calcium, and smooth muscle relaxation. This smooth muscle relaxation, along with decreased peripheral arteriolar resistance promotes blood inflow into the corporal tissues. In addition, adenosine, prostaglandins, and calcitonin gene-related peptides may activate cyclic adenosine monophosphate (cAMP), a similar mediator of smooth muscle relaxation (20). cGMP and cAMP are later degraded by phosphodiesterase type 5 (PDE5) and PDE4, respectively (21).

The discovery of NO as a signaling molecule and its part in the cascade that ultimately leads to an erection led to further exploration of the role of endothelial dysfunction in ED. Endothelial integrity is crucial to this process, and endothelial dysfunction is thought to be a common denominator between ED and CVD (22). Initial impairments to the endothelium-dependent vasodilation in penile tissues may lead to late structural changes, penile artery atherosclerosis, and flow-limiting stenosis similar to that seen in CAD (23).

The artery size hypothesis

Montorsi *et al.* introduced the artery size hypothesis as a

pathophysiologic mechanism to address the association between ED and CVD. The study proposed that, in cases of systemic atherosclerosis, all major vascular beds should be affected to the same extent. Symptoms, however, do not manifest equally at different points in the system, likely due to larger vessels being able to tolerate the same amount of obstruction better than smaller vessels. Given the smaller size of the penile vasculature (1–2 mm) compared to coronary vasculature (3–4 mm), ED is more likely to manifest earlier than CAD. This study was one of the first to propose that ED and CAD are different manifestations of the same systemic condition. It was also one of the first studies to introduce ED as a harbinger of CAD (24). A subsequent study supported this finding, suggesting that ED occurs prior to cardiac symptoms in virtually all patients with chronic coronary syndrome with a time interval of approximately 3 years. Those with acute coronary syndrome had a much lower prevalence of sexual dysfunction, although as the extent of CAD increased in these patients, so did the rate of ED (25). A study by Rogers *et al.* provided further support for the relationship between vessel size and symptoms, reporting that the degree of stenosis within the internal pudendal arteries (52–65%) was similar to stenosis found in coronary arteries of patients with ED unresponsive to PDE5 inhibitors (26).

Chang *et al.* characterized the phenotypes of coronary vasculature in CAD patients with and without ED. Thirty males with ED (average duration of 2.7 years) and asymptomatic CAD were compared to age-matched controls with angina pectoris and no ED. Subjects with ED and asymptomatic CAD had more coronary vessels involved than the angina group and were found to have a greater number of type C lesions (American Heart Association/American College of Cardiology grading system), which represent lesions with a chance of successful dilation of <60% and/or a high risk of abrupt complete vessel stenosis (27).

One limitation of the artery size hypothesis is the fact that not all cases of vasculogenic ED are caused solely by penile atherosclerosis. In fact, while evaluating a small cohort of 31 men over 45 years old undergoing autopsy, Ponholzer *et al.* found that clinically significant penile atherosclerosis was relatively rare (12.9%) compared to coronary (87%) or internal iliac vessel disease (77%) (28). Though this study was relatively small, it supports the conclusion that atherosclerotic lesions do not form uniformly in all vascular areas. It is likely that other factors such as microscopic endothelial damage and alterations of the NO-cGMP pathway may play a role as well.

The role of inflammation in CVD and ED

Several studies have suggested that chronic inflammation and circulating inflammatory markers affect systemic endothelial function. Chronic inflammation may, therefore, represent a link between ED and CVD. ED onset and severity are associated with increased expression of markers of inflammation. Markers and mediators such as C-reactive protein (CRP), intercellular adhesion molecule 1, interleukin (IL)-6, IL-10, IL-1B, and tumor necrosis factor alpha (TNF-α) were found to be expressed at higher levels in patients with ED. In addition, endothelial and prothrombotic factors such as von Willebrand factor (vWF), tissue plasminogen activator (tPA), plasminogen activator inhibitor 1 (PAI-1), and fibrinogen are also expressed at higher levels in ED patients [reviewed in (29)]. Vlachopoulos found that levels of circulating inflammatory markers were indeed elevated in men with ED in both the presence and absence of CAD. Marker levels were similar in patients with ED alone compared to patients with CAD alone, suggesting that ED and CAD are equivalent with respect to activation of inflammatory and prothrombotic pathways. The presence of ED is also thought to add to the negative impact of inflammation in patients with CAD (30).

Hypogonadism in CVD and ED

Androgens play an important role in both penile and vascular health, with cellular targets located in both endothelial and smooth muscle cells. Within the vasculature, androgens promote endothelial cell survival, inhibit proliferation and intimal migration of vascular smooth muscle cells, and reduce endothelial expression of pro-inflammatory markers. Within the penis, low androgen levels are associated with apoptosis of endothelial and smooth muscle cells as well as with pathologic structural remodeling (31).

Several studies have suggested a link between low testosterone and CVD. Lee *et al.* found that testosterone levels were negatively correlated with Framingham risk scores in patients with sexual dysfunction (32). Cao *et al.* studied a population of elderly males with CAD and found that compared to controls, these men had significantly lower levels of both total and free testosterone, as well as decreased expression of androgen receptors (33). Low androgen levels have also been associated with an increased

risk of cardiovascular death (34). Malkin *et al.* observed that androgen deficiency in men with CAD was associated with increased all-cause and vascular mortality (35). Corona *et al.* reported that low testosterone levels are significantly associated with cardiovascular death in patients with ED (34).

Testosterone's role in CVD

Our knowledge of the intersection between testosterone and cardiovascular risk continues to evolve. Animal studies suggest that testosterone plays a role in coronary artery vasodilation (36-38). Recently, multiple randomized, placebo-controlled trials have shown that testosterone therapy improves myocardial ischemia in men with CAD (39-41). English *et al.* observed that testosterone therapy decreased exercised-induced myocardial ischemia in men with stable angina. In addition, a significant decrease in pain perception, as well as role limitation due to physical problems was noted in the testosterone therapy group (39). Similarly, Rosano *et al.* demonstrated an increased time to 1 mm ST-segment depression in men with CAD receiving intravenous testosterone prior to exercise stress testing (40). It is important to note that these changes were seen with both transdermal and intravenous testosterone formulations.

The mechanism by which testosterone affects vasomotor response remains under investigation. Webb *et al.* demonstrated that physiologic levels of intracoronary testosterone led to increased coronary artery dilation as well as increased coronary blood flow in men with established CAD via an endothelium-independent pathway (42). Additional studies suggest that the most likely mechanism of action of testosterone on vascular smooth muscle is via modulation of non-ATP-sensitive potassium ion channels, calcium-activated potassium ion channels, voltage-sensitive potassium ion channels, and finally L-type calcium ion channels (43).

Testosterone is also thought to play a role in regulating ventricular repolarization. Prolongation of heart rate corrected QT interval (QTc), an accepted measure of ventricular repolarization, is associated with increased incidence of ventricular arrhythmias, including torsades de pointes (44). Charbit *et al.* examined the QTc interval in hypogonadal men and observed a significant negative correlation between QTc length and total testosterone levels, a finding echoed by van Noord *et al.* (45,46). Charbit *et al.* also examined the effects of a single intramuscular injection of testosterone enanthate on QTc and found that testosterone therapy shortened QTc. Its greatest effect was noted 2 days after administration, with statistically significant differences noted up to 4–6 weeks after administration (45).

An inverse correlation between testosterone levels and carotid intima-media thickness (IMT) has been demonstrated by several studies (47-49). IMT is considered a marker for preclinical atherosclerosis and is generally considered a risk factor for adverse cardiovascular events (50,51). The mechanism of action by which testosterone affects IMT remains unclear, but current data suggests endogenous testosterone may be protective against the development of atherosclerosis.

In addition to direct effects on the coronary vasculature, testosterone replacement may further affect CVD risk by modulating known CVD risk factors. Kalinchenko *et al.* showed that intramuscular testosterone therapy led to significant improvements in the BMIs of men with metabolic syndrome (MetS) (52). Corona *et al.* also revealed a reduction in fat mass after testosterone replacement therapy. Additionally, this same analysis revealed that testosterone therapy lowered hemoglobin A1c and fasting plasma glucose (53). Whitsel *et al.* demonstrated that intramuscular testosterone led to a reduction in both HDL and LDL, although studies published by Haddad and Isidori reported conflicting results (54-56).

A study done by Basaria *et al.* in 2010 was stopped prematurely due to an increased rate of adverse cardiovascular events observed in men receiving transdermal testosterone, raising concern that testosterone may carry significant cardiovascular risk (57). However, several limitations in this study have been pointed out. For example, the mean age of the study population was 74 years, with a very high percentage of the population suffering from serious chronic illnesses including diabetes, dyslipidemia, obesity, hypertension, and pre-existing heart disease. Significant limitations in mobility existed at baseline, as the purpose of this study was to measure improvement in physical strength. A number of adverse events reported may have been minor phenomena and not true cardiac events. Finally the sample size was thought to be relatively small. Several meta-analyses have investigated the association between testosterone therapy and adverse events. Calof *et al.* analyzed 19 randomized placebo controlled trials. No significant difference in rate of cardiovascular events was noted. An increased combined incidence of all prostate related adverse events was noted. These included

combined prostate events such as all incidents of prostate biopsies, PSA >4 ng/mL or an increase of 1.5 ng/mL during the study, prostate cancer, acute urinary frequency, and an increase in international prostate symptom score. Of note, none of these individual adverse events were significantly different than those observed in the placebo group. A significant rise in hematocrit >50% was observed in the testosterone group. Finally, skin irritation at the site of testosterone application was noted in studies using topical testosterone (58). A second analysis by Haddad *et al.* also failed to find a statistically significant difference in adverse cardiovascular events (56). Fernández-Balsells *et al.* analyzed 51 studies which included men receiving testosterone therapy for over 3 months. Again, a significant increase in hemoglobin and hematocrit levels was seen in the therapy group compared to those receiving placebo. No difference was found when comparing rate of death, MI, coronary revascularization procedures, or arrhythmias. No difference was seen in rates of prostate cancer, need for prostate biopsy, international prostate symptom score, increase in PSA, or combined prostate related adverse events (59).

MetS

MetS, now considered an important public health threat, is a constellation of several cardiovascular risk factors associated with a 2-fold increase of a 5- to 10-year risk of CVD. MetS is characterized by the presence or treatment of any three of the following: abdominal obesity (waist >94 cm), triglycerides >150 mg/dL, blood pressure >130/85 mmHg, fasting glucose >100 mg/dL, and HDL <40 mg/dL (60). Low levels of androgens are strongly associated with MetS and its components (61). In a study of men with low serum testosterone, García-Cruz *et al.* found that MetS was associated with significantly lower IIEF scores. Incidence of moderate to severe ED was higher among subjects with MetS versus those without. Severity of ED was found to be associated with severity of MetS, with an increased mean number of MetS components seen as ED severity increased. Multivariate analysis revealed that moderate and severe ED were the variables associated with the highest odds of MetS (62).

Yassin *et al.* followed 261 patients diagnosed with late onset hypogonadism and ED treated with testosterone undecanoate (TU). The mean duration of treatment was more than 4 years. The study assessed parameters affected by MetS, including body weight, waist circumference, BMI, total cholesterol, LDL, HDL, triglycerides, glucose, hemoglobin A1c, and blood pressure. Significant improvements in obesity parameters (BMI and waist circumference) were observed, along with a decrease in total cholesterol, LDL, triglycerides, fasting blood glucose, hemoglobin A1c, and blood pressure over the course of the study. Health related quality of life was significantly improved after testosterone therapy, with sustained improvement in erectile function and muscle and joint pain (63).

Screening for CVD

Given the evidence supporting a link between ED, CVD, and mortality, as well as the fact that ED may precede CV events by several years, it is recommended that men with ED be screened for CVD, with evaluation for related comorbidities where appropriate (64). However, controversy exists as to whether the presence ED improves the prediction of CVD beyond traditional risk factors. Araujo *et al.* found that ED did not improve risk assessment above traditional methods such as FRS (18). The joint 2013 American College of Cardiology/American Heart Association guideline on assessment of cardiovascular risk mentions ED as being investigated and considered as a risk predictor, but its contribution is awaiting further consideration (65). In 2012, the Princeton III Consensus Conference aimed to focus on the predictive value of vasculogenic ED in assigning cardiovascular risk to men of all ages. The consensus recognized ED to be, in itself, an independent marker of increased risk for CVD, CAD, stroke and all-cause mortality. The panel considered all men over 30 years of age with ED to be at an increased risk for CVD, recommending thorough noninvasive and, when indicated, invasive evaluation of CVD status (19).

While ED's role as a novel trigger for further testing may be under investigation, any sexual dysfunction evaluation is an opportunity for physicians to gather information regarding each patient's overall health profile, including any evidence of co-existing cardiac risk factors, such as hypertension, hyperlipidemia, diabetes, and smoking. Evaluation for obesity, including BMI as well as waist and hip measurements, should be considered. Validated questionnaires may also be utilized to assess the severity of sexual dysfunction [i.e., Sexual Health Inventory for Men (SHIM), IIEF] as well as assess for hypogonadism [Androgen Deficiency in the Aging Male (ADAM or qADAM)].

Initial laboratory testing includes assessment of the hypothalamic-pituitary-gonadal axis, lipid status, and

sugar metabolism. The International Conference on Sexual Medicine (ICSM) recommends testing fasting blood glucose, lipid levels, and gender-specific hormones during the evaluation of sexual dysfunction in men (66). Hemoglobin A1c is strongly associated with ED and may be considered in lieu of fasting blood glucose or in men with known diabetes (67). Evaluation of the hypothalamic-pituitary-gonadal-axis should include determination of testosterone, free testosterone, sex hormone-binding globulin, prolactin, luteinizing hormone, and follicle-stimulating hormone levels. Recommendations for routine hormonal blood tests remain controversial, but are supported by several groups such as the Princeton III Consensus Conference, British Society for Sexual Medicine, and the International Society for Sexual Medicine (19).

Patients should be risk stratified during their initial physician visit. The Princeton III Consensus Conference equated sexual activity to walking one mile on a flat surface in twenty minutes or climbing 2 flights of stairs in 10 seconds. Low-risk patients are those that can perform exercise of modest intensity without symptoms, and do not generally require additional cardiovascular workup prior to ED treatment. High-risk patients are those with cardiac conditions severe or unstable enough to pose a significant risk with sexual activity. Common profiles include unstable angina pectoris, uncontrolled hypertension, congestive heart failure (NYHA class IV), high risk arrhythmias (exercise induced ventricular tachycardia, implanted internal cardioverter defibrillator with frequent shocks, poorly controlled atrial fibrillation), obstructive hypertrophic cardiomyopathy, and moderate to severe valvular disease such as aortic stenosis. High-risk individuals should be referred to a cardiologist for further evaluation prior to initiation of treatment for ED and/or sexual activity. Patients considered at intermediate risk, such as those with mild or moderate angina pectoris, past MI (2–8 weeks) without intervention, congestive heart failure (NYHA class III), and non-cardiac sequelae of atherosclerotic disease (TIA, stroke, PAD), should be further evaluated with an exercise or chemical stress tests. Sexual activity is equivalent to 4 minutes of the Bruce treadmill protocol. These patients may then be categorized as low or high risk, and may proceed with treatment or further evaluation when appropriate (19).

Conclusions

ED is the most common male sexual dysfunction. Growing evidence has established that ED shares many risk factors with systemic conditions including CVD and the MetS. ED has been linked to CVD and is considered a potential harbinger of future cardiovascular events. Given this relationship, each encounter for ED should be viewed by healthcare providers as an opportunity to screen for CVD and other comorbid conditions that can significantly affect a man's overall health. Proper referral for additional testing should be pursued when warranted as well. While universally accepted screening guidelines do not yet exist, expert panel suggestions such as the Princeton III Consensus Conference provide an initial risk stratification method for men with ED. Further research on the relationship between ED, CVD and MetS is required. As our understanding of this link evolves, so should our approach to evaluating and treating patients presenting with ED.

Acknowledgements

Funding: AW Pastuszak is a K12 scholar supported by a Male Reproductive Health Research (MRHR) Career Development Physician-Scientist Award (grant No. HD073917-01 to Dolores J. Lamb) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) program.

Footnote

Conflicts of Interest: Dr. M Khera: Consultant—Lipocine, Endo, Abbvie, Coloplast, American Medical Systems. The other authors have no conflicts of interest to declare.

References

1. Porst H, Burnett A, Brock G, et al. SOP conservative (medical and mechanical) treatment of erectile dysfunction. J Sex Med 2013;10:130-71.
2. NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. JAMA 1993;270:83-90.
3. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007;120:151-7.
4. Raheem OA, Su JJ, Wilson JR, et al. The Association of Erectile Dysfunction and Cardiovascular Disease: A Systematic Critical Review. Am J Mens Health 2016. [Epub ahead of print].
5. Fung MM, Bettencourt R, Barrett-Connor E. Heart

disease risk factors predict erectile dysfunction 25 years later: the Rancho Bernardo Study. J Am Coll Cardiol 2004;43:1405-11.
6. Feldman HA, Goldstein I, Hatzichristou DG, et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994;151:54-61.
7. Feldman HA, Johannes CB, Derby CA, et al. Erectile dysfunction and coronary risk factors: prospective results from the Massachusetts male aging study. Prev Med 2000;30:328-38.
8. Derby CA, Mohr BA, Goldstein I, et al. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology 2000;56:302-6.
9. Bacon CG, Mittleman MA, Kawachi I, et al. A prospective study of risk factors for erectile dysfunction. J Urol 2006;176:217-21.
10. Bacon CG, Hu FB, Giovannucci E, et al. Association of type and duration of diabetes with erectile dysfunction in a large cohort of men. Diabetes Care 2002;25:1458-63.
11. Malavige LS, Levy JC. Erectile dysfunction in diabetes mellitus. J Sex Med 2009;6:1232-47.
12. Kalter-Leibovici O, Wainstein J, Ziv A, et al. Clinical, socioeconomic, and lifestyle parameters associated with erectile dysfunction among diabetic men. Diabetes Care 2005;28:1739-44.
13. Montorsi F, Briganti A, Salonia A, et al. Erectile dysfunction prevalence, time of onset and association with risk factors in 300 consecutive patients with acute chest pain and angiographically documented coronary artery disease. Eur Urol 2003;44:360-4; discussion 364-5.
14. Vlachopoulos C, Rokkas K, Ioakeimidis N, et al. Prevalence of asymptomatic coronary artery disease in men with vasculogenic erectile dysfunction: a prospective angiographic study. Eur Urol 2005;48:996-1002; discussion 1002-3.
15. Vlachopoulos CV, Terentes-Printzios DG, Ioakeimidis NK, et al. Prediction of cardiovascular events and all-cause mortality with erectile dysfunction: a systematic review and meta-analysis of cohort studies. Circ Cardiovasc Qual Outcomes 2013;6:99-109.
16. Dong JY, Zhang YH, Qin LQ. Erectile dysfunction and risk of cardiovascular disease: meta-analysis of prospective cohort studies. J Am Coll Cardiol 2011;58:1378-85.
17. Ponholzer A, Temml C, Obermayr R, et al. Is erectile dysfunction an indicator for increased risk of coronary heart disease and stroke? Eur Urol 2005;48:512-8; discussion 517-8.
18. Araujo AB, Hall SA, Ganz P, et al. Does erectile dysfunction contribute to cardiovascular disease risk prediction beyond the Framingham risk score? J Am Coll Cardiol 2010;55:350-6.
19. Nehra A, Jackson G, Miner M, et al. The Princeton III Consensus recommendations for the management of erectile dysfunction and cardiovascular disease. Mayo Clin Proc 2012;87:766-78.
20. Lin CS, Lin G, Lue TF. Cyclic nucleotide signaling in cavernous smooth muscle. J Sex Med 2005;2:478-91.
21. Jin L, Burnett AL. RhoA/Rho-kinase in erectile tissue: mechanisms of disease and therapeutic insights. Clin Sci (Lond) 2006;110:153-65.
22. Solomon H, Man JW, Jackson G. Erectile dysfunction and the cardiovascular patient: endothelial dysfunction is the common denominator. Heart 2003;89:251-3.
23. Montorsi P, Ravagnani PM, Galli S, et al. Common grounds for erectile dysfunction and coronary artery disease. Curr Opin Urol 2004;14:361-5.
24. Montorsi P, Ravagnani PM, Galli S, et al. The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. Am J Cardiol 2005;96:19M-23M.
25. Montorsi P, Ravagnani PM, Galli S, et al. Association between erectile dysfunction and coronary artery disease. Role of coronary clinical presentation and extent of coronary vessels involvement: the COBRA trial. Eur Heart J 2006;27:2632-9.
26. Rogers JH, Karimi H, Kao J, et al. Internal pudendal artery stenoses and erectile dysfunction: correlation with angiographic coronary artery disease. Catheter Cardiovasc Interv 2010;76:882-7.
27. Chang ST, Chu CM, Hsiao JF, et al. Coronary phenotypes in patients with erectile dysfunction and silent ischemic heart disease: a pilot study. J Sex Med 2010;7:2798-804.
28. Ponholzer A, Stopfer J, Bayer G, et al. Is penile atherosclerosis the link between erectile dysfunction and cardiovascular risk? An autopsy study. Int J Impot Res 2012;24:137-40.
29. Gandaglia G, Briganti A, Jackson G, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol 2014;65:968-78.
30. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, et al. Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. Eur Heart J 2006;27:2640-8.
31. Mirone V, Imbimbo C, Fusco F, et al. Androgens and morphologic remodeling at penile and cardiovascular

levels: a common piece in complicated puzzles? Eur Urol 2009;56:309-16.
32. Lee WC, Kim MT, Ko KT, et al. Relationship between Serum Testosterone and Cardiovascular Disease Risk Determined Using the Framingham Risk Score in Male Patients with Sexual Dysfunction. World J Mens Health 2014;32:139-44.
33. Cao J, Zou H, Zhu BP, et al. Sex hormones and androgen receptor: risk factors of coronary heart disease in elderly men. Chin Med Sci J 2010;25:44-9.
34. Corona G, Monami M, Boddi V, et al. Low testosterone is associated with an increased risk of MACE lethality in subjects with erectile dysfunction. J Sex Med 2010;7:1557-64.
35. Malkin CJ, Pugh PJ, Morris PD, et al. Low serum testosterone and increased mortality in men with coronary heart disease. Heart 2010;96:1821-5.
36. Yue P, Chatterjee K, Beale C, et al. Testosterone relaxes rabbit coronary arteries and aorta. Circulation 1995;91:1154-60.
37. Chou TM, Sudhir K, Hutchison SJ, et al. Testosterone induces dilation of canine coronary conductance and resistance arteries in vivo. Circulation 1996;94:2614-9.
38. O'Connor EK, Ivey JR, Bowles DK. Differential effects of androgens on coronary blood flow regulation and arteriolar diameter in intact and castrated swine. Biol Sex Differ 2012;3:10.
39. English KM, Steeds RP, Jones TH, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: A randomized, double-blind, placebo-controlled study. Circulation 2000;102:1906-11.
40. Rosano GM, Leonardo F, Pagnotta P, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. Circulation 1999;99:1666-70.
41. Webb CM, Adamson DL, de Zeigler D, et al. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. Am J Cardiol 1999;83:437-9, A9.
42. Webb CM, McNeill JG, Hayward CS, et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. Circulation 1999;100:1690-6.
43. Oskui PM, French WJ, Herring MJ, et al. Testosterone and the cardiovascular system: a comprehensive review of the clinical literature. J Am Heart Assoc 2013;2:e000272.
44. Morita H, Wu J, Zipes DP. The QT syndromes: long and short. Lancet 2008;372:750-63.
45. Charbit B, Christin-Maître S, Démolis JL, et al. Effects of testosterone on ventricular repolarization in hypogonadic men. Am J Cardiol 2009;103:887-90.
46. van Noord C, Dörr M, Sturkenboom MC, et al. The association of serum testosterone levels and ventricular repolarization. Eur J Epidemiol 2010;25:21-8.
47. Muller M, van den Beld AW, Bots ML, et al. Endogenous sex hormones and progression of carotid atherosclerosis in elderly men. Circulation 2004;109:2074-9.
48. van den Beld AW, Bots ML, et al. Endogenous hormones and carotid atherosclerosis in elderly men. Am J Epidemiol 2003;157:25-31.
49. Mäkinen J, Järvisalo MJ, Pöllänen P, et al. Increased carotid atherosclerosis in andropausal middle-aged men. J Am Coll Cardiol 2005;45:1603-8.
50. Crouse JR 3rd, Craven TE, Hagaman AP, et al. Association of coronary disease with segment-specific intimal-medial thickening of the extracranial carotid artery. Circulation 1995;92:1141-7.
51. Pignoli P, Tremoli E, Poli A, et al. Intimal plus medial thickness of the arterial wall: a direct measurement with ultrasound imaging. Circulation 1986;74:1399-406.
52. Kalinchenko SY, Tishova YA, Mskhalaya GJ, et al. Effects of testosterone supplementation on markers of the metabolic syndrome and inflammation in hypogonadal men with the metabolic syndrome: the double-blinded placebo-controlled Moscow study. Clin Endocrinol (Oxf) 2010;73:602-12.
53. Corona G, Monami M, Rastrelli G, et al. Type 2 diabetes mellitus and testosterone: a meta-analysis study. Int J Androl 2011;34:528-40.
54. Whitsel EA, Boyko EJ, Matsumoto AM, et al. Intramuscular testosterone esters and plasma lipids in hypogonadal men: a meta-analysis. Am J Med 2001;111:261-9.
55. Isidori AM, Giannetta E, Greco EA, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol (Oxf) 2005;63:280-93.
56. Haddad RM, Kennedy CC, Caples SM, et al. Testosterone and cardiovascular risk in men: a systematic review and meta-analysis of randomized placebo-controlled trials. Mayo Clin Proc 2007;82:29-39.
57. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22.
58. Calof OM, Singh AB, Lee ML, et al. Adverse events associated with testosterone replacement in middle-aged and older men: a meta-analysis of randomized, placebo-controlled trials. J Gerontol A Biol Sci Med Sci

2005;60:1451-7.
59. Fernández-Balsells MM, Murad MH, Lane M, et al. Clinical review 1: Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560-75.
60. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009;120:1640-5.
61. Laaksonen DE, Niskanen L, Punnonen K, et al. Sex hormones, inflammation and the metabolic syndrome: a population-based study. Eur J Endocrinol 2003;149:601-8.
62. García-Cruz E, Leibar-Tamayo A, Romero J, et al. Metabolic syndrome in men with low testosterone levels: relationship with cardiovascular risk factors and comorbidities and with erectile dysfunction. J Sex Med 2013;10:2529-38.
63. Yassin DJ, Doros G, Hammerer PG, et al. Long-term testosterone treatment in elderly men with hypogonadism and erectile dysfunction reduces obesity parameters and improves metabolic syndrome and health-related quality of life. J Sex Med 2014;11:1567-76.
64. Pastuszak AW. Current Diagnosis and Management of Erectile Dysfunction. Curr Sex Health Rep 2014;6:164-76.
65. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014;63:2935-59.
66. Hatzichristou D, Rosen RC, Derogatis LR, et al. Recommendations for the clinical evaluation of men and women with sexual dysfunction. J Sex Med 2010;7:337-48.
67. Weinberg AE, Eisenberg M, Patel CJ, et al. Diabetes severity, metabolic syndrome, and the risk of erectile dysfunction. J Sex Med 2013;10:3102-9.

Cite this article as: Sanchez E, Pastuszak AW, Khera M. Erectile dysfunction, metabolic syndrome, and cardiovascular risks: facts and controversies. Transl Androl Urol 2017;6(1):28-36. doi: 10.21037/tau.2016.10.01

