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REVIEW

Erectile dysfunction as a predictor of cardiovascular disease

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Although it has been recognized that erectile dysfunction (ED) and coronary artery disease share many of the same risk factors—smoking, dyslipidemia, diabetes and hypertension—just in the past few years several new studies now suggest that ED is an important early marker of the presence of coronary artery disease. Recent analyses suggest that ED symptoms occur prior to coronary artery disease symptoms and may be a predictor of future major cardiovascular events. Some of these new studies also suggest that ED is an independent risk factor for predicting cardiovascular events—that is independent of other well-established risk factors. Taken together, these new studies suggest that when a patient presents with ED, the patient should be questioned about cardiac health and cardiovascular risk factors. If cardiovascular risk factors are identified, they should be worked up and aggressively treated—as treatment of these risk factors may be life-saving.
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Introduction

It is now well recognized that risk factors for erectile dysfunction (ED) include the same risk factors as coronary artery disease, including smoking, dyslipidemia, diabetes, hypertension, lack of physical activity and obesity.[1–4] Over the past few years several new studies have taken this concept further, suggesting that ED may be an important early marker for the presence of coronary artery disease. Conversely patients with coronary artery disease have been shown to have a high prevalence of ED.

The purpose of this review is to describe some of the recent studies that suggest that ED may be an early marker for the development of coronary artery disease.

Early studies

The landmark Massachusetts Male Aging Study[3] increased awareness of the prevalence of ED in a general population of men as well as the link between ED and cardiovascular risk factors. The investigators studied 1290 healthy men aged 40–70 and observed that 52% claimed some degree of ED. ED was reported to be minimal in 17.2% of men, moderate in 25.2% and complete in 9.6% of men. The Massachusetts Male Aging Study assessed the risk factors associated with the development of ED. Age was a risk factor: complete ED was reported in 5.1% of men age 40 and increased to 15% in men age 70. Moderate ED increased from 17% in men aged 40 to 34% to those aged 70. Following adjustments for age, ED was associated with heart disease, hypertension, diabetes and inversely correlated with high-density lipoprotein (HDL, so-called 'good' cholesterol). In men with heart disease and hypertension, cigarette smoking was associated with a greater risk of complete ED. A higher probability of ED was also seen in men taking certain cardiac medicines, with increases in indices of anger and depression, and inversely with an index of dominant personality and serum dehydroepiandosterone. This paper has been viewed as a wake-up call to the fact that ED is a common problem in Western society and that it shares common risk factors with coronary artery disease. It suggests that much of ED in men of the ages of 40–70 is vasculogenic in nature and supports the concept that the common risk factors for ED and coronary artery disease (hypertension,

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dyslipidemia, smoking, diabetes) are associated with endothelial dysfunction and atherosclerosis.

O'Kane and Jackson[5] described two interesting case reports relevant to this concept. One patient developed ED 2 months before the onset of acute myocardial infarction. The patient had no previous history of coronary artery disease. A second patient had cardiovascular risk factors but only ED prompted his physician to obtain an exercise test that showed ST segment depression on the electrocardiogram (ECG). A subsequent cardiac catheterization showed significant three-vessel coronary artery disease.

Pritzker,[6] in a preliminary report, reviewed the stress test results, risk factor profiles and coronary angiograms in 50 men (ages 40–60) with ED but without overt cardiovascular disease. The results of exercise stress testing were positive for ischemia in 28 of 59 (56%) patients. In twenty of these patients who underwent coronary angiography, six demonstrated either left main coronary artery disease or severe three-vessel disease; seven had two-vessel coronary artery disease and seven had single-vessel disease. Pritzker concluded that ED may be an early warning of cardiovascular disease, and coined the term 'The Penile Stress Test'.

Our group[7] showed that in a population of men with known stable coronary artery disease that ED was very common. Men with chronic stable coronary artery disease were administered the Sexual Health Inventory in Men questionnaire. Of them, 75% had some degree of ED and in those with ED it was severe in 25%. Of note, most of these men had not previously discussed their ED with their cardiologist. These men presenting with ED should be screened for cardiovascular disease and the cardiovascular risk factors. Conversely, men with known heart disease or risk factors for heart disease should be asked about erectile function and their sexual health.

Recent studies (2003–2007)

Recent studies have confirmed and extended some of these earlier observations.[8] Blumentals *et al.*[9] reported data on 12 825 ED patients and an equal number of male patients without ED as part of a retrospective cohort study from a large managed care database that was carried out between 1 January 1997 and 31 March 2002. Men with ED had a twofold increased risk of acute myocardial infarction (odds ratio (OR) = 1.99; 95% confidence interval (CI) = 1.17–3.38) after adjusting for age, smoking, obesity and use of various medicines. The risk of having an acute myocardial infarction associated with ED increased with age. The authors concluded that physicians should monitor ED patients who may not necessarily present with cardiac symptoms.

Montorsi *et al.*[10] described 300 consecutive patients with chest pain and angiographically documented coronary artery disease. The prevalence of ED in this group of patients was 49% (147/300). Of interest, ED symptoms were reported to occur prior to symptoms of coronary artery disease in 99/147 (67%) of the patients. The mean time interval between the onset of ED and coronary artery disease symptoms was 39 months. All patients with type I diabetes mellitus developed sexual dysfunction before the onset of coronary artery disease. The authors concluded that a significant proportion of patients with angiographically documented coronary artery disease have ED and the symptoms of ED became evident prior to angina in about 70% of cases.

Speel *et al.*[11] studied 158 patients with ED, aged 40–69 who underwent a penile pharmacoduplex ultrasonogram. Patients aged 40–49 and 60–69 years had no significant difference in risk of developing coronary artery disease based on Framingham risk tables between patients with and without cavernous arterial insufficiency. However, those patients aged 50–59 who had cavernous arterial insufficiency did have a significantly greater risk of developing coronary artery disease. After 4 years, this cohort's estimated risk of developing coronary artery disease was 8.3% in those with versus 6.0% in those without cavernous arterial insufficiency. At 12 years this risk increased to 24% versus 19%. The authors concluded that men with cavernous arterial insufficiency aged 50–59 are prone to develop coronary artery disease based on Framingham functions. Roumeguère *et al.*[12] also observed that ED was associated with a high risk of coronary artery disease, based on Framingham risk tables. They compared 215 patients with ED (mean age 57.6 years) and 100 with no ED (mean age 59.7 years). Increased 10 year coronary heart disease risk was 57% in the ED groups versus 33% in the non-ED group ($P = 0.05$). They concluded that ED may serve as a sentinel event for coronary heart disease.

In 2004, Gazzaruso *et al.*[13] reported upon the relationship between ED and silent myocardial ischemia in apparently uncomplicated type II diabetic patients. They evaluated the prevalence of ED in 133 uncomplicated diabetic men with angiographically verified silent coronary artery disease and in 127 diabetic men without myocardial ischemia on exercise ECG, ambulatory ECG and stress echocardiography. The prevalence of ED was higher in patients with (34%) versus those without silent coronary artery disease (4.7%; $P = 0.000$). Multiple logistic regression analysis showed that the following factors were associated with silent coronary artery disease in uncomplicated type II diabetic patients: ED, apolipoprotein a polymorphism, smoking, microalbuminuria, HDL and low-density lipoprotein (LDL) cholesterol levels. Remarkably, among these various risk factors, ED was the most efficient predictor of silent coronary artery disease (OR = 14.8; 95% CI = 3.8–57). Gazzaruso *et al.*[13]

concluded that there was a strong and independent association between ED and silent coronary artery disease in type II diabetics. Furthermore, ED may become a potential marker to screen for silent coronary artery disease in these patients.

A very important paper by Thompson *et al.*[14] analyzed data from a 9-year prostate cancer prevention trial and showed a significant association between incident ED and subsequent angina, myocardial infarction and stroke. In this analysis, incident ED was defined as the first report of ED of any grade (developed during the study but not at entry) and prevalent ED was defined to include men with ED at study entry. There were a total of 9457 men in the study who were randomized to placebo; 3816 (47%) had ED at entry; 8063 (85%) had no history of cardiovascular disease at study entry. Of 4247 men who did not have ED at study entry, 2420 (57%) developed ED after 5 years. Incident ED was associated with an adjusted hazard ratio (HR) of 1.25 (95% CI = 1.02–1.53; $P = 0.04$) for subsequent cardiovascular events during the course of the protocol. Incident ED was associated with an unadjusted HR for development of angina of 1.73 (1.17–2.55; $P = 0.006$). Incident ED was associated with an unadjusted HR for developing myocardial infarction of 1.52 (1.15–2.00; $P = 0.003$); and incident ED was associated with an unadjusted HR for developing stroke of 1.96 (1.13–3.41; $P = 0.02$). The relationship of incident or prevalent (baseline) ED and incident cardiovascular disease was even more striking with an unadjusted HR of 1.99 (1.48–2.67; $P < 0.001$) for angina, 1.86 (1.50–2.30; $P < 0.001$) for myocardial infarction, 2.72 (1.76–4.20; $P < 0.001$) for stroke and 2.45 (1.45–4.12; $P = 0.001$) for transient ischemic attack. For patients with incident ED and no previous cardiac history, about 11% developed a cardiovascular event by 5 years and about 15% by 7 years. For incident cardiovascular events, the risk was 0.015 per person-year among men with no ED at study entry versus 0.024 per person-year for men with ED at study entry. The authors noted that the association between ED and subsequent risk of a cardiovascular event was in the range of risk of other common coronary artery disease risk factors such as current smoking, dyslipidemia or a family history of myocardial infarction. The authors conclude that in some men ED is a harbinger of cardiac events and that ED should prompt a work-up and treatment of cardiovascular risk factors.[14]

Min *et al.*[15] recently reported a study of 221 men referred for stress myocardial perfusion single-photon emission computed tomography (MPS) who were also then screened for ED with a validated questionnaire. ED was documented in 55% of these patients. Patients with ED had more severe coronary artery disease (MPS stress score > 8): 43% in those with ED versus 17% in those without ED; $P < 0.001$. Patients with ED were more likely to have lower left ventricular ejection fractions (<50%): 24.0% for those with ED versus 11.0% for those without ED; $P = 0.01$. In addition, ED was associated with shorter exercise times (8.0 versus 10.1 min in those without ED; $P < 0.001$). On multivariate analysis (taking into account referral for stress testing, age, hypertension, diabetes, tobacco use, hyperlipidemia, previous revascularization, medication use) ED was an independent predictor of summed stress score > 8, suggesting severe coronary artery disease (OR = 2.50; 95% CI = 1.24–5.04; $P = 0.01$). Also, on multivariate analysis, ED was an independent predictor of high-risk MPS (summed stress score > 8), transient ischemic dilation of the left ventricle or left ventricular ejection fraction <35% (OR = 2.86; 95% CI = 1.43–5.74; $P = 0.003$). Min *et al.*[15] concluded ED is common in men referred for stress testing and that ED is an independent predictor of severe coronary artery disease and high-risk MPS.

Baumhäkel and Böhm[16] recently described a correlation between ED and left ventricular dysfunction, and confirmed the concept that ED precedes cardiovascular events. A total of 192 patients with high cardiovascular risk answered an ED questionnaire. The prevalence of ED was high at 80.6%. There was a correlation between left ventricular ejection fraction (measured by magnetic resonance imaging, angiography or echocardiography) and ED such that patients with decreased IEFF scores had the lowest ejection fractions. Similar to other reports, the symptoms of ED appeared about 3 years prior to the first major cardiovascular event (myocardial infarction or stroke). The authors concluded that 'ED is suggested to be an early symptom of generalized cardiovascular disease and events'.[16]

Mechanisms for links between ED and coronary artery disease

One of the theories as to why ED may be a harbinger of coronary artery disease is that the diameter of the arteries that supply the penis are in general smaller (1–2 mm) than the coronary arteries (3–4 mm).[17] Thus, the same size atherosclerotic plaque burden affecting the penile arteries would be more likely to manifest with the symptoms of ED and if present in the coronary arteries would be less likely to cause significant obstruction to flow and less likely to manifest as angina pectoris. A greater plaque burden would be needed to compromise coronary blood flow and lead to angina. Hence the atherosclerotic process may manifest as symptoms of ED before it manifests as symptoms of coronary artery disease.

There are common links between ED and coronary artery disease including one of the earliest stages of the spectrum of atherosclerosis-endothelial dysfunction.[18–22] Endothelial dysfunction occurs when the inner lining of the blood vessels is damaged by

smoking, hypertension, dyslipidemia, diabetes and other noxious factors, such as inflammation or infection. One of the techniques for assessing endothelial function is by measuring brachial artery flow-mediated vasodilation following an episode of brachial artery occlusion induced by a pressure cuff. Kaiser *et al.*[23] reported that brachial artery flow-mediated vasodilation (endothelium-dependent) was reduced in patients with ED (1.3%) versus those patients without ED (2.4%; $P=0.014$). Also, vasodilation to nitroglycerin (endothelium-independent) was reduced in ED patients (13.0%) versus non-ED patients (17.8%; $P<0.05$). Other structural and functional vascular parameters (carotid and brachial artery diameters, intima-media thickness, compliance, distensibility, aortic pulse wave velocity and coronary calcification) were similar between patients with and without ED in this study. Thus, patients with ED but no clinical cardiovascular disease have a peripheral vascular defect in both endothelium-dependent and -independent vasodilation that occurs prior to development of onset of functional and structural vascular disease.

Kaya *et al.*[24] reported similar results. They examined 32 ED patients diagnosed with Doppler ultrasound and by the International Index of Erectile Function questionnaire who had no apparent cardiovascular disease or diabetes and compared them to 25 healthy men. Endothelial-dependent brachial artery flow-mediated vasodilation was lower in ED patients ($6.0 \pm 2.9\%$) versus normal men ($12.3 \pm 3.5\%$; $P<0.001$). Similar to the work by Kaiser *et al.*,[23] brachial artery response to nitroglycerin (endothelial-independent vasodilation) was also lower in ED patients ($12.8 \pm 5.2\%$; $P<0.001$) versus non-ED patients ($17.8 \pm 5.2\%$; $P<0.001$). Patients in this study had normal exercise stress tests and echocardiograms. The authors concluded that endothelial function was impaired in ED patients with no apparent cardiovascular disease or diabetes. As endothelial-independent vasodilation was also abnormal in ED patients it is conceivable that other structures (that is, vascular smooth muscle cells) are also abnormal as part of this disease state.

Bocchio *et al.*[25] examined endothelial cell activation in men with ED without cardiovascular risk factors and overt vascular damage. They evaluated biochemical measures in patients with ED to assess whether ED is a sentinel of atherosclerosis. Measures of endothelial cell activation (including circulating soluble P-selectin, intercellular adhesion molecule-1, vascular cell adhesion molecule-1 and endothelin-1 concentrations) were higher in men with ED but no cardiovascular risk factors than in healthy controls ($P<0.01$). Levels of endothelin-1 in men with ED and no cardiovascular risk factors was the best independent predictor of ED (OR = 5.37; 95% CI = 2.12–19.70). The structural parameter of intima-media thickness of the carotid arteries was comparable in healthy controls and in men with ED but no cardiovascular risk factors. The authors concluded that increased biochemical measures of endothelial cell activation were associated with ED independent of co-existing cardiovascular risk factors and overt vascular damage. This finding suggests that ED is a sentinel of early atherosclerosis.

Risk factor modification in men with ED

The work-up of patients with ED who have risk factors for cardiovascular disease is described in the Second Princeton Consensus reference[26] and other papers.[27] We recommend that all patients with ED have an assessment of their risk factors for vascular disease as well as treatment for these risk factors. Certainly the following modifiable risk factors need to be identified by history, physical and where appropriate, laboratory tests; and then treated: smoking, hypertension, dyslipidemia, diabetes, sedentary lifestyle and obesity. Specific goals have been established by various guideline documents and organizations. The goals may differ, depending on the recommendation of the specific organization. In our practice, for example, blood pressure goals are <140/90 mm Hg in the general population and <130/80 mm Hg in patients with diabetes or chronic kidney disease. LDL (the bad cholesterol) goals are <100 mg per 100 ml in patients with known coronary disease and <70 mg per 100 ml in high-risk patients with coronary disease (such as acute coronary syndrome, multiple risk factors); some guidelines recommend an LDL <130 mg per 100 ml for primary prevention in patients with some risk factors but many cardiologists now use the lower <100 mg per 100 ml goal as an option. HDL cholesterol (the good cholesterol) is recommended to be >40 mg per 100 ml. We recommend that patients stop smoking and refer patients to a smoking cessation program that covers behavioral modification as well as offers various medicines to aid patients in quitting smoking. If patients are cardiovascularly stable and do not have exercise-induced ischemia, we recommend that patients exercise (walking on a flat surface) for ~30 min a day at least 5 days a week. Fasting blood sugar should be <100 mg per 100 ml. The American Diabetes Association considers a fasting blood sugar of between 100 and 125 mg per 100 ml to be pre-diabetes and a fasting blood sugar of 126 mg per 100 ml or higher to be diabetes. In diabetics the Hbg Alc should be at least less than 7%. We liberally refer our overweight patients, patients with high cholesterol and diabetic patients to professional dieticians.

Does tight control of these risk factors reduce cardiovascular events in men with ED? Although the exact answer to this question is not known, there is no question that aggressive treatment of LDL

cholesterol and hypertension reduces cardiovascular and cerebrovascular events in patients with cardiovascular risk factors. Does aggressive risk factor management reduce the development or progression of ED? Though some studies suggest that smoking cessation, hypertension management (especially with angiotensin receptor blockers), management of lipids and physical activity programs may improve ED, there is some controversy regarding this concept.[28–34] One problem is that by the time ED develops in midlife it may be too late to fully reverse the vascular damage that has caused the ED.[28] There also have been suggestions that risk factor modification may improve the response of men with ED to PDE_5 inhibitors.[34] Until additional data are available, we recommend aggressive risk factor modification in anyone with ED with cardiovascular risk factors—primarily to reduce the risk of major adverse cardiovascular and cerebrovascular events and also hopefully to prevent the progression of ED, and perhaps actually improve ED in some patients or allow them to become more responsive to medical therapies.

Conclusions

Several very recent studies show that ED predicts the future development of coronary artery disease. In some of these studies ED was an independent predictor of future cardiovascular disease and equivalent to other common cardiovascular risk factors. Thus, health care professionals need to view ED as a potential cardiovascular risk factor and not just a urologic or psychogenic disorder. Patients presenting with ED should be questioned regarding cardiac history and worked up for cardiovascular risk factors as suggested by the recent Second Princeton Consensus paper.[26] Once, identified, these risk factors (hypertension, dyslipidemia, diabetes mellitus and smoking) should be treated. Patients with coronary artery disease often have ED. Coronary artery disease patients should be questioned about their sexual health. Endothelial dysfunction and perhaps smooth muscle dysfunction as well occur early in some ED patients as part of a marker for early atherosclerosis disease.

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