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Is erectile dysfunction an early precursor of silent coronary artery disease?: Review Article

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Abstract

Erectile dysfunction is defined as insufficiency in initiating, achieving and maintaining of penile erection necessary for satisfactory sexual intercourse. Its prevalence increases as the age progresses, but it is underestimated in routine clinical practice. An attempt is made to review the literature showing erectile dysfunction as silent risk factor for cardiovascular disease (atherosclerosis).

Keywords: Erectile dysfunction, coronary artery disease

Introduction

Erectile dysfunction (ED) is defined as the recurrent or persistent inability to achieve or maintain an erection in order for satisfactory intercourse to occur. In 19th century it was considered as age-related process (psychogenic). Age-related decline in erectile function was first documented by Kinsey et al in 1948.(1) However in 20th century it is recognised as an organic and physiologic problem that affects penile circulation as a part of generalised vascular disorder. An attempt is made to review the literature showing association of erectile dysfunction with cardiovascular disorders and its use as a screening method to find early onset of cardiovascular disease specially in young patients having silent underlying coronary artery disease.

Discussion

Prevalence of Erectile dysfunction: Epidemiological studies indicate the relationship between erectile dysfunction and advancing age.(1) The contemporary prevalence of ED is approximately 52% in the general population between 40 and 70 years of age; both the prevalence and the severity of ED increase with age.(2) It is estimated that ED affects 150 million people worldwide and this number is expected to more than double by the year 2025.(3)

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality globally. Effective interventions for primary and secondary prevention depend upon individual risk factors. However, it has been recognised that a significant proportion of cases of cardiovascular disease will occur in individuals without classic risk factors.(4) In many patients, erectile dysfunction may be the first manifestation of without known underlying cardiovascular disease that will progress to include coronary artery disease (CAD) and peripheral artery disease (PAD) at a later stage. Indeed, in men with CAD, the prevalence of ED is as high as 75%.(5) In men without known CVD, erectile dysfunction might be a sentinel symptom indicating the presence or increased risk of systemic CVD.(6)

Pathophysiology: After ruling out other causes for ED, major link between development of ED and cardiovascular disease is endothelial dysfunction.(7) Both clinical and animal studies on endothelial dysfunction have encouraged that atherosclerosis leads to increased cerebrovascular and cardiovascular morbidity.(7,8) Endothelial dysfunction, may simultaneously involve penile vascular structure.

Generally erectile dysfunction is attributed to the endothelial dysfunction in literature. The artery size hypothesis explains why patients with CAD frequently report ED before CAD detection.(9) According to this hypothesis, for a given atherosclerotic burden, the smaller penile arteries suffer obstruction earlier than the larger coronary arteries. The same concept holds true also in the case of non-obstructing atherosclerosis, since the smaller penile artery have a greater endothelial surface and erection requires a large degree of vasodilation to occur when compared with arteries in other organs. However the same degree of endothelial dysfunction will be symptomatic in these smaller vessels but subclinical in the larger ones (i.e. coronary arteries). Therefore ED could be considered the prima ballerina of asymptomatic atherosclerotic artery disease.(10)

A recent pathogenetichypothesis by Montorsi et al(11) when penile artery (diameter 1-2 mm) presents established obstruction, the blood flow is not yet impeded in both coronary and brain arteries, even less in the peripheral circulation, and symptoms, occurring after a 50% obstruction, are therefore absent.

Severity classification of Erectile Dysfunction

To asses the severity of ED the best validated score is the simplified international index of erectile function (IIEF-5):[12] 5questions on sexual activity are administered and the consequent possible scores range from 5 to 25; ED is classified into 5 categories: severe (5-7), moderate (8- 11), mild to moderate (12-16), mild (17-21) and no ED (22-25).

Window period and severity

Next consideration is if ED is present not due to primary or any other systemic diseases, what is the time duration between ED and onset of cardiovascular events. A number of studies have estimated the interval between the onset of ED symptoms and the occurrence of CAD symptoms as 2-3 years[13] and a cardiovascular event [myocardial infarction (MI) or stroke] as 3-5 years.[14] Montorsi et al examined 300 patients with coronary artery disease documented by coronary angiography, and showed that 147 (49%) had an ED and 99 (67%) of these had ED before the coronary event.[13]

Erectile dysfunction per se is unlikely to be a major independent cause of CVD, and it would be wise to say risk marker rather than a risk factor for CVD. It should be considered as a ''biomarker'', of the severity of underlying pathological processes such as atherosclerosis and endothelial dysfunction. All these studies demonstrate that pathphysiology is same i.e. endothelial dysfunction for ED and cardiovascular disorders. Men with ED generally exhibit more severe CAD and left ventricular dysfunction than those without ED,[15,16] and the severity of ED may also be correlated with the severity of CAD.[17]

Using Framingham risk scores, the relative risk of developing CAD within 10 years in men with moderate-severe ED has been estimated as 4.9% in those aged 30-39 years, increasing to 21.1% in those aged 60-69 years.[18] This compares with 4.3% and 16.6% in men without ED for the same age groups, i.e. an increase in relative risk of 1.14 and 1.27 respectively. The risk of experiencing a cardiovascular event within a 10-year timeframe is increased by 1.3-1.6 times in men with ED vs. men without ED.[19]

ED and Cardiovascular Common risk factors

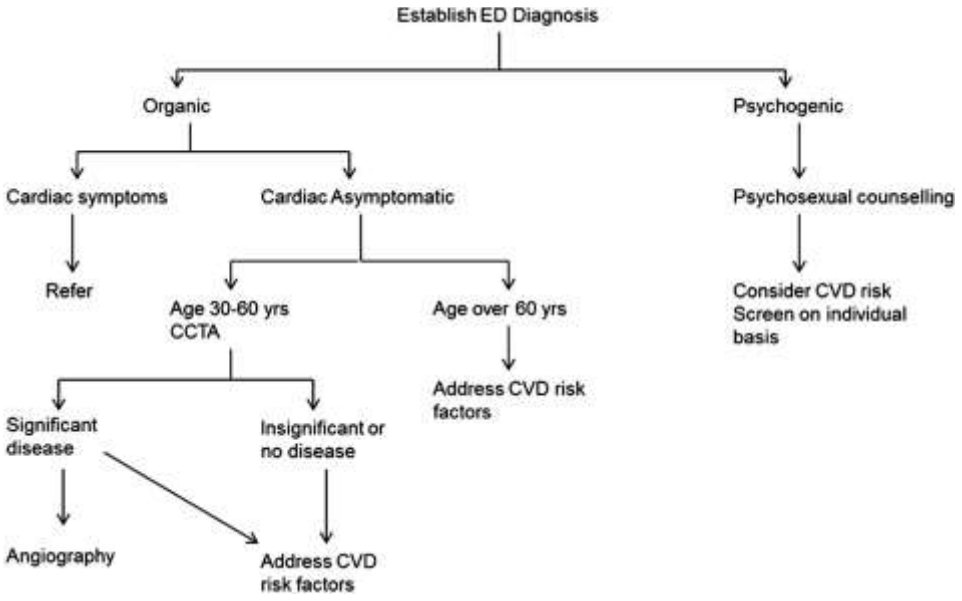
After adjusting age, modifiable risk factors for CVD which include, hypertension, hyperlipidaemia, diabetes, obesity, lack of physical exercise, cigarette smoking, poor diet, excess alcohol consumption, and psychological stress, including depression are associated with erectile dysfunction.[20] Metabolic syndrome and waist-to-rip ratio have been associated to more severe ED among those over 50 years old.[21] Sleep disorders are also more prevalent among ED men and their treatment could help in recovering sexual satisfaction.[22]

Some trials have shown the presence of vascular disease in men suffering from vasculogenic ED but without traditional risk factors, suggesting that ED as a clinical early cardiovascular risk marker.[23] Particularly among men less than 60 years old, ED seems to act as a risk factor independent of traditional markers. Recently laboratorial markers such as dimetilarginin asymmetric (ADMA)[24] and C-reactive protein were reported higher in ED men when compared with men without ED and similar risk factors.

But on the other side of window, as a multifactorial aspect, several conditions could promote ED without systemic vascular involvement such as pelvic surgeries, depression, Peyronie's disease, and prostatism. Probably this aspect is one among others to explain the lack of additional contribution of ED over traditional risk factors (Framingham score) during cardiovascular evaluation in some reports.[25]

Patient assessment: Detailed personal and sexual history must be taken.

1. One needs to be sure of the ED diagnosis and to establish whether there is premature ejaculation, decreased libido, or a combination of problems.
2. Medical assessment should include measurements of blood pressure, fasting glucose, glycosylated haemoglobin, lipid profile, waist circumference, thyroid function and testosterone.
3. If cause is organic, then check cardiac symptoms either symptomatic or asymptomatic.
4. Symptomatic patient is referred to a cardiologist. Asymptomatic patients must undergo screening radiological investigations for coronary atherosclerosis so that silent disease can be detected within the window period and secondary prevention can be done.
5. Stress testing for asymptomatic patients includes;
   a) Exercise, pharmacological stress, myocardial perfusion and stress echocardiography will only identify lesions influencing flow[26] (>50–70% coronary artery stenosis).
   b) Therefore an evaluation of subclinical (<50%) plaque is essential, especially in the younger men at intermediate risk. Outpatient coronary calcium screening or multi detector CT (MDCT)[27] shows clinical disease in men with ED and a normal exercise electrocardiogram (ECG). The advantage of MDCT is that it identifies non-calcified disease, which might be an issue in the younger men.[28]
6. Testosterone deficiency is often missed, and because it is frequently associated with type II diabetes or chronic illness such as heart failure, renal disease or hypertension. So it should be excluded.[29]



Flow chart showing approach for diagnosis of erectile dysfunction

Treatment options: Before starting treatment following issues should always be considered.

- Treatment of erectile dysfunction is secondary to cardiovascular symptoms.
- ED treatment should not have any negative impact on cardiovascular status of patient.
- Excercise tolerance should always be performed before starting ED treatment.
- Clinical evidence supports the use of PDE5 inhibitors as first-line therapy in men with CAD and comorbid ED.

Patients categorised as low-risk[30] require no special cardiac testing or evaluation prior to the initiation of treatment for ED and resumption of sexual activity, and they can be managed within primary care.

The high-risk[30] category consists of patients whose cardiac conditions are sufficiently severe and/or unstable that sexual activity may pose a significant risk of ischaemic events. These individual patients should be referred for specialised cardiac assessment and treatment. Sexual activity should be deferred until their cardiovascular status has been stabilised by treatment or a decision has been made by a cardiologist that sexual activity may be safely resumed.

Those patients considered as having an intermediate risk require further evaluation so that they can be definitively classified as low or high risk.

In men with mild-moderate chronic heart failure or stable CAD, sildenafil has been shown to improve erectile function and enhance intercourse, while being associated with few adverse cardiovascular effects and no adverse effects on exercise parameters.[31]

In men taking multiple antihypertensive agents, sildenafil and vardenafil improve erectile function and are well tolerated.[32] Tadalafil achieves improvements in men with ED and hypertension treated with or without thiazide diuretics, and vardenafil is effective in men with ED and comorbid hypertension and / or dyslipidaemia.[33] The short half-lives of sildenafil and vardenafil could be an advantage for patients with more severe cardiovascular disease, allowing early use of supportive treatment if an adverse clinical event occurs.[34]

Phosphodiesterase-5(PDE5) inhibitors are known to potentiate the effects of nitrates, leading to potentially clinically significant reductions in blood pressure, and are therefore contraindicated in patients taking these agents.[35] Two strategies may be adopted for the management of ED in such patients: using a different type of therapy for ED, or switching the patient to an alternative anti-ischaemic therapy and using a PDE5 inhibitor for the treatment of ED. Switching the anti-ischaemic therapy is an option because nitrates are a symptomatic treatment and are no more effective than placebo in reducing the risk of cardiovascular events in these patients.[35] If the second approach is chosen, an interval of at least 1 week should be allowed between the discontinuation of nitrate therapy and initiation of PDE5 treatment. When oral agents are not effective for the treatment of ED, intracavernous injection therapy, transurethral alprostadil, a vacuum pump and surgical implantation of a penile prosthesis are alternatives requiring specialised referral and advice.[36]

Testosterone (and selectively free testosterone) levels should be measured in all men with ED in accordance with contemporary guidance, particularly in those who fail to respond to PDE5 inhibitors or who have a chronic illness associated with low testosterone (e.g. heart failure, diabetes). While there is no clinical evidence that testosterone replacement therapy reduces cardiovascular risk or all-cause mortality (randomised trials are needed), there are clinical data to support a

symptomatic benefit in hypogonadal men with angina or heart failure.[37,38]

Table showing risk stratification:

Risk classification	Risk factors
Low	• Asymptomatic, < 3 cardiovascular risk factors • Controlled hypertension • Mild, stable angina pectoris Post revascularisation (no significant residual ischaemia) • MI > 6 weeks previously • Mild valvular disease • Left ventricular dysfunction (New York Heart Association class I) • Pericarditis • Mitral valve prolapsed • Atrial fibrillation with controlled ventricular response.
Intermediate	• Asymptomatic, >3 cardiovascular risk factors (excluding gender) • Moderate, stable angina pectoris • Recent MI (> 2 weeks, < 6 weeks) • Left ventricular dysfunction (NYHA class II) Non-cardiac sequelae of atherosclerotic disease (peripheral vascular disease, history of stroke or transient ischaemic attack)
High	• Unstable or refractory angina pectoris Uncontrolled hypertension • Congestive heart failure (NYHA class III or IV) • Recent MI (< 2 weeks) • High-risk arrhythmia • Obstructive hypertrophic cardiomyopathy Moderate–severe valvular disease, especially aortic stenosis

Conclusion

Available data make a strong argument for the role of ED as an early marker of cardiovascular disease. ED and generalized vascular disorders are linked pathophysiologically via endothelial dysfunction, activated inflammatory & thrombotic state and increase oxidative stress. ED is like a tip of iceberg. Patients with CAD very often have ED, and, importantly, patients presenting with ED as their initial condition have an increased prevalence of silent CAD. ED is associated with increased all-cause mortality primarily due to increased cardiovascular mortality. Recognizing this link between ED and CAD significant burden of sudden cardiac deaths and progression of CAD in young patients can be halted. Thus in summary:

1. A significant proportion of men with erectile dysfunction exhibit early signs of coronary artery disease, and this group may develop more severe CAD than men without ED.
2. The time interval among the onset of ED symptoms and the occurrence of CAD symptoms and cardiovascular events is estimated at 2-3 years and 3-5 years, this window period allows for risk factor reduction.
3. All men with ED should undergo a thorough medical assessment, including testosterone, fasting lipids, fasting glucose and blood pressure measurement. Following assessment, patients should be stratified according to the risk of future cardiovascular events. Those at high risk of cardiovascular disease should be evaluated by stress testing with selective use of computed tomography (CT) or coronary angiography.
4. In men with ED, hypertension, diabetes and hyperlipidaemia should be treated aggressively, keeping in mind the potential side effects
5. Management of ED is secondary to stabilising cardiovascular function, and controlling cardiovascular symptoms and exercise tolerance should be established prior to initiation of ED therapy
6. Clinical evidence supports the use of phosphodiesterase 5 (PDE5) inhibitors as first-line therapy in men with CAD and comorbid ED and those with diabetes and ED.
7. Testosterone replacement therapy may lead to symptomatic improvement (improved wellbeing) and enhance the effectiveness of PDE5 inhibitors.
8. Review of cardiovascular status and response to ED therapy should be performed at regular intervals

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