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Editorial

Erectile dysfunction: A present day coronary disease risk equivalent

Erectile dysfunction (ED) is a common medical condition that affects approximately 100 million men worldwide and is currently recognized as a major public health problem. It is estimated that nearly one-half of men older than 40 years have some degree of ED. While in 1995, ED affected over 152 million men worldwide, it is projected that by 2025, more than 320 million patients will be afflicted with the largest projected increases in the developing world[1,2].

Both ED and coronary artery disease (CAD) commonly coexist and share risk factors such as obesity, diabetes, smoking, hypertension, dyslipidaemia and metabolic syndrome. There is evidence that rather than being a disease of the penile vasculature, ED may be a manifestation of a systemic vascular disease. Since symptoms of ED often appear before that of CAD due to the smaller size of the penile vasculature, it can serve as a potential CAD risk equivalent[3,4].

Prevalence of ED

The overall prevalence of ED has been reported to be 16-25 per cent in the general population depending on the cohort of study and the definition of ED being applied[5]. Age is a strong determinant of occurrence of ED, and epidemiological studies indicate a strong relationship between ED and advancing age. While men aged 50-59 years have a 3.6 times higher risk of developing ED as compared to those aged 18-29 years, the risk is even higher (6-7 times) among males older than 70 yr[6]. Age-related hormonal, metabolic and inflammatory as well as increased prevalence of other risk factors for ED in the older population may be responsible for this association. When ED occurs in younger males, it is associated with a greater increase in the risk of future cardiac events as compared to its first detection in older males[7]. Therefore, younger men with early-onset ED may be the ideal candidates for intensive CV risk factor screening and medical interventions.

Clinical assessment of ED

The erectile function domain of the International Index of Erectile Function (IIEF), which contains 15 self-administered questions, is currently the gold standard for clinical assessment of ED, wherein each question is scored on a scale of 0 to 5 and ED defined as any value <25[8]. The IIEF-5 is a shorter version which includes questions 2, 4, 5, 7 and 15 of the IIEF-15[9]. The maximum score for IIEF-5 is 25 and a score of <21 is labelled as ED (mild ED: score 17-21, mild to moderate as 12-16, moderate as 8-11 and severe as <7). Peak penile systolic velocity measured by penile Doppler has a high negative predictive value; while a normal response in a patient with ED makes significant atherosclerotic CAD unlikely, values <35 cm/s should prompt a referral to a cardiologist for assessment of CAD.

Association with CAD

In patients with ED, the prevalence of CAD has been reported to vary from 5-56 per cent, while in symptomatic patients with CAD, the prevalence of ED has been reported to be 44-75 per cent[3,10]. A linear age-associated increase in ED has been reported (2, 6, 17 and 39% for men aged 40-49, 50-59, 60-69 and >69 yr, respectively)[11]. Patients with ED and without clinically manifested CAD have also been shown to have abnormal exercise stress tests, nuclear scans, reduced coronary flow velocity reserve and coronary calcifications[12,13].

A direct correlation between the extent of CAD, number of coronary vessels involved and the severity of ED as measured by the IIEF score has been reported. Greenstein *et al*[14] reported that patients with 2- or 3-vessel disease had a worse erectile function as compared to those with single vessel disease. Among 285 patients undergoing coronary angiography, Montorsi *et al*[4] observed that severe ED was 4-6 times

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more frequent in those with multi-vessel disease as compared to single vessel disease. In patients with single vessel disease, the prevalence of CAD was similar to that in controls indicating a low coronary and penile atherosclerotic burden. The prevalence of ED and the distribution of traditional CV risk factors were evaluated in 183 patients with angiographically documented CAD[15]; those with severe ED had a two-fold higher risk of CAD, suggesting that ED might be considered as a surrogate marker for the occurrence of CAD.

In a study of 175 Asian Indian patients undergoing coronary angiography, severe ED was found in 39 per cent and those with severe ED also had significantly higher prevalence of multi-vessel CAD and a higher number of mean coronary vessels involved compared with those with milder grades of ED[16]. Although most studies reported a correlation between severity of ED and extent of CAD, Montorsi and colleagues[3] found that although ED was common in patients with CAD, the clinical and angiographic characteristics were not different in those with and without CAD. Whether the mode of clinical presentation of CAD (acute coronary syndrome, ACS or chronic stable angina) affects the prevalence of ED, was assessed in the COBRA trial[4]. The prevalence of ED was lower in ACS and single vessel disease (24%) due to the low atherosclerotic burden of both the coronary as well as the penile vasculature. A higher atherosclerotic burden in chronic stable angina resulted in a higher prevalence of ED (65%), reflecting the opposite spectrum of the 'ED-atherosclerosis' relationship. However, other studies have not reported any significant difference in the clinical mode of presentation of CAD among patients with and without ED[3,16].

ED often precedes CAD

Symptoms related to ED usually predate symptomatic angina by two to three years and other major adverse CV events by three to five years[3,4,17,18]. This lag period provides an opportunity for timely risk-factor modification and potentially delays CV complications. This delay is related to the discrepancy of artery size between the penile and coronary vascular bed. The coronary vessels also have the ability to form collaterals in response to a reduction in blood flow while the cavernosal arteries, being end arteries, do not have this ability.

Evidence from various retrospective and prospective cohort studies has shown that the presence of ED is a predictor of the occurrence of major adverse cardiac events. Men with ED have been reported to have a two-fold higher risk for acute myocardial infarction (MI) after adjusting for covariates such as age, smoking, obesity and use of cardiac medications[19]. In a cross-sectional survey of 3921 Canadian men, aged 40-88 yr, Grover *et al*[20] reported that the presence of ED was associated with an unfavourable vascular risk and the association was even more robust in males older than forty. Males aged 30-39 yr and with moderate to severe ED were reported to have a 65 per cent increased risk for coronary heart disease (CHD) within next 10 years as estimated according to Framingham risk models[21]. The relative risk of developing CAD in 10 years in those with moderate to severe ED was 1.14 (those aged 30-39 yr) and 1.27 (those aged 60-69 yr) as compared to those without ED. Patients with ED also had a 43 per cent higher relative risk increase for stroke within next 10 yr versus those without ED[21]. ED was a significant predictor of all-cause death [hazard ratio (HR) 1.84], CV death (HR 1.93), MI (HR 2.02), hospitalization for heart failure (HR 1.2) and stroke (HR 1.1) in the ONTARGET and TRANSCEND trials[22]. Dong *et al*[23] preformed a meta-analysis of 12 prospective cohort studies including 36,744 participants and reported that the presence of ED was associated with an increased relative risk for cardiovascular disease (CVD) (1.48), CHD (1.46), stroke (1.35) and all-cause mortality.

Should patients with ED be routinely screened for CAD

Although ED is an early manifestation of atherosclerosis, an exhaustive cardiologic screening for all such patients might not prove cost-effective. Detailed cardiac screening would be more beneficial for selected patients with ED who are at high risk based on baseline CV risk assessment (*e.g.,* with multiple CV risk factors and those with ED onset at a younger age). The Princeton Consensus Panel guidelines and the 2010 evidence-based consensus recommend that all patients with ED undergo a detailed medical assessment along with measurement of BP, fasting lipid profile and glucose levels[24-26]. Patients are categorized into low, intermediate and high risk based on the long-term CV risk and the ability to sustain sexual activity based on their physiological reserve. High-risk patients need evaluation by specialized tests including echocardiography and exercise or nuclear stress testing to detect inducible myocardial ischaemia. In selected patients with equivocal stress testing results, coronary computed tomography angiography

may be considered. Other tests which assess surrogate measures of atherosclerosis may also be used, for example, brachial artery flow-mediated vasodilatation, peripheral arterial tonometry, carotid artery intimal medial thickness and ankle-brachial index.

Treatment of patients with ED

It is often challenging because of possible adverse CV effects of medications used to treat ED. It is important to stabilize CV status before initiating treatment for ED. Exercise tolerance should be assessed since sexual activity poses a small but definite risk of a cardiac event during and immediately afterwards. Low-risk patients can engage in sexual activity and participate safely in an exercise programme; they need regular follow up and drugs for ED may be prescribed without additional cardiac testing. For intermediate- to high-risk patients, CVD management should assume priority and they should avoid sexual activity till the cardiac condition is evaluated by detailed cardiac assessment, managed and stabilized.

Risk factor management for all patients with ED is essential and includes maintenance of optimal body weight, adequate physical activity, smoking cessation and management of associated risk factors. Lifestyle interventions, although unlikely to reverse ED, are usually recommended for the overall health benefits. Cardioactive drugs, for example, beta-blockers, calcium channel blockers, thiazide diuretics, fibrates and angiotensin converting enzyme (ACE) inhibitors, may either exacerbate underlying ED or may be associated with new-onset ED. Drug-induced ED usually develops or is precipitated within four weeks of initiation; in such cases, the drug should be either stopped or changed to a new one. Although conflicting reports exist regarding the role of statins in patients with ED, Kostis *et al*[27] in a meta-analysis, reported that statins led to an increase in the mean IIEF score by approximately 3.4 points and were thus associated with an improvement in the erectile function. The efficacy and safety of phosphodiesterase 5 (PDE5) inhibitors (sildenafil, tadalafil and vardenafil) in patients with underlying CVD are well established, and pooled data from more than 120 clinical trials indicate that these drugs do not increase the risk of MI or CV death[28]. PDE5 inhibitors are best avoided in patients taking nitrates since severe hypotension may be precipitated while caution should be exercised and reduced doses used in those on beta-blockers. For these patients, either the therapy for ED may be changed or an alternative anti-ischaemic agent therapy may be used, allowing PDE5 inhibitors to be prescribed. An interval of at least one week should be allowed between the discontinuation of nitrate therapy and initiation of PDE5 treatment. In case oral agents cannot be used or are ineffective, other options, for example, transurethral alprostadil, intracavernosal injection therapy, vacuum pumps and/or penile prosthesis, may be tried under the guidance of a urologist. The 2010 guidelines also recommend that testosterone levels be measured in all patients with ED, especially those with associated diabetes and heart failure or non-responders to PDE5 inhibitors[26]. The guidelines further reiterate that testosterone replacement therapy is not associated with an increased CV risk.

Recognizing and appropriately addressing the relationship between ED and CAD will potentially not only improve the quality of lives but also help and save lives.

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