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Review Article

Erectile Dysfunction and Cardiovascular Complications: A Literature Review

Reza Karbasi-Afshar[*1,2], Seyed Hasan Saadat[3], Morteza Izadi[4]

Abstract

Several studies have demonstrated that erectile dysfunction (ED) is associated with cardiovascular diseases; nonetheless, few physicians pay enough attention to take a precise history of potential sexual dysfunction in these patients. The magnitude of this correlation is to the extent that several authors have proposed ED as a cardiovascular risk equivalent. In this review article, we searched for the most significant studies performing in this issue, with special emphasize on prospective studies to provide a comprehensive and precise view on the matter in the cardiovascular disease context.

1. Atherosclerosis Research Center, Baqiyatallah University of Medical sciences;
2. Department of cardiology, Baqiyatallah University of Medical sciences;
3. Behavioral Science research Center; Baqiyatallah University of Medical Sciences; Tehran; Iran
4. Health Research Center, Baqiyatallah University of Medical Sciences; Tehran; Iran

*** Corresponding Author**
Reza Karbasi Afshar, Cardiovascular Research Center, Baqiyatallah University of Medical sciences, Vanaque Square, Tehran, Iran
E-mail: karbasi.afshar@gmail.com

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Introduction

Erectile dysfunction (ED), defined as the intermittent or constant incapacity to develop or maintain a penile erection in order to having suitable sexual performance, is a prevalent disorder, with an overall incident rate of 22% (95%CI, 19.4–24.6) in men, according to a study from the United States [1]. Although, it has long been known that major vascular injuries are among the main etiologies behind the ED [2]. Atherosclerosis of the internal iliac arteries and the smaller vessels supplying the penis are the backbone of pathogenesis of vasculopathy-induced ED. Nonetheless, very few cardiologists may ask their patients with cardiovascular disease about any potential complaints regarding obtaining or maintaining an erection.

In addition to the atherosclerotic etiology for ED, several studies have shown that, on the other hand, ED can also predict cardiovascular morbidities including coronary artery disease, hypertension and diabetes [2-4]. There are even reports indicating that significant correlation exists between the severity of ED and the number of coronary vessels involved [Greenstein]. In non-symptomatic individuals, ED has also been demonstrated to be a predictive of cardiovascular abnormalities [REFF]. Some studies have even proposed that ED can predict cardiovascular events [5,6] and associated mortality [7]. Due to the high prevalence of ED in the general population, and the cardiovascular relevance associated with this condition, a precise knowledge on this issue is of very high importance, so physicians become able to screen high risk people for further preventive and therapeutic endeavors. To attend this issue, in the current article, we aimed to review the existing literature to obtain and present the available data on the correlations between ED and associated cardiovascular threats.

Associations between ED and arterial diseases

There is a general tendency among researchers to consider ED as an early manifestation of a largely subclinical systemic vascular disorder than just a consequence of iliac artery atherosclerosis. Even some authors have proposed ED as a coronary artery risk equivalent [8]. Among risk factors playing major roles in the pathogenesis of atherosclerosis, endothelial dysfunction has gained increasing attention [9,10].

Nitric oxide (NO), a metabolite of L-arginine synthesis, is the key mediator of endothelium-dependent smooth muscle relaxation [11], which plays significant role in coronary artery diseases [12]. Likewise NO is the key mediator of penile erection [13]. NO can be synthesized and released by endothelial cells upon stimulation by acetylcholine through endothelial NO synthases (eNOS); or upon sexual stimulation get released from non-adrenergic, non-cholinergic nerve endings by specific neuronal synthases (nNOS) [14]. However, expression of eNOS and nNOS are dependent on complex regulatory mechanisms which are out of our discussion. However, any factor that disrupts this regulation can affect both the abovementioned pathways.

Some retrospective studies have also provided epidemiological data for possible associations between ED and cardiovascular injuries. Some studies have investigated the prevalence of cardiovascular diseases in ED patients, while some others have studies the incidence of ED in documented cardiovascular disease patients. El-Sakka and

Morsy [15] investigated the prevalence of cardiovascular disorders in 303 ED patients and reported that a reduced peak systolic velocity of the cavernous artery documented by Doppler ultrasonography is associated with ischemic heart disease. Montorsi et al. [16], on the other hand, observed the prevalence of ED in patients already diagnosed with acute coronary syndromes, with documented coronary vasculopathy by angiography. The prevalence of ED was 49% with 2/3rd of patients reporting Ed preceded their chest pain attack. These studies and similar ones demonstrated a mutual correlation between ED and cardiovascular disease; however, prospective studies were needed for more detailed knowledge about the nature of this relationship.

ED as a predictor for future cardiovascular disease

During the last decade, several studies have proposed significant correlation between ED and the development of cardiovascular diseases. However, most of these investigations have been conducted retrospectively, making it hard to find a cause-effect relationship. Nonetheless, some prospective cohort studies as well as population-based surveys have recently come into the literature, providing strong evidence for a causative role for ED in inducing cardiovascular injuries. Table 1 summarizes prospective studies as well as population based surveys that have found any causal effect for ED on the development of cardiovascular disorders. Thompson et al. [17], in a population based study, followed 8063 men aged ≥55 years old, every 3 months for 10 years, without history of cardiovascular disease at study entry, and found that incident erectile dysfunction was associated with a hazard ratio of 1.25 (95% confidence interval [CI], 1.02-1.53; P=0.04) for cardiovascular events happening during study follow-up. For men with either incident or prevalent erectile dysfunction, the hazard ratio was even higher (1.45; 95% CI, 1.25-1.69; p<0.001) [17]. Gazzaruso et al. [4] investigated the predictive value of ED in type 2 diabetic patients and reported that ED predicts major adverse cardiac events (MACE). Emily Banks [18] in a recent prospective study observed that severity of erectile dysfunction is also associated with acute coronary syndromes. Schouten et al. [19] in a study from Germany also reported that severity of erectile rigidity was associated with the incidence of cardiovascular events. Inman et al. [20], on the other hand, reported that the incidence densities of coronary artery disease associated with ED is highest in youngest age group (40-49 yr). Batty et al. [21], reported that, in multivariate analysis, having ED has independent relationship to cardiovascular events, coronary heart disease and cerebrovascular disease. Fung et al. [22], however, investigated conventional cardiovascular risk factors in ED patients. They found that mean age, body mass index, cholesterol, and triglycerides were each significantly associated with an increased risk of ED, and cigarette smoking was marginally more common in those with severe/complete ED, as compared with those without ED. In concordance with this study, Araujo et al. [23] reported that although there were significant relationships between ED and cardiovascular diseases, ED did not significantly improve the prediction of CVD incidence beyond traditional risk factors. Ponholzer et al. [24], also reported that despite increasing the risk of future cardiovascular events, ED was not an age-independent predictor of cardiovascular events in their cohort. However, Ma et al. [25] reported an independent association between ED and coronary heart diseases after adjustments for conventional risk factors.

Medication and ED

Cardiovascular therapy has been associated with disturbances in sexual function. Among anti-hypertensive medications, almost every class of them has been reported to induce erectile dysfunction. In the Treatment of Mild Hypertension Study (TOMHS), the incidence of ED was lowest in the patients taking an alpha blocker, and also the reversibility of drug-induced ED was highest in the same group [26]. ***Alpha blockers*** are known to interfere with corporal smooth muscle constriction, as well as inducing rare problems with emission and ejaculation have also been reported by using alpha blockers [27]. In type 2 diabetic patients, using alpha blockers has been associated with highest rate of ED development, compared to beta-blockers and calcium channel blockers [28]. However, there are also controversial reports indicating no role for alpha blockers to induce erectile dysfunction in patients with metabolic syndrome [29].

Beta blockers have probably received the highest attention regarding drug induced ED in cardiovascular patients. Although numerous studies have suggested significant effects for β-blockers in inducing ED [30,31], a more recent randomized trial of a large patient population found no significant association [32], and a meta-analysis of prospective data have failed to find such a significant relationship [33]. In TOMHS, beta blocker acebutolol was not associated with a significant increase in ED compared to placebo [Grimm], possibly due to its cardioselective nature. The strong presumption on the ED inducing property of beta-blockers potentially lies on propanolol due to its high lipophilicity and nonselective beta blockade [28]. In patients with metabolic syndrome, β-blockers have not been associated with ED development [29].

As a class, ***calcium channel blockers*** have been associated with a low incidence of ED [34]. In type 2 diabetes mellitus, these agents induced no significant effect on ED [28]. In this class of agents, nifedipine produced the least worsening of libido; although it resulted in deterioration in ejaculation and tumescence compared with atenolol and captopril [34]. In patients with metabolic syndrome, unlike alpha- and beta-blockers, calcium channel blockers were significantly associated with impairment of erectile function [29]. Despite their effect on ejaculation [35], erection problems in patients treated with calcium channel blockers appear to be similar to placebo-treated patients [36]; but with a lower adverse effect on male erectile function, compared to propranolol [37]. ***Angiotensin converting enzyme inhibitors (ACEI)*** are other cardiovascular agents that have been associated with ED. However, the majority of data suggests that the rates of ED are quite low with the use of ACEIs. They have even been shown to increase the frequency of sexual encounters and also to improve erectile function in cardiovascular risk patients [29].

Table 1. prospective studies investigating associations between erectile dysfunction (ED) and cardiovascular diseases.

Study	Population type	Sample size	Age specification	Follow up	Main findings
Thompson et al. (2005) [17]	Population-based	8063	≥55 yr	10 yr	After adjustment, incident erectile dysfunction was associated with a hazard ratio of 1.25 (95% confidence interval [CI], 1.02-1.53; *P*=.04) for subsequent cardiovascular events during study follow-up. For men with either incident or prevalent erectile dysfunction, the hazard ratio was 1.45 (95% CI, 1.25-1.69; *P*<0.001).
Gazzaruso et al. (2008) [4]	Type 2 diabetes	291	54.8 ± 7.3	47.2 ± 21.8 months	ED predicted MACE (hazard ratio [HR] 2.1; 95% CI, 1.6 to 2.6; p < 0.001). Among patients with CAD and ED, Cox regression analysis showed that statin use (HR 0.66; 95% CI 0.46 to 0.97; p < 0.036) reduced MACE.
Emily Banks (2013) [18]	Population based	95,038	≥45 yr	39 months	Among men without previous CVD, those with severe versus no erectile dysfunction had significantly increased risks of ischemic heart disease (adjusted relative risk [RR] = 1.60, 95% CI 1.31–1.95), heart failure (8.00, 2.64–24.2), peripheral vascular disease (1.92, 1.12–3.29), ‘‘other’’ CVD (1.26, 1.05–1.51), all CVD combined (1.35, 1.19–1.53), and all-cause mortality (1.93, 1.52–2.44).
Schouten et al. (2008) [19]	Schouten BW, Bohnen AM, Bosch JL, Bernsen RM, Deckers JW, Dohle GR, Thomas S. Erectile dysfunction prospectively associated with cardiovascular disease in the Dutch general population: results from the Krimpen Study. Int J Impot Res. 2008 Jan-Feb;20(1):92-9.	1248 CVD-free	50-75	7945 person-years	Incidence rates of cardiovascular events increased statistically significant from 5.1/1000 person-years in men with normal erections to 10.1/1000 person-years in men with reduced erectile rigidity to 19.0/1000 person-years in men with severely reduced erectile rigidity (Po0.05).
Inman et al. (2009) [20]	Population based	1402	>40	10 years	After adjustments for age, vascular risk factors, diabetes, hypertension, smoking status, and BMI, incident coronary artery disease was significantly associated with ED (HR, 2.1; 95% CI, 1.5-2.9)
Batty et al. (2010) [21]	Diabetes type 2	6304	55-88	5 years	After adjusting for a range of covariates, baseline ED was associated with an elevated risk of all CVD events (HR: 1.19; 95% CI: 1.08 to 1.32), CHD (HR: 1.35; 95% CI: 1.16 to 1.56), and cerebrovascular disease (HR: 1.36; 95% CI: 1.11 to 1.67) Men who experienced ED at baseline and at 2-year follow-up had the highest risk for these outcomes.
Fung et al. (2004) [22]	Population-based	1810	30-69	25 years in average	Mean age, body mass index, cholesterol, and triglycerides were each significantly associated with an increased risk of ED. Cigarette smoking was marginally more common in those with severe/complete ED, as compared with those without ED. Blood pressure and fasting blood glucose were not significantly associated with ED, likely due to selective mortality.
Araujo et al. (2009) [23]	Population-based without diabetes and cardiovascular diseases	1709	40-70	11.7 yr	During follow-up, 261 new cases of CVD occurred. ED was associated with CVD incidence controlling for age (HR: 1.42, 95% CI: 1.05, 1.90), age and traditional CVD risk factors (HR: 1.41, 95% CI: 1.05, 1.90), as well as age and Framingham risk score (HR: 1.40, 95% CI: 1.04–1.88). Despite these significant findings, ED did not significantly improve the prediction of CVD incidence beyond traditional risk factors
Ponholzer et al. (2010) [24]	Negative history of cardial or cerebral vascular disease	2506		6.5 yr	Men without ED at baseline developed a cardiovascular event in 1.9% as compared with 2.9% in those with ED. ED was not an independent risk factor for a cardiovascular event.
Ma et al. (2008) [25]	no clinical evidence of cardiovascular disease	2306	54.2 ± 12.7 years	4.0 [range 1.7 to 7.1] years),	Erectile dysfunction remained an independent predictor for CHD events (HR: 1.58, 95% CI 1.08 to 2.30, p = 0.018) after adjustment for other covariates along with age, duration of disease, and use of antihypertensive agents and albuminuria.

A large randomized trial has also consistently suggested a potential beneficial effect for these drugs regarding ED development [32]. In type 2 diabetic patients, however, ACEI use was associated with 47% higher rate of ED [28], but no similar correlation was found for patients with metabolic syndrome [29]. Angiotensin receptor blockers (ARBs), which have similar biological effects as that of ACEIs, have not been associated with ED in the literature.

Thiazides have been reported to contribute in the development of ED, decreased libido, and failed Ejaculation [37-43]. However, more recent studies have failed to find significant effects for thiazide diuretics on ED [36,44]. In patients with metabolic syndrome, a study has even suggested a beneficial effect for thiazide diuretics on sexual desire, frequency of sexual contacts and erectile function [29]. Similar finding has been reported from a study on type 2 diabetes mellitus patients [28].

Statins have been reported to increase the risk of ED [45]. In one study, patients with coronary artery disease developed ED one week after starting treatment with simvastatin, and sexual function was restored after stopping the treatment; however when two of the patients restarted simvastatin, ED recurred [46]. In patients with metabolic syndrome, statins have been associated with ED [29]. On the other hand, there are studies with controversial results. In a number of studies involving men with ED statins have been reported to significantly improve erectile function [47,48]. Evaluation of the incidence of ED in the Scandinavian simvastatin survival study, where 4444 patients with coronary heart disease were randomized to treatment with simvastatin or placebo for up to 6 year, ED was equally observed in the two groups [49]. Atorvastatin has been even successfully used for improving the beneficial effects associated with sildenafil for the treatment of ED in ED patients [50].

ED and stroke

Stroke is a neurovascular event which can end with the ischemic death of brain cells. This disease is the third leading cause of death in the developing countries, and the leading cause of cardiovascular events with long-term consequences [51]. Koperlainen et al probably provided the first evidence that stroke patients and their wives have some level of sexual life dissatisfaction [52]. Since then, several other studies have proposed such a relationship in different populations [53-56]. In a recent case-control study, Jung *et al.* [57] reported a significantly higher rate of decreased sexual desire and intercourse frequency in male stroke patients. An interesting finding of this study was that the type of sexual disorder was associated with the regional damage to the brain, where lesions in the right cerebellum was associated with ejaculation disorder while lesions in the left basal ganglia decreased sexual desire. Although there is controversy on the potential role of the regional damage to the brain and sexual dysfunction [54].

Besides the causal effects of stroke on the development of ED, on the other hand, ED also has been shown to be able to induce stroke events with catastrophic consequences. An interesting population-based cohort study in Taiwan, China, survival analyses showed that patients with ED were more likely to have a stroke during the 5-year follow-up period than patients in the comparison cohort (hazard ratio = 1.29, 95% confidence interval = 1.08 - 1.54) [58]. Similar findings have been reported in Dutch [19] and American studies [23]. Ponholzer *et al.* [24], reported an increased risk of stroke for 2,561 men with moderate to severe ED over 10 years of follow up than controls [24]. Another study from the Massachusetts Male Aging Study suggested that ED is an independent risk factor for stroke; in this study, 1,209 men were evaluated over a 15 year period and men with ED were almost three times more likely to develop a stroke than controls without ED [59]. As an explanation for the abovementioned observations, Vicenzini et al suggested that cerebrovascular reactivity was decreased in patients with ED representing no sign of clinical atherosclerosis [60].

Risk calculations, and recommendations for management

Considering the high prevalence of ED in the general population, and the strong evidence on the cardiovascular risk associated with this condition which has even proposed ED as a "cardiovascular risk equivalent", all men representing ED complains should be considered at high risk of cardiovascular disease. This importance would become more obvious when an individual already has cardiovascular risk factors, and simultaneously complain from ED. Jackson et al. [61] in the second Princeton consensus statement on sexual dysfunction and cardiac risk have categorized ED patients to low-, intermediate- and high-risk subcategories. Table 2 summarizes the statement provided by this expert panel. Low risk patients are mainly asymptomatic patients with less than 3 cardiovascular risk factors. In this category, patients are at low risk for the development of major cardiovascular complications due to sexual activities or treatment of ED. In this population, mostly non invasive diagnostic and therapeutic are recommended.

Patients categorized in the intermediate risk have more critical conditions, and before return back to sexual intercourse activities, they should be re-evaluated to be put in either the low- or high-risk category. The majority of patients in this category are asymptomatic, but they usually have more than 3 risk factors for coronary heart disease. So, most of these patients need to get under more invasive evaluating or therapeutic approaches, including exercise tolerance test.

Patients in the high risk category include those with moderate or severe symptoms, and they also are at high risk of representing cardiovascular symptoms during sexual activities. Patients with unstable angina, uncontrolled hypertension, and MI patients with less than 2 weeks of convalesces enter this category. These patients are recommended not to have sexual intercourse, until stabilization of their medical condition, and consultation with their physician.

Conclusion

Although the prevalence of ED in cardiovascular disease patients is quite high, and this condition is considered a crucial cardiovascular risk factor, few physicians discuss this issue during consultation.

Table 2. Cardiovascular risk evaluation and management of sexual activities from sexual activities recommended by the Second Princeton Consensus Conference [Jackson]

Main risk category	Patients in the subcategory	Risk evaluation	Recommendations
Low risk	Asymptomatic and <3 major risk factors* (excluding gender)		
	Controlled hypertension	Beta-blockers and thiazide diuretics may predispose to ED	
	Mild, stable angina pectoris		Noninvasive evaluation recommended Antianginal drug regimen may require modification
	Postrevascularization and without significant residual ischemia		ETT** may be beneficial to assess risk
	Post-myocardial infarction (MI) (>6–8 weeks), but asymptomatic and without ETT-induced ischemia, or post revascularization		If postrevascularization or no ETT-induced ischemia, intercourse may be resumed 3–4 weeks post-MI
	Mild valvular disease		
	LVD (NYHA class I)		
Moderate risk	Asymptomatic and >3 CAD risk factors* (excluding gender)	Increased risk for acute MI and death	ETT may be appropriate, particularly in sedentary patients
	Moderate, stable angina pectoris		ETT may clarify risk
	MI >2 weeks but <6 weeks	Increased risk of ischemia, reinfarction, and malignant arrhythmias	ETT may clarify risk
	LVD/congestive heart failure (CHF) (NYHA class II)	Moderate risk of increased symptoms	Cardiovascular evaluation and rehabilitation may permit reclassification as low risk
	Noncardiac atherosclerotic sequelae (peripheral arterial disease, history of stroke, or transient ischemic attacks)	Increased risk of MI	Cardiological evaluation should be considered
High risk	Unstable or refractory angina	Increased risk of MI	
	Uncontrolled hypertension	Increased risk of acute cardiac and vascular events (i.e., stroke)	
	CHF (NYHA class III, IV)	Increased risk of cardiac decompensation	
	Recent MI (<2 weeks)	Increased risk of reinfarction, cardiac rupture, or arrhythmias, but impact of complete revascularization on risk is unknown	
	High-risk arrhythmias	Rarely, malignant arrhythmias during sexual activity may cause sudden death	Risk is decreased by an implanted defibrillator or pacemaker
	Obstructive hypertrophic cardiomyopathies	Cardiovascular risks of sexual activity are poorly defined	Cardiological evaluation (i.e., exercise stress testing and echocardiography) may guide patient management
	Moderate to severe valve disease		Use vasoactive drugs with caution

* Major cardiovascular disease risk factors include age, male gender, hypertension, diabetes mellitus, cigarette smoking, dyslipidemia, sedentary lifestyle, and family history of premature CAD; ** ETT, exercise tolerance test;

However, according to the findings of the reviewed articles, adequate study to diagnose potential sexual dysfunction is needed to perform by general practitioners and cardiologists. Patients should be precisely evaluated and categorized according to the Princeton Consensus statement. Then patients should receive guidelines regarding their sexual activities, diagnostic tests and therapeutic endeavors. Unfortunately, no prospective study has been performed on Iranian population, and we recommend conducting such a study in our country.

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