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CARDIOVASCULAR PHYSIOLOGY AND ERECTILE DYSFUNCTION

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ABSTRACT

Erectile dysfunction (ED) is defined as the inability to initiate or maintain an erection that is not satisfactory or sufficient for sexual activity.

Erectile dysfunction affects the patient in many ways, especially the physical and psychosocial condition, and has extremely negative effects on the quality of life of the patient and his partner. There is increasing evidence that erectile dysfunction occurs in the early stages of coronary artery and peripheral vascular disease. This makes us think that ED is not only a condition that affects the quality of life but also a potential warning sign for cardiovascular diseases. Therefore, it is important to know the relationship between cardiovascular system physiology and erectile dysfunction. In this review, the relationship between cardiovascular system physiology and erectile dysfunction was evaluated in light of the literature.

KEY WORDS: cardiovascular system; erectile dysfunction; physiology; PDE-5

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INTRODUCTION

Erectile dysfunction (ED) is an important health problem that affects the quality of life. Erectile dysfunction is defined as the inability to adequately achieve and/or maintain an erection required for sexual performance [1].

Erectile dysfunction affects about 20% of men over the age of 50, and about 50% of men over 60. ED is thought to be associated with cardiovascular diseases (CVD). Age, hypertension, diabetes, insulin resistance, smoking, increased body mass index (BMI), cholesterol and low high-density lipoprotein (HDL) are common risk factors for ED and CVD [2–4].

The reason for the different values related to the frequency is due to the differences in the methods used in the studies. Penile erection is a complex process accompanied by hormonal control of arterial dilatation, trabecular smooth muscle relaxation, and corporeal venoocclusive mechanisms [5]. The most common cause of erectile dysfunction is atherosclerosis, so it is closely related to risk factors. These risk factors lead to oxidative stress and endothelial dysfunction, reducing nitric oxide production and therefore reducing nitric oxide release, which has a key role in normal erectile function [5, 6].

Other important causes of erectile dysfunction include thyroid dysfunction, drugs (especially beta-blockers, verapamil, spironolactone and thiazide diuretics, drugs such as digoxin, methyl-dopa), drugs with antiandrogenic effects, alcohol use, neurological and surgical disorders. Erectile dysfunction is common in those with cardiovascular disease. Age, diabetes mellitus, hypertension, obesity, dyslipidemia, smoking, sedentary lifestyle, male gender, family

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history of coronary artery disease at an early age (< 55 years in men, < 65 years in women) are risk factors for coronary artery disease. Therefore, controlling and treating these cardiovascular risk factors prevents the formation of ED. For this purpose, these risk factors should be specifically questioned in the evaluation of the patient with erectile dysfunction and, if any, they should be treated in accordance with the guidelines. Sexual activity requires a good exercise capacity in healthy individuals. Therefore, patients should undergo a cardiovascular evaluation to avoid cardiovascular events (angina, myocardial infarction, or cardiac death) during sexual performance [7, 8].

In this respect, the cardiovascular risk assessment should be performed in patients with erectile dysfunction. There is no need for additional cardiovascular testing before sexual activity recommendations or treatment for erectile dysfunction for low-risk patients. Cardiac evaluation should be made before sexual activity or erectile dysfunction treatment recommendations for this patient group. In these patients, a treadmill exercise test can be recommended for the presence of coronary ischemia after electrocardiographic and echocardiographic evaluation. Myocardial perfusion scintigraphy may be recommended for coronary ischemia investigation in patients who are found to be unsuitable for the treadmill test as a result of the electrocardiographic evaluation (presence of left bundle branch block, preexcitation, left ventricular hypertrophy, presence of a digital effect, presence of ST-T change at baseline), or who cannot exert effort due to orthopedic problems. Patients with no evidence of coronary ischemia in these tests are considered low-risk, and sexual activity restriction is not required. Patients with signs of ischemia in cardiological tests are considered high-risk. High-risk patients have severe and unstable cardiac disease. In this group of patients, sexual activity may worsen existing cardiac disease and lead to adverse cardiovascular events. Therefore, it is recommended to postpone sexual activity and erectile dysfunction treatment in this patient group [8–10].

MATERIAL AND METHODS

Search strategy

PubMed, Medline, Excerpta Medica Database (Embase), and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases are screened from 1980 to 2022."Cardiovascular system","Erectile Dysfunction", "Physiology", "PDE-5" terms were used as search term strategy. The references of selected articles were searched as well. The abstract and/ or full text of the article was assessed. The Cochrane Highly Sensitive Search Strategy was used to define articles in PubMed by using the aforementioned keywords along with Medical Subject Headings (MeSH) terms. We limited the search to articles on "Cardiovascular system", "Erectile Dysfunction", "Physiology", "PDE-5" in English. ". A total of 32 original articles, systematic reviews, and meta-analyses were included in this review.

Data extraction and management

Based on the pre-determined selection criteria, one author (LOS) independently selected all trials retrieved from the databases and bibliographies. Studies were reviewed to determine their relevance to "Cardiovascular system", "Erectile Dysfunction", "Physiology", "PDE-5".The full-text copies of the articles identified as potentially relevant by the review author.

Vasoconstrictor substances in the relationship between the cardiovascular system and erectile dysfunction

Angiotensin II (AT 2)

AT II is a peptide with potent vasoconstrictor properties that is part of the renin-angiotensin-aldosterone system.

It has an important role in the regulation of systemic blood pressure. High AT 2 levels play a role in the pathogenesis of hypertension by increasing vascular tone as well as salt retention. AT 2 plays an important role in the pathogenesis of erectile dysfunction. Some studies have shown that systemic AT 2 levels are elevated in men with ED. In patients with ED, AT 2 levels were found to be higher in cavernous blood compared to healthy individuals [11, 12]. AT II shows these effects through AT 1 and AT 2 receptors. Stimulation of AT 1 receptors leads to vasodilation, while stimulation of AT 1 receptors leads to vasoconstriction, vascular smooth muscle cell proliferation, inflammation, and sympathetic activation. AT 1 receptor blockade has been shown to correct ED. AT 2 causes an increase in the penile artery and cavernous vascular smooth muscle tone [13–15].

Endothelin 1

Endothelin 1 is a peptide synthesized in the endothelium and known to have potent constrictor effects on vascular tone. It acts on ET A and ET B receptors. Both types of receptors have been detected in the cavernous endothelium. It causes vasoconstriction via ET A receptors in the cavernous tissue of the penis. Stimulation of ET B receptors leads to vasodilator effects through the release of NO. Endothelin 1 not only causes vasoconstriction in the penile artery but also has been shown to cause vasoconstriction in the pudendal artery, which is the major artery supplying blood to the penis [16, 17].

Vasodilator substances in the relationship between the cardiovascular system and erectile dysfunction

ED may develop as a result of increased production of vasoconstrictor substances or increased sensitivity to these substances, as well as a decrease or insensitivity to vasodilator substances. All of these are classic signs of endothelial dysfunction.

Nitric Oxide (NO)

In hypertensive patients, there is a decrease in endothelial-derived NO levels due to reasons such as an increase in reactive oxygen products and a decrease in endothelial NO synthase expression. In hypertension, the balance of oxidants and antioxidants is impaired. Reactive oxygen products play an important role in many endothelial-related diseases as well as in atherogenesis. Reactive oxygen products convert NO to peroxynitrite. Peroxynitrite produces a weaker but slower and longer-lasting endothelial relaxation than NO, and ED occurs as a result of ineffective relaxation [18, 19].

Hydrogen Sulfide (H_2S)

H_2S consists of cystathionine B synthase (CBS) and cystathionine lyase (CLY) enzymes and L-cysteine. Its deficiency can contribute to hypertension. Inhibition of CLY secondary to drugs or genes may lead to impaired endothelial relaxation and hypertension [20]. Both enzymes have been demonstrated in smooth muscle cells in the penile artery and corpus cavernosum. Dose-dependent relaxation in cavernous tissue has been demonstrated by the administration of exogenous H_2S [21]. However, it is still unclear by which mechanisms of H_2S contribute to erectile function.

Hypertension and erectile dysfunction

Erectile Dysfunction is a problem of vascular origin. The penile endothelial bed is a specialized extension of the peripheral vascular system. It responds to stimuli to maintain normal homeostasis like other vascular systems [22]. The penis is a vascular organ sensitive to oxidative stress and systemic NO levels. Circulating neurotransmitters, hormones, and endothelial-derived factors regulate vascular smooth muscle tone. Changes in these factors in hypertensive patients lead to vascular contraction. All these explain that ED is more common in hypertensive patients. Apart from this, penile vessels are also affected by atherosclerosis like systemic vessels. Therefore, ED is not only associated with atherosclerosis but also strongly predicts atherosclerosis [23].

Abdominal obesity and erectile dysfunction

Abdominal obesity increases cardiac complications such as coronary heart disease, heart failure, acute MI and sudden death. In addition, the waist-to-hip ratio is an independent predictor of coronary artery disease in ED patients.

Men with a high waist circumference or obese BMI were approximately 50% more likely to have ED compared with men with a low waist circumference or a normal BMI [24–26].

Kidney function and erectile dysfunction

The 2012 Princeton III Consensus recommends the collection of serum creatinine (Cr) level (estimated glomerular filtration rate) and albumin to Cr ratio. Chronic kidney disease is a risk factor for the development of CVD. Men with serum Cr levels above 97.5 percent have an increased risk of death from cardiovascular and general causes. Baseline renal function values are a strong independent risk factor for adverse cardiovascular events. In addition, ED is quite common in men receiving hemodialysis treatment [27, 28].

Drugs used in the treatment of erectile dysfunction and cardiovascular system

One of the important cardiovascular issues in the treatment of erectile dysfunction is the use of phosphodiesterase 5 (PDE5) inhibitors.PDE5 inhibitors increase the concentration of cyclic guanyl monophosphate (cGMP) in the tissue by preventing the degradation of cGMP in penile erectile tissue, the intracellular increased concentration of cGMP lowers

intracellular calcium and relaxing penile cavernosal smooth muscle cells, ultimately leading to penile erection [29]. Sildenafil, tadalafil, vardenafil, and udenafil are available for medical use in the world.

All mentioned PDE5 inhibitors are metabolized in the liver. The half-life of sildenafil and vardenafil is approximately 4 hours, while that of tadalafil is approximately 18 hours and that of udenafil is approximately 10 hours. Although PDE5 inhibitors do not have a direct adverse effect on the cardiovascular system, caution should be exercised when using them because of their potential to cause fatal drug interactions and hypotension [30]. In healthy young men, sildenafil reduces mean systolic and diastolic blood pressure by 8.5 and 5.5 mmHg, respectively, while vardenafil reduces 8 and 7 mmHg, respectively. Tadalafil decreases by 1.6 and 0.8 mmHg, respectively [29]. Orthostatic hypotension may occur, especially in case of simultaneous use with alpha--adrenergic receptor blockers. To prevent this, treatment should be started with a low-dose PDE5 inhibitor, and if the patient needs to use alpha-adrenergic receptor blockers simultaneously, care should be taken to ensure that there is at least a 6-hour difference between taking this drug and PDE5 inhibitor. Although PDE5 inhibitors do not cause severe hypotension when used alone, guidelines recommend starting these drugs for those with a blood pressure of 90/60 mmHg and above.

Patients describing Canadian Cardiovascular Society (CCS) III or IV angina pectoris, presence of acute coronary syndrome, uncontrolled hypertension (SBP > 180 mmHg), presence of congestive heart failure with Newyork Herat Association (NYHA) class III or IV, dyspnea, recent myocardial infarction (< 14 days), presence of risky arrhythmia [ventricular tachycardia, high ventricular rate atrial fibrillation (resting heart rate > 110/min), presence of 2nd or 3rd degree AV block, presence of severe bradycardia (heart rate < 40/min)], presence of hypertrophic cardiomyopathy and presence of moderate and severe valvular heart disease defines high-risk patients. Sexual activity should not be recommended in these high-risk patients.

It should be noted that initiation of PDE5 inhibitors in this patient group is contraindicated.

Another issue to keep in mind with PDE5 inhibitors is drug interactions. PDE5 inhibitors induce peripheral vasodilation via cGMP and thus causeing blood pressure reduction to varying degrees [29–31]. Concomitant use of nitrate-derived drugs (such as isosorbide mononitrate, isosorbide dinitrate, and nitroglycerin) that use the same pathway as PDE5 inhibitors may result in fatal hypotension. Nitrate-derived drugs are frequently used in cardiology practice in coronary artery disease, relief of anginal complaints, and treatment of heart failure [31]. Therefore, it should be questioned whether there is a nitrate-derived drug among the drugs used by the patient who will be started on a PDE5 inhibitor. If the need to use nitrate-derived drugs arises in a patient using a PDE5 inhibitor, it is necessary to wait to follow the guideline recommendations. While this period is 24 hours after sildenafil and vardenafil use, it is 48 hours for tadalafil, which has a longer half-life [8, 30, 31]. Although no time has been specified for Udenafil, it may be appropriate to wait 36 hours, given that its half-life is 10 hours. In patients receiving nitrate therapy, nitrate should be discontinued for PDE5 inhibitor use, and other antianginal agents (such as beta-blockers, trimetazidine, and calcium channel blockers) can be started instead of nitrate. In these patients, however, it is recommended to wait at least 24–48 hours before starting a PDE5 inhibitor to avoid possible interference [32]. Vardenafil, unlike other PDE5 inhibitors, can cause mild QT interval prolongation on electrocardiography. As a result, it should not be used in patients with congenital long QT syndrome. In addition, it should not be used together with antiarrhythmic drugs such as quinidine, procainamide, amiodarone, and sotalol that prolong the QT interval [30–32].

CONCLUSION

Erectile dysfunction is closely associated with cardiovascular risk factors. Cardiovascular evaluation should be recommended before sexual activity and erectile dysfunction treatment in these patients. In high-risk patients, sexual activity and treatment of erectile dysfunction should be delayed. The parallel relationship between ED and CVD may be helpful in screening for cardiovascular risk factors in men with ED. In addition, it should never be used with nitrate-derived drugs used in the treatment of coronary artery disease due to the potential to cause fatal drug interactions.

Conflict of interest

Author declares no conflict of interest.

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