Erectile Dysfunction, Sleep Disorders, and Endothelial Function

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ABSTRACT: Erectile dysfunction (ED) is a syndrome associated with endothelial dysfunction, which may predict cardiovascular events in men presenting with this syndrome. It has been shown to be associated with a higher rate of acute myocardial infarction and cardiovascular mortality, vascular inflammation, and impaired endothelial function. In this review we present the literature findings and describe the mechanistic pathways that are known to be involved in this syndrome and its related clinical consequences.

IMAJ 2019; 21: 408–411

KEY WORDS: endothelial function, erectile dysfunction, nitric oxide (NO), sleep medicine, sudden death

ERECTILE DYSFUNCTION AND CARDIOVASCULAR RISK

Vascular erectile dysfunction (ED) is mechanistically related with vascular disease and endothelial dysfunction. It is caused by an impaired ability of the smooth muscle cells lining the penile arterioles to relax, thereby inhibiting vasodilatation. Patients with vascular ED have significantly more ischemic heart disease events compared with men without ED [1]. Penile erection is a hemodynamic process that is composed of two synchronized components. The first (active) requires a competent vascular endothelial function. The second (passive) is based on a proper veno-occlusive mechanism. Lifestyle modification may have a positive effect on ED, and it has been shown that in patients without type 2 diabetes mellitus (T2DM), a greater decrease in systolic blood pressure was associated with greater improvement in erectile function. This beneficial effect of lowering blood pressure was observed in patients with hypertension and in patients with dyslipidemia [2].

Erectile dysfunction is one of the earliest signs of endothelial dysfunction and should be part of a routine screening of men older than 45 years of age

AGING

Aging changes sex hormones and causes endothelial dysfunction, expressed also as ED.

ANIMAL MODELS

A trial that examined whether exercise training could protect from ED by enhanced penile endothelial nitric oxide synthase (e-NOS) levels in aging rats showed that exercise training increased serum testosterone levels in all age groups. Exercise training protected against aging-induced decrease in e-NOS and e-NOS protein levels in the penis [3].

HUMAN STUDIES

In a cohort study that included 802 patients (40–80 years old), blood samples were drawn to measure testosterone levels. Endothelial function was assessed by the flow mediated dilatation of the brachial artery, and erectile dysfunction was assessed by the International Index of Erectile Function 5 questionnaire (available from http://www.croesoffice.org/Portals/0/Short_IIEF.pdf). The composite endpoint was major adverse cardiovascular events (MACEs). It was found that subjects with lower serum testosterone levels had higher prevalence of traditional risk factors such as hypertension, T2DM, dyslipidemia, obesity, and endothelial dysfunction. Acute myocardial infarction (AMI), death after AMI, major stroke, and all clinical events were more frequent in patients with testosterone levels < 300 ng/dl. Using multiple logistic regression analysis, it was found that dyslipidemia, obesity, low testosterone level, and ED were independent predictors of future MACEs [4].

ED is associated with cardiovascular disease and mortality; however, the mechanism is not clear. A study that examined endothelial function using the brachial artery method of measuring flow mediated dilatation percent change (FMD%), carotid intima-media thickness (IMT), coronary artery calcification, and other vascular functions such as the ankle brachial

index, toe-brachial index, and pulse wave velocity, found that ED was associated with a 2.64% reduction in FMD% compared to subjects without ED. Patients with ED also had a 0.09 mm thicker IMT compared to those without ED. This study demonstrated that ED is associated with subclinical mechanisms leading to clinical atherosclerotic events and shows the need and the importance of an aggressive cardiovascular risk assessment and management of patients with ED [5].

A study that screened ED and associated cardiovascular risk factors in 19,131 Israeli men (aged 34.0 ± 7.1 years) found that one out of four men (25.2%) presented with ED, which was mild in 18.9%, mild to moderate in 4.4%, moderate in 1.1%, and severe in 0.7%. In the severe group 45.2% had dyslipidemia, 25.6% were active smokers, 4.2% had essential hypertension, and 1.6% had T2DM. ED was significantly associated with age and diabetes mellitus ($P < 0.0001$) [6].

CAN WE PREDICT THE CLINICAL OUTCOME OF PATIENTS WITH ERECTILE DYSFUNCTION?

The Henry Ford Exercise Testing Project (1991–2009) examined the prognostic impact of maximal exercise capacity on the cardiovascular event rate of men (40–60 years of age) treated for ED. The study found that among the 1152 men who were followed, each one metabolic equivalent of fitness was associated with a 16% lower risk of death with a non-significant reduction in major adverse cardiovascular events and T2DM. A higher baseline fitness was associated with improved cardiovascular prognosis in middle-aged men treated for ED [7].

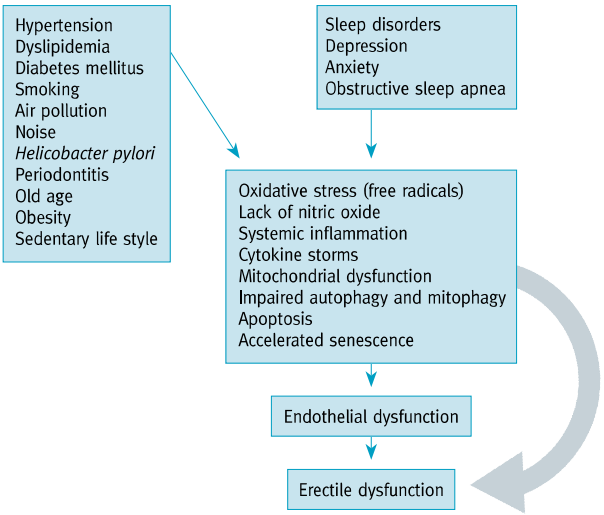
Smoking and obesity are risk factors that may be a cause of erectile dysfunction in young men

The Multi-Ethnic Study of Atherosclerosis examined the association between cardiovascular health and endothelial function and the future development of ED. This study comprised 1136 men. Their erectile dysfunction status was evaluated at baseline, as well as their endothelial function, measured by the brachial artery method. The FMD% was better among men without ED. ED prevalence was lower in men with a better cardiovascular health. Future erectile dysfunction could be predicted by the cardiovascular health and the cardiovascular risk score. Maintaining a healthy lifestyle profile may improve quality of life for men on the long run [8].

COULD ERECTILE DISFUNCTION PREDICT THE DEVELOPMENT OF ACUTE MYOCARDIAL INFARCTION

A study that investigated the prevalence of ED in patients with AMI and after 2 years of follow-up found that 40% of the patients admitted with AMI had ED. After a 2-year follow-up, post-AMI, the percentage of patients without ED increased by 13% while the percentage of patients with severe ED significantly decreased by 15%. Patients with ED had higher B type natriuretic peptide levels and lower levels of nitric oxide. During the 2-year follow-up, 9 patients died (69% had ED) and 22 were re-admitted to the hospital (59% had ED). Low levels of nitric oxide were the best predictors of ED during AMI and after 2 years. ED predicted the worst outcomes of AMI: death and re-hospitalization [9]. Interestingly, a study that evaluated arterial stiffness and cardiac function in patients with ED found that phosphodiesterase-5 inhibitor (tadalafil), given for ED, reduced pulse pressure, systolic blood pressure, and diastolic blood pressure, while increasing aortic dispensability and aortic strain. Tadalafil positively affected arterial stiffness and left ventricular diastolic function in patients with ED who did not have a known atherosclerotic risk factor or cardiac disease [10].

Figure 1. Mechanistic pathways leading to erectile dysfunction



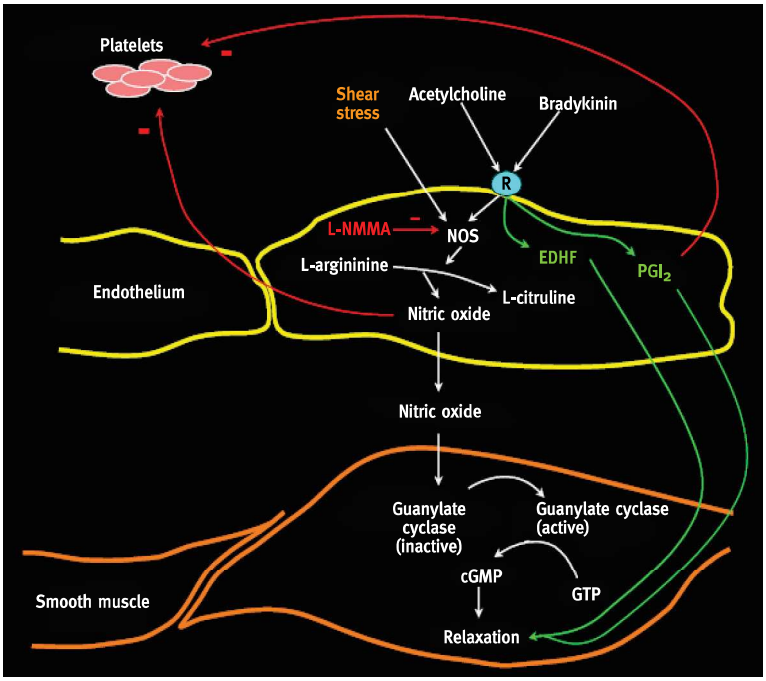
ERECTILE DYSFUNCTION AND SLEEP APNEA SYNDROME

ED is quite common in men with obstructive sleep apnea syndrome (OSA). Studies showed that treating OSA by continuous positive airway pressure (CPAP) improved ED. A controlled study was designed to examine this hypothesis, and 60 men with moderate to severe OSA and ED were randomized to 12 weeks of CPAP treatment (or sham CPAP) with 10 mg daily of vardenafil (or a placebo) in a 2 × 2 factorial design. It was found that CPAP increased the frequency of sleep related erections, overall sexual satisfaction, and arterial stiffness. However, it did not change erectile dysfunction and neither did a 10 mg dose of vardenafil. CPAP improved overall sexual satisfaction, sleep related erections, and arterial stiffness [11].

SLEEP DISORDERS AND ERECTILE DYSFUNCTION

Both obstructive sleep apnea (OSA) and ED are prevalent and underdiagnosed. They co-exist, so that about half of the male

Figure 2. Nitric oxide production in endothelial cells (endothelial nitric oxide syntahse). Lack of nitric oxide leads to endothelial dysfunction, and erectile dysfunction is one of the earliest clinical events expressing endothelial dysfunction. Sleep disorders lead to endothelial dysfunction and to ED through ROS pathways with activation of inflammatory genes and pro-inflammatory cytokines



ED = erectile dysfunction, EDHF = endothelium-derived hyperpolarizing factor, NOS = nitric oxide synthase, ROS = reactive oxygen species

subjects with OSA also have ED and vice versa. OSA is associated with cardiovascular mortality, and ED could be used as a phenotypic marker of cardiovascular disease. It could be that endothelial dysfunction may be the common pathophysiological mechanism linking OSA and ED to cardiovascular morbidity and mortality [12].

Sleep disorders are associated with endothelial dysfunction as well as cardiovascular death, cardiac events, and erectile dysfunction

Clinical studies have demonstrated a link between ED and sleep disorders. A MEDLINE search found an association between ED and sleep disorders, and hormonal, neural and endothelial mechanisms have been implicated in linking sleep disorders with ED.

More than that, treating sleep disorders by continuous positive airway pressure (CPAP) has been shown to improve ED [13].

POSSIBLE MECHANISTIC PATHWAYS: NITRIC OXIDE, INFLAMMATION, AND OXIDATIVE STRESS

There are several possible pathways, and most of them are related to nitric oxide-dependent pathways, vascular inflammation, and oxidative stress.

INFLAMMATION

Roumeguere and colleagues [14] investigated markers of inflammation and oxidative stress in the corpus cavernosum. They examined the impact of inflammatory markers on erectile function and endothelial function. The researchers recruited 97 subjects without ED who completed the ED questionnaire. Lipid profile, myeloperoxidase-dependent oxidized low-density lipoprotein (LDL), interleukin 8 (IL-8), and interleukin 18 (IL-18) were measured. After RNA extraction, e-NOS level was measured as well. IL-18, myeloperoxidase-dependent oxidized LDL, and myeloperoxidase/Apo B levels were significantly increased in the corpus cavernosum compared to arm blood. ED score correlated with IL-18 levels in the venous blood, in the corpus cavernosum, and also with IL-8. IL-18 and myeloperoxidase-dependent LDL significantly inhibited e-NOS mRNA expression in human aortic endothelial cell line. This study demonstrated the important role of inflammation and oxidative stress in the mechanism of erectile function.

OBESITY

Obesity was related to ED. To examine the effect of obesity on erectile function, two groups of mice were studied. One group consisted of lean mice (Zucker lean) and the other group was composed of fat mice (Zucker fat). Insulin tolerance and erectile function were evaluated and the researchers found that erectile function was significantly impaired in the group of fat mice. However, low intensity extracorporeal shockwave therapy significantly improved the erectile function. Endothelial cells from the penis of the fat mice were damaged, with a significant regeneration after the shockwave therapy. This study clearly showed that obesity impairs erectile function by causing smooth muscle cells atrophy, endothelial dysfunction, and lipid accumulation in the corpus cavernosum. Low intensity extracorporeal shockwave therapy restored penile hemodynamics of the penile endothelium in the fat mice, improved endothelial function, and reduced lipid accumulation. Further studies showed that the mechanism was related to enhancement of activation of endothelial progenitor cells that prompted cellular proliferation and accelerated penile tissue regeneration [15].

FOLATE PATHWAY

Another related pathway is the folate-homocysteine pathway. Homocysteine impaired erectile function via several mechanisms. Patients with ED had lower levels of folic acid and higher levels of homocysteine compared to those without ED [16].

GENETICS

A strong link between vascular endothelial growth factor (VEGF) and penile erectile function has been documented. VEGF can regulate blood flow to the corpus cavernosus and control the penile vasomotor tone. A study that investigated

VEGF polymorphisms and their relationship to ED among 688 men (≥ 55 years old) showed that subjects who had T2DM, hypertension, or the VEGF 2578A allele also presented with ED. All three VEGF genes (460C, 1154A, and 2578A) were significantly associated with coronary artery disease. Those with hypertension had the 1154A and 2578A alleles. A significant association (logistic regression analysis) was found between the VEGF 2578A allele carrier and ED. The prevalence and severity of ED were significantly increased with an increment of the 2578A allele number [17].

Since nitric oxide bioavailability is impaired in ED, the gene encoding e-NOS could be of interest for understanding the physiology of ED. A study that investigated the association between the G894 polymorphism in the e-NOS gene and ED among 449 men found that ED was associated with T2DM, hypertension, sleep apnea syndrome, older age, body mass index, and testosterone level. In a multiple regression analysis, age was found to be the only independent factor associated with ED. No association was found between ED and any genotype or allelic form [18].

THE FUTURE: STEM CELLS TRANSPLANTATION

Several novel therapeutic options have been suggested in recent years, including stem cells transplantation.

Animal model studies investigated several cells transplantation approaches:

- The combined transplantation of mesenchymal stem cells (MSCs) and endothelial progenitor cells (EPCs) on restoration of ED in rats with cavernous nerve injury (human MSCs and EPCs were injected to the per prostatic area) and erectile function was measured 2 weeks later. Combined transplantation of MSCs and EPCs improved ED much better than a single cell-type transplantation with a much higher expression of nitric oxide level, and increased endothelial and smooth muscle contents of the corpus cavernosum [19].
- Another approach is to transplant adipose derived stem cells to improve erectile dysfunction. It was found that adipose-derived stem cells (ADSCs) secreted higher levels of insulin growth factor, beta fibroblast growth factor, and VEGF. Transplantation of ADSCs to aged rats partially normalized levels of these growth factors and enriched the contents of cavernous smooth muscle and endothelium in the corpus cavernosus of these rats [20].

CONCLUSIONS

In this review we described the known data on ED and the mechanistic pathways leading to this syndrome and to its cardiovascular complications. We believe that understanding the mechanism will lead to the development of new medications and clinical management that will improve the ED and its cardiovascular complications.

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References

1. Azab SS, El Din Hosni H, El Far TA, et al. The predictive value of arteriogenic erectile dysfunction for coronary artery disease in men. *J Sex Med* 2018; 15 (6): 880-7.
2. Kalka D, Gebala J, Rusiecki L, et al. Relation of postexercise reduction of arterial blood pressure and erectile dysfunction in patients with coronary heart disease. *Am J Cardiol* 2018; 122 (2): 229-34.
3. Seo DY, Lee SR, Kwak HB, et al. Exercise training causes a partial improvement through increasing testosterone and eNOS for ereectile function in middle aged rats. *Exp Gerontol* 2018; 108: 131-138.
4. Iacona R, Bonomo V, Di Piazza M, et al. Five-year prospective study on cardiovascular events, in patients with erectile dysfunction and hypotestosterone. *Arch Ital Urol Androl* 2017; 89 (4): 313-15.
5. Osondu CU, Vo B, Oni ET, et al. The relationship of erectile dysfunction and subclinical cardiovascular disease: a systemic review and meta-analysis. *Vasc Med* 2018; 23 (1): 9-20.
6. Heruti RJ, Steinvil A, Shochat T, et al. Screening for erectile dysfunction and associated cardiovascular risk factors in Israeli men. *IMAJ* 2008; 10: 686-90.
7. Same RV, Al Rifai M, Feldman DI, et al. Prognostic value of exercise capacity among men undergoing pharmacologic treatment for erectile dysfunction: the FIT project. *Clin Cardiol* 2017; 40 (11): 1049-54.
8. Lane-Cordova AD, Kershaw K, Liu K, et al. Association between cardiovascular health and endothelial function with future erectile dysfunction: the Multi-Ethnic Study of Atherosclerosis. *Am J Hypertens* 2017; 30 (8): 815-21.
9. Apostolovic S, Stanojevic D, Jankovic-Tomasevic R, et al. Erectile dysfunction as a predictor of two-year prognosis in acute myocardial infarction. *Cardiol J* 2017; 24 (4): 393-402.
10. Ozdabakoglu O, Gullulu S, Sag S, et al. Evaluation of arterial stiffness and cardiac function in patients with vascular erectile dysfunction: acute effects of phosphodiesterase-5 inhibitor tadalafil. *Int J Impot Res* 2017; 29 (3): 96-100.
11. Melehan KL, Hoyos CM, Hamilton GS, et al. Randomized trial of CPAP and vardenafil on erectile and arterial function in men with obstructive sleep apnea and erectile dysfunction. *J Clin Endocrinol Metab* 2018; 103 (4): 1601-11.
12. Hoyos CM, Melehan KL, Phillips CL, et al. To ED or not to ED – is erectile dysfunction in obstructive sleep apnea related to endothelial dysfunction? *Sleep Med Rev* 2015; 20: 5-14.
13. Jankowski JT, Seftel AD, Strohl KP. Erectile dysfunction and sleep related disorders. *J Urol* 2008; 179 (3): 837-41.
14. Roumeguere T, Van Antertpen P, Fathi H, et al. Relationship between oxidative stress and erectile function. *Free Radic Res* 2017; 51 (11-12): 924-31.
15. Ruan Y, Zhou J, Kang N, et al. The effect of low-intensity extracorporeal shockwave therapy in an obesity-associated erectile dysfunction rat model. *BJU Int* 2018; 122 (1): 133-42.
16. Sansone M, Sansone A, Romano M, et al. Folate: a possible role in erectile dysfunction? *Aging Male* 2018; 21 (2): 116-20.
17. Lee YC, Huang SP, Tsai CC, et al. Associations of VEGF gene polymorphisms with erectile dysfunction and related risk factors. *J Sex Med* 2017; 14 (4): 510-17.
18. Andersen ML, Guindalini C, Santos-Silva R, et al. Association analysis of endothelial nitric oxide synthase G894T gene polymorphism and erectile dysfunction complaints in a population-based survey. *J Sex Med* 2010; 7 (3): 1229-36.
19. Fang JF, Huang XN, Han XY, et al. Combined transplantation of mesenchymal stem cells and endothelial progenitor cells restores cavernous nerve injury related erectile dysfunction. *J Sex Med* 2018; 15 (3): 284-95.
20. Yang J, Zhang Y, Zang G, et al. Adipose derived stem cells improve erectile function partially through the secretion of IGF-1, bFGF, and VEGF in aged rats. *Andrology* 2018; 6 (3): 498-509.