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Review article

Endothelial dysfunction: The hidden link between erectile dysfunction and cardiovascular disease

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Abstract Erectile dysfunction (ED), often regarded as a quality-of-life issue for middle-aged and older men, is increasingly recognized as a predictor of atherosclerotic cardiovascular disease (CVD), particularly in younger men. Endothelial dysfunction may be an early marker of vascular erectile dysfunction. This article explores the pathophysiological mechanisms connecting endothelial dysfunction, ED, and CVD. By reviewing current research, we highlight the significance of ED as a predictor of cardiovascular events and discuss approaches for early detection and intervention to enhance cardiovascular health.

Key words erectile dysfunction, coronary artery disease, endothelial dysfunction, cardiovascular events

Introduction

Erectile dysfunction (ED) affects millions of men worldwide, with approximately 40% of men over the age of 40 experiencing some degree of ED[1]. While psychological and hormonal factors can contribute to ED, vascular causes are the most common and often seen as an early manifestation of endothelial dysfunction. Endothelial dysfunction is a key factor in the development of atherosclerosis and cardiovascular disease (CVD)[1,2]. The *artery size hypothesis* provides a mechanistic link between ED and CVD[1]. Atherosclerosis impacts all major vascular beds uniformly, but smaller arteries, such as penile arteries, are more susceptible to becoming occluded before larger ones like coronary arteries due to their smaller diameter. As a result, ED often precedes the clinical signs of CVD, serving as an early warning indicator.

The interconnectedness of ED and CVD is further illustrated by the numerous shared risk factors (Figure 1). A growing body of literature documents ED as an independent risk factor for the development of CVD. A meta-analysis involving over 36,000 men found that ED was associated with a significantly increased risk of coronary heart disease and all-cause mortality[3]. These associations persisted even after adjusting for traditional cardiovascular risk factors. ED commonly precedes CVD symptoms by two to five years, providing a critical window for early cardiovascular risk assessment and intervention[4].

Recognizing ED as an early marker of CVD has significant implications for clinical practice. Studies have shown that men with ED have an increased relative risk of cardiovascular disease. Specifically, ED is associated with a 1.5-fold increased risk of experiencing a cardiovascular event and a 1.6-fold increased risk of coronary artery disease[5]. Men presenting with ED should be evaluated for cardiovascular risk factors, even in the absence of overt symptoms of CVD[5]. This proactive approach can lead to the identification of subclinical disease and facilitate early intervention. Lifestyle modifications and pharmacotherapy aimed at mitigating cardiovascular risk and addressing endothelial dysfunction can improve both erectile function and overall vascular health.

Figure 1. ED & CVD Shared Risk Factors

An Intimate connection: A common pathophysiology

Endothelial dysfunction is a systemic disorder characterized by an imbalance between vasodilating and vasoconstricting substances produced by or acting on the

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endothelium[2]. Nitric oxide (NO), synthesized by endothelial nitric oxide synthase (eNOS), is a crucial vasodilator that maintains vascular tone and inhibits platelet aggregation and smooth muscle proliferation. Reduced NO bioavailability, due to decreased production or increased degradation by reactive oxygen species, leads to impaired endothelium-dependent vasodilation[6].

In erectile physiology, NO plays a pivotal role in initiating and maintaining erections by relaxing the smooth muscle of the corpus cavernosum and dilating penile arteries[7]. Endothelial dysfunction impairs this mechanism, leading to ED. This impairment is not confined to the penile vasculature but reflects a generalized vascular disorder affecting multiple arterial beds, including coronary, cerebral, and peripheral arteries[8].

Several risk factors contribute to both endothelial dysfunction and the development of ED and CVD. Hypertension exerts mechanical stress on the endothelium, promoting vascular remodeling and stiffness, and impairing endothelial function by reducing NO availability and increasing oxidative stress. These changes contribute to the pathophysiology of both ED and CVD by decreasing vascular compliance, promoting atherosclerosis, and impairing the vasodilatory response needed for normal erectile function and coronary blood flow.

Diabetes mellitus leads to chronic hyperglycemia, which causes endothelial damage and reduced eNOS expression. Diabetic neuropathy further exacerbates ED by impairing the neural pathways essential for erection[9]. Obesity and metabolic syndrome also play critical roles. Excess adipose tissue secretes pro-inflammatory cytokines that impair endothelial function, and insulin resistance associated with metabolic syndrome further reduces NO production. These metabolic disturbances contribute to both ED and CVD by accelerating atherosclerotic processes and endothelial dysfunction.

Dyslipidemia contributes to the formation of atherosclerotic plaques. Oxidized low-density lipoprotein (LDL) cholesterol induces endothelial dysfunction by promoting inflammation and oxidative stress. Treatments for dyslipidemia, such as statins, can help mitigate endothelial dysfunction by reducing LDL levels and improving vascular health. Moreover, smoking is another significant risk factor for both ED and CVD due to its detrimental effects on vascular health, including reduced NO availability and increased endothelial permeability.

The underlying endothelial dysfunction shared by ED and CVD is further highlighted by the hypoxic episodes of obstructive sleep apnea (OSA). These episodes further increase oxidative stress and promote systemic inflammation, damaging endothelial cells and reducing NO bioavailability. OSA also activates the sympathetic nervous system, causing vasoconstriction and hypertension. The endothelial dysfunction resulting from OSA affects the penile vasculature, contributing to ED, and increases the risk of CVD. Addressing OSA through interventions like continuous positive airway pressure (CPAP) therapy can improve endothelial function and reduce cardiovascular risk[10].

Understanding the common pathophysiological mechanisms underlying ED and CVD underscores the importance of endothelial dysfunction as a unifying factor. The interplay between reduced nitric oxide bioavailability, oxidative stress, and inflammation contributes to vascular impairment across multiple arterial beds. Recognizing that conditions such as hypertension, diabetes mellitus, obesity, dyslipidemia, smoking, and sleep apnea adversely affect endothelial function highlights the need for a comprehensive approach to patient care. By addressing these shared risk factors and their impact on endothelial health, clinicians can not only improve erectile function but also mitigate the progression of cardiovascular disease.

Diagnostic evaluation

Endothelial dysfunction is the earliest detectable stage of cardiovascular disease (CVD) and represents a critical window for intervention. Unlike atherosclerotic plaques, endothelial dysfunction is reversible with appropriate lifestyle and pharmacological interventions. Early detection and treatment of endothelial dysfunction can prevent progression to more advanced cardiovascular pathology, making early testing essential.

In some patients, erectile dysfunction (ED) may be the first and sole clinical manifestation of subclinical coronary artery disease (CAD). For these individuals, ED serves as an early indicator of potential vascular abnormalities, warranting a comprehensive cardiovascular evaluation even in the absence of other symptoms. While for patients without established CVD or diabetes, cardiovascular evaluation should focus on assessing exercise capacity and identifying potential risks associated with sexual activity. Stress testing is recommended in men with ED who have multiple cardiovascular risk factors or reduced exercise ability. Evaluating exercise tolerance helps stratify the risk of cardiovascular events during sexual activity, which is an exertional activity comparable to moderate physical exercise. Men who can perform exercise of modest intensity without symptoms are typically considered to be at low risk for cardiovascular events during sexual activity[12].

In patients with established CVD or diabetes, additional testing may be warranted to evaluate cardiovascular stability before initiating or resuming sexual activity. Stress testing and imaging studies can help determine the patient's exercise tolerance and identify any underlying ischemia that could pose a risk during sexual activity. Coronary artery calcium scoring may also be considered in men at intermediate cardiovascular risk to further guide management decisions. This imaging technique is particularly useful for reclassifying risk in individuals with ambiguous risk profiles, providing a more precise evaluation of coronary plaque burden[13]. Calcium scoring helps identify patients who might benefit from more intensive preventive interventions, including lifestyle modifications and pharmacotherapy. It serves as a useful tool for determining the need for additional testing or more aggressive treatment, thereby optimizing patient outcomes. Further advanced imaging techniques, such as coronary computed tomography angiography (CCTA), can be utilized in the detection of subclinical atherosclerosis in men with ED[14].

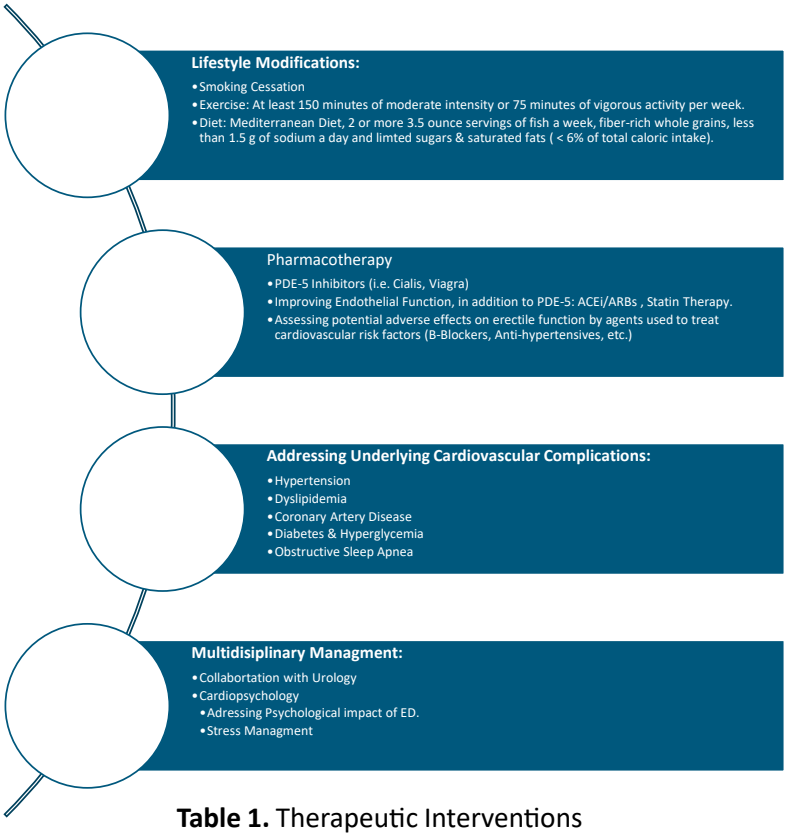

Table 1. Therapeutic Interventions

Cardiac evaluation in asymptomatic individuals, particularly those presenting with ED, can benefit from the use of biomarkers and endothelial function testing. Biomarkers such as high-sensitivity C-reactive protein provide insight into systemic inflammation, which is closely linked to endothelial health. Definitive endothelial function testing in the catheterization lab involves the use of intracoronary acetylcholine to assess endothelium-dependent vasodilation. This method provides a direct and detailed assessment of coronary endothelial function. It is particularly useful in evaluating patients with suspected coronary endothelial dysfunction and provides critical information about coronary vascular health. However, non-invasive testing, such as flow-mediated dilation of the brachial artery and reactive hyperemia, offers valuable insights into systemic endothelial health without the need for invasive procedures. Reactive hyperemia, in particular, measures the ability of blood vessels to dilate following a temporary occlusion, providing an important non-invasive measure of endothelial responsiveness. These tests are highly relevant for patients with ED, as they can help assess the degree of vascular impairment and predict future cardiovascular risk.

Therapeutic interventions

Addressing endothelial dysfunction can improve both erectile and cardiovascular health. Recent studies have demonstrated improvements in endothelial health and a reduction in ED symptoms with the adoption of certain lifestyle changes, including regular physical activity, weight loss, smoking cessation, and a diet rich in antioxidants and omega-3 fatty acids, which have been shown to enhance endothelial function[15]. Exercise is a crucial component of lifestyle modification, with recommendations of at least 150 minutes per week of moderate-intensity activity or 75 minutes of vigorous activity. The Mediterranean diet, which emphasizes fruits, vegetables, whole grains, and healthy fats, has been shown to reduce the risk of cardiovascular events by 30% and is recommended for individuals with ED and increased cardiovascular risk[15].

Pharmacological treatments targeting endothelial dysfunction include phosphodiesterase type 5 inhibitors (PDE5i), statins, ACE inhibitors, and angiotensin receptor blockers. PDE5i not only improve erectile function but also exhibit beneficial effects on endothelial function and cardiovascular outcomes[17]. It is essential to manage underlying cardiovascular conditions such as hypertension, diabetes, and dyslipidemia in collaboration with cardiologists, as these conditions significantly contribute to both ED and CVD.

Supplementation with L-arginine has been shown to improve endothelial function and alleviate symptoms of ED by enhancing NO production and promoting vasodilation[18]. However, L-arginine supplementation often undergoes extensive pre-systemic metabolism, which limits its effectiveness. This highlights the role of L-citrulline supplementation, which is better absorbed and subsequently converted to L-arginine in the body, resulting in a more sustained elevation of L-arginine levels and nitric oxide production[19].

Testosterone replacement therapy may be considered for men with low testosterone levels, and recent studies suggest it may improve some cardiovascular risk factors such as insulin sensitivity, lipid profiles, and body composition, though it has not shown a substantial reduction in overall CVD incidence[20]. A recent meta-analysis indicated that testosterone therapy improved erectile function and quality of life in hypogonadal men without

significantly increasing cardiovascular risk when appropriately monitored[21].

Medications affecting the cardiovascular system, such as beta-blockers and certain antihypertensives, should be reconciled for their impact on erectile function, with the goal of optimizing cardiovascular treatment while minimizing negative effects on sexual health. Ultimately, a combination of lifestyle modifications, pharmacological treatments, and supplementation can effectively target endothelial dysfunction, potentially not only improving erectile function, but also curtailing future cardiovascular risk.

Conclusion | Emerging therapies & future directions

Erectile dysfunction serves as a critical window into a patient's vascular health, signaling potential underlying endothelial dysfunction and future cardiovascular disease. Early recognition and comprehensive management of ED not only enhance sexual function, but also provide an opportunity to improve cardiovascular outcomes. Therefore, clinicians should prioritize cardiovascular evaluations in patients presenting with ED to implement timely interventions that enhance both quality of life and long-term health.

Educating patients about the link between ED and cardiovascular health is essential. By raising awareness, patients are empowered to seek medical advice promptly, leading to early detection of potential cardiovascular risks. Discussing the vascular implications of ED during consultations can motivate patients to adopt healthier lifestyles and adhere to treatment plans aimed at improving endothelial function.

Advancements in regenerative medicine offer new avenues for treating endothelial dysfunction. Research into endothelial progenitor cell therapy and gene therapy targeting eNOS shows promise in restoring endothelial function[22]. However, these therapies face challenges, such as the difficulty of efficient cell delivery, potential immune reactions, and the need for long-term safety and efficacy studies before they can be widely adopted in clinical practice. Novel pharmacological agents, such as Rho-kinase inhibitors and anti-inflammatory therapies, are also being explored to address the underlying mechanisms of endothelial dysfunction[23]. Further studies are needed to evaluate the long-term efficacy and safety of these treatments.

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Sažetak

Endotelna disfunkcija: Skrivena veza između erektilne disfunkcije i kardiovaskularnih bolesti

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Erektilna disfunkcija (ED), koja se često smatra problemom kvaliteta života za sredovečne i starije muškarce, sve se više prepoznaje kao prediktor aterosklerotske kardiovaskularne bolesti (KVB), posebno kod mlađih muškaraca. Endotelna disfunkcija može biti rani marker vaskularne erektilne disfunkcije. Ovaj članak istražuje patofiziološke mehanizme koji povezuju endotelnu disfunkciju, ED i KVB. Pregledom trenutnih istraživanja, naglašavamo značaj ED kao prediktora kardiovaskularnih događaja i razmatramo pristupe za rano otkrivanje i intervenciju za poboljšanje kardiovaskularnog zdravlja.

Ključne reči: *erektilna disfunkcija, koronarna arterijska bolest, endotelna disfunkcija, kardiovaskularni događaji*