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# Mechanisms of dyslipidemia-induced erectile dysfunction: a narrative review

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**Background:** Dyslipidemia is strongly associated with obesity, metabolic syndrome, and atherosclerosis, and is increasingly recognized as an independent risk factor for erectile dysfunction (ED). Emerging evidence suggests lipid-specific mechanisms that may directly impair erectile function, beyond the effects of obesity.
**Objective:** To summarize the pathophysiological mechanisms linking dyslipidemia to the development and progression of ED.
**Methods:** A narrative review of studies published between 2000 and 2025 was conducted using PubMed, Web of Science, Scopus, and Google Scholar, including experimental, clinical, observational, and review studies.
**Results and conclusion:** Dyslipidemia contributes to ED through multiple interconnected pathways, including vascular dysfunction, neural impairment, oxidative stress, inflammation, and endocrine alterations. These mechanisms may increase susceptibility to ED in affected patients. However, direct evidence remains limited, and confounding by coexisting metabolic, cardiovascular and neural conditions complicates interpretation. Further research is needed to clarify the independent effects of dyslipidemia and to identify potential therapeutic strategies.

KEYWORDS
**cholesterol, dyslipidemia, endocrine, erectile dysfunction, mechanism, vascular**

## 1 Introduction

Dyslipidemia refers to a pathological state where the concentration of one or more lipid components in serum falls outside the upper and lower limits of the normal reference range, and it is recognized as one of leading but modifiable risk factors for the development of atherosclerotic cardiovascular disease (ASCVD) and endothelial dysfunction (1). Its core features are abnormally elevated levels of serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG), as well as pathologically reduced high-density lipoprotein cholesterol (HDL-C), a combination frequently seen in clinical settings (2). Clinically, this metabolic disorder is mainly classified into four standardized phenotypes: isolated hypercholesterolemia (elevated serum TC and/or LDL-C), isolated hypertriglyceridemia (markedly elevated serum TG), mixed dyslipidemia (concurrently elevated serum TC/LDL-C and TG), and isolated hypoalphalipoproteinemia (isolated reduction in serum HDL-C) (3). Due to its high prevalence, it represents a substantial

burden to health systems and the economy worldwide. According to a World Health Organization (WHO) estimate, the global prevalence of raised plasma total cholesterol levels among adults aged ≥25 years was approximately 39% in 2008 (2). Furthermore, a 2025 global systematic review and meta-analysis estimated the global prevalence of hypercholesterolemia, hypertriglyceridemia, low HDL-C, and high LDL-C at 24.1%, 28.8%, 38.4%, and 18.93%, respectively, with marked regional variation (4). Driven by adverse global shifts in lifestyle and dietary structure, both the prevalence and incidence of dyslipidemia are increasing annually, particularly among younger populations (5).

Erectile dysfunction (ED) is defined as the persistent or recurrent inability to achieve and maintain a sufficient penile erection to complete satisfactory sexual intercourse (6). It is a growing male health problem worldwide (7). Epidemiological studies show that the overall prevalence of ED in men over 40 is approximately 20%-40% (8), increasing significantly with age, reaching up to 50% by age 70 (9). Notably, ED is no longer considered merely a condition of the elderly, as its incidence in younger populations is also rising, closely related to metabolic disorders caused by modern lifestyles (10). Among these metabolic conditions, dyslipidemia has emerged as a particularly important factor.

Many studies indicate a significant correlation between dyslipidemia and ED (11). Although dyslipidemia frequently coexists with obesity and metabolic syndrome, research suggests the existence of lipid-specific mechanisms that may directly impair penile vascular and neural function (11). Population-based analyses have also reported associations between dyslipidemia-related metabolic indices and ED (12, 13). Therefore, this review aims to outline the multi-mechanism theoretical framework of dyslipidemia-associated ED (Figure 1).

## 2 Methods

The research strategy followed in producing this article is that of a narrative review, which was used to gather and synthesize evidence on dyslipidemia-induced ED. We searched PubMed, Web of Science, Scopus, and Google Scholar for English-language publications from 2000 until December 2025, using keywords related to dyslipidemia ("dyslipidemia", "hyperlipidemia", "hypercholesterolemia", "hypertriglyceridemia", "low HDL", "hypoalphalipoproteinemia") combined with terms for ED ("erectile dysfunction", "impotence", "erection mechanisms").

In contrast to a systematic review, the study selection for this narrative review was not exhaustive but prioritized based on relevance, novelty, and mechanistic insight. Articles of experimental studies, clinical observational studies, meta-analyses, and high-quality narrative or systematic reviews were first selected. Case reports and studies without mechanistic relevance were generally excluded.

Focusing on studies that explore the dyslipidemia-ED association, we critically appraised and synthesized the selected literature to construct a cohesive conceptual framework. Rather than conducting a formal meta-analysis, we thematically organized the evidence into four key pathogenic domains: Vascular Injury, Endocrine Disturbances, Neurological Mechanisms, and the Interplay of Chronic Inflammation and Oxidative Stress. This integrative process followed academic standards to ensure a logical and structured evidence presentation.

Notably, this narrative review provides a comprehensive overview of possible biologically plausible mechanisms potentially linking dyslipidemia to ED, rather than focusing exclusively on studies with direct causal evidence obtained from ED-specific experimental or clinical research. The included evidence integrates findings from both systemic and ED-specific studies to develop a theoretical framework of potential pathogenic mechanisms.

## 3 Physiological basis of normal erection

Penile erection is a complex neurovascular event dependent on precisely regulated hemodynamic changes and molecular signaling (14). The erection process can be divided into three phases: initiation, tumescence, and maintenance (15),each involving unique physiological mechanisms (Figure 2). Erection initiation begins with sexual stimuli (visual, tactile, or imaginative) transmitted via afferent nerves to the spinal cord and related brain regions, followed by efferent signals from the autonomic nervous system (primarily parasympathetic). These nerve signals promote dilation of the penile cavernous arteries, a sharp increase in blood flow, and relaxation of the trabecular smooth muscle and dilatation of the sinusoids. As the intracavernous pressure rises, the subtunical venous plexus is compressed, forming a venous occlusion mechanism that traps blood within the penis, ultimately resulting in a rigid erection (16).

At the molecular level, the nitric oxide (NO)-cyclic guanosine monophosphate (cGMP) signaling pathway is the core mechanism mediating erection (17, 18). Nitric oxide (NO) plays a key role in regulating vasodilation, arterial blood pressure and penile erection. Endothelial nitric oxide synthase (eNOS) is the key enzyme for NO production, and its activity is regulated by various factors, including blood flow shear stress, hormone levels, and oxidative stress status (19, 20). Furthermore, substances such as L-arginine and L-citrulline can increase NO production, supporting sexual function and vascular health (21). Nerve impulses promote the release of NO from endothelial cells. NO activates guanylate cyclase, increasing intracellular cGMP levels, leading to relaxation of cavernous smooth muscle, thereby increasing penile blood flow and achieving erection.

## 4 Vascular injury mechanisms

### 4.1 Endothelial dysfunction

Endothelial dysfunction is the possible primary trigger in dyslipidemia-induced impairment of erectile function. Indeed,

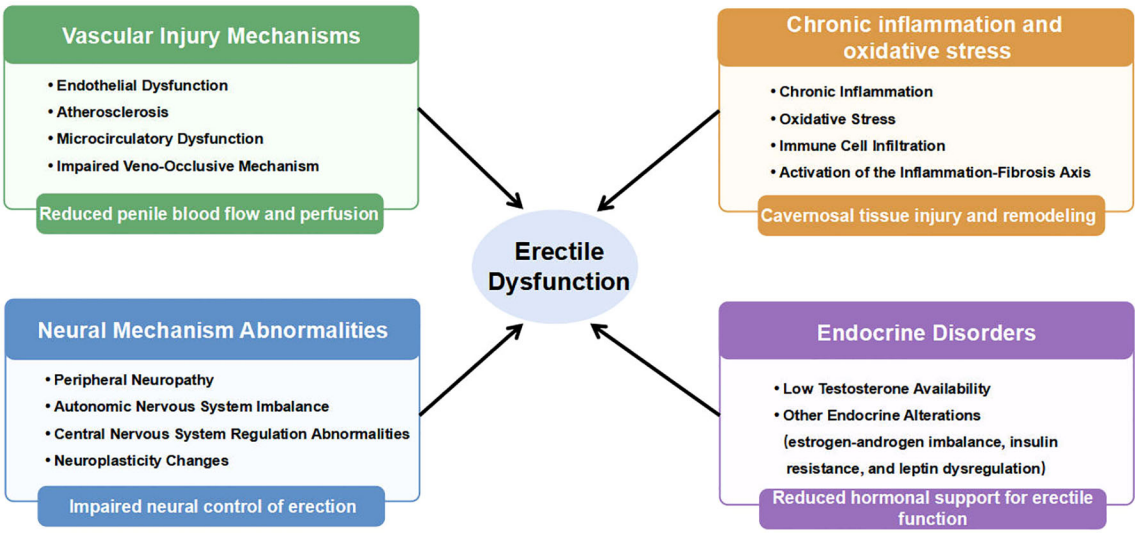



FIGURE 1
Potential mechanisms linking dyslipidemia to ED. A conceptual overview of the major mechanistic domains discussed in this review.

dyslipidemia can lead to impaired penile endothelial function, thereby affecting erection, through multiple mechanisms: oxidation of low-density lipoprotein (LDL) leading to stimulation of endothelial cells to release endothelin and reactive oxygen species (ROS), which further reduce NO bioavailability (22); increase of oxidative stress in endothelial cells, leading to inactivation of eNOS, thereby reducing NO production (23). Additionally, postprandial dyslipidemia also impairs endothelial function. High-fat diet-induced obese rats showed reduced endothelium-dependent relaxation of penile arteries in response to acetylcholine and the mitochondrial ATP-sensitive potassium channel activator BMS191095, indicating impaired endothelial function and a decreased ability of endothelial cells to synthesize and release nitric oxide (NO), thus reducing NO bioavailability (24, 25).

In a study of 40 premenopausal women and 40 age- and BMI-matched men (26), the number and activity of circulating endothelial progenitor cells (EPCs-bone marrow-derived cells involved in vascular repair and endothelial homeostasis) and NO levels in plasma or

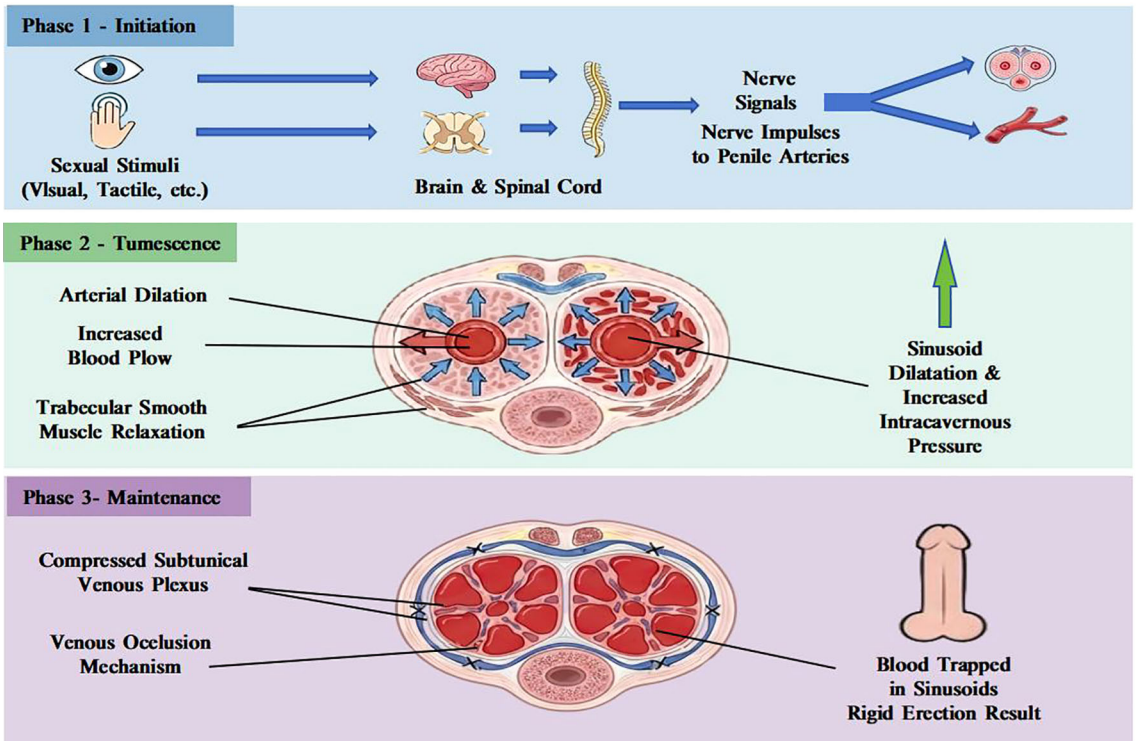



FIGURE 2
Normal erectile physiological mechanism.

culture medium were significantly reduced in dyslipidemic men. In contrast, EPC number and activity, as well as NO production, were preserved in premenopausal hypertriglyceridemic women (26). These findings suggest a role for sex differences in hypertriglyceridemia-associated vascular injury, which may impair erectile function via the nitric oxide-cyclic guanosine monophosphate (NO-cGMP) signaling pathway. Furthermore, these changes can reduce vasodilatory capacity, thereby affecting normal blood flow regulation and erectile function (27).In a prospective randomized trial, 10 subjects treated for 4 weeks with ezetimibe -a selective cholesterol absorption inhibitor that blocks intestinal cholesterol uptake by targeting the Niemann-Pick C1-like 1 (NPC1L1) transporter-showed significant attenuation of postprandial elevations in triglycerides, remnant lipoprotein cholesterol, and apolipoprotein B-48 levels, along with improvement in postprandial endothelial function, as assessed by brachial artery flow-mediated dilation (28).

## 4.2 Atherosclerosis

Dyslipidemia, particularly LDL-C elevation, causes lipid deposition in the arterial wall, triggering plaque formation (29). Studies showed that the LDL/HDL ratio is negatively correlated with the peak systolic velocity (PSV) of the cavernous artery, while HDL-C is positively correlated with PSV (30). In patients with dyslipidemia, this leads to hemodynamic changes in the penile arteries, shown by ultrasound as a significant decrease in cavernous artery PSV and an increase in resistance index (RI), reflecting arterial inflow dysfunction, thereby affecting erectile function (31). Pathological studies further confirmed that in dyslipidemia animal models, the number of small arteries in penile tissue decreases, the vascular wall thickens, and the lumen narrows (32). In men with coronary artery disease (CAD), the incidence of ED is higher, and the severity of CAD is associated with an increased risk of ED. In a study of 316 CAD patients, about 55.1% had ED. Multivariate analysis showed that CAD severity was an independent risk factor for ED (OR = 4.11, 95% CI = 1.69 - 9.97). The greater the number of affected coronary arteries and the degree of stenosis, the higher the risk of ED (OR = 3.74, 95% CI = 1.72 - 8.09). Age (OR = 1.23, 95% CI = 1.18 - 1.29) and BMI (OR = 1.26, 95% CI = 1.13 - 1.41) were also independent predictors of ED (33).

The penile cavernous arteries are small in diameter (about 0.3-0.5 mm) and particularly susceptible to atherosclerosis. Therefore, based on the association between atherosclerosis and ED, researchers have also proposed that ED can be an early marker of systemic atherosclerosis (34).

## 4.3 Microcirculatory dysfunction

The penile corpus cavernosum is rich in a microvascular network, the integrity of which is crucial for maintaining erectile function. Hypercholesterolemia, an important component of dyslipidemia, can lead to decreased capillary density, reduced expression of vascular endothelial growth factor (VEGF), and abnormal vascular remodeling (35). Concurrently, downregulation of angiogenic factors and their downstream signaling molecules can further exacerbate ED (36). Compared to normal rats, diabetic dyslipidemic rats showed a 37% reduction in microvascular branches and a 19% reduction in microvascular length density (37). Studies have also found that Angiopoietin-1 (Ang1), an angiogenic growth factor, can promote the generation of stable and functional vasculature and rescue erectile function in hypercholesterolemic mice (38).

## 4.4 Impaired veno-occlusive mechanism

During erection, venous occlusion allows blood to accumulate within the corpus cavernosum, a process essential for maintaining penile rigidity. Dyslipidemia may impair veno-occlusive function through both direct structural remodeling of the corpus cavernosum and indirect hemodynamic effects (39–41). On the one hand, dyslipidemia promotes atherosclerosis, reducing penile arterial inflow; the resulting arterial insufficiency may prevent an adequate rise in intracavernosal pressure (41, 42). In addition, chronic arterial insufficiency can induce cavernosal hypoxia and ischemia, which promote progressive tissue remodeling and ultimately impair veno-occlusive function (41).Experimental evidence from hypercholesterolemic rabbit models has demonstrated endothelial and smooth muscle dysfunction in the corpus cavernosum, along with ultrastructural abnormalities in smooth muscle cells, elastic fibers, and collagen, indicating disruption of the structural basis required for effective venous occlusion (39). Long-term hypercholesterolemia has also been shown to cause chronic cavernosal tissue injury that may be only partially reversible after lipid normalization (40).

On the other hand, direct clinical evidence linking dyslipidemia to venogenic ED remains limited. However, interventional studies support the central role of the veno-occlusive mechanism in maintaining erectile function. In patients with mixed arteriovenous ED who did not benefit from arterial revascularization alone, additional venous leak embolization significantly improved outcomes. Only 11.5% (3/26) of patients achieved the primary feasibility endpoint (an increase in IIEF-5 score ≥ 4 points) 6 weeks after arterial revascularization alone, whereas this proportion increased to 65.4% (17/26) following additional venous leak embolization (43). Furthermore, in a cohort of 50 patients with severe ED secondary to venous leakage treated with venous embolization, 68% (34/50) reached the primary feasibility endpoint at 6-week follow-up, further confirming the importance of the veno-occlusive mechanism in erectile function (44).Taken together, these findings underscore the importance of intact veno-occlusive function in maintaining penile rigidity, although they do not establish dyslipidemia as a direct cause of venous leakage. Nevertheless, impaired veno-occlusive function may contribute to reduced erection hardness and shorter erection duration in patients with dyslipidemia-associated ED.

# 5 Chronic inflammation and oxidative stress

Dyslipidemia contributes to the pathogenesis of ED through a deeply integrated pathway of chronic inflammation and oxidative

stress (45, 46). The process begins with the oxidation of elevated LDL to form oxidized LDL (ox-LDL) (47). Acting as a damage-associated molecular pattern, ox-LDL not only triggers an innate immune response but also stimulates excessive production of reactive oxygen species (ROS), creating a pathogenic feed-forward loop (48). This interplay critically undermines vascular endothelial function and reduces NO bioavailability. As the pathology advances, immune cell infiltration and the activation of the inflammation-fibrosis axis drive irreversible structural fibrotic remodeling of the corpus cavernosum (46).

## 5.1 Chronic inflammation

Low-grade chronic inflammation is one of the possible underlying mechanisms by which dyslipidemia induces ED (49). Studies indicated that inflammation is closely related to ED. In a study of US adults, the Dietary Inflammatory Index (DII) was positively correlated with ED. After adjusting for age, race, education level, and other factors, the odds ratio for the association between DII score and ED was 1.12, indicating a link between the inflammatory potential of diet and ED (50). Another study found that systemic inflammation indicators such as the multi-inflammatory index 1 (MII-1) and MII-2 were significantly higher in the ED group than in the non-ED group and were negatively correlated with the International Index of Erectile Function (IIEF) (51).

In an asthma model in rats, inflammatory factors damaged vascular endothelial cells, leading to ED. Treatment with the traditional Chinese medicine Xuefu Zhuyu Decoction (XFZYD) could inhibit inflammation, increase the number of penile erections, and improve erectile function, while reducing the expression levels of inflammatory factors such as interleukin-6 (IL-6), vascular endothelial growth factor A (VEGFA), and tumor necrosis factor (TNF) in penile tissue. This indicates that chronic inflammation primarily affects erectile function by damaging vascular endothelial cells, and inhibiting inflammation can improve this condition (52).

## 5.2 Oxidative stress

Oxidative stress is an important possible mechanism in dyslipidemia-induced ED. Under normal physiological conditions, the body's oxidation and antioxidant systems remain balanced. However, dyslipidemia can lead to increased oxidative stress, producing excessive ROS that damage penile tissue. Studies showed that in dyslipidemic rat models, ROS levels in penile cavernous tissue are elevated (53).

Oxidative stress can affect erectile function through multiple pathways. On one hand, ROS can damage vascular endothelial cells, causing endothelial dysfunction and reducing the production and release of NO. In studies on diabetic ED rats, oxidative stress led to decreased expression of eNOS in penile cavernous tissue and reduced NO production. Administration of the antioxidant hesperidin activated the Nrf2-HO-1/GPX4 axis, inhibited oxidative stress and ferroptosis, and improved erectile function (54). Furthermore, oxidative stress can induce apoptosis of penile cavernous smooth muscle cells or sympathetic overactivity and downregulation of soluble guanylate cyclase (55, 56), disrupting the tissue structure and function related to erection.

## 5.3 Immune cell infiltration

Immune cell infiltration is involved in dyslipidemia-related ED. Dyslipidemia is associated with monocyte/macrophage infiltration and activation in penile tissue, which may enhance local inflammatory injury through the release of pro-inflammatory mediators and downstream effectors, including matrix metalloproteinases (MMPs) (57). MMPs may further promote cavernosal remodeling by disturbing extracellular matrix turnover (58). Macrophages may acquire a pro-inflammatory M1 phenotype, which amplifies local inflammatory responses (59) and promotes endothelial dysfunction and impaired penile perfusion.

Experimental studies have shown that macrophage-specific TLR9 signaling is associated with cavernosal dysfunction in high-fat diet-fed C57BL/6 mice (60). In addition, high-fat diet-induced ED models have shown activation of the IL-18/NLRP3/caspase-1 pathway together with reduced eNOS expression (61). Hypercholesterolemic ApoE−/− mice fed a Western diet also showed corpus cavernosum remodeling accompanied by altered MMP-related structural changes (58). Overall, these findings suggest that dyslipidemia-associated monocyte/macrophage infiltration and inflammatory activation may participate in the progression of ED.

## 5.4 Activation of the inflammation-fibrosis axis

Activation of the inflammation-fibrosis axis leads to irreversible structural changes in the corpus cavernosum (62). Mendelian randomization studies have suggested that dyslipidemia is associated with an elevated risk of ED, in which inflammatory mediators serve as a critical contributor (63). In the corpus cavernosum, dyslipidemia activates two synergistic inflammatory pathways. First, oxidized low-density lipoprotein (ox-LDL) induces oxidative stress and activates the nuclear factor-κB (NF-κB) signaling pathway (48, 64, 65), leading to endothelial dysfunction and promoting macrophage-mediated inflammatory changes in cavernosal tissue (60); Second, lipid overload activates the NLRP3 inflammasome and maintains a state of meta-inflammation (61).

Persistent inflammatory stimuli activate fibroblasts and myofibroblasts, resulting in excessive extracellular matrix deposition (58). The inflammatory cytokine IL-17A reprograms corpus cavernosum smooth muscle cells (CCSMCs) via the mTORC2–ACACA pathway, enhancing lipid synthesis and the secretion of fibromatrix proteins (66); transforming growth factor-β (TGF-β) drives the differentiation of fibroblasts into myofibroblasts and promotes collagen production (66); tumor necrosis factor-α (TNF-α) amplifies TGF-β signaling and facilitates CCSMC apoptosis (67). The consequent collagen accumulation impairs CCSMC compliance and disrupts veno-occlusive function, thereby leading to refractory ED (68, 69). Collectively, these findings indicate that the inflammation–fibrosis axis represents a central driver in the

pathogenesis of dyslipidemia-induced ED and a promising therapeutic target (70, 71).

# 6 Neural mechanism abnormalities

## 6.1 Peripheral neuropathy

Dyslipidemia may cause various forms of damage to the peripheral nervous system, including direct axonal injury, myelin loss, and progressive conduction deficits (72, 73). Elevated LDL-C, particularly its oxidized form (oxLDL), may promote oxidative stress and inflammation in neurons and Schwann cells (74). In addition, oxidized lipids may contribute to myelin abnormalities and impaired nerve function (72, 73). Elevated triglyceride (TG) levels may alter membrane lipid composition and lipid raft organization, thereby impairing neuronal signal transduction and slowing nerve conduction velocity (73, 75).

The specific mechanisms may involve disorders of neural lipid metabolism and mitochondrial function, which may damage peripheral nerves, slow nerve conduction velocity, and induce nerve fiber damage, thereby potentially contributing to the development of ED (73, 74, 76). However, direct ED-specific evidence linking dyslipidemia to peripheral neuropathy remains limited.

## 6.2 Autonomic nervous system imbalance

Dyslipidemia can contribute to autonomic dysregulation, which may negatively affect erectile function. In healthy young men, acute experimental hyperlipidemia has been shown to reduce baroreflex sensitivity and impair cardiovascular reflexes (77). Clinical evidence also indicates that disordered lipid metabolism is linked to cardiac autonomic dysfunction (78, 79). In patients with recent-onset type 2 diabetes, higher plasma lipid metabolites have been linked to early cardiac autonomic dysfunction (78).

Moreover, hypertriglyceridaemia has been associated with small nerve fibre damage and cardiac autonomic dysfunction even in individuals without diabetes (79). Experimental diet-induced metabolic models similarly demonstrate impaired baroreflex sensitivity (80). Because penile erection depends on parasympathetic-mediated vasodilation and is counteracted by sympathetic activation, dyslipidemia-related autonomic dysregulation may contribute to ED by promoting vasoconstriction and reducing penile perfusion (81).

## 6.3 Central nervous system regulation abnormalities

The hypothalamic preoptic area, limbic system, and cerebral cortex are the primary centers for erection. These regions regulate the spinal erection centers by integrating sensory and emotional inputs. The hypothalamus is especially important for controlling systemic metabolism and reproductive function.

Studies in animal models show that a high-calorie environment activates hypothalamic CD4+ T cells and microglia, promotes macrophage infiltration, and reduces hypothalamic regulatory T cells (Tregs), thereby exacerbating hypothalamic immune activation (82). Dyslipidemia-related metabolic stress, particularly during high-fat feeding, rapidly7 induces hypothalamic inflammation. In rodents, inflammatory signaling emerges within 1–3 days of high-fat diet exposure, followed by reactive gliosis and markers of neuronal injury within the first week; similar mediobasal hypothalamic gliosis has also been documented in humans with obesity (83). Because the medial preoptic area and paraventricular nucleus, together with dopaminergic circuits, are central to sexual behavior and penile erection (84, 85), hypothalamic injury may impair the central integration of sexual stimuli and weaken descending input to the spinal erection centers. Consistently, dopamine release in the medial preoptic area rises before and during copulation, and electrical stimulation of this region elicits intracavernous pressure responses in rats, whereas the paraventricular nucleus is a critical node in erectile control (84–86). Thus, central nervous system dysregulation may represent an important mechanism by which dyslipidemia contributes to erectile dysfunction.

## 6.4 Neuroplasticity changes

Neuroplasticity describes the nervous system's capacity to remodel its structure and function in response to stimuli, including neurogenesis, axonal regeneration, and synaptic remodeling, which is critical for sustaining the neural pathways mediating penile erection. Studies have demonstrated that dyslipidemia may directly disrupt intracavernosal neuroplasticity: it downregulates the intracavernosal expression of nerve growth factor (NGF) and vascular endothelial growth factor (VEGF), two core mediators of neural repair, an effect that impedes neural repair processes and reduces the regenerative capacity of nerve fibers (87–89), thereby impairing erectile-related neural signal transduction and contributing to the onset and progression of ED.

Furthermore, evidence indicates that dyslipidemia is significantly associated with neural aging-related phenotypes and reduced neuroplasticity, which can further impair the function of the cavernous nerve plexus and central erectile regulatory circuits, serving as a potential indirect pathway for dyslipidemia to impair erectile function (90, 91).However, neuroplasticity's specific role in dyslipidemia-associated ED remains to be elucidated and warrants further investigation.

# 7 Endocrine disorders

## 7.1 Low testosterone availability

Numerous clinical studies indicate that dyslipidemia can affect testosterone levels through various pathways: a high-cholesterol diet can induce endoplasmic reticulum stress in the testes, thereby inhibiting the expression of steroidogenic enzymes and leading to decreased testosterone levels (92). Inflammatory factors may also affect testosterone synthesis by inhibiting the function of the hypothalamic-pituitary-gonadal (HPG) axis (93).

Studies have found that oxidized low-density lipoprotein (oxLDL) can inhibit testosterone synthesis in Leydig cells by

affecting mitochondrial function and the p38 MAPK/COX-2 signaling pathway, thereby reducing testosterone availability and leading to ED (94). In a multicenter cross-sectional study of 411 patients (mean age 63.19 years), 91.73% had varying degrees of ED. Total testosterone levels decreased from a median of 7.05 ng/mL in patients with normal erectile function to 3.56 ng/mL in patients with severe symptoms, and free testosterone levels gradually decreased, with the median free testosterone level in all ED groups below the normal lower threshold (95). In addition, studies on ED patients found that parameters in the testosterone-deficient group, such as the number of nocturnal erections per night, average event rigidity, erection duration, and percentage of erection exceeding baseline in the nocturnal penile tumescence and rigidity (NPTR) test, were significantly lower than those in the normal testosterone group (96).

Dyslipidemia may also contribute to testosterone deficiency through modulation of the gut microbiota, particularly via enrichment of testosterone-degrading species (97). In male patients with dyslipidemia, the relative abundance of Pseudomonas nitroreducens, a Gram-negative intestinal commensal capable of metabolizing testosterone, is significantly higher than in controls (98). This bacterium expresses the 3/17β-hydroxysteroid dehydrogenase (3/17β-HSD) gene, which encodes a key enzyme involved in testosterone catabolism. Specifically, 3/17β-HSD catalyzes the oxidation of hydroxyl groups in the testosterone molecule, converting biologically active testosterone into inactive androgen metabolites, thereby reducing circulating testosterone levels (98, 99). The presence of this gene has been associated with both testosterone degradation and dyslipidemia, suggesting that intestinal testosterone-degrading bacteria may contribute to the pathogenesis of dyslipidemia-associated ED through reduced testosterone availability (97, 99). However, whether this microbial alteration is attributable to dyslipidemia itself or to coexisting obesity-related metabolic disturbances remains uncertain, and the independent contribution of dyslipidemia requires further clarification.

### 7.2 Other endocrine alterations

Other endocrine and metabolic alterations, including estrogen-androgen imbalance, insulin resistance, and leptin dysregulation, may coexist in patients with dyslipidemia. However, current evidence does not establish a direct causal link between these changes and dyslipidemia itself, as they are more commonly associated with obesity and related metabolic disturbances. Therefore, these mechanisms should be interpreted cautiously, and their contribution to dyslipidemia-associated ED remains uncertain.

## 8 Interaction among mechanisms

Dyslipidemia-induced ED arises not from isolated pathogenic mechanisms but from an integrated network of vascular, endocrine, neural, and immunometabolic disturbances that mutually reinforce one another (100). Central to this network is endothelial injury, which arises from the accumulation of circulating lipids, particularly low-density lipoprotein cholesterol and triglycerides (101). As lipid deposition progresses, localized oxidative stress and inflammation intensify, resulting in the depletion of nitric oxide and a consequent impairment of endothelium-dependent vasodilation (64, 100, 102, 103). This initial endothelial dysfunction serves as a pathogenic trigger, from which downstream disruptions across vascular, neural, endocrine, and immune systems subsequently ensue.

Unmitigated oxidative and inflammatory stress eventually forces structural remodeling of the corpus cavernosum. This environment promotes fibroblast activation and extracellular matrix deposition, culminating in progressive fibrosis (63, 104). Because these structural shifts reduce smooth muscle compliance, the veno-occlusive mechanism becomes mechanically compromised (105). Concurrent endocrine and neural dysregulation only compound this vascular decline. Therefore, the pathogenesis of dyslipidemia-associated ED involves numerous overlapping mechanisms.

## 9 Limitations

This review has some limitations. Most of the available evidence is indirect and based on systemic vascular, inflammatory, endocrine, and neural changes rather than studies directly performed in erectile ED. These mechanisms may help explain the association between dyslipidemia and ED, but they are not established causes. In humans, dyslipidemia frequently co-occurs with obesity, insulin resistance, hyperglycemia, and chronic inflammation, making it difficult to isolate its effects. Animal models also do not fully replicate human dyslipidemia, particularly regarding low HDL-C. Therefore, there is a clear need for ED studies that specifically address low HDL-C and distinguish the effects of lipids from other metabolic factors.

## 10 Conclusion and future perspectives

In summary, dyslipidemia may affect the male reproductive system through multiple interrelated mechanisms, including vascular injury, chronic inflammation, oxidative stress, neural dysregulation, and endocrine alterations, all of which can contribute to the development and progression of ED. Although the link between dyslipidemia and ED is increasingly recognized, understanding remains limited due to the complexity of its pathogenesis and the scarcity of direct, ED-specific evidence.

Future research should focus on several key directions. First, ED-specific preclinical and clinical studies are urgently needed to provide direct causal evidence and systematically elucidate the molecular mechanisms of dyslipidemia-induced ED. Particular emphasis should be placed on endothelial dysfunction-related signaling pathways, the impact of dyslipidemia on testosterone biosynthesis, regulation of cavernous nerve plasticity, and

inflammation-driven fibrotic remodeling of the corpus cavernosum. These studies should also carefully distinguish the independent effects of dyslipidemia from confounding metabolic factors, including obesity, insulin resistance, hyperglycemia, and chronic low-grade inflammation, and clarify the specific role of low HDL-C in ED pathogenesis.

Second, mechanism-targeted therapeutic strategies should be systematically explored and validated using robust ED-specific experimental data. Additionally, integrating multimodal clinical data-such as lipid profiles, hormonal status, vascular imaging, and lifestyle factors-into machine learning-based risk prediction models may enable early identification of high-risk individuals and facilitate preemptive interventions. Such approaches hold substantial promise for improving quality of life and advancing lifelong health management.

## Author contributions

DL: Writing – original draft. DS: Writing – original draft. EC: Writing – review & editing. L-PP: Investigation, Writing – review & editing. SW: Investigation, Writing – review & editing. JG: Funding acquisition, Supervision, Writing – review & editing. HW: Writing – review & editing, Supervision. JZ: Funding acquisition, Supervision, Writing – review & editing.

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## Conflict of interest

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## References

1. Du Z, Qin Y. Dyslipidemia and cardiovascular disease: current knowledge, existing challenges, and new opportunities for management strategies. *J Clin Med*. (2023) 12:363. doi: 10.3390/jcm12010363

2. Pirillo A, Casula M, Olmastroni E, Norata GD, Catapano AL. Global epidemiology of dyslipidaemias. *Nat Rev Cardiol*. (2021) 18:689–700. doi: 10.1038/s41569-021-00541-4

3. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Atherosclerosis*. (2019) 290:140–205. doi: 10.1016/j.atherosclerosis.2019.08.014

4. Ballena-Caicedo J, Zuzunaga-Montoya FE, Loayza-Castro JA, Vásquez-Romero LEM, Tapia-Limonchi R, De Carrillo CIG, et al. Global prevalence of dyslipidemias in the general adult population: a systematic review and meta-analysis. *J Health Popul Nutr*. (2025) 44:308. doi: 10.1186/s41043-025-01054-3

5. Liu LY, Aimaiti X, Zheng YY, Zhi XY, Wang ZL, Yin X, et al. Epidemic trends of dyslipidemia in young adults: a real-world study including more than 20,000 samples. *Lipids Health Dis*. (2023) 22:108. doi: 10.1186/s12944-023-01876-2

6. Mazzilli F. Erectile dysfunction: causes, diagnosis and treatment: an update. *J Clin Med*. (2022) 11:6429. doi: 10.3390/jcm11216429

7. Huang D, Wu H, Huang Y. Novel indicator for erectile dysfunction: the CALLY index, evidence from data of NHANES 2001-2004. *Front Endocrinol Lausanne*. (2025) 16:1527506. doi: 10.3389/fendo.2025.1527506

8. Çayan S, Kendirci M, Yaman Ö, Aşçı R, Orhan İ, Usta MF, et al. Prevalence of erectile dysfunction in men over 40 years of age in Turkey: results from the Turkish Society of Andrology Male Sexual Health Study Group. *Turk J Urol*. (2017) 43:122–9. doi: 10.5152/tud.2017.24886

9. Viigimaa M, Vlachopoulos C, Doumas M, Wolf J, Imprialos K, Terentes-Printzios D, et al. Update of the position paper on arterial hypertension and erectile dysfunction. *J Hypertens*. (2020) 38:1220–34. doi: 10.1097/HJH.0000000000002382

10. Ruiz-García A, Arranz-Martínez E, Cabrera-Vélez R, Palacios-Martínez D, Rivera-Teijido M, García-Álvarez JC, et al. Prevalence of erectile dysfunction in Spanish primary care setting and its association with cardiovascular risk factors and cardiovascular diseases. SIMETAP-ED study. *Clin Investig Arterioscler*. (2019) 31:101–10. doi: 10.1016/j.arteri.2019.01.002

11. Zhu Q, Tan Y, Zou X, Lu L. Association of high LDL concentrations with erectile dysfunction from a Mendelian randomization study. *Sci Rep*. (2023) 13:22252. doi: 10.1038/s41598-023-49771-1

12. Xu N, Zou H, Xu H, Chen Y, Wen Q, Xing X, et al. Association between five novel anthropometric indices and erectile dysfunction in US adults from NHANES database. *Sci Rep*. (2025) 15:1625. doi: 10.1038/s41598-024-80878-1

13. Santi D, Spaggiari G, Simoni M, Granata ARM. Accurate and time-saving, two-step intracavernosal injection procedure to diagnose psychological erectile dysfunction. *Andrology*. (2022) 10:852–62. doi: 10.1111/andr.13175

14. Andreev-Andrievskiy A, Lagereva E, Popova A. Reflex erection in the rat: reciprocal interplay between hemodynamic and somatic events. *BMC Urol*. (2018) 18:36. doi: 10.1186/s12894-018-0352-5

15. Giuliano F, Rampin O. Central control of erection and its pharmacological modification. *Curr Opin Urol*. (2000) 10:629–33. doi: 10.1097/00042307-200011000-00017

16. Torenvlied HJ, Trip E, Olthuis W, Segerink LI, Beck JJH. 'Staying hot': investigating the influence of overnight conditions on the penile skin temperature during male sexual arousal-a novel methodology for nocturnal erection detection. *BJUI Compass*. (2024) 5:439–46. doi: 10.1002/bco2.328

17. Morelli A, Filippi S, Zhang XH, Luconi M, Vignozzi L, Mancina R, et al. Peripheral regulatory mechanisms in erection. *Int J Androl*. (2005) 28:23–7. doi: 10.1111/j.1365-2605.2005.00550.x

18. Burnett AL. Phosphodiesterase 5 mechanisms and therapeutic applications. *Am J Cardiol*. (2005) 96:29M–31M. doi: 10.1016/j.amjcard.2005.07.008

19. Sabri M, Ai J, Lass E, D'abbondanza J, Macdonald RL. Genetic elimination of eNOS reduces secondary complications of experimental subarachnoid hemorrhage. *J Cereb Blood Flow Metab*. (2013) 33:1008–14. doi: 10.1038/jcbfm.2013.49

20. Su Y. Regulation of endothelial nitric oxide synthase activity by protein-protein interaction. *Curr Pharm Des*. (2014) 20:3514–20. doi: 10.2174/13816128113196660752

21. Sağır S, Unsal V, Oner E, Yıldız R, Mert BD. Comparison of PDE-5 inhibitors used in erectile dysfunction with some candidate molecules: a study involving molecular docking, ADMET, DFT, biological target, and activity. *BMC Urol*. (2025) 25:47. doi: 10.1186/s12894-025-01727-5

22. Janaszak-Jasiecka A, Płoska A, Wierońska JM, Dobrucki LW, Kalinowski L. Endothelial dysfunction due to eNOS uncoupling: molecular mechanisms as potential therapeutic targets. *Cell Mol Biol Lett*. (2023) 28:21. doi: 10.1186/s11658-023-00423-2

23. Yunoki K, Nakamura K, Miyoshi T, Enko K, Kohno K, Morita H, et al. Ezetimibe improves postprandial hyperlipemia and its induced endothelial dysfunction. *Atherosclerosis*. (2011) 217:486–91. doi: 10.1016/j.atherosclerosis.2011.04.019

24. Gómez Del Val A, Sánchez A, Freire-Agulleiro Ó, Martínez MP, Muñoz M, Olmos L, et al. Penile endothelial dysfunction, impaired redox metabolism and blunted mitochondrial bioenergetics in diet-induced obesity: compensatory role of H2O2. *Free Radic Biol Med*. (2025) 230:222–33. doi: 10.1016/j.freeradbiomed.2025.02.004

25. Zaric B, Obradovic M, Trpkovic A, Banach M, Mikhailidis DP, Isenovic ER. Endothelial dysfunction in dyslipidaemia: molecular mechanisms and clinical implications. *Curr Med Chem*. (2020) 27:1021–40. doi: 10.2174/0929867326666190903112146

26. Ren Z, Guo J, Xiao X, Huang J, Li M, Cai R, et al. The effect of sex differences on endothelial function and circulating endothelial progenitor cells in hypertriglyceridemia. *Cardiol Res Pract*. (2020) 2020:2132918. doi: 10.1155/2020/2132918

27. Jamwal S, Sharma S. Vascular endothelium dysfunction: a conservative target in metabolic disorders. *Inflammation Res*. (2018) 67:391–405. doi: 10.1007/s00011-018-1129-8

28. Xu D, Xie L, Cheng C, Xue F, Sun C. Triglyceride-rich lipoproteins and cardiovascular diseases. *Front Endocrinol Lausanne*. (2024) 15:1409653. doi: 10.3389/fendo.2024.1409653

29. Ference BA, Braunwald E, Catapano AL. The LDL cumulative exposure hypothesis: evidence and practical applications. *Nat Rev Cardiol*. (2024) 21:701–16. doi: 10.1038/s41569-024-01039-5

30. Flores JM, West M, Mulhall JP. Efficient use of penile Doppler ultrasound for investigating men with erectile dysfunction. *J Sex Med*. (2024) 21:734–9. doi: 10.1093/jsxmed/qdae070

31. Zou X, Wang H, Cai L, Li K, Zhang W, Ding Y, et al. Effects of serum lipid smoothness on the progression and vulnerability of atherosclerotic plaques in rabbits. *PloS One*. (2014) 9:e93686. doi: 10.1371/journal.pone.0093686

32. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. *Eur Urol*. (2014) 65:968–78. doi: 10.1016/j.eururo.2013.08.023

33. Hamidi Madani A, Mirbolouk F, Naghshbandi M, Hasandokht T, Gholipour M, Zabihi MS, et al. Associated factors for erectile dysfunction occurrence in patients with coronary artery disease: a cross-sectional study. *Iran J Med Sci*. (2025) 50:37–43. doi: 10.30476/ijms.2024.100731.3312

34. Xie D, Annex BH, Donatucci CF. Growth factors for therapeutic angiogenesis in hypercholesterolemic erectile dysfunction. *Asian J Androl*. (2008) 10:23–7. doi: 10.1111/j.1745-7262.2008.00372.x

35. Ryu JK, Shin HY, Song SU, Oh SM, Piao S, Han JY, et al. Downregulation of angiogenic factors and their downstream target molecules affects the deterioration of erectile function in a rat model of hypercholesterolemia. *Urology*. (2006) 67:1329–34. doi: 10.1016/j.urology.2005.12.027

36. Benedict KF, Coffin GS, Barrett EJ, Skalak TC. Hemodynamic systems analysis of capillary network remodeling during the progression of type 2 diabetes. *Microcirculation*. (2011) 18:63–73. doi: 10.1111/j.1549-8719.2010.00069.x

37. Ryu JK, Kim WJ, Koh YJ, Piao S, Jin HR, Lee SW, et al. Designed angiopoietin-1 variant, COMP-angiopoietin-1, rescues erectile function through healthy cavernous angiogenesis in a hypercholesterolemic mouse. *Sci Rep*. (2015) 5:9222. doi: 10.1038/srep09222

38. Grammaticos PC, Baloyiannis SJ, Kokkas V. Circulatory system and neurosciences. Some perspectives in diagnosis and treatment. *Hell J Nucl Med*. (2019) 22:10–3. doi: 10.1967/s002449910953

39. Yeşilli C, Yaman O, Anafarta K. Effect of experimental hypercholesterolemia on cavernosal structures. *Urology*. (2001) 57:1184–8. doi: 10.1016/s0090-4295(01)00974-8

40. Karaboga R, Kilic O, Yaman O, Percinel S, Anafarta K. Long-term effect of experimental hypercholesterolemia on cavernosal tissues. *Urology*. (2006) 67:431–4. doi: 10.1016/j.urology.2005.08.049

41. Wang T, Soker S, Atala A, Siroky MB, Azadzoi KM. Alterations in angiogenic growth factors and neuronal nitric oxide synthase expression in chronic cavernosal ischemia. *Int J Impot Res*. (2004) 16:403–11. doi: 10.1038/sj.ijir.3901186

42. Li M, Ma Z, Zhang XL, Guo LQ, Yuan MZ. Significance of blood lipid parameters as effective markers for arteriogenic erectile dysfunction. *Andrology*. (2020) 8:1086–94. doi: 10.1111/andr.12776

43. Diehm N, Hirschle D, Kalka C, Keo HH, Mohan V, Schumacher MC, et al. Venous leak embolization results in clinical improvement of patients with mixed arterio-venous erectile dysfunction not responding to arterial revascularization alone. *Cardiovasc Intervent Radiol*. (2025) 48:184–93. doi: 10.1007/s00270-024-03910-x

44. Diehm N, Pelz S, Kalka C, Keo HH, Mohan V, Schumacher MC, et al. Venous leak embolization in patients with venogenic erectile dysfunction via deep dorsal penile vein access: safety and early efficacy. *Cardiovasc Intervent Radiol*. (2023) 46:610–6. doi: 10.1007/s00270-023-03412-2

45. Kaltsas A, Zikopoulos A, Dimitriadis F, Sheshi D, Politis M, Moustakli E, et al. Oxidative stress and erectile dysfunction: pathophysiology, impacts, and potential treatments. *Curr Issues Mol Biol*. (2024) 46:8807–34. doi: 10.3390/cimb46080521

46. Lyu F, Long W, Ma L. Atherosclerosis-induced arterial erectile dysfunction: pathogenesis, diagnosis, and therapeutic strategies. *Transl Androl Urol*. (2025) 14:2732–53. doi: 10.21037/tau-2025-241

47. Vergnani L, Hatrik S, Ricci F, Passaro A, Manzoli N, Zuliani G, et al. Effect of native and oxidized low-density lipoprotein on endothelial nitric oxide and superoxide production: key role of L-arginine availability. *Circulation*. (2000) 101:1261–6. doi: 10.1161/01.cir.101.11.1261

48. Musicki B, Liu T, Lagoda GA, Strong TD, Sezen SF, Johnson JM, et al. Hypercholesterolemia-induced erectile dysfunction: endothelial nitric oxide synthase uncoupling in the mouse penis by NAD(P)H oxidase. *J Sex Med*. (2010) 7:3023–32. doi: 10.1111/j.1743-6109.2010.01880.x

49. Kaya-Sezginer E, Gur S. The inflammation network in the pathogenesis of erectile dysfunction: attractive potential therapeutic targets. *Curr Pharm Des*. (2020) 26:3955–72. doi: 10.2174/1381612826666200424161018

50. Ruan Z, Xie X, Yu H, Liu R, Jing W, Lu T. Association between dietary inflammation and erectile dysfunction among US adults: a cross-sectional analysis of the National Health and Nutrition Examination Survey 2001-2004. *Front Nutr*. (2022) 9:930272. doi: 10.3389/fnut.2022.930272

51. Feng J, Deng S, Gong X, Wang B, Sun L, Zhang H, et al. Bioinformatics combined with experimental modeling to study the molecular mechanism of Xuefu Zhuyu decoction to improve erectile dysfunction associated with asthma in rats. *Am J Mens Health*. (2024) 18:15579883241293936. doi: 10.1177/15579883241293936

52. Taskiran M, Dogan K. The efficacy of systemic inflammatory response and oxidative stress in erectile dysfunction through multi-inflammatory index: a prospective cross-sectional analysis. *J Sex Med*. (2023) 20:591–6. doi: 10.1093/jsxmed/qdad037

53. Olopade EO, Adefegha SA, Alao JO, Adepoju AE, Fakayode AE, Oboh G. Ameliorative role of β-caryophyllene on antioxidant biomarkers in a paroxetine-induced model of male sexual dysfunction. *Basic Clin Pharmacol Toxicol*. (2025) 136:e70010. doi: 10.1111/bcpt.70010

54. Xin S, Song W, Mao J, Hu P, Chen Z, Liu J, et al. Therapeutic potential of hesperidin in diabetes mellitus-induced erectile dysfunction through Nrf2-mediated ferroptosis and oxidative stress. *Andrology*. (2024) 13:1702–14. doi: 10.1111/andr.13814

55. de Almeida Feitosa MS, de Almeida AJPO, Dantas SH, de Lourdes Assunção Araújo de Azevedo F, de Souza Júnior JF, Gonçalves TAF, et al. Carvacrol prevents D-(+)-galactose-induced aging-associated erectile dysfunction by improving endothelial dysfunction and oxidative stress in rats. *Naunyn Schmiedebergs Arch Pharmacol*. (2024) 397:10061–73. doi: 10.1007/s00210-024-03264-8

56. Silva FH, Lanaro C, Leiria LO, Rodrigues RL, Davel AP, Claudino MA, et al. Oxidative stress associated with middle aging leads to sympathetic hyperactivity and downregulation of soluble guanylyl cyclase in corpus cavernosum. *Am J Physiol Heart Circ Physiol*. (2014) 307:H1393–400. doi: 10.1152/ajpheart.00708.2013

57. Miyata Y, Matsuo T, Nakamura Y, Mitsunari K, Ohba K, Sakai H. Pathological significance of macrophages in erectile dysfunction including Peyronie's disease. *Biomedicines*. (2021) 9:1658. doi: 10.3390/biomedicines9111658

58. Sturny M, Anguenot L, Costa-Fraga FP, Bragina ME, Lima AM, da Silva RF, et al. Apelin-13 protects corpus cavernosum against fibrosis induced by high-fat diet in an MMP-dependent mechanism. *J Sex Med*. (2021) 18:875–88. doi: 10.1016/j.jsxm.2021.02.004

59. Giagulli VA, Lisco G, De Tullio A, Guastamacchia E, Triggiani V, Jirillo E. The pathogenic role of the immune system in erectile dysfunction and Peyronie's disease: focusing on immunopathophysiology and potential therapeutic strategies. *Sex Med Rev*. (2024) 12:210–20. doi: 10.1093/sxmrev/qead055

60. Priviero F, Calmasini F, Dela Justina V, Wenceslau CF, McCarthy CG, Webb RC. Macrophage-specific toll like receptor 9 (TLR9) causes corpus cavernosum dysfunction in mice fed a high fat diet. *J Sex Med*. (2021) 18:723–31. doi: 10.1016/j.jsxm.2021.01.180

61. Zhu B, Niu Y, Niu L, Zhang X, Liu F. Exploring the application of sildenafil for high-fat diet-induced erectile dysfunction based on interleukin-18-mediated NLRP3/Caspase-1 signaling pathway. *Sex Med*. (2023) 11:qfad044. doi: 10.1093/sexmed/qfad044

62. Rao WT, Jiang S, Shen YH, Wang YH, Liu SN, Tang JD, et al. Myofibroblasts: a new factor affecting the hyperlipidemia-induced elastic abnormality of corpus cavernosum in rabbits detected by 2-D shear wave elastography. *Ultrasound Med Biol*. (2023) 49:2336–45. doi: 10.1016/j.ultrasmedbio.2023.07.010

63. Yu J, Liang P. A Mendelian randomization study on associations between plasma lipidome, circulating inflammatory proteins, and erectile dysfunction. *Transl Androl Urol*. (2024) 13:2724–34. doi: 10.21037/tau-24-378

64. Fraga-Silva RA, Costa-Fraga FP, Savergnini SQ, De Sousa FB, Montecucco F, da Silva D, et al. An oral formulation of angiotensin-(1-7) reverses corpus cavernosum damages induced by hypercholesterolemia. *J Sex Med*. (2013) 10:2430–42. doi: 10.1111/jsm.12262

65. Lu-Chen, Yu KW, Zhuang QZ, Jing-Yu, Zhao JJ, Lai BC, et al. MS4A6A regulates ox-LDL-induced endothelial dysfunction and monocyte adhesion in atherosclerosis via the IKK/NF-kappaB pathway. *Int Immunopharmacol*. (2025) 152:114404. doi: 10.1016/j.intimp.2025.114404

66. Yang W, Fang J, Zhai J, Qiu C, Liang Z, Liu Q, et al. IL-17A exacerbates corpus cavernosum fibrosis and neurogenic erectile dysfunction by inducing CSMC senescence via the mTORC2-ACACA pathway. *BMC Med*. (2024) 22:376. doi: 10.1186/s12916-024-03609-3

67. Ding W, Fan JH, Zhong LR, Wang NX, Liu LH, Zhang HB, et al. N-acetylcysteine ameliorates erectile dysfunction in rats with hyperlipidemia by inhibiting oxidative stress and corpus cavernosum smooth muscle cells phenotypic modulation. *Asian J Androl*. (2024) 26:99–106. doi: 10.4103/aja202324

68. Zhou W, Zhang Y, Li L, Gao J, Zheng H, Huang M, et al. Evaluation of arterial erectile dysfunction using shear wave elastography: a feasibility study. *J Ultrasound Med*. (2021) 40:1209–16. doi: 10.1002/jum.15502

69. Stern N, Bajic P, Campbell J, Capogrosso P, Domes T, Miranda EP, et al. Evolving medical management of erectile dysfunction: recommendations from the Fifth International Consultation on Sexual Medicine (ICSM 2024). *Sex Med Rev*. (2025) 13:513–37. doi: 10.1093/sxmrev/qeaf035

70. Ihrig CM, Montgomery MM, Nomura Y, Nakano M, Pandey D, La Favor JD. Histone deacetylase 6 inhibition prevents hypercholesterolemia-induced erectile dysfunction independent of changes in markers of autophagy. *Sex Med*. (2025) 12:qfae096. doi: 10.1093/sexmed/qfae096

71. Li R, Wang G, Feng C, Diao T, Liu S, Fu Q. Inhibition of Galectin-3 by ADSC-derived exosomes after cavernous nerve injury ameliorates erectile dysfunction by modulating oxidative stress and inflammatory profibrotic cascades. *Stem Cell Res Ther*. (2025) 16:627. doi: 10.1186/s13287-025-04749-w

72. Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. *Nat Rev Neurol*. (2011) 7:573–83. doi: 10.1038/nrneurol.2011.137

73. Rumora AE, Guo K, Hinder LM, O'Brien PD, Hayes JM, Hur J, et al. A high-fat diet disrupts nerve lipids and mitochondrial function in murine models of neuropathy. *Front Physiol*. (2022) 13:921942. doi: 10.3389/fphys.2022.921942

74. Vrentzos GE, Paraskevas KI, Mikhailidis DP. Dyslipidemia as a risk factor for erectile dysfunction. *Curr Med Chem*. (2007) 14:1765–70. doi: 10.2174/092986707781058931

75. Wiggin TD, Sullivan KA, Pop-Busui R, Amato A, Sima AA, Feldman EL. Elevated triglycerides correlate with progression of diabetic neuropathy. *Diabetes*. (2009) 58:1634–40. doi: 10.2337/db08-1771

76. Iqbal Z, Bashir B, Ferdousi M, Kalteniece A, Alam U, Malik RA, et al. Lipids and peripheral neuropathy. *Curr Opin Lipidol*. (2021) 32:249–57. doi: 10.1097/MOL.0000000000000770

77. Reimann M, Rüdiger H, Weiss N, Ziemssen T. Acute hyperlipidemia but not hyperhomocysteinemia impairs reflex regulation of the cardiovascular system. *Atheroscler Suppl*. (2015) 18:8–15. doi: 10.1016/j.atherosclerosissup.2015.02.004

78. Ziegler D, Strom A, Straßburger K, Knebel B, Bönhof GJ, Kotzka J, et al. Association of cardiac autonomic dysfunction with higher levels of plasma lipid metabolites in recent-onset type 2 diabetes. *Diabetologia*. (2021) 64:458–68. doi: 10.1007/s00125-020-05310-5

79. Bashir B, Pasha R, Kamath A, Malik RA, Ferdousi M, Soran H. Small nerve fibre damage and cardiac autonomic dysfunction in patients with hypertriglyceridaemia. *Atherosclerosis*. (2025) 405:119186. doi: 10.1016/j.atherosclerosis.2025.119186

80. Ai J, Liang F, Zhou H, Zhao J, Wang N, Zhu S, et al. Mechanism of impaired baroreflex sensitivity in Wistar rats fed a high-fat and -carbohydrate diet. *Br J Nutr*. (2010) 104:291–7. doi: 10.1017/S0007114510000450

81. Dogru MT, Basar MM. Comparison of the differences in circadian autonomic function in hyperlipidemic men with and without erectile dysfunction. *Int Urol Nephrol*. (2010) 42:589–96. doi: 10.1007/s11255-009-9658-2

82. Becker M, Kälin S, Neubig AH, Lauber M, Opaleva D, Hipp H, et al. Regulatory T cells in the mouse hypothalamus control immune activation and ameliorate metabolic impairments in high-calorie environments. *Nat Commun*. (2025) 16:2744. doi: 10.1038/s41467-025-57918-z

83. Thaler JP, Yi CX, Schur EA, Guyenet SJ, Hwang BH, Dietrich MO, et al. Obesity is associated with hypothalamic injury in rodents and humans. *J Clin Invest*. (2012) 122:153–62. doi: 10.1172/JCI59660

84. Dominguez JM, Hull EM. Dopamine, the medial preoptic area, and male sexual behavior. *Physiol Behav*. (2005) 86:356–68. doi: 10.1016/j.physbeh.2005.08.006

85. Argiolas A, Melis MR. Central control of penile erection: role of the paraventricular nucleus of the hypothalamus. *Prog Neurobiol*. (2005) 76:1–21. doi: 10.1016/j.pneurobio.2005.06.002

86. Sato Y, Christ GJ. Differential ICP responses elicited by electrical stimulation of medial preoptic area. *Am J Physiol Heart Circ Physiol*. (2000) 278:H964–70. doi: 10.1152/ajpheart.2000.278.3.H964

87. Gholami SS, Rogers R, Chang J, Ho HC, Grazziottin T, Lin CS, et al. The effect of vascular endothelial growth factor and adeno-associated virus mediated brain derived neurotrophic factor on neurogenic and vasculogenic erectile dysfunction induced by hyperlipidemia. *J Urol*. (2003) 169:1577–81. doi: 10.1097/01.ju.0000055120.73261.76

88. Ryu JK, Cho CH, Shin HY, Song SU, Oh SM, Lee M, et al. Combined angiopoietin-1 and vascular endothelial growth factor gene transfer restores cavernous angiogenesis and erectile function in a rat model of hypercholesterolemia. *Mol Ther*. (2006) 13:705–15. doi: 10.1016/j.ymthe.2005.10.016

89. Zhang HY, Jin XB, Lue TF. Three important components in the regeneration of the cavernous nerve: brain-derived neurotrophic factor, vascular endothelial growth factor and the JAK/STAT signaling pathway. *Asian J Androl*. (2011) 13:231–5. doi: 10.1038/aja.2010.162

90. Nishimatsu H, Suzuki E, Saito Y, Niimi A, Nomiya A, Fukuhara H, et al. Senescent cells impair erectile function through induction of endothelial dysfunction and nerve injury in mice. *PloS One*. (2015) 10:e0124129. doi: 10.1371/journal.pone.0124129

91. Lénárt N, Szegedi V, Juhász G, Kasztner A, Horváth J, Bereczki E, et al. Increased tau phosphorylation and impaired presynaptic function in hypertriglyceridemic ApoB-100 transgenic mice. *PloS One*. (2012) 7:e46007. doi: 10.1371/journal.pone.0046007

92. Yu C, Jiang F, Zhang M, Luo D, Shao S, Zhao J, et al. HC diet inhibited testosterone synthesis by activating endoplasmic reticulum stress in testicular Leydig cells. *J Cell Mol Med*. (2019) 23:3140–50. doi: 10.1111/jcmm.14143

93. Wang G, Cheng S, Zhang S, Zhu Y, Xiao Y, Ju L. LPS impairs steroidogenesis and ROS metabolism and induces PPAR transcriptional activity to disturb estrogen/androgen receptor expression in testicular cells. *Mol Biol Rep*. (2020) 47:1045–56. doi: 10.1007/s11033-019-05196-6

94. Jing J, Ding N, Wang D, Ge X, Ma J, Ma R, et al. Oxidized-LDL inhibits testosterone biosynthesis by affecting mitochondrial function and the p38 MAPK/COX-2 signaling pathway in Leydig cells. *Cell Death Dis*. (2020) 11:626. doi: 10.1038/s41419-020-02751-z

95. Porav-Hodade D, Gherasim RD, Kosovski IB, Voidazan TS, Crisan N, Bogdan P, et al. Hormones, age, and erectile dysfunction: should routine testing be part of the initial evaluation? *Diagnostics Bsl*. (2025) 15:294. doi: 10.3390/diagnostics15030294

96. Yuli F, Qi Z, Haojie Y, Zedong L, Wenjie H, Runnana X, et al. Association between testosterone levels and RigiScan parameters of patients with erectile dysfunction. *Sex Med*. (2024) 12:qfad072. doi: 10.1093/sexmed/qfad072

97. Leelani N, Bole R, Khooblall P, Bajic P, Lundy SD. The role of the microbiome in erectile dysfunction. *Curr Sex Health Rep*. (2023) 15:132–7. doi: 10.1007/s11930-023-00365-y

98. Tao J, Dai W, Lyu Y, Liu H, Le J, Sun T, et al. Role of intestinal testosterone-degrading bacteria and 3/17β-HSD in the pathogenesis of testosterone deficiency-induced hyperlipidemia in males. *NPJ Biofilms Microbiomes*. (2024) 10:123. doi: 10.1038/s41522-024-00599-1

99. Su Q, Tang Q, Ma C, Wang K. Advances in the study of the relationship between gut microbiota and erectile dysfunction. *Sex Med Rev*. (2024) 12:664–9. doi: 10.1093/sxmrev/qeae049

100. Wang H, Guo J, Chung E. Metabolic syndrome-associated erectile dysfunction: multiple vascular endothelial dysfunction mechanisms and potential therapeutic targets. *Int J Biol Sci*. (2025) 21:5842–58. doi: 10.7150/ijbs.120980

101. Higashi Y. Endothelial function in dyslipidemia: roles of LDL-cholesterol, HDL-cholesterol and triglycerides. *Cells*. (2023) 12:1293. doi: 10.3390/cells12091293

102. Wen W, Chi Y, Liu M, Gao M, Xie B, Yan Y, et al. Inflammation mediated glycolipid dysregulation in coronary microvascular disease pathogenesis. *Sci Rep*. (2025) 15:22694. doi: 10.1038/s41598-025-08057-4

103. Zhu D, Pham QM, Wang C, Colonnello E, Yannas D, Nguyen BH, et al. Erectile dysfunction and oxidative stress: a narrative review. *Int J Mol Sci*. (2025) 26:3073. doi: 10.3390/ijms26073073

104. Li R, Cui K, Wang T, Wang S, Li X, Qiu J, et al. Hyperlipidemia impairs erectile function in rats by causing cavernosal fibrosis. *Andrologia*. (2017) 49:e12693. doi: 10.1111/and.12693

105. Aleksandra R, Aleksandra S, Iwona R. Erectile dysfunction in relation to metabolic disorders and the concentration of sex hormones in aging men. *Int J Environ Res Public Health*. (2022) 19:7576. doi: 10.3390/ijerph19137576