

## REVIEW ARTICLE



# Endocrine-metabolic crosstalk in erectile dysfunction: mechanistic insights and therapeutic implications

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Erectile dysfunction (ED) is a prevalent male sexual disorder frequently coexisting with cardiometabolic diseases. Although phosphodiesterase type 5 inhibitors remain the first-line therapy, limited efficacy or safety concerns in some patients highlight the need for alternative approaches. Emerging evidence demonstrates that endocrine abnormalities—including dysregulation of testosterone, estradiol, prolactin, and thyroid hormones—play crucial roles in the pathogenesis of ED. These hormones influence erectile capacity through central neuroendocrine and peripheral vascular mechanisms, while their interaction with metabolic disorders such as obesity and diabetes further exacerbates disease severity. We searched PubMed, Web of Science, and Embase up to August 2025 for studies examining hormonal mechanisms, clinical manifestations, and therapeutic interventions in ED. Current findings indicate that androgen deficiency impairs erection via a threshold mechanism; estradiol exerts bidirectional effects on libido and endothelial function; both hyper- and hypoprolactinemia disrupt sexual performance; and thyroid dysfunction is associated with ED, with restoration of euthyroidism being linked to improvement in erectile function in selected patients. Therapeutic options include testosterone replacement, selective estrogen receptor modulators, aromatase inhibitors, dopamine agonists, and thyroid hormone therapy, often combined with metabolic or lifestyle interventions. Integrating multi-hormonal regulation with metabolic health may shift ED management from symptomatic control toward precision, individualized medicine.

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## INTRODUCTION

Erectile dysfunction (ED) is one of the most common male sexual disorders, with the prevalence increasing markedly with age [1]. ED frequently coexists with cardiovascular disease and metabolic disorders, including metabolic syndrome and diabetes, while a strong association with depression has also been reported in multiple population-based studies [1–3]. These associations underscore ED's role as a marker of systemic health rather than a purely localized condition [4]. Despite being the primary therapeutic option, phosphodiesterase type 5 (PDE5) inhibitors are ineffective or unsuitable in a substantial proportion of men, underscoring the need for alternative or adjunctive treatment strategies [5].

In the past decade, increasing attention has been directed toward the contribution of endocrine abnormalities to ED [6]. Accumulating evidence suggests that disruptions in testosterone, estradiol, prolactin (PRL), and thyroid hormones can influence erectile function through both central and peripheral pathways [6–9]. Moreover, interactions between endocrine disturbances and metabolic disorders such as obesity and diabetes may further contribute to the risk and severity of ED [6, 10]. Consequently, ED should be considered not merely the result of isolated hormonal defects, but rather a manifestation of complex multi-hormonal imbalances in the context of metabolic dysregulation.

Nevertheless, current clinical management remains largely symptom-focused, and the therapeutic implications of these multi-hormonal interactions for precision medicine are still underexplored. This review therefore aims to synthesize current evidence on the mechanistic and clinical roles of key endocrine hormones in ED, assess their interplay with metabolic health, and highlight recent therapeutic advances. In doing so, we seek to provide insights that may facilitate the development of more individualized, endocrine-based management strategies for ED.

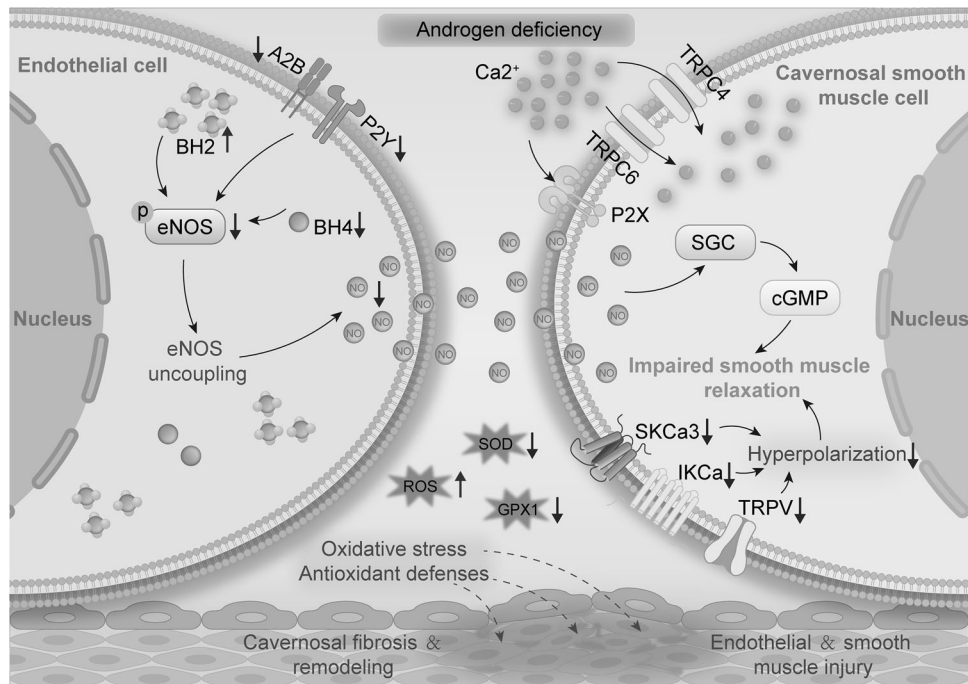
## METHODS

The literature search was conducted primarily through PubMed, Web of Science, and Embase, covering publications available up to August 2025. Search terms included “erectile dysfunction,” “androgens,” “testosterone,” “estrogens,” “prolactin,” “thyroid hormones,” “hormone therapy,” and “metabolic syndrome,” in combination with relevant Medical Subject Headings (MeSH) terms. This study was conducted as a narrative review. To enhance conceptual clarity and transparency, the review question and search scope were informed by the PICOS framework as a guiding structure, including the population (men with ED), key exposures or conditions (endocrine and metabolic disturbances), outcomes of interest (erectile function and related vascular, neuroendocrine,

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**Fig. 1 Mechanistic overview of androgen deficiency-associated ED.** Schematic illustration summarizing the molecular mechanisms by which androgen deficiency contributes to ED. Androgen deficiency impairs nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) signaling through reduced endothelial nitric oxide synthase (eNOS) activity, decreased tetrahydrobiopterin (BH4) availability, and eNOS uncoupling, resulting in reduced NO bioavailability and increased oxidative stress. Dysregulation of neuronal nitric oxide synthase (nNOS) further compromises neurogenic NO release. Androgen deficiency also disrupts ion channel homeostasis in cavernosal smooth muscle. Upregulation of transient receptor potential canonical (TRPC) channels and P2X receptors enhances  $Ca^{2+}$  influx and contraction, while downregulation of small-conductance calcium-activated potassium channels (SKCa3), intermediate-conductance calcium-activated potassium channels (IKCa), and transient receptor potential vanilloid (TRPV) channels reduces hyperpolarization and impairs relaxation. In addition, androgen deficiency promotes oxidative stress by increasing reactive oxygen species (ROS) and reducing antioxidant defenses, including superoxide dismutase (SOD) and glutathione peroxidase (GPX). These changes contribute to apoptosis and fibrotic remodeling of the corpus cavernosum, ultimately leading to endothelial dysfunction and impaired erectile function.

or metabolic endpoints), and relevant study designs. PICOS was used for conceptual framing rather than as a formal eligibility or screening tool. The literature selection focused primarily on original experimental and clinical studies relevant to ED. Review articles and meta-analyses were consulted selectively for background context and for identifying key primary studies, while original research was prioritized throughout the manuscript. Seminal publications of enduring relevance were also included where appropriate.

## RESULTS AND DISCUSSION

### Androgens and ED

The androgen family of steroid hormones, including testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate, is predominantly synthesized in the gonads and adrenal cortex, with additional tissues contributing to local steroid metabolism and intracrine signaling [11]. Among numerous endocrine mediators, androgens, particularly testosterone, are important modulators of normal erectile function [12]. At the central level, androgens modulate hypothalamic and limbic neural circuits that govern sexual motivation and arousal, which are integral to the initiation of sexual behavior and subsequent erectile responses [13, 14]. Functional MRI studies have shown that men with hypogonadism display reduced activation of these regions in response to erotic stimuli, which can be restored by testosterone supplementation [15]. This evidence suggests that androgens may indirectly facilitate erectile function by modulating sexual desire and central arousal mechanisms. Peripherally, androgens are crucial for maintaining

the structural and functional integrity of the corpus cavernosum. Animal studies have demonstrated that castration reduces smooth muscle cell content, cavernous sinus area, and endothelial progenitor cell numbers in the rat corpus cavernosum, while simultaneously increasing collagen fiber deposition and decreasing elastic fibers. These changes ultimately lead to corporal fibrosis and reduced compliance [16]. Testosterone supplementation, however, reverses many of these alterations [17]. Furthermore, androgens are indispensable for modulating the nitric oxide (NO) signaling pathway within the penis, where NO functions as the principal neurovascular mediator initiating and sustaining erection [18].

Androgen deficiency disrupts the balance of erection by interfering with multiple molecular pathways, ultimately resulting in ED. Among these, the NO/cyclic guanosine monophosphate (NO/cGMP) pathway is a central regulator of penile erection [18]. Nitric oxide synthase (NOS), produced by endothelial and neuronal cells within the corpus cavernosum, activates guanylyl cyclase, thereby initiating the synthesis of cGMP. Elevated cGMP reduces calcium influx, promotes smooth muscle relaxation, and initiates penile erection [19].

Androgen deficiency has been shown to impair NO/cGMP signaling through multiple mechanisms, including reduced phosphorylation and activation of endothelial NOS (eNOS), altered purinergic receptor expression (e.g., A2B and P2Y receptors), and disruption of tetrahydrobiopterin (BH4) availability, leading to eNOS uncoupling and oxidative stress [20]. It also decreases BH4 while increasing its oxidized product BH2, leading to eNOS uncoupling, a condition in which superoxide anions rather than NO are generated, further exacerbating oxidative stress [21]. In

addition, an association has been reported between erectile performance and the number of neuronal NOS (nNOS)-immunoreactive branches in the dorsal penile nerve, whereas abnormalities such as impaired phosphorylation and nNOS uncoupling within the corpus cavernosum contribute to functional decline [22]. Regulation of nNOS is also mediated by androgens acting via the androgen receptor (AR). In animal models, nerve injury leads to a decline in arterial nNOS expression, yet responsiveness to sodium nitroprusside remains unaffected. Replacement with testosterone or dihydrotestosterone reinstates normal nNOS expression [23].

Beyond NO signaling, androgen deficiency disrupts ion channel homeostasis, promoting smooth muscle contraction and impairing relaxation. In experimental models, androgen deficiency has been shown to upregulate transient receptor potential canonical (TRPC) channels (TRPC4, TRPC6) and P2X receptors, thereby enhancing  $\text{Ca}^{2+}$  influx and triggering contraction [24, 25]. This process also involves downregulation of small-conductance calcium-activated potassium channel 3 (SKCa3), intermediate-conductance calcium-activated potassium channels (IKCa), and transient receptor potential vanilloid (TRPV) channels, which diminishes hyperpolarization capacity and disrupts normal smooth muscle relaxation [26].

Ultimately, a lack of androgens accelerates oxidative stress, apoptosis, and fibrotic remodeling, all of which are pivotal processes in the progression of ED. It increases reactive oxygen species (ROS) within the corpus cavernosum while reducing antioxidant gene expression, such as superoxide dismutase (SOD) and glutathione peroxidase 1 (GPX1) [27]. These pathological changes promote oxidative stress, apoptosis, and fibrotic remodeling of the corpus cavernosum, leading to endothelial and cavernosal smooth muscle injury and impaired erectile capacity. Collectively, these processes culminate in pathological fibrotic remodeling of the corpus cavernosum, impairing its capacity to accommodate blood and sustain erection. The integrated molecular mechanisms linking androgen deficiency to ED are summarized in Fig. 1.

From a clinical perspective, the profound molecular and structural alterations induced by androgen deficiency are not always adequately captured by measurements of total testosterone alone. In men with ED, particularly those with concomitant metabolic disturbances, obesity, insulin resistance, and chronic low-grade inflammation are frequently associated with alterations in sex hormone-binding globulin (SHBG) concentrations. These changes may result in a disproportionate reduction in circulating free testosterone (cFT), even when total testosterone levels remain within the reference range [28]. Under such conditions, cFT may provide a more functionally relevant indicator of biologically active androgen availability at target tissues, including endothelial cells and cavernosal smooth muscle, thereby offering a plausible explanation for erectile impairment in men with apparently normal total testosterone concentrations [28, 29].

Clinical studies have demonstrated that endogenous androgen levels and erectile function exhibit a distinct threshold or saturation effect. Data from major epidemiological cohorts, notably the EMAS study, reveal that diminished libido, loss of morning erections, and ED are independently related to androgen deficiency, provided that circulating total testosterone decreases below about 11 nmol/L or estimated free testosterone is below 220 pmol/L [30]. Beyond this threshold, additional increases in testosterone exert minimal impact on penile blood flow. Evidence from animal models reinforces this concept. Expression of PDE5 in the penis is closely linked to AR expression, yet significant downregulation of PDE5 occurs only in hypogonadal states corresponding to the lowest quintile of testosterone [31]. Within the normal range, PDE5 expression does not rise further with increasing testosterone, underscoring that androgens function primarily as “permissive factors” rather than direct “stimulatory factors” in erectile regulation.

In summary, androgens regulate erection at multiple levels through central and peripheral mechanisms. Androgen deficiency disrupts the NO/cGMP pathway, alters ion channel activity, and promotes oxidative stress and fibrosis, ultimately culminating in ED. The “threshold effect” highlights the indispensable yet incomplete role of androgens in sexual function. Understanding this mechanism more fully underpins the scientific justification for appropriate clinical deployment of testosterone replacement therapy (TRT).

### Estrogen and ED

Estrogens, together with androgens, constitute essential components of the male sex hormone milieu. In men, estradiol is primarily generated through aromatization of testosterone and is highly expressed within the male reproductive system [8]. Emerging evidence indicates that estradiol plays an important role in central sexual arousal and desire, and that disruption of estradiol homeostasis—either deficiency or excess—may adversely affect male sexual function [32, 33]. Although sexual desire and erectile function represent distinct physiological processes, impaired libido may indirectly exacerbate ED by attenuating psychogenic arousal. Clinical observations further support this notion: interventions that markedly reduce estradiol levels, such as aromatase inhibition, may paradoxically impair sexual desire despite increasing circulating testosterone [34, 35]. Collectively, these findings highlight the necessity of balanced estradiol signaling for normal male sexual function, while underscoring the importance of distinguishing its central effects on libido from its peripheral actions on erectile physiology. The following discussion therefore focuses on estrogen-related mechanisms that are directly relevant to ED rather than broader aspects of male sexual desire.

Although testosterone contributes to maintaining erectile function, most men can still achieve normal erections even when testosterone levels fall slightly below the lower limit of the normal range. In eugonadal men, elevated serum testosterone does not appear to exert a decisive influence on erectile function; instead, estradiol levels have been identified as an independent risk factor in some clinical studies. In young male patients with organic ED, serum estradiol concentrations are significantly elevated, accompanied by an increased estradiol-to-testosterone ratio [36]. Consistently, increased estradiol levels have been associated with a reduced frequency of spontaneous and nocturnal erections in men [37]. Findings from clinical studies suggest that elevated estradiol levels in combination with low testosterone are associated with greater ED severity, and that an increased estradiol-to-testosterone ratio is linked to a higher likelihood of ED occurrence [38]. Notably, in experimental models, administration of exogenous estradiol has been shown to impair erectile function, in part by suppressing endogenous testosterone production. Findings from animal models indicate that exogenous estrogen is associated with suppression of testosterone and structural alterations of the corpus cavernosum, characterized by reduced smooth muscle content and increased connective tissue deposition [39]. Early exposure of rats to exogenous estrogen disrupts normal penile development, leading to reduced bulbospongiosus muscle volume, diminished cavernous spaces, and adipocyte accumulation within lacunae—pathological changes that culminate in ED in adulthood. Beyond structural remodeling, estrogen also exerts profound effects on penile vascular regulation. A case-control study of male outpatients with ED complicated by venous leakage reported that elevated estradiol levels were a distinguishing feature compared with controls [40]. Investigators concluded that estradiol enhances venous permeability via vascular endothelial growth factor (VEGF), thereby aggravating venous leakage and impairing erectile function. Importantly, when elevated estrogen levels cause ED, testosterone therapy alone cannot restore erectile function within a persistent

estrogenic milieu, underscoring estrogen's independent and direct impact on erectile physiology [41].

Estrogen therefore exhibits a biphasic effect in male ED: moderate levels are indispensable for preserving vascular and erectile homeostasis, whereas both excessively low and excessively high levels impair erectile function. Thus, the balance between estradiol and testosterone is more critical than the absolute level of either hormone. A deeper understanding of estrogen's role in ED provides a theoretical basis for future therapeutic strategies, including selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and individualized testosterone-to-estradiol (T:E2) ratio management.

### Prolactin and ED

PRL, produced by lactotrophs in the anterior pituitary, is a polypeptide hormone with a molecular structure comprising 199 amino acids. Beyond its classical role in stimulating lactation, PRL participates in a wide range of physiological processes, including behavioral regulation, neurodevelopment, immune modulation, fluid balance, and reproductive function [42]. In males, PRL modulates the secretion of gonadotropin-releasing hormone (GnRH), which in turn governs the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), thereby indirectly affecting testicular function [43]. The expression of PRL receptors in testicular interstitial, Sertoli, and germ cells supports a functional role in spermatogenesis and endocrine regulation of male reproductive function.

However, knockout of the prolactin receptor (PRLR) in male mice leads to infertility, although only 20%–40% of these animals display abnormal mating behavior [44]. Collectively, these findings suggest that PRL serves primarily as a supportive factor in male reproductive function rather than an indispensable determinant [45, 46].

The role of PRL in male sexual function is complex and bidirectional. Traditionally, hyperprolactinemia has been linked to reduced libido and sexual dysfunction, primarily through suppression of the GnRH–gonadal axis, leading to hypogonadism and subsequent loss of sexual desire and ED [47]. Notably, testosterone supplementation alone cannot fully restore sexual function in men with elevated PRL, whereas normalization of PRL levels markedly improves libido and erectile capacity, suggesting that PRL itself directly regulates sexual function [48]. On the other hand, several studies have identified hypoprolactinemia as a potential factor associated with ED. Evidence from penile color Doppler ultrasonography after prostaglandin E1 challenge indicated that subjects in the lowest quartile of PRL levels were more likely to experience ED and exhibited diminished penile blood flow [49]. Further confirmation arises from longitudinal cohort data, which demonstrate that men suffering from moderate-to-severe ED have substantially lower serum PRL than counterparts with mild ED [43].

Experimental data provide additional mechanistic insights. In rats with impaired sexual function, PRL injection (5–10 µg/kg, but not 50 µg/kg) restored complete sexual behavior and increased extracellular dopamine and serotonin metabolites in the striatum, whereas prolonged administration produced the opposite effect [50]. These findings suggest that acute elevation of PRL may facilitate sexual behavior, whereas sustained elevation exerts inhibitory effects, possibly via modulation of central serotonergic and dopaminergic systems. In humans, functional MRI in 12 heterosexual men demonstrated a positive correlation between baseline PRL levels and brain activity during sexual responses to visual stimuli, further supporting the notion that central PRL may facilitate acute neural responses to sexual stimuli [51].

In summary, both excessively high and low PRL levels may be detrimental to erectile function. This bidirectional effect highlights the importance of maintaining physiological PRL levels for sexual health and provides a theoretical basis for clinical interventions.

### Thyroid hormones and ED

Thyroid hormones play a crucial role in male sexual function and the onset and progression of ED. Thyroid dysfunction, including both hypothyroidism and hyperthyroidism, can impair reproductive function through multiple mechanisms [52]. In animal studies, hypothyroidism has been shown to reduce testicular volume, decrease sperm production, enhance oxidative stress, and increase apoptosis. Restoration of thyroid function, by contrast, improves testicular performance and spermatogenesis [53]. Clinically, hypothyroidism is strongly associated with male sexual dysfunction: more than 59% of affected men report symptoms such as ED, reduced libido, and delayed ejaculation [54]. A study by Krassas and coworkers, comprising 44 hypothyroid men and 71 healthy controls, showed that ED affected 63% of hypothyroid subjects compared with 34% of controls ( $P < 0.0001$ ) [55]. The underlying mechanisms include decreased total and free testosterone, reduced SHBG, and in some cases, hyperprolactinemia. In addition, hypothyroidism is frequently accompanied by fatigue, depression, and metabolic abnormalities, all of which further compromise sexual function [56]. Notably, administration of T4 in hypothyroid men restores cFT, SHBG, and PRL concentrations to normal ranges, accompanied by resolution of sexual dysfunction over a clinically meaningful period [57].

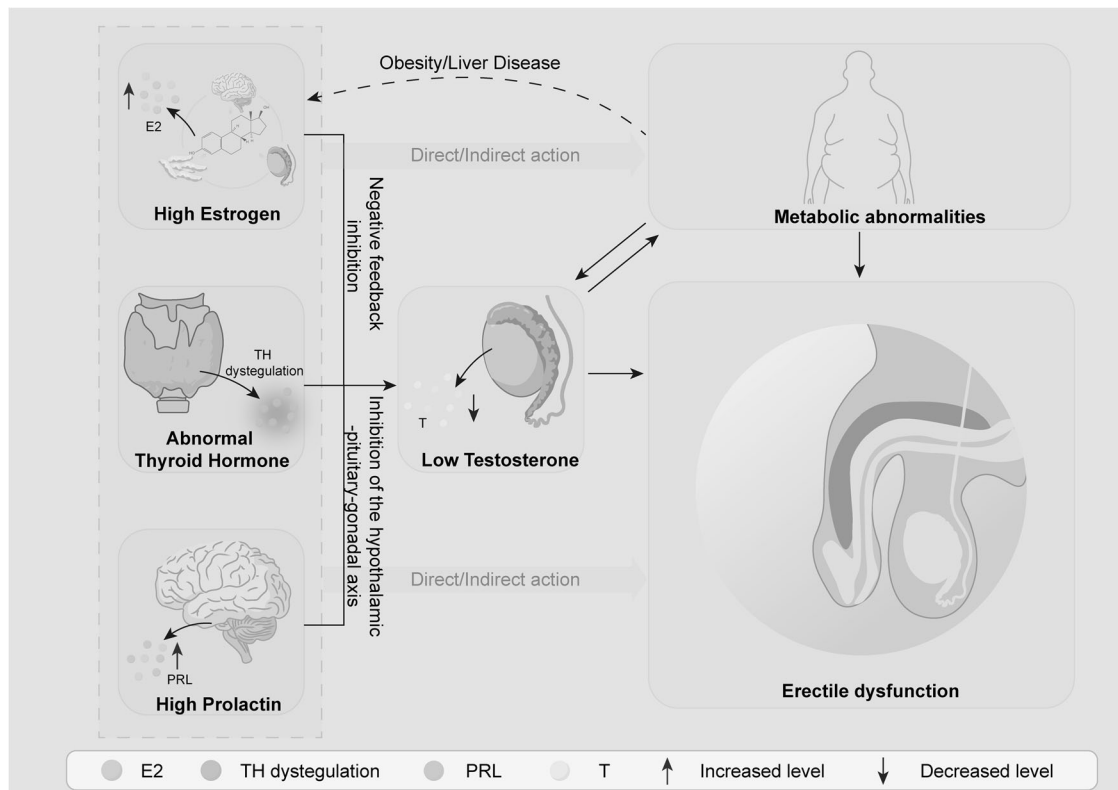
Although the exact mechanisms remain debated, increasing evidence supports a link between hyperthyroidism and ED. According to clinical evidence, severe ED occurs in 62% of men with overt hyperthyroidism and in 25% of those with subclinical disease, frequently presenting as a lack of spontaneous organic erections [58]. Mechanistically, thyroid hormones in hyperthyroid states upregulate  $\beta$ -adrenergic receptors, increasing sensitivity to catecholamines and thereby inhibiting relaxation of penile cavernosal arteries [59]. In addition, thyroid hormone receptors have been identified in human cavernosal tissue, suggesting a direct role in impairing NO-mediated vasodilation. Epidemiological evidence reinforces these findings [60]. A 2024 systematic review showed that restoration of euthyroidism—through antithyroid drugs, surgery, or radiotherapy—leads to significant improvements in International Index of Erectile Function (IIEF) and Sexual Health Inventory for Men (SHIM) scores, particularly in erectile function and sexual satisfaction [61].

Overall, whether caused by hypothyroidism or hyperthyroidism, sexual dysfunction is often markedly reversible once thyroid function is normalized. Given the high prevalence of thyroid disorders among young men, systematic screening and early treatment hold substantial clinical value for preventing and managing ED [62, 63].

### The interaction between hormones and metabolic health

In male health, hormonal balance is fundamental not only to reproductive function but also to metabolic regulation. Testosterone, estrogen, PRL, and thyroid hormones interact to maintain endocrine homeostasis and influence metabolic pathways that are closely associated with the development and severity of ED [6]. Among these, androgens—particularly testosterone—play a central role by sustaining sexual function while simultaneously regulating metabolic health.

Testosterone is converted into estrogen via aromatase, and the balance between these two hormones is critical. Testosterone deficiency results in relatively elevated estrogen, and disruption of this balance has been associated with MetS, obesity, insulin resistance, and ED. Wang et al. reported that men with low testosterone exhibit a higher incidence of MetS, which in turn further increases their risk of ED [64]. Excessive estrogen levels—arising from obesity, liver disease, or exogenous hormone supplementation—are likewise associated with metabolic disturbances and impaired sexual function, particularly in men with abdominal obesity. Evidence from experimental models indicates that estrogen influences fat distribution, vascular endothelial



**Fig. 2 Endocrine–metabolic interactions contributing to ED.** Diagram illustrating the bidirectional interactions between endocrine factors and metabolic disturbances in ED. Testosterone, estrogen, prolactin, and thyroid hormones interact to maintain endocrine homeostasis and regulate metabolic pathways. Disruption of this balance—such as androgen deficiency, estrogen excess, hyperprolactinemia, or thyroid dysfunction—contributes to metabolic abnormalities including obesity, insulin resistance, diabetes, and metabolic syndrome. In turn, these metabolic disturbances further impair hormonal regulation by altering sex hormone synthesis, increasing aromatase activity, and disrupting hypothalamic–pituitary–gonadal axis function, thereby creating a self-reinforcing cycle. This endocrine–metabolic crosstalk ultimately promotes endothelial dysfunction, metabolic imbalance, and impaired sexual function, leading to the onset and progression of ED.

function, and glucose metabolism, thereby predisposing men to metabolic disorders and exacerbating ED risk [65]. The interaction between testosterone and estrogen not only affects sexual function but also modulates energy balance through pathways involving insulin sensitivity and lipid metabolism. Clinical evidence suggests that the association between low testosterone and central obesity, insulin resistance, and hyperglycemia is well established [66]. This body of evidence provides a mechanistic rationale for the observed benefits of TRT on sexual function and metabolic parameters in selected patient populations.

The role of PRL in men is complex: while it supports reproductive health, it can also impair sexual function when dysregulated. Elevated PRL suppresses the hypothalamic–pituitary–gonadal axis, reducing testosterone synthesis and leading to decreased libido and ED [67]. Beyond reproduction, PRL also influences metabolic health by regulating lipid and glucose metabolism. Clinical evidence, particularly from patients with antipsychotic-induced hyperprolactinemia, shows that hyperprolactinemia is closely associated with insulin resistance and obesity, which in turn aggravate ED [68]. The negative feedback between PRL and testosterone is clinically relevant, as low PRL levels may reflect relative androgen excess in some contexts, whereas elevated PRL directly suppresses testosterone, negatively impacting both sexual and metabolic health [67]. Thus, modulation of PRL levels offers therapeutic potential for restoring sexual function and improving metabolic outcomes, particularly in men with obesity and diabetes.

Thyroid hormones, especially in hyperthyroidism, exert profound effects on male sexual function and metabolic regulation. Hyperthyroidism accelerates metabolism and disrupts energy

balance, thereby altering testosterone synthesis and metabolism and increasing the risk of ED [61]. Liu et al. reported that the prevalence of ED is significantly higher in hyperthyroid men than in healthy controls, with ED risk rising in parallel with thyroid hormone levels [69]. Thyroid hormones not only regulate sex hormone synthesis but also modulate glucose, lipid, and protein metabolism, contributing to insulin resistance and fatty acid dysregulation [70]. These metabolic disturbances commonly accompany hyperthyroidism and further exacerbate ED. Conversely, hypothyroidism is frequently associated with hypogonadism, which may increase ED risk through overlapping mechanisms [71].

The relationship between hormones and metabolic health is inherently bidirectional (Fig. 2). Low testosterone interacts with metabolic disorders such as MetS, obesity, and diabetes in a reinforcing cycle. Beatrice et al. found a negative correlation between the metabolic score and testosterone levels in men, particularly pronounced among those with diabetes and MetS [72]. These findings highlight the complex feedback mechanisms through which multiple hormones jointly influence metabolic health and sexual function in men.

#### Management for ED related to low testosterone levels

For men with testosterone deficiency, TRT remains the cornerstone of management [73]. Conventional formulations include oral, injectable, and transdermal gel preparations. Novel oral testosterone undecanoate formulations significantly increase serum testosterone levels in hypogonadal men and demonstrate good safety and tolerability with long-term use [74]. However, discontinuation of therapy often results in recurrent hypogonadism, underscoring the need for long-term follow-up and dynamic

monitoring. In a 12-year follow-up study, injectable formulations have been shown to improve ED, reductions in cardiovascular and metabolic risk factors, and a potential decrease in prostate cancer incidence [75]. Nevertheless, dosing intervals and amounts must be individualized to avoid fluctuations in drug concentration and associated complications [76]. Transdermal gels, increasingly used in recent years, effectively restore serum testosterone to a normal range, eliminate injection-related discomfort, and improve patient adherence [77].

Although TRT enhances libido and overall sexual quality of life, its effect on erectile function alone is limited. Pencina et al. reported that TRT produces only small-to-moderate improvements in IIEF scores in men with low testosterone, highlighting the modest overall benefit and the need for careful patient selection [78]. Accordingly, in hypogonadal men with poor response to PDE5 inhibitors, combination therapy with TRT and PDE5 inhibitors is commonly considered, as this strategy achieves superior outcomes compared with either therapy alone [79].

Combination interventions represent a promising therapeutic direction. TRT combined with lifestyle modifications—such as weight loss, exercise, and dietary changes—may further enhance clinical outcomes, particularly in obese and diabetic patients, by improving insulin sensitivity, reducing body fat, and ameliorating glucose metabolism [80]. These metabolic improvements indirectly support the recovery of sexual function. Clinical and interventional studies suggest that regular exercise is associated with reduced oxidative stress, enhanced NO bioavailability, and improvements in serum testosterone levels and erectile function, supporting the concept that integrating pharmacotherapy with exercise may yield additional clinical benefits [81].

Emerging research has also investigated stem cell therapy for hypogonadism-related ED. Stem cells may restore tissue function by counteracting apoptosis, fibrosis, and inflammation associated with low testosterone through their self-renewal and differentiation capacities [82]. However, current clinical evidence remains limited, and further investigation is required to validate both efficacy and underlying mechanisms.

#### Treatment of ED related to abnormal estrogen levels

Estrogen exerts a biphasic effect on male erectile function, with both excess and deficiency impairing libido and erectile capacity. Therefore, the therapeutic goal is not simply to reduce or supplement estrogen, but rather to maintain the physiological balance of the T:E2 ratio.

For patients with estrogen excess or T:E2 imbalance, clinical interventions commonly include AIs and SERMs. AIs such as letrozole and anastrozole act by preventing androgen-to-estrogen conversion, thereby lowering circulating estradiol, restoring the T:E2 ratio, and improving sexual performance [83]. However, long-term use may reduce bone density, necessitating regular monitoring of bone metabolism and bone mineral density [84]. SERMs such as clomiphene and enclomiphene antagonize estrogen feedback, activate the hypothalamic–pituitary–gonadal axis, and increase LH and FSH secretion, thereby boosting endogenous testosterone while preserving physiological estradiol levels [83]. A 2024 review concluded that clomiphene significantly increased testosterone concentrations and improved hypogonadal symptoms such as libido and sexual function in many patients, although the degree of improvement varied across studies. Unlike TRT, SERMs do not suppress spermatogenesis, making them especially suitable for men who desire fertility preservation [85].

In contrast, men with estrogen deficiency often present with reduced libido. Although exogenous estrogen supplementation may partly improve sexual desire, it also suppresses testosterone synthesis and can worsen ED [41]. Therefore, it is not recommended for routine clinical use. Importantly, management should avoid excessively lowering estradiol. Evidence suggests that libido may decline when estradiol levels fall below approximately 10 pg/

mL, whereas markedly elevated estradiol levels are likewise detrimental to sexual function [86]. This E2 window highlights the need for dynamic monitoring of testosterone and estradiol during therapy, with careful drug and dosage selection to ensure efficacy and safety.

#### Treatment of ED related to abnormal prolactin levels

Abnormalities in PRL can contribute to male ED, though the underlying mechanisms and therapeutic strategies differ markedly between hyperprolactinemia and hypoprolactinemia. Hyperprolactinemia is a well-established pathogenic factor: excess PRL suppresses the hypothalamic–pituitary–gonadal axis, reduces gonadotropin release, and consequently leads to decreased libido and ED [87]. The 2023 Pituitary Society international consensus explicitly recommends dopamine agonists (DAs) as first-line therapy, which effectively lower PRL, increase testosterone levels, and improve sexual function in approximately 70–90% of patients [88]. In drug-induced hyperprolactinemia, medications should be adjusted or substituted under specialist supervision. If replacement is not possible and secondary hypogonadism is significant, TRT may be considered [89]. However, testosterone supplementation alone is generally insufficient to overcome central suppression of sexual function caused by elevated PRL, and correction of hyperprolactinemia remains the fundamental treatment. Importantly, although DAs improve sexual outcomes, they may exacerbate psychiatric disorders, warranting caution in patients with psychiatric history [90].

In contrast, growing recognition has emerged of the link between hypoprolactinemia and ED. Clinical studies suggest that low PRL is associated with MetS, insulin resistance, and dyslipidemia, and may impair central reward pathways, thereby reducing libido and contributing to ED [47]. At present, no established medication directly increases PRL. Management therefore focuses on avoiding overtreatment with DAs and addressing comorbidities. Because psychological factors such as anxiety and depression are common in men with low PRL, psychotherapy and cognitive-behavioral interventions represent important therapeutic options. Notably, some psychotropic medications, including certain antidepressants, can elevate PRL levels but may simultaneously cause sexual dysfunction, requiring careful risk–benefit assessment [43].

Hyperprolactinemia is commonly associated with obesity, insulin resistance, and adverse metabolic profiles. While current evidence for reducing PRL levels and improving metabolic outcomes primarily derives from pharmacological approaches such as dopamine agonists, lifestyle modifications including weight loss, dietary optimization, and regular physical activity may also confer benefits on insulin sensitivity and sexual function, either independently or in conjunction with medical therapy [91]. Ultimately, comprehensive management should integrate endocrine regulation, psychological support, and metabolic control to restore PRL balance and optimize erectile outcomes.

#### Treatment of ED related to thyroid hormone abnormalities

Thyroid dysfunction, including both hypothyroidism and hyperthyroidism, is closely associated with ED in men, and correction of the underlying thyroid abnormality often leads to significant improvement in sexual function. For hypothyroidism, levothyroxine, a synthetic form of thyroxine (T<sub>4</sub>), remains the standard replacement therapy [92]. Clinical evidence suggests that restoration of euthyroidism with levothyroxine may be associated with improvement in erectile function in some men with hypothyroidism. For example, an early study of 44 hypothyroid patients reported significant improvement in SHIM scores after treatment, with scores positively correlated with free T<sub>4</sub> levels [55]. In 2020, an RCT involving 40 subclinical hypothyroid men showed that levothyroxine therapy achieving euthyroidism was associated with significant increases in both IIEF-5 scores and cavernosal

arterial peak systolic velocity, whereas the control group remained unchanged [93]. These findings suggest that thyroid hormone replacement enhances endothelial function and improves sexual outcomes.

Treatment of hyperthyroidism likewise focuses on restoring thyroid function, typically through antithyroid medications (e.g., propylthiouracil or methimazole), surgical thyroidectomy, or radioactive iodine ablation [94]. Clinical evidence indicates that improvement in sexual function is closely linked to the achievement of euthyroidism. Krassas et al. found that among 27 hyperthyroid men treated with methimazole, SHIM scores improved significantly. Prior to treatment, 70.4% met ED criteria, whereas after treatment only 25.9% met diagnostic criteria for ED, with mean SHIM scores rising from 14.5 to 23.0 ( $P < 0.0001$ ) [55]. Another study of 34 hyperthyroid men similarly demonstrated that normalization of thyroid function significantly increased total IIEF scores, with the greatest improvements observed in erectile function and sexual satisfaction [95]. A comparative summary of endocrine-based therapeutic modalities, their hormonal and metabolic associations, and major clinical considerations is provided in Table 1.

### LIMITATIONS AND FUTURE PERSPECTIVES

Current evidence on the role of endocrine abnormalities in ED remains limited by several methodological and clinical factors. A substantial proportion of the available literature is derived from cross-sectional observational studies and small- to moderate-sized clinical cohorts, typically ranging from tens to several hundred participants, which inherently limits causal inference and precludes firm conclusions regarding temporal relationships between hormonal disturbances and ED. Second, mechanistic investigations are often fragmented, with many studies focusing narrowly on individual hormonal pathways rather than examining the integrated effects of multi-hormonal and metabolic networks. Third, evidence on the long-term safety, tolerability, and adherence of hormone-targeted therapies remains scarce, particularly with respect to long-term outcomes in diverse patient populations such as younger men, individuals with obesity, and individuals with diabetes.

To address these gaps, future research should increasingly prioritize large-scale, longitudinal, and multicenter studies to clarify the causal and temporal links between hormonal dysregulation and ED. Integrating multi-omics technologies such as genomics, proteomics, and metabolomics may yield a more holistic view of how testosterone, estradiol, PRL, thyroid hormones, and metabolic health interact in complex ways. In addition, real-world evidence is needed to evaluate both the effectiveness and safety of hormone-based and combination interventions across broader clinical settings. Ultimately, integrating hormonal balance with metabolic optimization, and tailoring interventions to individual endocrine–metabolic profiles, holds promise for advancing ED management toward precision and personalized medicine.

### CONCLUSION

Endocrine abnormalities—including androgen deficiency, estrogen imbalance, PRL dysregulation, and thyroid dysfunction—are central contributors to the development and progression of ED. Increasing evidence suggests that ED is not driven by a single hormonal disturbance but rather by complex, multi-hormonal interactions that are further compounded by metabolic dysregulation.

From a therapeutic perspective, available interventions include testosterone replacement, SERMs, AIs, DAs, and thyroid hormone replacement, all of which provide opportunities for individualized management. Yet, the limited efficacy of these monotherapies

**Table 1.** Endocrine-based therapeutic approaches and their hormonal–metabolic relevance in ED.

Therapeutic approach	Core indications	Hormonal associations	Metabolic associations	Advantages	Limitations / Cautions
Exercise & lifestyle intervention	Mild-to-moderate ED with MetS/obesity	↑T; optimized T/E2 ratio	Improves insulin resistance, blood lipids, and blood pressure	Favorable safety profile	Requires cardiovascular risk assessment prior to exercise initiation
Testosterone replacement therapy	Confirmed hypogonadism with ED	Exogenous T supplementation	Improves insulin sensitivity, body composition, and some glucose/lipid metabolic parameters	Improves libido and metabolic parameters	Risk of erythrocytosis; prostate-related issues; potential cardiovascular risk
Selective estrogen receptor modulators	Secondary hypogonadism, fertility desired	Blocks estrogen feedback, ↑endogenous T	May indirectly improve metabolism by restoring testosterone levels	Preserves fertility potential	Inconsistent improvement in erectile function; requires monitoring of hormone levels
Aromatase inhibitors	Obesity or age-related low T	↓E2, ↑T, improved T/E2 ratio	May indirectly improve metabolism in obesity-related low testosterone	Increases endogenous testosterone	Risk of decreased bone mineral density; limited evidence for ED efficacy
Dopamine agonists	Hyperprolactinemia-induced ED	↓PRL, ↑T	Hyperprolactinemia associated with metabolic syndrome	Targets the underlying etiology (elevated PRL)	Can cause nausea, hypotension, impulse control disorders
Thyroid function correction	ED with hypo-/hyperthyroidism	Normalizes T	Thyroid dysfunction increases metabolic and cardiovascular risks	Etiological treatment, ED often improves	Requires achieving and maintaining euthyroidism for months prior to reassessment

T, testosterone; E<sub>2</sub>, estradiol; PRL, prolactin; MetS, metabolic syndrome.

underscores the need for more comprehensive approaches. Integrating hormonal optimization with metabolic interventions may therefore represent a paradigm shift in ED management, moving beyond symptomatic relief toward precision medicine and holistic, multi-dimensional care.

## DATA AVAILABILITY

The data in this paper can be found by searching the listed references on PubMed, Web of Science, and Embase.

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## AUTHOR CONTRIBUTIONS

XH was responsible for writing the manuscript. ST and YJ participated in the literature screening. DG designed the structure of the article and assisted in manuscript preparation. DS and WC provided revisions to the manuscript. BJ contributed the research topic.

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### COMPETING INTERESTS

The authors declare no competing interests.

### ADDITIONAL INFORMATION

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