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Review

Androgens and erectile dysfunction: from androgen deficiency to treatment

Yuan Wang, MS and Rui Jiang, MD, PhD*

Department of Urology, The Affiliated Hospital of Southwest Medical University, Luzhou, 646000, China

*Corresponding author: Department of Urology, The Affiliated Hospital of Southwest Medical University, Luzhou, 646000, China.
Email: jiangrui@126.com; jiangrui610@swmu.edu.cn.

Abstract

Introduction: Androgens play important roles in regulating the growth and development of the male reproductive system and maintaining libido and erectile function. The specific mechanisms by which androgen deficiency leads to erectile dysfunction (ED) are not yet fully understood.
Objectives: To understand the mechanisms and treatment of androgen deficiency–related ED.
Methods: A literature search in the past 10 years was conducted in PubMed and Google Scholar to determine the effects of androgen deficiency on erectile function and the treatment of androgen deficiency.
Results: Androgen deficiency can be caused by hypothalamic-pituitary lesions and injuries, testicular-related diseases and injuries, endocrine and metabolic disorders, the side effects of medication, and age. Androgen deficiency can lead to ED by inhibiting the NOS/NO/cGMP pathway (nitric oxide synthase/nitric oxide/cyclic guanosine monophosphate) and altering the expression of ion channel proteins, as well as by inducing oxidative stress, death, and fibrosis in penile corpus cavernosum cells. Testosterone replacement therapy is effective at improving the serum testosterone levels and erectile function in patients with androgen deficiency. For patients who need to maintain a low androgenic state, erectile function can be improved by lifestyle changes, treatment with phosphodiesterase type 5 inhibitors, low-intensity extracorporeal shock wave therapy, and stem cell therapy.
Conclusions: Androgen deficiency can affect the structure and function of the penile corpus cavernosum, leading to ED. Areas of further study include how androgen replacement therapy can improve erectile function and how to improve the maintenance of erectile function in patients with hypoandrogenic status.

Keywords: androgens; erectile dysfunction.

Introduction

Androgens, which are steroid hormones, include testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, and dehydroepiandrosterone sulfate. Androgens are produced mainly by the testes, ovaries, adrenal glands, placenta, brain, and skin.[1] The testes and ovaries are the main organs that produce testosterone, which is metabolized in target tissues by the enzyme alpha-reductase to produce the more reactive dihydrotestosterone.[2] Androgen production at different sites is regulated by different factors. The hypothalamic-pituitary-gonadal (HPG) axis has an important role in regulating androgen production. Gonadotropin-releasing hormone is secreted by the hypothalamus; it acts on the pituitary via the hypothalamic-pituitary portal circulation to stimulate the secretion of gonadotropins, mainly luteinizing hormone and follicle-stimulating hormone. Luteinizing hormone acts on the Leydig cells of the testes and the membranous cells of the ovaries in a way that causes them to produce testosterone, which negatively regulates the hypothalamus and the pituitary gland.[3] Although androgens play roles in many organs throughout the body, their most important role is the regulation of sexual and reproductive development. Hypogonadism can lead to androgen deficiency.[4] Androgens help maintain and regulate the growth and function of a range of cells in penile tissue. Endothelial progenitor cells, smooth muscle cells, and cavernous sinusoids are significantly reduced in the cavernous body of the penis of denuded rats, and testosterone supplementation restores the number and function of these cells.[5,6] Androgen deficiency also leads to alterations in signaling pathways such as the nitric oxide (NO) pathway in penile tissues, as well as to a decrease in elastic fibers and a significant increase in collagen fibers, both of which ultimately lead to erectile dysfunction (ED).[7,8] ED refers to the persistent inability to achieve and maintain sufficient erectile capacity to achieve satisfactory sexual behavior.[9] Therefore, understanding the causes of androgen deficiency and its effects on erectile function can help prevent and treat ED due to androgen deficiency.

Methods

A complete literature search was conducted on published peer-reviewed articles in the PubMed and Google Scholar databases, including original research and systematic reviews. The search terms were as follows: androgen, androgen deficiency, hypogonadism, orchiectomy, testosterone, testosterone replacement therapy, erection, erectile dysfunction, and treatment. This article summarizes what we consider to be the most important research findings.

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Table 1. Pathophysiologic factors of androgen reduction.

Classification	Disease or injury	Mechanisms of androgen reduction	Studies
Hypothalamic-pituitary lesions and injuries	Prader-Willi syndrome, craniocerebral tumor, and traumatic brain injury	Regulation of androgen production by destroying the HPGA	Napolitano et al, 2021[11]; Li uet al, 2022[13]; Baydar et al, 2021[14]; Schneider et al, 2007[16]
Testicular-related diseases and injuries	Ischemia–reperfusion injury, testicular cancer, orchitis, testicular torsion, and cryptorchidism	Inhibition of androgen synthesis by Leydig cells	Mohamed et al, 2021[18]; Hisasue et al, 2018[20]; Li et al, 2021[21]; Clarke et al, 2018[22]
Endocrine and metabolic disorders	Diabetes, obesity, and hyperthyroidism	Reduce testosterone production	Anupam et al, 2020[25]; Gianatti et al, 2020[26]; Molina-Vega et al, 2019[27]; Kjaergaard et al, 2021[29]
Side effects of clinical treatment	Abuse of androgens, psychotropic drugs and painkillers, tumor resection, and side effects of chemotherapy and radiotherapy	Effect of HPGA on androgen regulation	Koch et al, 2023[31]; Rasmussen et al, 2016[32]; Salata et al, 2022[33]; Asker et al, 2022[34]; Thirumalai et al, 2022[35]
Age	Aging	HPGA disorder and decreased testosterone synthesis	Kaufman et al, 2019[36]; Bhasin et al, 2011[37]; Harman et al, 2001[38]; Anawalt et al, 2022[40]

Abbreviation: HPGA, hypothalamic-pituitary-gonadal axis.

Results and discussion

Causes of androgen deficiency and its effect on erectile function

As one of the most important classes of sex hormones in the body, androgens are regulated centrally and peripherally and are usually maintained in a relatively balanced state. Androgen deficiency may result when certain diseases affect the central nervous system or the sex organs. The prevalence of androgen deficiency is as high as 20% in adolescent and young adult males, and androgen levels tend to decrease over time.[10] There are many causes of androgen deficiency (Table 1).

Hypothalamic-pituitary lesions and injuries

The injury or disruption of the hypothalamus and pituitary gland disrupts the regulation of androgen production through the hypothalamus-pituitary-gonadal axis, leading to a decrease in androgen production. Prader-Willi syndrome is a rare genetic disorder characterized by hypogonadism and mental retardation and is associated with the absence of a functional paternal copy of chromosome 15q11-q13. In individuals with Prader-Willi syndrome, hypothalamic and pituitary dysfunction reduces androgen production and ultimately leads to ED.[11] Patients with pituitary tumors, craniopharyngiomas, or ventricular meningiomas may have enlarged tumors that compress the pituitary gland, resulting in significantly lower androgen levels; in such cases, the size and histologic type of the tumor are associated with erectile function, and surgical removal of the tumors to relieve compression can improve androgen levels and erectile function.[12-15] Hypopituitarism following brain injury (eg, traumatic brain injury or aneurysmal subarachnoid hemorrhage) can lead to reduced androgen levels and ED. Lesions of or damage to the hypothalamus and pituitary gland cause the HPG axis to lose its ability to regulate androgens, and these alterations may cause a lack of androgen in the body.

Testicular diseases and injuries

Leydig cells of the testis are the primary cells that produce androgens, which they synthesize from cholesterol.[17] Diseases and injuries associated with the testis can affect the function of Leydig cells in synthesizing androgens. Ischemia reperfusion is the most common form of testicular injury, which mainly involves oxidative stress, inflammatory reactions, and a decrease in androgen levels. Paeonol (2′-hydroxy-4′-methoxyacetophenone) has antioxidant stress and anti-inflammatory effects, which can reduce oxidative stress and inflammation after testicular ischemia–reperfusion injury and prevent a decrease of serum testosterone levels in rats. It is a potential drug for treating ischemia–reperfusion injury.[18] However, there are currently no reports of this compound being applied to patients. Testicular cancer, the most common solid tumor in young men, can be treated with orchiectomy, chemotherapy, and radiation, but all of these modalities increase the risk of androgen deficiency.[19,20] Bacteria and viruses are common causes of testicular inflammation, and high-throughput sequencing has shown that the presence of an inflammatory microenvironment induces senescence and apoptosis of Leydig cells and thereby suppresses androgen production.[21] Animal studies have demonstrated that testicular torsion has little effect on Leydig cells or androgens for a short period after torsion but, after 5 hours, leads to a significant decrease in Leydig cell function and androgen production.[22] In patients with cryptorchidism, surgery after the age of 2 years does not prevent fertility deterioration or androgen deficiency, and surgery before the age of 2 years is needed to minimize the impact on fertility and androgen levels.[23] Exposure to heavy metals (cadmium and lead) and chemicals (formaldehyde and benzene) can also cause testicular damage, ultimately affecting Leydig cell function and androgen production and leading to ED.[24]

Endocrine and metabolic disorders

Androgens regulate endocrine functions and metabolism, and endocrine and metabolic disorders (eg, diabetes mellitus, obesity, and hyperthyroidism) can affect androgen synthesis and secretion. Decreased androgen levels are common in men with diabetes mellitus, especially men with type 2 diabetes mellitus. This association is characterized mainly by a normal gonadotropin response to gonadotropin-releasing hormone stimulation but an inverse relationship between body mass index and androgen levels.[25,26] Insulin resistance, inflammation, and oxidative stress induced by prolonged

hyperglycemia may be the main causes of decreased androgen levels in such individuals.[26] Obesity itself is also a major cause of decreased androgen levels. In a group of young men who were nondiabetic and obese, approximately 25% had hypoandrogenemia.[27] Factors such as altered levels of micronutrients (eg, zinc, vitamin A, and vitamin E) and excess adiposity in the bodies of obese men may be the primary causes of decreased androgen levels, and weight loss can significantly improve androgen levels.[28] Thyroid hormones secreted by the thyroid gland regulate testicular and penile corpus cavernosum development and sex hormone bioavailability by increasing hepatic nuclear factor 4 alpha concentrations, which in turn increases the concentrations of sex hormone–binding globulins. Because sex hormone–binding globulin has a greater binding affinity for testosterone than estradiol, increased sex hormone–binding globulin levels in individuals with hyperthyroidism can lead to ED.[29] Androgens can be metabolized into estrogen under the action of peripheral aromatase. The low level of androgen and the imbalance between androgen and estrogen can further cause endocrine and metabolic disorders.[30]

Side effects of medication

A variety of clinical treatments may lead to decreased androgen levels and ED by affecting androgen production and secretion. Although anabolic androgens (AASs) can effectively alleviate the clinical symptoms caused by androgen deficiency, abuse of AASs leads to a decrease in androgen levels and a significant decrease in serum testosterone years after discontinuation of the drug. This is mainly attributed to the fact that the drastic elevation in androgen levels that occurs after abuse of AASs inhibits androgen regulation via the HPG axis.[31] Some drugs used to treat psychosis (eg, risperidone, olanzapine, and quetiapine) can cause decreased androgen levels by increasing serum prolactin levels through blockade of dopamine receptors, which can lead to ED.[32] Opioids affect sexual function primarily by affecting the HPG axis, and approximately half of long-term opioid users are affected by sexual dysfunction.[33] Androgen deficiency and ED occur in patients with prostate cancer who are undergoing postradical androgen deprivation therapy.[34] The side effects of medication for prostate cancer, testicular cancer, leukemia, lymphoma, and other diseases may include damage to organs such as the testes, leading to decreased androgen synthesis and ED.[35]

Aging

Aging is an important cause of decreased androgen levels and sexual dysfunction in men. Many cross-sectional and longitudinal studies have shown (1) that serum testosterone levels peak in the second and third decades of life and then decrease gradually at a rate of approximately 1% per year and (2) that total and free testosterone concentrations are lower in older men than younger men, even when the effects of obesity, sampling time, comorbidities, drug use, and lifestyle factors are excluded.[36,37] A 9-year longitudinal mass spectrometry study showed that serum total and free testosterone concentrations decreased at annualized rates of 2.0% and 2.9%, respectively, in men with a baseline age of 75 years.[38] In a cross-sectional study of >10 000 Australian men 35 to 100 years of age, total serum testosterone levels measured by mass spectrometry decreased progressively at a rate of approximately 0.5% per year after 35 years of age, followed by a more rapid decrease between 60 and 70 years and a still more rapid decrease after 80 years.[39] Aging-associated decreases in androgen levels are mainly associated with decreased secretion of gonadotropin-releasing hormone and decreased responsiveness of testicular interstitial cells to stimulation by luteinizing hormone as a result of disorders of the HPG axis.[40] In addition, obesity, long-term use of drugs such as opioids or corticosteroids, and systemic diseases can further affect the function of the HPG axis and testicular interstitial cells.

Molecular mechanisms of ED due to androgen deficiency

The process of male penile erection is complex in that it requires blood vessels, nerves, and muscles to work together; thus, the structural and functional integrity of these tissues plays an important role in penile erection. Under conditions of sexual stimulation, nerve endings release diastolic factor, which acts on vascular endothelial cells and smooth muscle cells, leading to arterial vasodilatation and congestion; the congested arteries further prevent venous blood from returning to the venous sinus, which ultimately leads to penile erection.[41] The NO/cyclic guanosine monophosphate (NO/cGMP) signaling pathway may be the most important pathway that acts on the penile vasculature and smooth muscle; it also plays an important regulatory role in the erectile process. Nerve cells and endothelial cells in the corpus cavernosum produce and release NO synthase (NOS), which activates guanylyl cyclase and produces cGMP; this reduces the inward flow of Ca^{+}, leading to smooth muscle relaxation and penile erection.[42] Androgen deficiency can affect endothelial and smooth muscle cells by affecting endothelial NOS (eNOS) activity, the opening and closing of ion channels, oxidative stress, apoptosis, and fibrosis through a variety of pathways leading to ED (Figure 1).

Androgen deficiency inhibits the NOS/NO/cGMP pathway

eNOS activity is regulated in a variety of ways, including post-translational phosphorylation, eNOS coupling, and protein-protein interactions. ATP is an important signaling molecule in the activation of NOS, and the purinergic receptors P1 (including the A1, A_{2A}, A_{2B}, and A3 isoforms) and P2 (P2X and P2Y) are involved in the metabolism of ATP.[43] Androgen deficiency inhibits the AKT/eNOS/cGMP signaling pathway and cAMP production in the corpus cavernosum of denuded rats by downregulating the expression of A_{2B} receptors, leading to ED.[44] P2X receptors are nonselective cation channel proteins; adenosine triphosphate released by sympathetic nerves acts on the P2X1, P2X2, and P2X4 receptors of vascular smooth muscle cells to cause contraction of smooth muscle cells, a process that is associated with the activation of RhoA/Rho-kinase. In the penile corpus cavernosum of denuded rats, expression of the P2X1, P2X2, P2X3, ROCK1, and ROCK2 proteins was significantly elevated, whereas the animals' serum testosterone concentrations, maximum intracavernous pressure/mean arterial pressure, NO levels, and phospho-eNOS/eNOS ratios were significantly reduced. This may be one of the mechanisms by which androgen deficiency leads to ED.[8] Activated P2Y receptors couple with G proteins to activate phospholipase C and calmodulin (CaM), and calcium/CaM binds to the CaM-binding domain of eNOS, leading to a conformational change in and activation of eNOS. CaM also activates calcium/CaM-dependent protein kinase II, leading to the phosphorylation

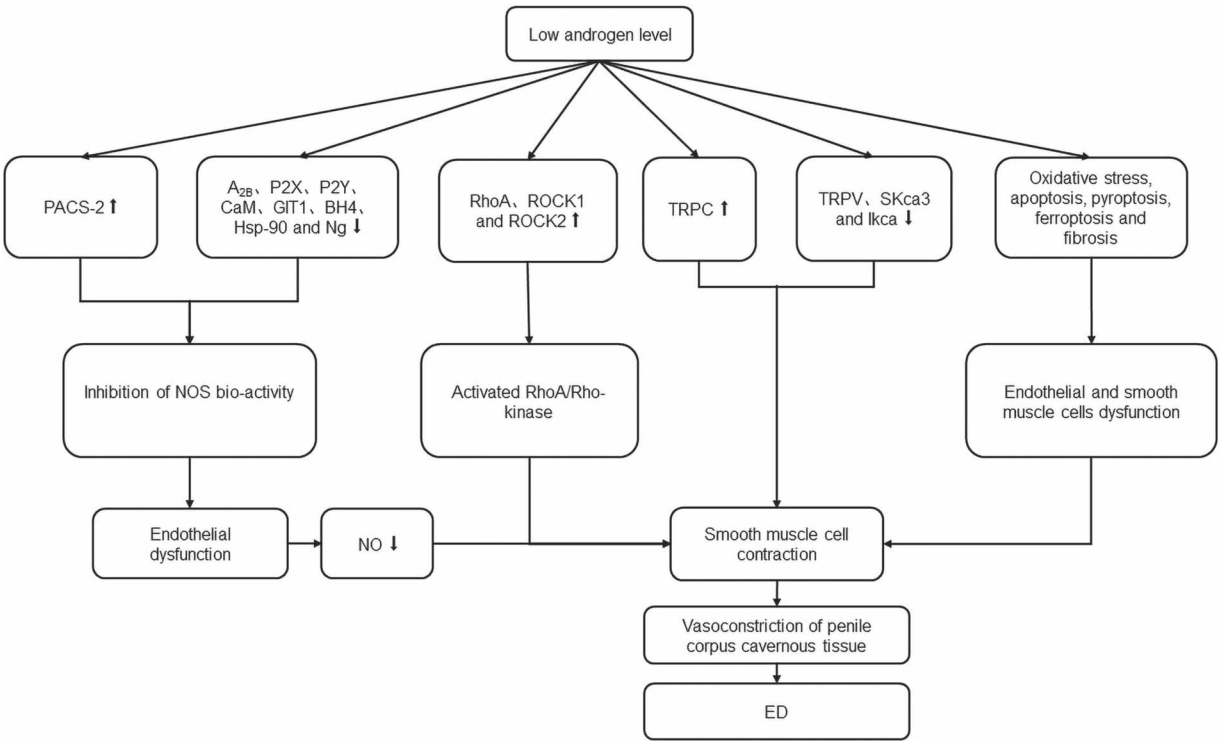

Figure 1. The pathophysiological mechanism of low androgen levels leading to ED. The increased expression of PACS-2 and the decreased expression of A2B, P2X, P2Y, CaM, GIT1, BH4, Hsp-90, and Ng caused by low androgen status inhibit the bio-activity of NOS, leading to endothelial dysfunction and reduced NO production, ultimately causing contraction of smooth muscle cells in penile corpus cavernosum. Low androgen status can directly lead to smooth muscle cell contraction by activating RhoA/Rho kinase. Low androgens status can also promote smooth muscle cell contraction by up-regulating TRPC channel expression and down-regulating TRPV, SKca3, and Ikca channel expression. In addition, low androgen level can cause cellular oxidative stress, apoptosis, pyroptosis, ferroptosis, and tissue fibrosis changes, leading to dysfunction of endothelial cells and smooth muscle cells. Contraction of smooth muscle cells in the penile corpus cavernosum causes ED. ED,Erectile Dysfunction; PACS-2, Phosphofurin acidic cluster sorting protein 2; P1 (A2B) and P2 (P2X and P2Y), Purine receptors;CaM, calmodulin;GIT1, G protein-coupled receptor kinase interactor 1; BH4, tetrahydrobiopterin;Hsp-90, heat shock protein-90;Ng, neurogranulin;RhoA,Ras homolog gene family member A; ROCK, Rho-associated coiled-coil kinase;TRPC,Transient receptor potential canonical;TRPV,Transient receptor potential vanilloid; NOS,Nitric Oxide Synthase; NO,Nitric Oxide.

of eNOS and further activation of EnoS.[45] A hypoandrogenic state downregulates P2Y1, P2Y2, P2Y4, and P2Y6 receptor expression and decreases the ratio of phospho-eNOS/eNOS and eNOS activity.[46] Androgen deficiency leads to elevated levels of PACS-2: a proapoptotic protein that is expressed in the mitochondria-associated membrane and binds to the dephosphorylated apoptotic protein Bid, initiating apoptosis-related pathways and inhibiting the phosphorylation of eNOS, which in turn reduces the synthesis and release of NO and inhibits erectile function.[47] GIT1 (G protein–coupled receptor kinase interactor 1) also interacts with eNOS, leading to eNOS phosphorylation, and androgen deficiency decreases GIT1 expression and thus inhibits eNOS phosphorylation.[48]

eNOS monomers form eNOS dimers that catalyze the production of NO, and tetrahydrobiopterin (BH4) is a key cofactor in stabilizing the activity of eNOS dimers. De novo synthesis of BH4 by eNOS involves the sequential activation of 3 enzymes; the major control point in this synthetic pathway is GTP cyclohexyl hydrolase I, and the recycling and recovery pathway ensures that the level of BH4 is maintained strictly within the normal physiologic range. However, BH4 is prone to self-oxidation, leading to the release of superoxide radicals and inflammation and the production of BH2, a nonactive form of BH4 that reduces its bioavailability.[49] Androgen deficiency leads to a decreased BH4/BH2 ratio and elevated levels of 3-nitrotyrosine, inducing eNOS uncoupling.[50] BH4 can be oxidized to BH2 by increased O_2^- via an oxidation reaction with NO to generate peroxynitrite; this reduces the activity and stability of the eNOS dimer and leads to eNOS uncoupling. Nitration of tyrosine residues of proteins to 3-nitrotyrosine by oxynitrite also induces eNOS uncoupling.[51] Oxidative stress has been observed in the penile tissues of denuded rats, but whether the conversion of BH4 to BH2 that occurs in the hypoandrogenic state is related to the oxidative response is unclear and requires further investigation.

eNOS interacts with a variety of proteins, resulting in its activation and in the promotion of NO formation and release. Heat shock protein 90, CaM, vesicle protein 1, and NOS-interacting protein can increase NO production by interacting with eNOS.[52,53] In the penile corpus cavernosum, CaM can activate calcium/CaM-dependent protein kinase II, leading to the phosphorylation of eNOS, a process that is regulated by the activation of the P2Y receptor.[45] Neurogranulin is a calcium-sensitive CaM-binding protein. Androgen deficiency inhibits neurogranulin expression in rat penile corpus cavernosum tissue, leading to elevated CaN expression, and high expression of CaN reduces eNOS phosphorylation and NO production by inhibiting AKT phosphorylation.[54]

Androgen deficiency inhibits the NOS/NO/cGMP pathway by altering neuronal NOS (nNOS) expression. The number of small nNOS-positive branches in the dorsal penile nerve shows a significant correlation with erectile function.[55] An increase in nNOS phosphorylation and uncoupling in the penile corpus cavernosum affects nNOS function and the

NOS/NO/cGMP pathway, ultimately leading to ED.[56] Androgens can regulate nNOS production and function by interacting with the androgen receptor.[57,58] In animal experiments, denervation leads to a decrease in arterial nNOS expression, whereas the vasodilatory responsiveness of NO donor sodium nitroprusside is unaffected, and supplementation with testosterone or dihydrotestosterone elevates nNOS expression.[59]

Androgen deficiency alters ion channel protein expression

Smooth muscle contraction and diastole are related mainly to the opening and closing of Ca^+ channels, a process that is also affected by K^+. Thus, androgen deficiency can affect erectile function by altering the status of Ca^+ and K^+ channels.

The major types of Ca^+-permeable channels are transient receptor potential channels, ligand-gated cation channels (P2Xs), and cyclic nucleotide-gated channels. TRPC proteins comprise a superfamily of Ca^+-permeable cation channels that are located in the cell membrane, and activation of TRPC proteins induces smooth muscle contraction. Androgen deficiency upregulates the expression of TRPC3, TRPC4, and TRPC6 in rat penile corpus cavernosum tissues, and activation of TRPC4 promotes Ca^+ entry into the cell, causing smooth muscle contraction through voltage-dependent calcium channels and leading to ED.[60] Similarly, androgen deficiency leads to decreased expression of the TRPC subfamily proteins TRPV3 and TRPV4, an alteration that inhibits acetylcholine-induced NO-dependent vasodilation and NO-independent endothelium-dependent hyperpolarization (EDH) pathway–induced vasodilation.[61] P2X receptors, which include 7 isoforms (P2X1-7), are a class of nonselective cation channel proteins that are distributed mainly in smooth muscle cells, epithelial cells, neurons, and endothelial cells in various tissues. Androgen deficiency–induced increases in the expression of P2X1 and P2X2 may lead to ED by affecting smooth muscle cell contraction.[8] In addition, increased intraendothelial calcium concentrations cause the opening of SKCa3 (small conductance calcium-activated potassium channel 3) and IKCa (intermediate conductance calcium-activated potassium channels), thereby creating hyperpolarizing potentials that activate smooth muscle cells through endothelial–smooth muscle cell gap junctions or through K^+ efflux, leading to smooth muscle cell hyperpolarization and vasodilation. Androgen deficiency can downregulate the expression of SKCa3 and IKCa, inhibit vasodilation, and lead to ED.[62] Current studies have focused on observing the effects of androgen deficiency on the expression of ion channel proteins in the penile corpus cavernosum of animals; fewer studies have reported the effects of low androgen status on penile corpus cavernosum endothelial and smooth muscle cell ion channels at the cellular level. Studies performed at the cellular level can more directly reveal the effects of androgen deficiency on ion channels in penile cavernous endothelial cells and smooth muscle cells; thus, the effects of androgen deficiency on ion channels need to be further explored.

Androgen deficiency induces alterations, including oxidative stress, cell death, and tissue fibrosis, in penile corpus cavernosum cells

Androgens regulate endothelial progenitor cells in penile tissue, and androgen-deficient rats have significantly fewer endothelial progenitor cells in the cavernous body of the penis.[5] Observation of the ultrastructure of the cavernous body of the penis in denuded rats revealed that the amount of smooth muscle, the area of the cavernous sinus, and the total area of the cavernous body of the penis were significantly reduced in rats that underwent orchiectomy.[6]

One of the mechanisms underlying ED is the increase in reactive oxygen species (ROS) levels in the corpus cavernosum tissue caused by androgen deficiency.[63] Oxidative stress and elevated ROS levels induced by androgen deficiency promote endothelial dysfunction; androgen supplementation therapy reduces ROS levels and thus improves erectile function through its antioxidant effects in deprived rats.[64] Depotting decreases the expression of antioxidant genes (*GCLC*, *GPX1*, *Prdx3*, *Prdx5*, *NQO1*, *Sod2*, *Sod3*, and *Hmox1*), and long-term administration of resveratrol and MitoQ upregulates the expression of several key antioxidant genes, including *Cat*, *SOD1*, *GSTM1*, and *Prdx3*.[65] Zinc improves erectile function by inhibiting xanthine oxidase/uric acid-induced oxidative stress and upregulating testosterone through Nrf2 signaling.[66]

Cell death involves multiple modalities and multiple signaling pathways. Androgen deficiency induces apoptosis of endothelial cells via the S1P1/Akt/FOXO3a signaling pathway.[67] PACS-2, which is highly expressed in animals with androgen deficiency, can act as a proapoptotic protein and release cytochrome C upon binding to the dephosphorylated apoptotic protein Bid, which activates the caspase 3 signaling pathway, leading to apoptosis of endothelial cells.[47] Furthermore, androgen deficiency inhibits autophagy and promotes apoptosis in cavernous smooth muscle cells by modulating BECN1-Bcl2 interactions.[68] In addition to oxidative stress and cell death, androgen deficiency can cause changes such as fibrosis in penile cavernous tissue.[69-71] These alterations ultimately affect the structure and function of endothelial and smooth muscle cells, ultimately causing ED.

Treatment of low androgen-induced ED

The primary goal of testosterone replacement therapy (TRT) is to ameliorate the signs and symptoms of testosterone deficiency, including decreased libido, ED, mood depression, anemia, and decreased muscle and bone mass, by bringing serum testosterone levels to levels within the normal physiologic range. TRT has been used for many years, and various pharmaceutical preparations are available to ameliorate androgen deficiency in vivo via oral, nasal, dermal, subcutaneous, and intramuscular routes (Tables 2 and 3). However, there is no uniform view regarding the route of administration and the specific treatment method when TRT is used to ameliorate androgen deficiency and the resulting ED, and the therapeutic efficacy and side effects of TRT are the first things that we should focus on.

Oral administration has the advantages of convenience and not causing pain, making it one of the most acceptable treatment modalities. Oral testosterone gel improves sexual function in patients who are hypoandrogenic, but the risks associated with testosterone therapy cannot be judged over a short period, such as 1 year.[72,73] A new oral formulation of testosterone undecanoate significantly improves testosterone levels in patients who are hypoandrogenic, and it is safe and effective for long-term administration (2 years).[74,75] However, the reemergence of hypogonadism in patients after cessation of testosterone therapy requires a search for new solutions.[76] Intravenous or intramuscular injections can be painful, and frequent injections tend to cause pain and redness at the injection site. Long-term treatment with testosterone undecanoate

Table 2. Basic research on testosterone replacement therapy.

Study design	Sample size	Therapy method	Study period	Result	Studies
RCT	45	Daily subcutaneous injection of 3 mg/kg of testosterone propionate	4 wk	TRT may improve erectile function by modulating EPCs in patients with hypogonadism	Hwang et al (2016)[5]
RCT	36	3 mg/kg of testosterone was subcutaneously injected every other day	4 and 8 wk	TRT may improve erectile function by inhibiting eNOS uncoupling	Xiong et al (2020)[50]
RCT	40	Received 100 mg/kg/mo of testosterone	1 mo	Testosterone reduced ROS production and increased phospho-eNOS/eNOS ratio in castrated rats	Li et al (2016)[64]
RCT	36	Injected with testosterone propionate (3 mg/kg) subcutaneously every other day after surgery	4 and 8 wk	Testosterone may improve erectile function by modulating fibrosis and NO synthesis	Chen et al (2021)[70]

Abbreviations: eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; NO, nitric oxide; RCT, randomized controlled trial; ROS, reactive oxygen species; TRT, testosterone replacement therapy.

Table 3. Clinical study of testosterone replacement therapy.

Study design	Sample size	Therapy method	Study period	Result	LOE/SOR	Study
Placebo-controlled experiments	790	Oral testosterone gel (5 g every day*)	1 y	Testosterone is maintained in the normal range and has moderate benefits to sexual function	2b/B	Snyder et al (2016)[72]
Randomized, active-controlled, open-label study	222	Oral testosterone undecanoate or topical testosterone (oral, 237 mg twice per day*; injectable: 60 mg every day*)	3-4 mo	Testosterone recovery to intermediate gonadal levels in hypogonadal cases	2c/B	Swerdloff et al (2020)[74]
Open, multicenter, randomized, active-controlled trial	69	Oral testosterone undecanoate (316 mg twice per day*)	2 y	Total serum testosterone was maintained in the physiologic range, and the sexual function was improved.	2c/B	Honig et al (2022)[75]
Randomized controlled trial	60	Intravenous injection of testosterone undecanoate and tadalafil (group 1, 1000 mg/ample + 10-20 mg of *tadalafil; group 2, 1000 mg/ample + 5 mg of *tadalafil)	36 wk	Erectile function has been significantly improved	1b/A	Park et al (2015)[77]
Longitudinal observation and study of a single center	126	Injection of testosterone decanoate (1000 mg/ample*)	12.1 y	Increasing intervals between TU injections were performed 44% more often in the elderly vs younger patients and time between TU injections were prolonged 4% more in the elderly patients.	2b/B	Abildgaard et al (2022)[79]
Open uncontrolled study	139	Topical testosterone replacement gel (start at 23 mg/d* and adjust to 69 mg/d* after 2 wk)	90 d	Serum testosterone levels return to physiologic range	2c/B	Cunningham et al (2017)[80]
Randomized, double-blind, placebo-controlled, parallel-group study	1161	Randomized to receive 1.62% testosterone gel or placebo gel	2 y	Testosterone replacement therapy improved hypogonadal symptoms and sexual desire but not erectile function.	2b/B	Pencina et al (2024)[81]
Open-label randomized trials	81	Intranasal testosterone gel or intramuscular testosterone cypionate (intranasal, 5.5 mg 3 times per day*; intramuscular, 200 mg* once every 2 wk)	2.2 y	It can increase the level of serum testosterone, and the effect of intramuscular injection is better.	2c/B	Rivero et al (2023)[86]

Abbreviations: LOE, level of evidence; SOR, strength of recommendation, TU: testosterone undecanoate, *Initial dose at start of treatment.

via injection with daily tadalafil significantly improves erectile function, which is well maintained even after treatment is stopped.[77] A 12-year clinical study showed that testosterone undecanoate injection therapy relieves ED, improves cardiovascular and metabolic risk factors, and reduces the incidence of prostate cancer.[78] However, long-term testosterone undecanoate injection therapy requires adjustment of the injection interval, regular clinical follow-up, and dose adjustment.[79] To avoid the pain caused by injections, a new topical testosterone replacement gel is being used to treat patients with hypogonadism, and it is effective at restoring men's serum testosterone levels to the physiologic range.[80] Although the TRAVERSE trial suggests that testosterone therapy can significantly improve overall sexual activity and libido in middle-aged and elderly men with hypogonadism, it cannot improve erectile function.[81] This may be related to the high prevalence of cardiovascular disease and diabetes among these patients, which may weaken the erectile response to TRT. Meanwhile, there are research reports noting that, for these patients, TRT combined with phosphodiesterase type 5 inhibitor (PDE5i) is better for improving erectile function than just 1 drug. This indicates that testosterone plays an important role in the erection process of male patients with hypogonadism.

A study found that exercise can reduce oxidative stress and increase the production of lactate, NO, and cortisol, thereby increasing total testosterone content and improving erectile function.[82] Therefore, strengthening exercise while administering medication can better improve the patient's testosterone levels and erectile function.

Although TRT can improve testosterone levels and erectile function in patients with low androgen levels, androgen abuse is becoming an increasing concern. The results of a prospective, cross-sectional, questionnaire survey showed that androgen abuse in the studied population was characterized by infertility (64.24%), ED (59.60%), abnormal semen and abnormal hormone levels (follicle-stimulating hormone, luteinizing hormone, testosterone, and estradiol; 94.70%), and decreased testicular size (50.33%) and that these populations were less aware of the adverse effects of androgen abuse.[83] The main adverse effects of TRT are acne, oily skin, elevated hematocrit, decreased fertility, and metastatic prostate and breast cancer, the latter of which are absolute contraindications to the use of testosterone.[84] In conclusion, TRT can be effective at improving serum testosterone levels and erectile function in patients who are androgen deficient, but it should be administered in consultation with a medical professional and discontinued in the event of adverse effects.[85]

Improved maintenance of erectile function in a low androgen state

TRT may improve erectile function by restoring serum testosterone, but some patients, such as those with prostate cancer or those who have an increased risk of prostate cancer, should avoid TRT and maintain androgens at lower levels.[87,88] Therefore, there is a need to find new ways to improve erectile function in patients who maintain a low androgen status. Lifestyle changes, PDE5is, low-intensity extracorporeal shock wave therapy (LI-ESWT), and stem cell therapy may be beneficial in improving erectile function in patients with low androgen status.

Regular physical activity improves erectile function through a variety of mechanisms, including raising androgen levels, regulating glucose and lipid metabolism, modulating arterial pressure, and increasing NO production.[89] Pelvic floor muscle exercises can improve blood circulation and muscle contractility, thereby effectively improving erectile function.[90,91] Smoking-related ED is mainly associated with endothelial damage, decreased NO availability, and oxidative stress, and smoking cessation is beneficial for recovery of erectile function.[92] Polyphagia, alcohol consumption, diabetes, and high blood pressure have been linked to the development of ED.[93] Therefore, moderate exercise, smoking cessation, and a healthy diet can improve erectile function.

PDE5is inhibit the degradation of cGMP by phosphodiesterase type 5 and thus increase the cGMP concentration within cells; this relaxes smooth muscle cells and increases blood flow to the penile corpus cavernosum, improving erectile function. Commonly used PDE5is such as sildenafil, tadalafil, vardenafil, and avanafil significantly improve erectile function when used alone or in combination with testosterone preparations.[94,95]

Shock wave therapy is a safe noninvasive treatment. LI-ESWT improves erectile function by increasing neovascularization, stimulating mechanosensors, improving microcirculation, and promoting nerve regeneration and the remodeling of tissues.[96,97] Observation of penile hemodynamics before and after treatment with LI-ESWT for 3 months revealed that LI-ESWT significantly improved penile hemodynamics.[98] The use of L-arginine and tadalafil with LI-ESWT results in significant efficacy and extends the duration of the effects of LI-ESWT.[99] In addition, patients with PDE5i-refractory ED experience great improvement in erectile function after the application of LI-ESWT.[100,101] LI-ESWT does not appear to affect androgen levels when applied to patients with ED and Peyronie's disease.[102] Although LI-ESWT does not directly affect serum androgen levels, it may improve function of endothelial cells and smooth muscle cells by increasing angiogenesis, improving microcirculation, and remodeling tissue. Stem cells can self-renew and differentiate to produce a variety of cell types; therefore, they have great therapeutic potential in repairing cellular damage. Animal experiments have demonstrated that stem cells can improve erectile function through numerous mechanisms. Transplanted mesenchymal stem cells can differentiate into neuron-like cells while increasing the cavernous collagen area, the number of cavernous neurons and endothelial cells, and smooth muscle content, and this in turn improves erectile function.[103] Transplantation of adipose-derived mesenchymal stem cells and bone marrow–derived mesenchymal stem cells into the corpus cavernosum of rats with ED increases the expression of eNOS, promotes vascular regeneration, reverses functional cellular damage, and restores erectile function in rats.[104] Human umbilical cord mesenchymal stem cells restore erectile function in aged rats by inhibiting TLR4, alleviating cavernous fibrosis, and increasing eNOS expression.[105] However, the role of stem cells in hypoandrogenic ED is unclear, and whether stem cell transplantation affects serum testosterone levels requires further study. Small clinical trials have demonstrated that stem cell therapy has a good safety profile and that it improves erectile function in the treatment of ED.[106] Yet, there is a lack of data from large randomized human phase 2 trials. Therefore, additional clinical studies are needed to determine the safety and efficacy of stem cell therapy for ED. The impact of stem cells on serum testosterone is currently unclear, although the self-renewal and differentiation ability of stem cells may

improve pathologic conditions such as apoptosis, pyroptosis, and fibrosis caused by low androgen levels. Therefore, LI-ESWT and stem cells have potential in the treatment of ED caused by low androgen level. Further research is needed on the efficacy and mechanism of LI-ESWT and stem cells in treating low-androgen ED.

Conclusion

Androgen deficiency can be caused by hypothalamic-pituitary lesions and injuries, testicular disease, testicular injury, endocrine and metabolic disorders, clinical treatments, and age. Androgen deficiency leads to ED because it inhibits endothelial cell function and smooth muscle cell diastole through several pathways, including inhibition of eNOS activity and alterations in ion channel protein expression, as well as induction of apoptosis, pyroptosis, ferroptosis, oxidative stress, and fibrosis in penile corpus cavernosum cells. TRT can improve erectile function by restoring androgen levels in the body and is currently the main treatment for androgen deficiency–induced ED. Moreover, how to improve and maintain erectile function in patients with long-term maintenance of low androgen status needs further study.

Author contributions

Conception and design: R.J. Acquisition of data: Y.W. Analysis and interpretation of data: Y.W., R.J. Drafting the article: Y.W., R.J. Revising it for intellectual content: Y.W., R.J. Final approval of the completed article: Y.W., R.J.

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Conflicts of interest

None declared.

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