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Testosterone and Erectile Function: From Basic Research to a New Clinical Paradigm for Managing Men with Androgen Insufficiency and Erectile Dysfunction

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Abstract

Objectives—Androgens are essential for the development and growth of the penis, and they regulate erectile physiology by multiple mechanisms. Our goal is to provide a concise overview of the basic research and how this knowledge can be translated into a new clinical paradigm for patient management. In addition, this new paradigm may serve as a basis for stimulating constructive debate regarding the use of testosterone in men, and to promote new, innovative basic and clinical research to further understand the underlying mechanisms of androgen action in restoring erectile physiology.

Methods—A literature review was performed utilizing the US National Library of Medicine's PubMed database.

Results—On the basis of evidence derived from laboratory animal studies and clinical data, we postulate that androgen insufficiency disrupts cellular-signaling pathways and produces pathologic alterations in penile tissues, leading to erectile dysfunction. In this review, we discuss androgen-dependent cellular, molecular, and physiologic mechanisms modulating erectile function in the animal model, and the implication of this knowledge in testosterone use in the clinical setting to treat erectile dysfunction. The new clinical paradigm incorporates many of the consensed points of view discussed in traditional consensed algorithms exclusively designed for men with androgen insufficiency. There are, however, novel and innovative differences with this new clinical paradigm. This paradigm represents a fresh effort to provide mandatory and optional management strategies for men with both androgen insufficiency and erectile dysfunction.

Conclusions—The new clinical paradigm is evidence-based and represents one of the first attempts to address a logical management plan for men with concomitant hormonal and sexual health concerns.

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1. Introduction

The health of the penile vascular tissues and the perineal and ischiocavernosus muscles that support the proximal penis is essential for normal erectile function [1–4]. The role of androgens in regulating erectile physiology in humans is of considerable importance and merits continued investigation. The literature is replete with articles and anecdotes suggesting that androgens have little or a passive role in erectile function. In contrast, a significant and accumulating body of knowledge suggests that androgens play an important role in erectile physiology in humans. These inconsistencies may be due to the fact that much of the literature is based on clinical studies with varying methodologies and patient populations. In addition, genetic, health, and cultural factors are usually not considered. Nevertheless, animal studies have provided some basic foundation for our understanding of erectile physiology and the role androgens play in this process. In this review, we discuss knowledge gained from animal studies to provide a succinct analysis of the cellular, molecular, and physiologic mechanisms of androgens in erectile physiology, and how such knowledge may be translated into a new clinical paradigm for the management of patients with androgen deficiency and erectile dysfunction (ED). Our objective is to engage readers in a constructive and stimulating debate regarding the use of testosterone in men, and to promote new, innovative basic and clinical research to further understand the underlying cellular and molecular mechanisms of androgen action in restoring erectile physiology.

2. Modulation of erectile physiology by androgens: cellular, molecular, and physiologic mechanisms

2.1. Testosterone regulates nerve structure and function

The studies of Meusburger and Keast [5] and Keast et al [6] have provided elegant demonstrations on the potential role of androgens in maintaining the structure and function of many pelvic ganglion neurons. They suggest that testosterone is critical for the maturation and maintenance of terminal axon density and neuropeptide expression in the vas deferens. Giuliano et al [7] suggested that testosterone acting peripherally to the spinal cord enhances the erectile response of the cavernous nerve. Rogers et al [8] demonstrated that castration altered the dorsal nerve ultrastructure in the rat concomitant with loss of erectile function. The authors further showed that testosterone treatment of castrated animals restored the nerve fibers and myelin sheath structure, similar to that observed in the sham (control) group. Baba et al [9,10] reported that the integrity of NADPH diaphorase-stained nerve fibers in the rat corpus cavernosum and dorsal nerve is dependent on androgens. Recently, we examined the effects of castration on the structural integrity and function of the cavernosal nerve (Traish et al, unpublished observations). We noted that there were marked structural changes in the cavernosal nerve from castrated animals compared with control (sham-operated animals) or castrated animals treated with androgens (Fig. 1). These structural alterations may be responsible in part for the marked reduction in the intracavernosal pressure (attenuated blood flow) observed in the experimental animals [11]. In addition, recent studies have demonstrated that penile erection in rats, elicited by stimulation of the medial preoptic area, is testosterone-dependent [12]. Thus, testosterone may regulate central mechanisms of penile erection, as well as peripheral neural mechanisms. Clearly, more in-depth investigations are warranted to define the exact role of androgens on the penile nerve network and to determine how androgens modulate penile response to sexual stimulation.

2.2. Testosterone regulates nitric oxide synthase expression and activity

The nitric oxide synthase/cyclic guanosine monophosphate (NOS/cGMP) pathway has been deemed critical for erectile function [13]. Nitric oxide (NO) mediates relaxation of the vascular smooth muscle of the resistance arteries of the corpus cavernosum and the trabeculae to

facilitate penile erection. A preponderance of evidence supports a role for androgens in regulating the expression and activity of NOS isoforms in the corpus cavernosum in animal models [14–25]. In castrated animals, testosterone or 5α-dihydrotestosterone (DHT) administration restored the erectile response and NOS expression in the penis [9–11,16,18, 19,21,23,24]. Interestingly, very few studies ventured beyond these initial observations demonstrating effects of testosterone on NOS expression. Further studies are needed to delineate the molecular basis of androgen receptor activation of the NOS genes and the battery of factors that modulate androgen receptor activity in penile tissue. While the focus on the NOS/cGMP pathway provided a stimulus for understanding the physiology of erection, many other pathways have received little attention. For instance, the role of prostanoids/eicosanoids and growth factors in regulating erectile physiology has yet to be fully investigated. Reassessment of the multiple pathways involved in this very critical physiologic function is warranted.

2.3. Testosterone regulates phosphodiesterase (type) 5

Phosphodiesterase (type) 5 (PDE5) hydrolyzes cGMP in vascular and trabecular smooth muscle into GMP. Activation of PDE5 terminates NO-induced, cGMP-mediated smooth muscle relaxation, resulting in restoration of basal smooth muscle contractility and penile flaccidity. In penile tissue, the balance between the intracellular levels of cGMP and GMP is primarily regulated by the activities of NOS and PDE5. Thus, it is likely that any disruption in the expression or activity of these enzymes will lead to pathophysiology. Castration has been shown to reduce the expression and activity of PDE5 in rabbits and rats [11,27,28], and androgen supplementation has been shown to upregulate the expression and activity of PDE5 [11,26–28]. Further, administration of PDE inhibitor alone to medically or surgically castrated animals has little effect on the intracavernosal pressure in response to pelvic nerve stimulation [27,29], suggesting that androgens are critical not only for regulating NOS activity, but also in modulating PDE5 activity. While these actions may be seen as a paradox, in that androgens are upregulating both signal initiators (NOS) and signal terminators (PDE5), we interpret this to be a homeostatic mechanism that maintains a relatively constant ratio of critical enzymes for this pathway (Fig. 2). We postulate that PDE5 expression may be controlled by NO. Upregulation of NOS by androgens may lead to increased NO synthesis, which then upregulates PDE5 expression and activity. Conversely, NOS downregulation by androgen deprivation results in downregulation of PDE5 expression and activity. Studies are underway to define this delicate and crucial mechanism in androgen action.

2.4. Testosterone regulates cellular growth and differentiation

Androgen deprivation by surgical or medical castration results in a significant reduction in trabecular smooth muscle content and marked increase in connective tissue deposition [26, 29]. These structural alterations are also associated with loss of erectile function. Using transmission electron microscopy, the cavernosal smooth muscle in castrated animals appears disorganized with a large number of cytoplasmic vacuoles, whereas, in the intact animals, the smooth muscle cells exhibit normal morphology and are arranged in clusters [1,8]. Shen et al [30] have demonstrated that the structure of the tunica albuginea in rats is also influenced by androgens. Four weeks after castration, the tunica was thinner with fewer elastic fibers, and the collagen appeared more disorganized. Depletion of elastic fibers and replacement fibrosis was also noted in intact rats treated with finasteride, although the thickness of the tunica did not differ from intact controls. Taken together, these results suggest that androgens have a profound effect on cellular structure and organization of the corpus cavernosum, and that these alterations may contribute to the loss of erectile function. Such studies have not been performed in human penile tissue.

In addition to the alterations in smooth muscle and connective tissue, fat-containing cells have been observed in the subtunical region of penile tissue sections from orchiectomized animals [31]. The alterations in cavernosal tissue composition and structure were accompanied by a reduced erectile response to pelvic nerve stimulation [11,31]. It is interesting to speculate that the presence of fat cells in the subtunical region of the corpus cavernosum may contribute to venous leakage in the orchiectomized or androgen-deficient animal. Abnormal deposition of fat-containing cells and reduced relaxation response to nitroprusside and acetylcholine has also been observed in penile corpus cavernosum of intact rabbits that were administered the endocrine disrupters bisphenol A and tetrachlorodibenzodioxin (TCDD) [32,33]. Specifically, bisphenol A has been shown to accelerate terminal differentiation of 3T3L1 fibroblasts into adipocytes through the PI_3 kinse pathway [34]. Interestingly, in developmental studies, Goyal et al [35–38] have shown that administration of estradiol valerate or the estrogen receptor agonist diethylstilbestrol into 2-day-old rats resulted in infertile mature animals (120 d) and accumulation of fat-containing cells in the penile corpus cavernosum. In contrast, animals treated with vehicle exhibited no fat-containing cells and remained fertile. The authors demonstrated that estrogen treatment was associated with low plasma testosterone levels, which may have contributed to alterations in penile anatomy and morphology, infertility, and ED. Since estrogens are known to act as antiandrogens in some tissues [39–41], these studies point to the potential importance of androgens in maintaining penile corpus cavernosum structure.

There is renewed interest in understanding the mechanisms by which androgens regulate growth and differentiation of vascular smooth muscle cells. Bhasin et al [42] and Singh et al [43,44] hypothesized that androgens promote the commitment of pluripotent stem cells into a muscle lineage and inhibit their differentiation into an adipocyte lineage. The total number of circulating vascular progenitor cells may also be dependent on testosterone levels [45]. Regulation of progenitor cell differentiation is a complex process, dependent on numerous hormones, growth factors, and specific activation of a cascade of gene expression [42,46–51].Critical regulators of adipocyte differentiation include C/EBPα (CCAAT/enhancer binding protein), PPARγ2 (peroxisome proliferator-activated receptor), and LPL (lipoprotein lipase) [47,48,52–57]. Alternatively, transdifferentiation of smooth muscle cells into other phenotypes may occur [58–61]. Inhibition of 5α-reductase activity induces stromal remodeling and smooth muscle dedifferentiation in the prostate, suggesting that 5α-DHT deficiency promotes smooth muscle dedifferentiation [62]. While these mechanisms of precursor cell differentiation or smooth muscle transdifferentiation have yet to be investigated in penile tissue, future studies using expression of biochemical markers as well as changes in ultrastructure are needed to test these hypotheses in the corpus cavernosum under varying states of androgen deprivation and supplementation. Thus, the penis is a unique model system that contains multiple tissue types with differing androgen responses. We postulate that, in the penile corpus cavernosum, androgens are critical for promoting and maintaining the myogenic lineage (Fig. 3).

2.5. Testosterone restores erectile function in diabetic animals

Zhang et al [63] have demonstrated that alloxan-induced diabetes in rabbit and streptozotocin-induced diabetes in rats resulted in reduced plasma testosterone and atrophy of androgen-dependent accessory glands. Supplementation with testosterone in diabetic rats increased the erectile response, and the expression of PDE5 and endothelial and neural NO synthases. In organ baths, relaxation to acetylcholine was enhanced in corpus cavernosum tissue strips from diabetic animals treated with testosterone. The authors concluded that normalizing plasma testosterone in diabetic animals restores NOS and PDE5, and reinstates sensitivity to relaxant stimuli and responsiveness to sildenafil in vivo.

2.6. Erectile function depends on a threshold dose of testosterone

Armagan et al [11] have demonstrated that erectile function in rats is maintained by a wide range of systemic testosterone levels, as low as 10–12% of normal physiologic plasma concentrations. However, below these concentrations, erectile function is significantly attenuated, and this attenuation is positively correlated with the plasma concentration of testosterone. Testosterone levels in the range of 10% of the normal physiologic plasma concentration may represent a threshold value, below which erectile function declines in a dose-dependent fashion. This concept of threshold value is supported by recent clinical studies [64]. Interestingly, in rats, prostate tissue mass was positively correlated to plasma testosterone levels across the entire range of testosterone concentrations examined. In addition, the significance of the correlation between plasma testosterone and androgen-dependent tissue growth (weights) was variable, with the seminal vesicles exhibiting the most significant correlation. These data suggest that different androgen-dependent tissues have varying sensitivities to circulating testosterone levels that can be manifested through both trophic and functional responses.

3. A clinical paradigm for the combined management of androgen insufficiency and ED

Androgens have been used to treat sexual problems [65] as well as to augment vasodilation [66–69] in patients with angina and claudication for more than six decades. In light of the established historic link of androgens to both facilitating sexual function and vasodilatory function, it is not surprising that the contemporary management of aging men and their sexual health concerns involves frequent use of PDE5 inhibitors and off-label use of androgens [70–76]. These clinical uses are based in part on the recent explosion of basic science and clinical data concerning androgens and erectile physiology [1,3,77–83]. Such basic science and clinical trial data support an evidence-based diagnostic and treatment paradigm for men with both androgen insufficiency and ED. Prevalence rates of androgen insufficiency and ED in aging men have been reported from 1.7% [84] to 35% [85], which translates to millions of men being afflicted with both disorders. In the following section, we outline an integrated approach for the management of men with both androgen insufficiency and ED, including step care strategies that engage identification of the hormonal and sexual problems, patient and partner education, modification of reversible causes, hormonal and nonhormonal therapies, and other treatments (Fig. 4). The remaining sections of this review encompass information from guidelines provided by the European Association of Urology, International Society of Andrology (ISA), and International Society for the Study of the Aging Male (ISSAM) [86]. In addition, we propose a new clinical paradigm for patient management based on knowledge gained from basic science research. The new clinical paradigm incorporates many of the consensed points of view discussed in traditional consensed algorithms exclusively designed for men with androgen insufficiency. There are, however, novel and innovative differences that represent a fresh effort to provide mandatory and optional management strategies for aging men with not just androgen insufficiency alone, but for men with both androgen insufficiency and ED.

3.1. Step care 1: Identification of androgen insufficiency and ED

Androgen insufficiency [82,83] is considered to exist as a syndrome in which there are (1) nonspecific signs and symptoms, such as low sexual interest, muscle weakness, feeling sad and melancholy, or having an inadequate erectile response to PDE5 inhibitors in a man with ED and (2) biochemical blood test values suspicious for low levels of physiologically relevant androgens. ED is the persistent or consistent inability to obtain and/or maintain a sufficient erection for satisfactory sexual activity [87]. Presenting symptoms exist in several other syndromes and vary widely among individuals. Thus, a detailed medical workup is required [4].

3.1.1. Sexual, psychosocial, and medication history—The sexual symptoms of androgen insufficiency are varied and include decreased sexual interest; diminished erectile quality, particularly of nocturnal erections; muted, delayed or absent orgasms; decreased genital sensation; and reduced sexual pleasure [82,83,86,88–90]. In addition, sexual dysfunction may affect the patient's self-esteem, coping ability, and occupational and social roles [4]. Androgen insufficiency is associated with changes in mood, diminished well-being, blunted motivation, changes in spatial orientation, reduced intellectual ability, fatigue, depression, and anger/irritability [82,83,86,88–90].

Failure to respond to a maximum dose of oral PDE5 with maximum erection hardness may be the first sign of androgen insufficiency [70–76]. This perspective is based on the observation that androgens may directly control the expression and activity of NOS in human corpus cavernosum [91–94]. The clinical responsiveness of PDE5 inhibitors appears to be strongly linked to NOS activity in vascular tissues [70–76].

3.1.2. Screening questionnaires—Screening questionnaires may be used to aid in the clinical diagnosis of androgen insufficiency. Androgen Deficiency of the Aging Male (ADAM) is useful for identifying the presence or absence of androgen insufficiency symptoms [95,96], but has poor specificity in aging men. The Aging Male Scale (AMS) is a more extensive, validated instrument [97]. The low testosterone screener of Smith and colleagues [98] is also useful to reliably detect androgen insufficiency. Similarly, ANDROTEST is a structured interview for the screening of androgen insufficiency in men with sexual dysfunction [99]. However, it should be noted that validated questionnaires cannot replace a detailed history and physical examination [4,82,83]. Questionnaires are separate and unique aspects of the “identification” aspect of the new clinical paradigm. Some of the questionnaires are psychometrically validated and distinct, and used for outcomes assessment.

3.1.3. Physical examination—A focused physical examination including endocrinologic examination should be performed on every patient, especially if the response to a PDE5 inhibitor is not robust. Androgen insufficiency is associated with small, less firm testes; decreased beard and body hair growth; skin thinning; a decrease in lean body mass; an increase in body fat and decrease in muscle mass and strength; and the development of breast tissue [82,83]. Small, less firm testes are consistent with hypergonadotrophic hypogonadism (primary testicular failure). However, this characteristic may not be the case in hypogonadothrophic hypogonadism.

3.1.4. Mandatory laboratory testing—In this new clinical paradigm, laboratory tests are subdivided into mandatory and optional in men with both androgen insufficiency and ED. In this section, we describe the mandatory laboratory tests (Fig. 4).

3.1.4.1. Testosterone: The diagnosis of androgen insufficiency in men is based on a suggestive clinical picture and the biochemical demonstration of androgen deficiency. Abnormal total testosterone values [82,83] alone are not sufficient reason to institute therapy. In men with minimal symptoms and markedly reduced testosterone values (eg, <200 ng/dl), a discussion should ensue with the patient concerning risks and benefits of therapy. It should be noted that the various laboratory ranges currently considered normal for androgens in men are not always reliable [82,83] and are, at best, an approximation of androgen status. They do not take into account the localized, tissue-specific metabolism of androgens into bioactive metabolites (intracrine mechanisms) or differences in androgen sensitivity, in which the response of target organs to a given androgen concentration will vary in different individuals [82,83].

There is no universally accepted cut-off value of total testosterone that unambiguously defines the state of androgen insufficiency [64,86,100,101]. Since total testosterone values fall with

age and change with circadian rhythm, the ideal time to clinically measure total testosterone is in the early morning. Because of loss of pulsatile hypothalamic functions with aging, starting as early as age 40 [100], blood tests can be measured at any time in aging men [82,83,102].

Total testosterone measurements can be misleading, because only unbound testosterone can act within cells to regulate gene expression. In normal males, 2% of testosterone is free (unbound), 30–60% is bound to sex hormone–binding globulin (SHBG) with high affinity, and the remainder is bound with much lower avidity to albumin and other proteins [103]. SHBG has a higher affinity for testosterone than for estradiol, and changes in SHBG reduce or amplify the hormonal milieu. Thus SHBG, in part, regulates androgen function, and it is clinically relevant in each patient suspected of having androgen insufficiency to be aware of the SHBG value. High values of SHBG will lower the unbound physiologically available testosterone [82,83].

The health care provider should assess free testosterone in all patients. However, it should be stressed that different assay techniques can yield different measurements. Antibody-based, free testosterone assays using a testosterone analogue are considered unreliable. Equilibrium dialysis, the gold standard, is usually difficult and time-consuming, and therefore not widely used clinically [104]. Bioavailable testosterone measures free and albumin-bound fractions of testosterone, and is reliable and accessible. Bioavailable testosterone values fall with increasing age, especially as total testosterone falls and SHBG values increase [82,83].

A contemporary management strategy for the health care provider is to determine total testosterone (ng/dl), SHBG (nmol/l), and albumin (g/dl) concentrations. These values can then be used to determine free testosterone with a calculator [82,83,86] that is available on the Web page of the ISSAM (www.issam.ch/freetesto.htm). The use of this calculator is free of charge and results in values that correlate well to free testosterone determined by equilibrium dialysis. In most cases of “healthy” men, the albumin value can be assumed to be 4.3 g/dl. However, when doing clinical research or in aging men with a chronic disorder, it is advisable to determine the individual's actual albumin value. A calculated free testosterone value less than 5 ng/dl is considered abnormal. When the total testosterone value is borderline, calculated free testosterone values are useful to help confirm androgen insufficiency [105]. In studies using this approach, 17.6% of men with ED had criteria for androgen insufficiency [106]. Further, hypertension, aging, absence of nocturnal erections, and low erectile function scores were associated with low calculated free testosterone levels [106].

3.1.4.2. Prostate-specific antigen: Androgen administration is absolutely contraindicated in men with or suspected of having carcinoma of the prostate [82,83,86]. Determination of serum prostate-specific antigen ((PSA) [107,108] and digital rectal examination (DRE) are mandatory as baseline measurements of prostate health prior to therapy with androgens. Many health care providers now consider a PSA of 0–2.5 ng/ml as low and values greater than 2.6 to 10 ng/ml as elevated. Both PSA and DRE examinations should be repeated every 3–6 mo for the first 12 mo, and annually thereafter. Transrectal biopsy of the prostate is indicated if the DRE or the PSA are abnormal or if the PSA increases 0.75 ng/ml in one calendar year [107–110]. If the PSA increases during androgen therapy and the biopsy is negative for prostate cancer, androgen therapy can continue with repeated PSA testing and DRE every 3–6 mo. While there is no evidence that androgen therapy causes prostate cancer, it may accelerate an existing underlying prostate cancer [107–110].

3.1.5. Optional laboratory testing

3.1.5.1. Dihydrotestosterone: Serum dihydrotestosterone (DHT) determination may be valuable, because for some androgen-dependent functions, testosterone is a prohormone peripherally converted to DHT via the enzyme 5-alpha reductase. Supraphysiologic levels of

DHT may be observed following topical testosterone gel administration, which is associated with acne and scalp hair loss [111]. The presumed mechanism is related to the presence of high concentrations of 5-alpha reductase enzyme in skin and the much greater skin surface area of testosterone application using the gels compared with the patch. Successful management of side effects may be achieved with low doses of 5-alpha reductase enzyme inhibitors.

Subphysiologic levels of DHT may occur with the medical treatment for lower urinary tract symptoms (LUTS) that engages clinical use of 5-alpha reductase inhibitors and lowers the circulating level of DHT by as much as 80% [112]. The 5-alpha reductase inhibitors finasteride and dutasteride are reportedly associated with a greater risk of ED, ejaculatory dysfunction, and decreased libido compared with placebo [113,114]. In animal studies, finasteride treatment resulted in significantly lower DHT levels, and multiple ultrastructural alterations of the tunica albuginea and penile erectile tissues [30]. DHT has also been shown to be an independent hormonal predictor of increased frequency of orgasms in men [115].

3.1.5.2. Prolactin: Hyperprolactinemia is an uncommon cause of androgen insufficiency and ED [82,83]. However, if a patient presents with signs and symptoms of diminished sexual interest and gynecomastia, and has biochemical evidence of androgen insufficiency, determination of serum prolactin is recommended [116]. Direct role of prolactin in male libido has been proposed [117]. Although rare, elevated serum prolactin levels are associated with potentially high morbidity disease and pituitary tumors.

3.1.5.3. Estradiol: For men undergoing exogenous testosterone therapy, serum estradiol determination may be of value. Estradiol is synthesized in men in peripheral organs by metabolism of testosterone via the enzyme aromatase. In aging and obese men, estradiol values increase over time [118]. Basar and colleagues [119] studied the relationship between scores of the Aging Male Symptoms and serum sex steroid levels and found that estradiol levels were greater in men with aging male symptoms. Since androgens are the precursors of estrogens, administration of exogenous testosterone will result in a potential increase in estradiol values. Recording periodic follow-up estradiol values in men on exogenous testosterone therapy is good medical practice. Estradiol has been shown to inhibit luteinizing hormone (LH) secretion in men (decreasing endogenous testosterone synthesis) and to increase the liver synthesis of SHBG (decreasing free unbound physiologically available testosterone) [82,83]. High estradiol values are considered detrimental to male sexual function. Estradiol values have been noted to be significantly higher in ED patients with venous leak than in controls, supporting the hypothesis that estradiol level can adversely influence penile smooth muscle function [120].

3.1.5.4. Dehydroepiandrosterone: The physiologic role of dehydroepiandrosterone (DHEA) and DHEA sulphate (DHEA-S) are not well investigated. DHEA may be involved in cognitive, memory, metabolic, vascular, immune, and sexual functions [121]. DHEA is an androgen precursor produced by the adrenal glands that exerts its effects via downstream conversion to testosterone and estradiol [122]. DHEA deficiencies in men have been reportedly associated with various drugs, and endocrine, nonhormonal, and age-related disorders (DHEA steadily decreases from age 40). DHEA-S levels were significantly lower in men with sexual dysfunction, as determined by the International Index of Erectile Function (IIEF) score [119]. Patients with ED and type 1 diabetes had lower levels of DHEA and DHEA-S compared with diabetics without ED [123]. Also, low levels of DHEA and DHEA-S, but not free or total testosterone, were strongly associated with ED. No well-designed clinical trials have definitively substantiated the role of DHEA in these functions in humans, or even the safety and efficacy of DHEA therapy [124]. In a small study, Reiter and colleagues [125] evaluated the efficacy of DHEA replacement in the treatment of ED and found it was associated with higher mean scores for all five domains of the IIEF with no impact on mean serum levels of PSA or testosterone.

3.1.5.5. Thyroid-stimulating hormone: Both hyperthyroidism and hypothyroidism have been shown to adversely affect sexual function [126,127]. It is likely that androgen therapy would not be successful until thyroid function has been normalized. In examining the clinical and hormonal profiles of patients, screening is performed by obtaining a thyroid-stimulating hormone (TSH) blood value for primary hypothyroidism. In suspected cases of central hypothyroidism, serum-free thyroxine (T4) is considered the best indicator [128]. In men presenting for initial evaluation and therapy of ED, 4.0% had increased TSH [129].

3.1.5.6. Follicle-stimulating hormone and LH: Serum LH and follicle-stimulating hormone (FSH) determination may also be of value in men with ED and androgen insufficiency. Knowledge of these gonadotropin values will define whether the androgen insufficiency is due to hypogonadotropic hypogonadism versus hypergonadotropic hypogonadism [82,83].

3.2. Step care 2: Patient and partner education

A partner's sexual health can be affected by the patient's sexual dysfunction [130–134]. Thus, an essential component in the management of androgen insufficiency and ED is patient and partner education that is uniquely matched to individual needs [4]. Educational subjects include an overview of pertinent anatomy and physiology, relevant pathophysiology, full disclosure of risks and benefits, and appropriate discussion of expectations with treatment. Efforts are made to translate the results of the history taking, physical examination, and laboratory testing into understandable management strategies in the presence of the patient and partner, if possible, with patient and partner's preferences for management respected and taken into consideration [4].

3.3. Step care 3: Modifying reversible causes

Both androgen insufficiency and ED are potentially reversible if specific potentially reversible etiologic factors can be addressed. For example, weight loss has been shown to improve testosterone levels, reducing fat mass and estrogen levels [135,136]. Modification may apply to changing prescription or nonprescription drug use and/or altering psychosocial factors [4].

3.4. Step care 4: Hormonal and nonhormonal pharmacologic treatment

Safe and effective government-approved pharmacologic agents are available to treat androgen insufficiency and ED separately. Pharmacologic treatments are prescribed considering cost and ease of administration. Should optional hormonal blood testing be performed and suspicions for abnormal hormonal blood tests be identified, considerations for hormonal treatment should be discussed with the patient. Hormonal agents [82,83] include testosterone, DHEA, clomiphene citrate, aromatase inhibitors, 5-alpha reductase inhibitors, dopamine agonists, and thyroid therapies [82,83]. For androgen insufficiency, androgen delivery systems, listed chronologically, include oral testosterone [137], intramuscular depot injections [138], scrotal transdermal patch systems [139], nongenital skin transdermal patch systems [140], hydroalcoholic testosterone gels, [141,142], adhesive buccal tablets [143], and, recently, long-acting intramuscular depot injections [144]. Nonhormonal treatments include vasodilators such as PDE5 inhibitors and intracavernosal/intraurethral agents [145]. Before considering treatment for androgen insufficiency, a patient should show signs and symptoms and biochemical confirmation of androgen insufficiency, a PSA and DRE not consistent with prostate cancer or a negative prostate biopsy, and an absent history of breast cancer [82,83]. The patient should also meet the definition of ED [4].

3.4.1. Testosterone—Isidori and colleagues [146] determined that exogenous testosterone improved the number of nocturnal erections and successful intercourses, sexual thoughts, scores of erectile function, and overall sexual satisfaction in men with low testosterone, but

had no effect on eugonadal men. They concluded that the effect of testosterone tended to decline over time and was progressively smaller with increasing baseline T levels, and that long-term safety data were not available [146]. Relative contraindications to be considered include elevated hematocrit, abnormal liver function studies, LUTS, and sleep apnea. A rare adverse event is the enlargement of prostate size, which can be prevented by the administration of finasteride [147,148]. It has also been suggested that large numbers of men with low to low-normal testosterone levels would benefit from testosterone screening when they are evaluated for ED and that testosterone therapy may improve the response of PDE5 inhibitors [70,71, 73].

3.4.2. Dehydroepiandrosterone—Many men take DHEA without physician supervision, because it is sold over the counter. Saad and colleagues [122] noted DHEA supplementation had positive effects on the cardiovascular system, body composition, bone mineral density, skin, central nervous system, the immune system, and sexual function. DHEA use may be justified in aging men with periodic evaluations to maintain serum concentrations in the physiologic range [149]. Recent evidence suggests that DHEA has a physiologic role through interaction with specific membrane receptors on the endothelium [150].

3.4.3. Clomiphene citrate—Exogenous testosterone may be deleterious in men with relative infertility, because it suppresses gonadotropins [82,83]. Alternatively, clomiphene citrate increases gonadotropins [133] and may be beneficial when the androgen insufficiency is due to hypogonadotropic hypogonadism. Guay et al [152] and Shabsigh et al [153] administered off-label clomiphene citrate to men with hypogonadotropic hypogonadism and found significant increases in LH and free testosterone, and improved sexual function. Erectile improvement was lower in men with aging, diabetes, hypertension, coronary artery disease, and multiple medication use. In another study, sexual function improved in ED patients using clomiphene in limited parameters in younger and healthier ED men [154].

3.4.4. Aromatase inhibitors—Administration of exogenous testosterone will result in increased estradiol values by aromatization. Anastrozole is a potent, highly selective aromatase inhibitor with no intrinsic steroid hormone agonist or antagonist activities [155]. In a recent study, anastrozole administration increased serum bioavailable and total testosterone levels in older men with mild hypogonadism, while estradiol levels remained normal [156]. The sexual benefits of aromatase inhibitor therapy were reported in a case report in which use of an aromatase inhibitor normalized the testosterone level and improved sexual functioning, possibly by a central alteration in the testosterone/estrogen ratio [157].

3.4.5. 5-Alpha reductase inhibitors—Common, distressing side effects of androgen therapy are hirsutism and acne [158]. The most efficacious pharmacologic therapy to reduce DHT is via 5-alpha reductase inhibition. Mechanical therapies for hirsutism and topical and systemic acne therapies are also available.

3.4.6. Dopamine agonists—Dopamine agonists have been reported to improve sexual function [159] on the basis of research showing that sexual motivation is modulated by a number of central nervous system neurotransmitter and receptor changes induced, in part, by the action of sex steroids and by the central neurotransmitter dopamine. Dopamine neurotransmitter systems may play a critical intermediary role in the central regulation of sexual arousal and excitation, mood, and incentive-related sexual behavior, particularly in the motivational responses to conditioned external stimuli [160–164]. Although their use is controversial, more research is needed with dopamine agonists for men with androgen insufficiency and ED.

3.4.7. Thyroid hormones—If a patient with androgen insufficiency and ED has a concomitant thyroid abnormality, it is likely that androgen therapy would not be successful until the thyroid state was normalized. In men diagnosed with abnormalities in both thyroid function and sexual function (decreased sexual desire, ED, premature or delayed ejaculation), treatment with methimazole (for hyperthyroidism) or thyroxine (for hypothyroidism) for 8 wk without concomitant PDE5 inhibitor therapy resulted in an improvement in sexual function [126]. In animal studies, hypothyroidism resulted in autonomic neuropathy and endothelial dysfunction, adversely influencing the release or synthesis of NO from nitrergic nerves and endothelium [127].

3.4.8. Phosphodiesterase inhibitors—Oral PDE5 inhibitors are approved for on-demand administration and are effective in facilitating and enhancing erections following sexual stimulation [145]. In a recent review [165], a synergistic effect for testosterone therapy and efficacy of PDE5 inhibitor therapy in men with androgen insufficiency and ED was shown. In patients with androgen insufficiency, in whom treatment with testosterone supplementation alone failed, combined treatment with a PDE5 inhibitor and testosterone gel improved erectile function [72]. Likewise, aging men with androgen insufficiency who failed first-line oral PDE5 inhibitor treatment and in whom androgens were not contraindicated had improved erectile function and quality of life when treated with a combination of testosterone and PDE5 inhibitors [74–76]. These findings provide clinical support to the experimental knowledge of the importance of androgens in regulating smooth muscle function. Of interest, sustained improvement in sexual function after 12 mo of PDE5 inhibitor administration has been associated with increased testosterone to estradiol ratio, mainly related to reduction of estradiol levels [166].

3.4.9. Follow-up strategies—Patients undergoing hormonal treatment for androgen insufficiency and ED should undergo reassessment at regular intervals to ensure optimum patient-physician communication to assess the progress of therapy and the sexual, general medical, and psychosocial status of the patient and partner [4]. Total testosterone, SHBG, albumin (if appropriate), PSA, and DRE should be performed every 3–6 mo until the values are stable and in the appropriate range. Hematocrit and hemoglobulin, liver function tests, and bone density and lipid profile evaluations should be monitored annually. Follow-up also provides the occasion for critical continued education, addressing any relevant patient concerns regarding the treatments, including dose titration or change in medication. Adverse drug reactions or drug interaction effects should be carefully monitored [82,83].

3.5. Step care 5: Other treatments

Men with androgen insufficiency and ED may not respond to the previously discussed interventions and may need to consider such options as a vacuum erection device, intraurethral or intracavernosal administration of alprostadil or other vasoactive agents, or surgical intervention with penile prostheses or reconstructive surgery such as penile revascularization [4].

4. Summary, conclusions, and future directions

Androgen-dependent mechanisms that regulate genital tissue remodeling in the adult have been poorly defined. Characterization of the molecular and cellular mechanisms by which androgens regulate genital tissue structure and function would provide significant gains in knowledge and understanding of important pathogenic processes. These mechanisms need to be investigated using well-established experimental approaches to assess changes in penile hemodynamics, tissue structure, and cell-specific biomarkers. Such studies in animal models would initiate a novel line of investigation in genital physiology and may provide further scientific rationale

for the judicious use of androgens in the management of male ED in men with androgen insufficiency. In light of the similarities in systemic and penile vascular disease, and the role of adipogenesis in the metabolic syndrome, this line of investigation may also stimulate future work on the role of androgens in systemic metabolic and vascular disease. While the NO/cGMP pathway plays a key role in erectile physiology, our knowledge of the downstream events that regulate gene expression in the penis is rudimentary at best. New approaches are needed to develop better understanding of the interplay between PDE5 expression and activation of the NO/cGMP pathway. The effects of androgens on the cavernosal and dorsal nerves also merit further investigation, and defining the effect of androgens on neurotransmitter synthesis and release would be of scientific and clinical value. Finally, tissue remodeling at the vascular, trabecular, and tunica albuginea levels is of paramount importance if we are to understand the relationship between androgen deficiency and venous leakage, and its restoration by androgen treatment.

Both the conditions of androgen insufficiency and ED are highly prevalent medical disorders in aging men with associated multiple risk factors. Good clinical practice requires the use of appropriate step care strategies for patient and goal-directed management. The future will likely see new basic science investigations that will lead to novel treatment strategies. In this fashion, management can be delivered in a more safe and effective manner for the majority of afflicted patients (and partners). It is appreciated that there are some who argue that there is little or no role for androgens in the management of ED. Indeed, healthy skepticism is warranted, but one must keep an open mind and weigh the evidence in making such an important scientific judgment. The emergence of clinical data from well-designed studies should provide the foundation for evidence-based medicine. We must recognize that humans have multiple pathways of generating androgens, not only in the endocrine glands but also in the periphery. It should be noted that a “back door” biosynthetic pathway for the production of 5α-DHTfrom progesterone was reported only recently [167]. Ultimately, the common and binding goal of both clinicians and scientists is to develop better understanding of the role of androgens and erectile function in human health, and to be able to provide the best possible treatment strategies for patients afflicted with androgen deficiency and ED.

Take-home message

Both conditions of androgen insufficiency and ED are highly prevalent medical disorders in aging men with associated multiple risk factors. Good clinical practice requires the use of appropriate step care strategies for patient and goal-directed management. The future will likely see new basic science investigations that will lead to new, safe, and effective treatment strategies. The emergence of clinical data from well-designed studies should provide the foundation for evidence-based medicine. We must recognize that humans have multiple pathways of generating androgens, not only in the endocrine glands but also in the periphery. Ultimately, the common and binding goals of both clinicians and scientists are to develop better understanding of the role of androgens in human health and to be able to provide the best possible treatment strategies for patients afflicted with androgen deficiencies.

References

1. Traish A, Kim N. The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function. J Sex Med 2005;2:759–70. [PubMed: 16422801]
2. Traish AM, Kim N. Weapons of penile smooth muscle destruction: androgen deficiency promotes accumulation of adipocytes in the corpus cavernosum. Aging Male 2005;8:141–6. [PubMed: 16390736]
3. Traish AM, Guay AT. Are androgens critical for penile erections in humans? Examining the clinical and preclinical evidence. J Sex Med 2006;3:382–404. [PubMed: 16681465]

4. Lue TF, Giuliano F, Montorsi F, et al. Summary of the recommendations on sexual dysfunctions in men. J Sex Med 2004;1:6–23. [PubMed: 16422979]
5. Meusburger SM, Keast JR. Testosterone and nerve growth factor have distinct but interacting effects on structure and neurotransmitter expression of adult pelvic ganglion cells in vitro. Neuroscience 2001;108:331–40. [PubMed: 11734365]
6. Keast JR, Gleeson RJ, Shulkes A, et al. Maturational and maintenance effects of testosterone on terminal axon density and neuropeptide expression in the rat vas deferens. Neuroscience 2002;112:391–8. [PubMed: 12044456]
7. Giuliano F, Rampin O, Schirar A, et al. Autonomic control of penile erection: modulation by testosterone in the rat. J Neuroendocrinol 1993;5:677–83. [PubMed: 8680441]
8. Rogers RS, Graziottin TM, Lin CM, et al. Intracavernosal vascular endothelial growth factor (VEGF) injection and adeno-assoicated virus-mediated VEGF gene therapy prevent and reverse venogenic erectile dysfunction in rats. Int J Impot Res 2003;15:26–37. [PubMed: 12605238]
9. Baba K, Yajima M, Carrier S, et al. Effect of testosterone on the number of NADPH diaphorase-stained nerve fibers in the rat corpus cavernosum and dorsal nerve. Urology 2000;56:533–8. [PubMed: 10962339]
10. Baba K, Yajima M, Carrier S, et al. Delayed testosterone replacement restores nitric oxide synthase-containing nerve fibres and the erectile response in rat penis. BJU Int 2000;85:953–8. [PubMed: 10792181]
11. Armagan A, Kim NN, Goldstein I, et al. Dose-response relationship between testosterone and erectile function: evidence for the existence of a critical threshold. J Androl 2006;27:517–26. [PubMed: 16582415]
12. Suzuki N, Sato Y, Hisasue SI, et al. Effect of testosterone on intracavernous pressure elicited with electrical stimulation of the medial preoptic area and cavernous nerve in male rats. J Androl. 2006In press
13. Burnett AL, Lowenstein CJ, Bredt DS, et al. Nitric oxide: a physiologic mediator of penile erection. Science 1992;257:401–3. [PubMed: 1378650]
14. Lugg JA, Rajfer J, Gonzalez-Cadavid NF. Dihydrotestosterone is the active androgen in the maintenance of nitric oxide-mediated penile erection in the rat. Endocrinology 1995;136:1495–1501. [PubMed: 7534702]
15. Muller SC, Hsieh JT, Lue TF, et al. Castration and erection. An animal study. Eur Urol 1988;15:118–24. [PubMed: 3215226]
16. Zvara P, Sioufi R, Schipper HM, et al. Nitric oxide mediated erectile activity is a testosterone dependent event: a rat erection model. Int J Impot Res 1995;7:209–19. [PubMed: 8770664]
17. Park KH, Kim SW, Kim KD, et al. Effects of androgens on the expression of nitric oxide synthase mRNAs in rat corpus cavernosum. BJU Int 1999;83:327–33. [PubMed: 10233504]
18. Reilly CM, Zamorano P, Stopper VS, et al. Androgenic regulation of NO availability in rat penile erection. J Androl 1997;18:110–5. [PubMed: 9154504]
19. Reilly CM, Lewis RW, Stopper VS, et al. Androgenic maintenance of the rat erectile response via a non-nitric-oxide-dependent pathway. J Androl 1997;18:588–94. [PubMed: 9432131]
20. Garban H, Vernet D, Freedman A, et al. Effect of aging on nitric oxide-mediated penile erection in rats. Am J Physiol 1995;268:H467–75. [PubMed: 7530924]
21. Penson DF, Ng C, Cai L, et al. Androgen and pituitary control of penile nitric oxide synthase and erectile function in the rat. Biol Reprod 1996;55:567–74. [PubMed: 8862773]
22. Shen Z, Chen Z, Lu Y, et al. Relationship between gene expression of nitric oxide synthase and androgens in rat corpus cavernosum. Chin Med J (Engl) 2000;113:1092–5. [PubMed: 11776143]
23. Marin R, Escrig A, Abreu P, et al. Androgen-dependent nitric oxide release in rat penis correlates with levels of constitutive nitric oxide synthase isoenzymes. Biol Reprod 1999;61:1012–6. [PubMed: 10491638]
24. Schirar A, Bonnefond C, Meusnier C, et al. Androgens modulate nitric oxide synthase messenger ribonucleic acid expression in neurons of the major pelvic ganglion in the rat. Endocrinology 1997;138:3093–102. [PubMed: 9231755]
25. Seo SI, Kim SW, Paick JS. The effects of androgen on penile reflex, erectile response to electrical stimulation and penile NOS activity in the rat. Asian J Androl 1999;1:169–74. [PubMed: 11225889]

26. Traish AM, Park K, Dhir V, et al. Effects of castration and androgen replacement on erectile function in a rabbit model. Endocrinology 1999;140:1861–8. [PubMed: 10098525]
27. Zhang XH, Morelli A, Luconi M, et al. Testosterone regulates PDE5 expression and in vivo responsiveness to tadalafil in rat corpus cavernosum. Eur Urol 2005;47:409–16. [PubMed: 15716209]
28. Morelli A, Filippi S, Mancina R, et al. Androgens regulate phosphodiesterase type 5 expression and functional activity in corpora cavernosa. Endocrinology 2004;146:2253–63. [PubMed: 14764637]
29. Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. J Androl 2003;24:381–7. [PubMed: 12721214]
30. Shen ZJ, Zhou XL, Lu YL, et al. Effect of androgen deprivation on penile ultrastructure. Asian J Androl 2003;5:33–6. [PubMed: 12647000]
31. Traish AM, Toselli P, Jeong SJ, et al. Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for venoocclusive dysfunction in androgen deficiency. J Androl 2005;26:242–8. [PubMed: 15713830]
32. Moon DG, Sung DJ, Kim YS, et al. Bisphenol A inhibits penile erection via alteration of histology in the rabbit. Int J Impot Res 2001;13:309–16. [PubMed: 11890520]
33. Moon DG, Lee KC, Kim YW, et al. Effect of TCDD on corpus cavernosum histology and smooth muscle physiology. Int J Impot Res 2004;16:224–30. [PubMed: 15184913]
34. Masuno H, Kidani T, Sekiya K, et al. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. J Lipid Res 2002;43:676–84. [PubMed: 11971937]
35. Goyal HO, Braden TD, Williams CS, et al. Exposure of neonatal male rats to estrogen induces abnormal morphology of the penis and loss of fertility. Reprod Toxicol 2004;18:265–74. [PubMed: 15019723]
36. Goyal HO, Braden TD, Williams CS, et al. Abnormal morphology of the penis in male rats exposed neonatally to diethylstilbestrol is associated with altered profile of estrogen receptor-alpha protein, but not of androgen receptor protein: a developmental and immunocytochemical study. Biol Reprod 2004;70:1504–17. [PubMed: 14749301]
37. Goyal HO, Braden TD, Williams CS, et al. Permanent induction of morphological abnormalities in the penis and penile skeletal muscles in adult rats treated neonatally with diethylstilbestrol or estradiol valerate: a dose response study. J Androl 2005;26:32–43. [PubMed: 15611564]
38. Goyal HO, Braden TD, Williams CS, et al. Estrogen induced abnormal accumulation of fat cells in the rat penis and associated loss of fertility depends upon estrogen exposure during critical period of penile development. Toxicol Sci 2005;87:242–54. [PubMed: 15976194]
39. Luthy IA, Begin D, Labrie F. Mediation by the androgen receptor of the stimulatory and antiandrogenic actions of 17 beta-estradiol on the growth of androgen-sensitive Shionogi mammary carcinoma cells in culture. Endocrinology 1988;123:1418–24. [PubMed: 3402389]
40. Tindall DJ, French FS, Nayfeh SN. Estradiol-17 beta inhibition of androgen uptake, metabolism and binding in epididymis of adult male rats in vivo: a comparison with cyproterone acetate. Steroids 1981;37:257–68. [PubMed: 6453438]
41. Wilson EM, French FS. Binding properties of androgen receptors. Evidence for identical receptors in rat testis, epididymis, and prostate. J Biol Chem 1976;251:5620–9. [PubMed: 184085]
42. Bhasin S, Taylor WE, Singh R, et al. The mechanisms of androgen effects on body composition: mesenchymal pluripotent cell as the target of androgen action. J Gerontol 2003;58A:1103–10.
43. Singh R, Artaza JN, Taylor WE, et al. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology 2003;144:5081–8. [PubMed: 12960001]
44. Singh R, Artaza JN, Taylor WE, et al. Testosterone inhibits adipogenic differentiation in 3T3-L1 cells: nuclear translocation of androgen receptor complex with beta-catenin and T-cell factor 4 may bypass canonical Wnt signaling to down-regulate adipogenic transcription factors. Endocrinology 2006;147:141–54. [PubMed: 16210377]
45. Foresta C, Caretta N, Lana A, et al. Reduced number of circulating endothelial progenitor cells in hypogonadal men. J Clin Endocrinol Metab 2006;91:4599–602. [PubMed: 16926245]

46. Anderson LA, McTernan PG, Harte AL, et al. The regulation of HSL and LPL expression by DHT and flutamide in human subcutaneous adipose tissue. Diabetes Obes Metab 2002;4:209–13. [PubMed: 12047400]
47. Rosen ED, Hsu CH, Wang X, et al. C/EBPalpha induces adipogenesis through PPARgamma: a unified pathway. Genes Dev 2002;16:22–6. [PubMed: 11782441]
48. Wright HM, Clish CB, Mikami T, et al. A synthetic antagonist for the peroxisome proliferator-activated receptor gamma inhibits adipocyte differentiation. J Biol Chem 2000;275:1873–7. [PubMed: 10636887]
49. Dieudonne MN, Pecquery R, Boumediene A, et al. Androgen receptors in human preadipocytes and adipocytes: regional specificities and regulation by sex steroids. Am J Physiol 1998;274:C1645–52. [PubMed: 9611130]
50. Garcia E, Lacasa M, Agli B, et al. Modulation of rat preadipocyte adipose conversion by androgenic status: involvement of C/EBPs transcription factors. J Endocrinol 1999;161:89–97. [PubMed: 10194532]
51. Belanger C, Luu-The V, Dupont P, et al. Adipose tissue intracrinology: potential importance of local androgen/estrogen metabolism in the regulation of adiposity. Horm Metab Res 2002;34:737–45. [PubMed: 12660892]
52. Rosen ED. Molecular mechanisms of adipocyte differentiation. Ann Endocrinol (Paris) 2002;63:79–82. [PubMed: 11994665]
53. Rosen ED, Spiegelman BM. PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem 2001;276:37731–4. [PubMed: 11459852]
54. Wong YC, Tam NNC. Dedifferentiation of stromal smooth muscle as a factor in prostate carcinogenesis. Differentiation 2002;70:633–45. [PubMed: 12492504]
55. Chen W, Yang CC, Sheu HM, et al. Expression of peroxisome proliferator-activated receptor and CCAAT/enhancer binding protein transcription factors in cultured human sebocytes. J Invest Dermatol 2003;121:441–7. [PubMed: 12925198]
56. Bostrom K, Tintut Y, Kao SC, et al. HOXB7 overexpression promotes differentiation of C3H10T1/2 cells to smooth muscle cells. J Cell Biochem 2000;78:210–21. [PubMed: 10842316]
57. Hu E, Tontonoz P, Spiegelman BM. Transdifferentiation of myoblasts by the adipogenic transcription factors PPAR gamma and C/EBP alpha. Proc Natl Acad Sci USA 1995;92:9856–60. [PubMed: 7568232]
58. Antonioli E, Della-Colleta HH, Carvalho HF. Smooth muscle cell behavior in the ventral prostate of castrated rats. J Androl 2004;25:50–6. [PubMed: 14662786]
59. Johnson JL, van Eys GJ, Angelini GD, et al. Injury induces dedifferentiation of smooth muscle cells and increased matrix-degrading metalloproteinase activity in human saphenous vein. Arterioscler Thromb Vasc Biol 2001;21:1146–51. [PubMed: 11451743]
60. Rong JX, Shapiro M, Trogan E, et al. Transdifferentiation of mouse aortic smooth muscle cells to a macrophage-like state after cholesterol loading. Proc Natl Acad Sci USA 2003;100:13531–6. [PubMed: 14581613]
61. Rucker-Martin C, Pecker F, Godreau D, et al. Dedifferentiation of atrial myocytes during atrial fibrillation: role of fibroblast proliferation in vitro. Cardiovasc Res 2002;55:38–52. [PubMed: 12062707]
62. Corradi LS, Goes RM, Carvalho HF, et al. Inhibition of 5α-reductase activity induces stromal remodeling and smooth muscle de-differentiation in adult gerbil ventral prostate. Differentiation 2004;72:198–208. [PubMed: 15270776]
63. Zhang XH, Filippi S, Morelli A, et al. Testosterone restores diabetes-induced erectile dysfunction and sildenafil responsiveness in two distinct animal models of chemical diabetes. J Sex Med 2006;3:253–64. [PubMed: 16490018]
64. Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab 2006;91:4335–43. [PubMed: 16926258]
65. Stanley LL. An analysis of one thousand testicular substance implantations. Endocrinology 1922;6:787.
66. Edwards E, Hamilton J, Duntley S. Testosterone propionate as a therapeutic agent in patients with organic disease of peripheral vessels. N Engl J Med 1939;220:865.

67. Hamm L. Testosterone propionate in the treatment of angina pectoris. J Clin Endocrinol 1942;2:325–8.
68. Levine SA, Likoff WB. The therapeutic value of testosterone propionate in angina pectoris. N Engl J Med 1943;229:770–2.
69. Lesser MA. Testosterone propionate therapy in one hundred cases of angina pectoris. J Clin Endocrinol 1946;6:549–57.
70. Amar E, Grivel T, Hamidi K, Lemaire A, et al. Ageing men's sexual functions decline and the erectile dysfunction (ED) increase. Prog Urol 2005;15:6–9. [PubMed: 15822384]
71. Shabsigh R. Testosterone therapy in erectile dysfunction and hypogonadism. J Sex Med 2005;2:785–92. [PubMed: 16422803]
72. Greenstein A, Mabjeesh NJ, Sofer M, et al. Does sildenafil combined with testosterone gel improve erectile dysfunction in hypogonadal men in whom testosterone supplement therapy alone failed? J Urol 2005;173:530–2. [PubMed: 15643239]
73. Rosenthal BD, May NR, Metro MJ, et al. Adjunctive use of AndroGel (testosterone gel) with sildenafil to treat erectile dysfunction in men with acquired androgen deficiency syndrome after failure using sildenafil alone. Urology 2006;67:571–4. [PubMed: 16527581]
74. Aversa A, Isidori AM, Greco EA, et al. Hormonal supplementation and erectile dysfunction. Eur Urol 2004;45:535–8. [PubMed: 15082192]
75. Aversa A, Isidori AM, Spera G, et al. Androgens improve cavernous vasodilation and response to sildenafil in patients with erectile dysfunction. Clin Endocrinol (Oxf) 2003;58:632–8. [PubMed: 12699447]
76. Shamloul R, Ghanem H, Fahmy I, et al. Testosterone therapy can enhance erectile function response to sildenafil in patients with PADAM: a pilot study. J Sex Med 2005;2:559–64. [PubMed: 16422854]
77. Rhoden EL, Morgentaler A. Risks of testosterone-replacement therapy and recommendations for monitoring. N Engl J Med 2004;350:482–92. [PubMed: 14749457]
78. Shabsigh R, Rajfer J, Aversa A, et al. The evolving role of testosterone in the treatment of erectile dysfunction. Int J Clin Pract 2006;60:1087–92. [PubMed: 16939550]
79. Wald M, Meacham RB, Ross LS, et al. Testosterone replacement therapy for older men. J Androl 2006;27:126–32. [PubMed: 16474018]
80. Nieschlag E. Testosterone treatment comes of age: new options for hypogonadal men. Clin Endocrinol (Oxf) 2006;65:275–81. [PubMed: 16918944]
81. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males: ISA, ISSAM, and EAU recommendations. Int J Androl 2005;28:125–7. [PubMed: 15910536]
82. Morales A, Buvat J, Gooren LJ, et al. Endocrine aspects of sexual dysfunction in men. J Sex Med 2004;1:69–81. [PubMed: 16422986]
83. Morales A, Heaton JP. Hypogonadism and erectile dysfunction: pathophysiological observations and therapeutic outcomes. BJU Int 2003;92:896–9. [PubMed: 14632842]
84. Hatzichristou D, Hatzimouratidis K, Bekas M, et al. Diagnostic steps in the evaluation of patients with erectile dysfunction. J Urol 2002;168:615–20. [PubMed: 12131320]
85. Spark RF, White R, Connolly PB. Impotence is not always psychogenic. Newer insights into hypothalamic-pituitary-gonadal dysfunction. JAMA 1980;243:750–5. [PubMed: 7351816]
86. Nieschlag E, Swerdloff R, Behre HM, et al. Investigation, treatment and monitoring of late-onset hypogonadism in males – ISA, ISSAM, and EAU recommendations. Eur Urol 2005;48:1–4. [PubMed: 15951102]
87. NIH Consensus Development Panel on Impotence. NIH Consensus Conference. Impotence. JAMA 1993;270:83–90. [PubMed: 8510302]
88. Jockenhovel F. Testosterone therapy—what, when and to whom? Aging Male 2004;7:319–24. [PubMed: 15799128]
89. Gooren LJ, Bunck MC. Androgen replacement therapy: present and future. Drugs 2004;64:1861–91. [PubMed: 15329035]
90. Schulman C, Lunenfeld B. The ageing male. World J Urol 2002;20:4–10. [PubMed: 12088188]

91. Vignozzi L, Corona G, Petrone L, et al. Testosterone and sexual activity. J Endocrinol Invest 2005;28:39–44. [PubMed: 16042359]
92. Morelli A, Vignozzi L, Filippi S, et al. Erectile dysfunction: molecular biology, pathophysiology and pharmacological treatment. Minerva Urol Nefrol 2005;57:85–90. [PubMed: 15951732]
93. Morelli A, Filippi S, Zhang XH, et al. Peripheral regulatory mechanisms in erection. Int J Androl 2005;28:23–7. [PubMed: 16236060]
94. Gooren LJ, Saad F. Recent insights into androgen action on the anatomical and physiological substrate of penile erection. Asian J Androl 2006;8:3–9. [PubMed: 16372114]
95. Morley JE, Perry HM 3rd, Kevorkian RT, et al. Comparison of screening questionnaires for the diagnosis of hypogonadism. Maturitas 2006;53:424–9. [PubMed: 16140484]
96. Tancredi A, Reginster JY, Schleich F, et al. Interest of the androgen deficiency in aging males (ADAM) questionnaire for the identification of hypogonadism in elderly community-dwelling male volunteers. Eur J Endocrinol 2004;151:355–60. [PubMed: 15362965]
97. Heinemann LA, Saad F, Heinemann K, et al. Can results of the Aging Males' Symptoms (AMS) scale predict those of screening scales for androgen deficiency? Aging Male 2004;7:211–8. [PubMed: 15669540]
98. Smith KW, Feldman HA, McKinlay JB. Construction and field validation of a self-administered screener for testosterone deficiency (hypogonadism) in ageing men. Clin Endocrinol (Oxf) 2000;53:703–11. [PubMed: 11155092]
99. Corona G, Mannucci E, Petrone L, et al. ANDROTEST: a structured interview for the screening of hypogonadism in patients with sexual dysfunction. J Sex Med 2006;3:706–15. [PubMed: 16839327]
100. Luboshitzky R, Shen-Orr Z, Herer P. Middle-aged men secrete less testosterone at night than young healthy men. J Clin Endocrinol Metab 2003;88:3160–6. [PubMed: 12843160]
101. Lazarou S, Reyes-Vallejo L, Morganthaler A. Wide variability in laboratory reference values for serum testosterone. J Sex Med 2006;3:1085–1089. [PubMed: 17100942]
102. Bremner WJ, Vitiello MV, Prinz PN. Loss of circadian rhythmicity in blood testosterone levels with aging in normal men. J Clin Endocrinol Metab 1983;56:1278–81. [PubMed: 6841562]
103. Lepage R. Measurement of testosterone and its sub-fractions in Canada. Clin Biochem 2006;39:97–108. [PubMed: 16376328]
104. Vermuelen A, Verdonck L, Kaufman JM. A critical evaluation of simple methods for the estimation of free testosterone in serum. J Clin Endocrinol Metab 1999;84:3666–72. [PubMed: 10523012]
105. Morris PD, Malkin CJ, Channer KS, et al. A mathematical comparison of techniques to predict biologically available testosterone in a cohort of 1072 men. Eur J Endocrinol 2004;151:241–9. [PubMed: 15296480]
106. Martinez-Jabaloyas JM, Queipo-Zaragoza A, Pastor-Hernandez F, et al. Testosterone levels in men with erectile dysfunction. BJU Int 2006;97:1278–83. [PubMed: 16686726]
107. Brawer MK. Assays for complexed prostate-specific antigen and other advances in the diagnosis of prostate cancer. Rev Urol 2003;5:S10–6. [PubMed: 16985971]
108. Wilt TJ. Prostate cancer: epidemiology and screening. Rev Urol 2003;5:S3–9. [PubMed: 16985974]
109. Guay AT, Perez JB, Fitaihi WA, et al. Testosterone treatment in hypogonadal men: prostate-specific antigen level and risk of prostate cancer. Endocr Pract 2000;6:218–21. [PubMed: 11421536]
110. Svetec DA, Canby ED, Thompson IM, et al. The effect of parenteral testosterone replacement on prostate specific antigen in hypogonadal men with erectile dysfunction. J Urol 1997;158:1775–7. [PubMed: 9334599]
111. Mazer N, Bell D, Wu J, Fischer J, et al. Comparison of the steady-state pharmacokinetics, metabolism, and variability of a transdermal testosterone patch versus a transdermal testosterone gel in hypogonadal men. J Sex Med 2005;2:213–26. [PubMed: 16422889]
112. Clark RV, Hermann DJ, Cunningham GR, et al. Marked suppression of dihydrotestosterone in men with benign prostatic hyperplasia by dutasteride, a dual 5alpha-reductase inhibitor. J Clin Endocrinol Metab 2004;89:2179–84. [PubMed: 15126539]
113. Giuliano F. Impact of medical treatments for benign prostatic hyperplasia on sexual function. BJU Int 2006;97:34–8. [PubMed: 16507052]

114. Miner M, Rosenberg MT, Perelman MA. Treatment of lower urinary tract symptoms in benign prostatic hyperplasia and its impact on sexual function. Clin Ther 2006;28:13–25. [PubMed: 16490576]
115. Mantzoros CS, Georgiadis EI, Trichopoulos D. Contribution of dihydrotestosterone to male sexual behaviour. BMJ 1995;310:1289–91. [PubMed: 7773040]
116. Buvat J, Lemaire A. Endocrine screening in 1,022 men with erectile dysfunction: clinical significance and cost-effective strategy. J Urol 1997;158:1764–7. [PubMed: 9334596]
117. Buvat J. Hyperprolactinemia and sexual function in men: a short review. Int J Impot Res 2003;15:373–7. [PubMed: 14562140]
118. Cohen PG. The role of estradiol in the maintenance of secondary hypogonadism in males in erectile dysfunction. Med Hypotheses 1998;50:331–3. [PubMed: 9690769]
119. Basar MM, Aydin G, Mert HC, et al. Relationship between serum sex steroids and Aging Male Symptoms score and International Index of Erectile Function. Urology 2005;66:597–601. [PubMed: 16140085]
120. Mancini A, Milardi D, Bianchi A, et al. Increased estradiol levels in venous occlusive disorder: a possible functional mechanism of venous leakage. Int J Impot Res 2005;17:239–42. [PubMed: 15578040]
121. Webb SJ, Geoghegan TE, Prough RA, et al. The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab Rev 2006;38:89–116. [PubMed: 16684650]
122. Saad F, Hoesl CE, Oettel M, et al. Dehydroepiandrosterone treatment in the aging male—what should the urologist know? Eur Urol 2005;48:724–33. [PubMed: 16137821]
123. Alexopoulou O, Jamart J, Maiter D, et al. Erectile dysfunction and lower androgenicity in type 1 diabetic patients. Diabetes Metab 2001;27:329–36. [PubMed: 11431598]
124. Lunenfeld B. Androgen therapy in the aging male. World J Urol 2003;21:292–305. [PubMed: 14576959]
125. Reiter WJ, Schatzl G, Mark I, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction in patients with different organic etiologies. Urol Res 2001;29:278–81. [PubMed: 11585284]
126. Carani C, Isidori AM, Granata A, et al. Multicenter study on the prevalence of sexual symptoms in male hypo- and hyperthyroid patients. J Clin Endocrinol Metab 2005;90:6472–9. [PubMed: 16204360]
127. Kilicarslan H, Bagcivan I, Yildirim MK, et al. Effect of hypothyroidism on the NO/cGMP pathway of corpus cavernosum in rabbits. J Sex Med 2006;3:830–7. [PubMed: 16942528]
128. Alexopoulou O, Beguin C, De Nayer P, et al. Clinical and hormonal characteristics of central hypothyroidism at diagnosis and during follow-up in adult patients. Eur J Endocrinol 2004;150:1–8. [PubMed: 14713273]
129. Bodie J, Lewis J, Schow D, et al. Laboratory evaluations of erectile dysfunction: an evidence based approach. J Urol 2003;169:2262–4. [PubMed: 12771765]
130. Oberg K, Sjogren Fugl-Meyer K. On Swedish women's distressing sexual dysfunctions: some concomitant conditions and life satisfaction. J Sex Med 2005;2:169–80. [PubMed: 16422883]
131. Patrick DL, Althof SE, Pryor JL, et al. Premature ejaculation: an observational study of men and their partners. J Sex Med 2005;2:358–67. [PubMed: 16422867]
132. Fisher WA, Rosen RC, Mollen M, et al. Improving the sexual quality of life of couples affected by erectile dysfunction: a double-blind, randomized, placebo-controlled trial of vardenafil. J Sex Med 2005;2:699–708. [PubMed: 16422828]
133. Shindel A, Quayle S, Yan Y, et al. Sexual dysfunction in female partners of men who have undergone radical prostatectomy correlates with sexual dysfunction of the male partner. J Sex Med 2005;2:833–41. [PubMed: 16422807]
134. Goldstein I, Fisher WA, Sand M, et al. Vardenafil Study Group. Women's sexual function improves when partners are administered vardenafil for erectile dysfunction: a prospective, randomized, double-blind, placebo-controlled trial. J Sex Med 2005;2:819–32. [PubMed: 16422806]
135. Niskanen L, Laaksonen DE, Punnonen K, et al. Changes in sex hormone-binding globulin and testosterone during weight loss and weight maintenance in abdominally obese men with the metabolic syndrome. 2004 Diabetes Obes Metab 2004;6:208–15. [PubMed: 15056129]

136. Kaukua J, Pekkarinen T, Sane T, et al. Sex hormones and sexual function in obese men losing weight. Obes Res 2003;11:689–94. [PubMed: 12805389]

137. Nieschlag E, Mauss J, Coert A, et al. Plasma androgen levels in men after oral administration of testosterone or testosterone undecanoate. Acta Endocrinologica 1975;79:366–74. [PubMed: 1173495]

138. Schulte-Beerbühl M, Nieschlag E. Comparison of testosterone, dihydrotestosterone, luteinizing hormone, and follicle stimulating hormone in serum after injection of testosterone enanthate or testosterone cypionate. Fert Steril 1980;33:201–3.

139. Behre HM, von Eckardstein S, Kliesch S, et al. Long-term substitution therapy of hypogonadal men with transscrotal testosterone over 7–10 years. Clin Endocrinol 1999;50:629–35.

140. Dobs AS, Meikle W, Arver S, et al. Pharmacokinetics, efficacy, and safety of a permeation-enhanced testosterone transdermal system in comparison with bi-weekly injections of testosterone enanthate for the treatment of hypogonadal men. J Clin Endocrinol Metab 1999;84:3469–78. [PubMed: 10522982]

141. Wang C, Cunningham G, Dobs A, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. J Clin Endocrinol Metab 2004;89:2085–98. [PubMed: 15126525]

142. Steidle C, Schwartz S, Jacoby K, et al. AA2500 testosterone gel normalizes androgen levels in aging males with improvements in body composition and sexual function. J Clin Endocrinol Metab 2003;88:2673–81. [PubMed: 12788872]

143. Korbonits M, Slawik M, Cullen D, et al. A comparison of a novel testosterone bioadhesive buccal system, Striant, with a testosterone adhesive patch in hypogonadal males. J Clin Endocrinol Metab 2004;89:2039–43. [PubMed: 15126518]

144. Schubert M, Minnemann T, Hübler D, et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. J Clin Endocrinol Metab 2004;89:5429–34. [PubMed: 15531493]

145. Padma-Nathan H, Christ G, Adaikan G, et al. Pharmacotherapy for erectile dysfunction. J Sex Med 2004;1:128–40. [PubMed: 16422967]

146. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. Clin Endocrinol (Oxf) 2005;63:381–94. [PubMed: 16181230]

147. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab 2005;90:1502–10. [PubMed: 15572415]

148. Amory JK, Watts NB, Easley KA, et al. Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab 2004;89:503–10. [PubMed: 14764753]

149. Buvat J. Androgen therapy with dehydroepiandrosterone. World J Urol 2003;21:346–55. [PubMed: 14551720]

150. Liu D, Dillon JS. Dehydroepiandrosterone activate endothelial cell nitric-oxide synthase by a specific plasma membrane receptor coupled to Galpha(i2,3). J Biol Chem 2002;277:21379–88. [PubMed: 11934890]

151. Hayes FJ, DeCruz S, Seminara SB, et al. Differential regulation of gonadotropin secretion by testosterone in the human male: absence of a negative feedback effect of testosterone on follicle-stimulating hormone secretion. J Clin Endocrinol Metab 2001;86:53–8. [PubMed: 11231978]

152. Guay AT, Jacobson J, Perez JB, et al. Clomiphene increases free testosterone levels in men with both secondary hypogonadism and erectile dysfunction: who does and does not benefit? Int J Impot Res 2003;15:156–65. [PubMed: 12904801]

153. Shabsigh A, Kang Y, Shabsigh R, et al. Clomiphene citrate effects on testosterone/estrogen ratio in male hypogonadism. J Sex Med 2005;2:716–21. [PubMed: 16422830]

154. Guay AT, Bansal S, Heatley GJ. Effect of raising endogenous testosterone levels in impotent men with secondary hypogonadism: double blind placebo-controlled trial with clomiphene citrate. J Clin Endocrinol Metab 1995;80:3546–52. [PubMed: 8530597]

155. Dukes M, Edwards PN, Large M, et al. The preclinical pharmacology of “Arimidex” (anastrozole; ZD1033)—a potent, selective aromatase inhibitor. J Steroid Biochem Mol Biol 1996;58:439–45. [PubMed: 8903429]

156. Leder BZ, Rohrer JL, Rubin SD, et al. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. J Clin Endocrinol Metab 2004;89:1174–80. [PubMed: 15001605]

157. Harden C, MacLusky NJ. Aromatase inhibition, testosterone, and seizures. Epilepsy Behav 2004;5:260–3. [PubMed: 15123030]

158. Moghetti P, Toscano V. Treatment of hirsutism and acne in hyperandrogenism. Best Pract Res Clin Endocrinol Metab 2006;20:221–34. [PubMed: 16772153]

159. Nickel M, Moleda D, Loew T, et al. Cabergoline treatment in men with psychogenic erectile dysfunction: a randomized, double-blind, placebo-controlled study. Int J Impot Res. 2006In press

160. Giraldi A, Marson L, Nappi R, et al. Physiology of Female Sexual Function: Animal models. J Sex Med 2004;1:237–53. [PubMed: 16422954]

161. Giuliano F, Allard J. Dopamine and male sexual function. Eur Urol 2001;40:601–8. [PubMed: 11805404]

162. Pfaus JG. Revisiting the concept of sexual motivation. Ann Rev Sex Res 1999;10:120–57. [PubMed: 10895250]

163. Pfaus JG, Kippin TE, Coria-Avila G. What can animal models tell us about human sexual response? Ann Rev Sex Res 2003;14:1–63. [PubMed: 15287157]

164. Pfaus JG, Shadiack A, Van Soest T, et al. Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist. Proc Natl Acad Sci USA 2004;101:10201–4. [PubMed: 15226502]

165. Greco EA, Spera G, Aversa A. Combining testosterone and PDE5 inhibitors in erectile dysfunction: basic rationale and clinical evidences. Eur Urol 2006;50:940–7. [PubMed: 16979814]

166. Greco EA, Pili M, Bruzziches R, et al. Testosterone: estradiol ratio changes associated with long-term tadalafil administration: a pilot study. J Sex Med 2006;3:716–22. [PubMed: 16839328]

167. Auchus RJ. The backdoor pathway to dihydrotestosterone. Trends Endocrinol Metab 2004;15:432–8. [PubMed: 15519890]

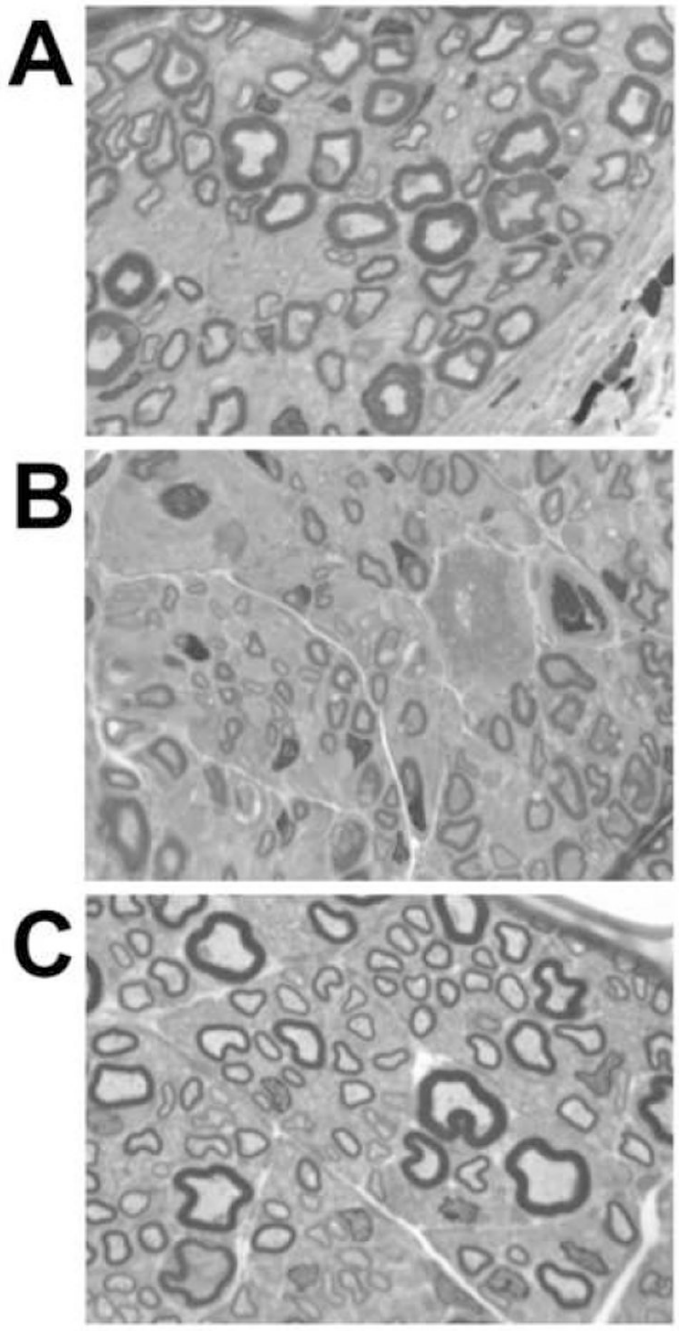

Fig. 1.

Effect of androgens on rat penile cavernosal nerve structure. Tissue sections of cavernosal nerves from intact (sham-operated) or castrated rats were fixed in glutaraldehyde and stained with toluidine blue to visualize myelinated nerve fibers (magnification = 1000×, oil immersion). Castrated rats infused with vehicle (B) exhibited decreased nerve fiber density and thinner myelin sheaths compared with intact rats (A) or castrated rats infused with testosterone (C). Myelinated nerve fibers can be seen throughout each section and appear as darkened circular or irregularly shaped profiles.

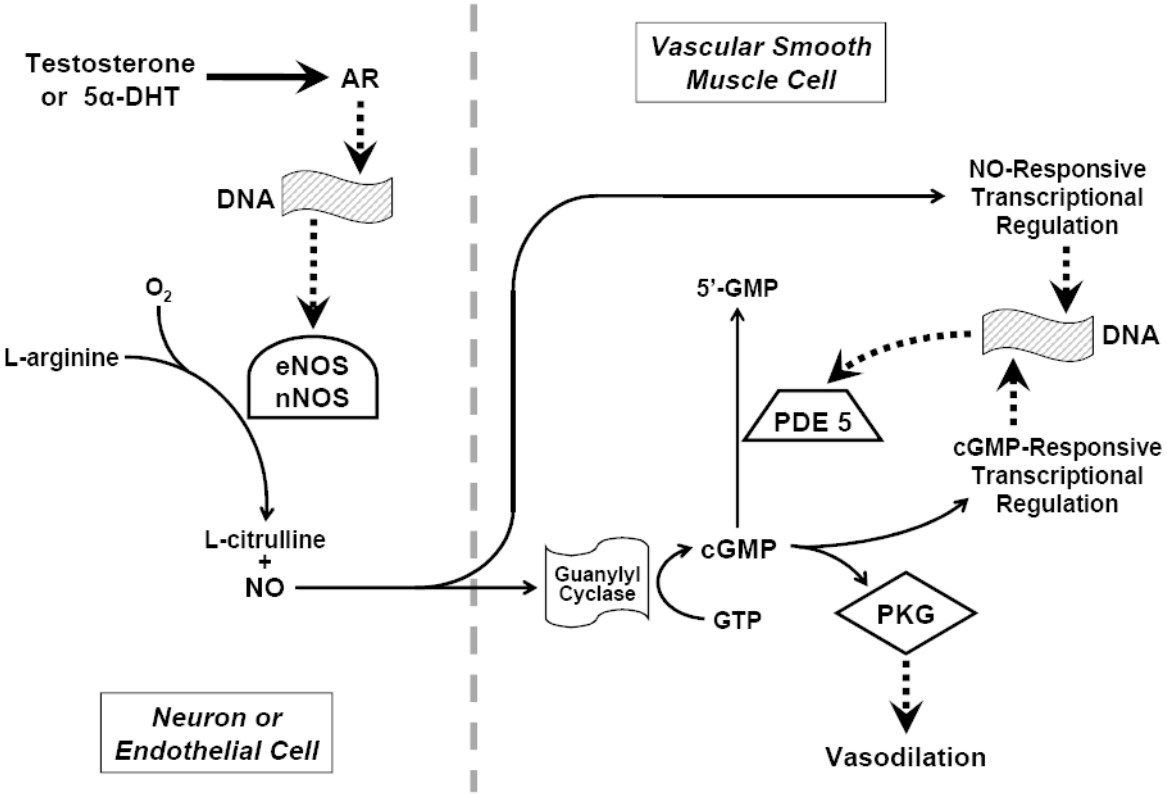

Fig. 2.

Potential regulation of nitric oxide synthase (NOS) and phosphodiesterase (type) 5 (PDE5) by androgens. Hypothetical mechanism by which androgens may upregulate both NOS and PDE5 proteins.

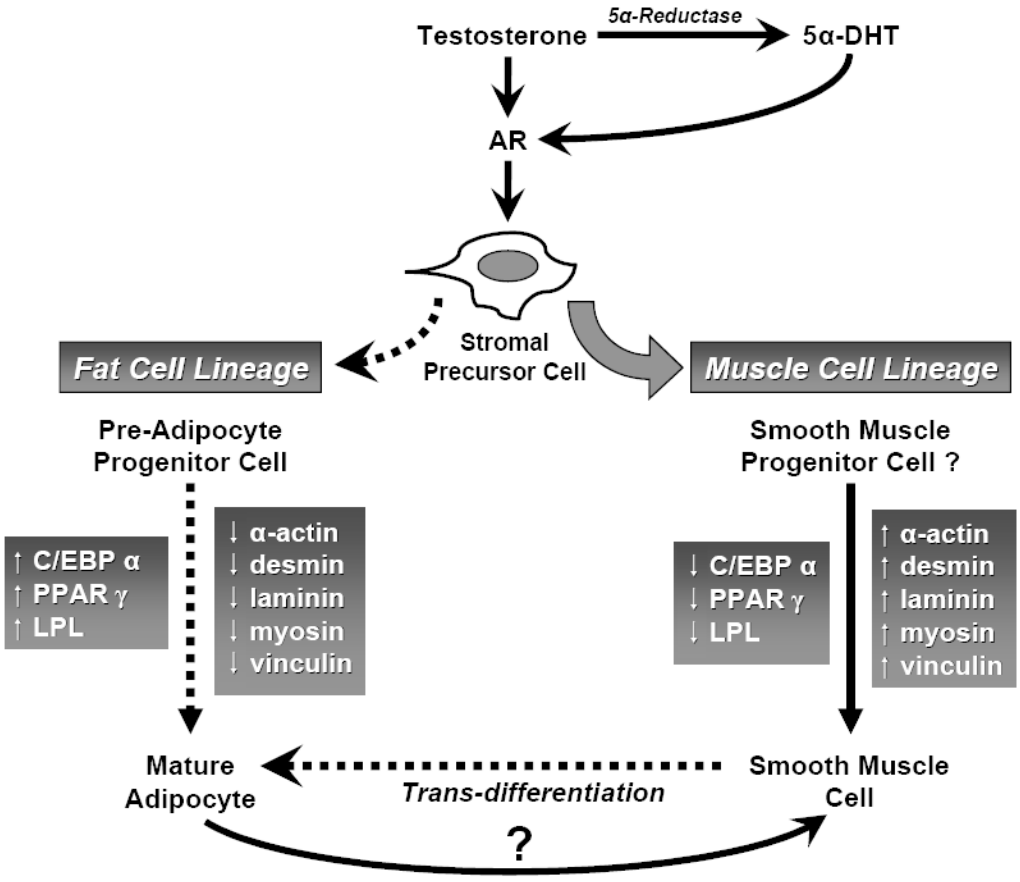

Fig. 3.

Proposed mechanism of regulation of cellular differentiation by androgens in penile corpus cavernosum. Androgens, through the activation of androgen receptors (ARs), may stimulate stromal precursor cells to differentiate into smooth muscle cells (solid lines/arrows). Normal smooth muscle cell content is predicted to result in abundant amounts of smooth muscle marker proteins (α-actin, desmin, laminin, myosin, vinculin) and decreased levels of adipocyte marker proteins (C/EBPα [CCAAT/enhancer binding protein], PPARγ2 [peroxisome proliferator-activated receptor], and LPL [lipoprotein lipase]). Androgen deprivation may inhibit the smooth muscle differentiation pathway and stimulate differentiation of stromal precursor cells into adipocytes and/or transdifferentiation of smooth muscle cells (dashed lines/arrows). Either of these states is predicted to result in increased levels of adipogenic markers and decreased levels of smooth muscle marker proteins.

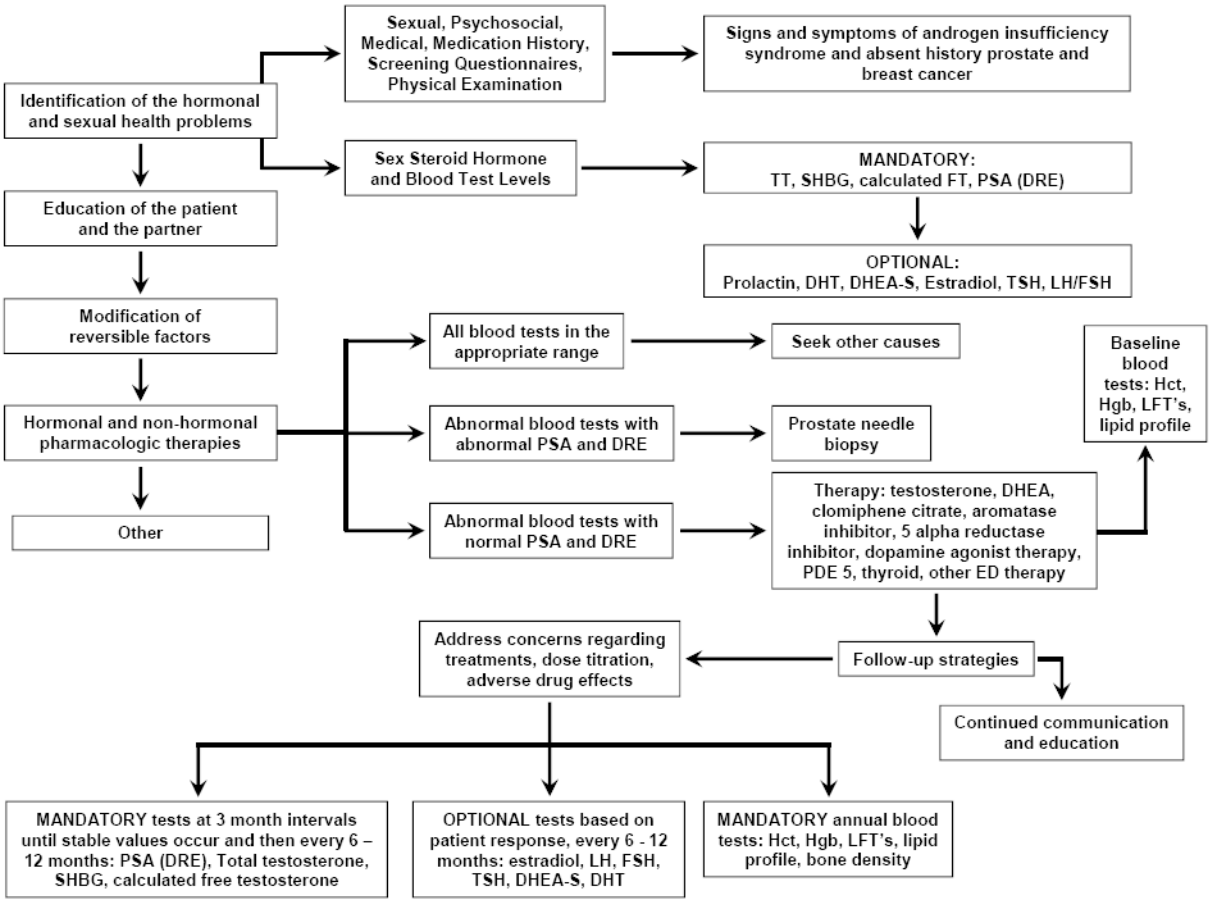

Fig. 4.
Diagnosis and treatment algorithm for androgen insufficiency and erectile dysfunction.