A Clinical Paradigm for the Combined Management of Androgen Insufficiency and Erectile Dysfunction

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Androgen insufficiency and erectile dysfunction (ED) have historically been considered separate and distinctly different conditions affecting the aging man. Men who had ED were historically treated with a psychologic focus [1]. Current data from basic science laboratories and clinical investigations have shown that the most frequent biologic pathophysiologies of ED are endothelial dysfunction and vasculopathy [2,3].

Hormonal pathophysiologies of ED were considered rare [1]. New information on the cellular mechanisms of erectile physiology has led to the consistent observation that erectile physiology, especially vascular and endothelial function, is strongly dependent on sex steroid hormonal integrity [4,5]. Clinical interest in androgen insufficiency and ED has increased [6–9].

Since the isolation and synthesis of testosterone in the mid-1930s [10], testosterone has been clinically available for use in aging men. Edwards and colleagues first reported the effects of testosterone on the vasculature in 1939 [11]. In the 1940s, several investigators used testosterone to treat angina in men who had coronary artery disease [12,13]. Androgens have not been popular therapies for sexual dysfunction, in part due to fear of prostate cancer facilitation [7,9]. Another problem was the lack of basic science to support a direct relationship between testosterone and sexual dysfunction. In addition, testosterone delivery systems were not user friendly and were associated with side effects or marked variations in blood levels. The recent advent of the hydroalcoholic testosterone gels [14,15] has enabled, for the first time, patient-friendly drug delivery of stable, eugonadal testosterone

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values, and the prostate-specific antigen (PSA) blood test [16] has simplified the clinical strategy to monitor for prostate cancer.

Contemporary basic science laboratory and clinical research data consistently show synergy between androgen insufficiency and ED. There are shared physiologic and pathophysiologic mechanisms [17,18]. Published prevalence rates of androgen insufficiency in men who have ED vary but are as high as 35% [19]. Increased numbers of patients (and partners) [20–22] are seeking combined health care management of androgen insufficiency and ED. A general approach to the management of ED related to other etiologies is discussed by Brant and colleagues elsewhere in this issue. This article focuses on a rational, evidence-based clinical management paradigm (Fig. 1) that combines the diagnosis and treatment of men who have androgen insufficiency and ED [6,23–30]. There is close interplay with hormonal, sexual, medical, and lifestyle variables in aging men, and appropriate clinical management needs to engage all these contributing variables [31].

Identification of androgen insufficiency and erectile dysfunction

A comprehensive sexual, psychosocial, medical, and medication history [23], physical examination, and laboratory testing are essential for the diagnosis and management of androgen insufficiency and ED (Fig. 1A, B). Androgen insufficiency [32,33] is a syndrome in which there are signs and symptoms in conjunction with a biochemical blood test. The signs and symptoms are nonspecific and not sufficient for the diagnosis of androgen insufficiency.

History

The medical history should include focused questions on the patient's medical history, including possible risk factors and associated medical conditions of androgen insufficiency and ED, such as diabetes, cardiovascular disease, and depression [32,33]. Androgen insufficiency is associated with an increase in visceral fat and a decrease in lean body mass with associated diminution in muscle volume and strength. Androgen insufficiency is also related to a decrease in body hair, skin alterations, and decreased bone mineral density, resulting in osteoporosis [32–36].

The sexual history should include past and present characteristics of the patient's erectile qualities and other aspects of sexual function, such as sexual interest, sexual orgasm and ejaculatory function, penile sensation capabilities, and sexual pleasure and satisfaction. Some symptoms of androgen insufficiency exist in several other syndromes, such as depression and hypothyroidism, and may have broad variation in patients. The sexual symptoms of androgen insufficiency include decreased sexual interest; diminished erectile quality (particularly of nocturnal erections); muted, delayed, or absent orgasms; decreased genital sensation; and reduced sexual pleasure [32,33].

A

Identification of the hormonal and sexual health problems

⬇

Education of the patient and the partner

⬇

Modification of reversible factors

⬇

First Line Treatments - including hormonal and non-hormonal therapies

⬇

Other

B

Sexual, Psychosocial, Medical, Medication History, Screening Questionnaires, Physical Examination

→

Signs and symptoms of androgen insufficiency syndrome, absent history prostate and breast cancer

TT, SHBG, calculated FT, PSA (DRE), Prolactin, DHT, DHEA-S, estradiol TSH, LH/FSH

←

Sex Steroid Hormone and Blood Test Levels

DRE=Digital Rectal Exam,
PSA=ProstateSpecific Antigen, TT=Total Testosterone
DHT=dihydrotestosterone
FT=Free Testosterone
SHBG = Sex hormone binding globulin
LH=Luteinizing Hormone, FSH=Follicle Stimulating Hormone
TSH=thyroid stimulating hormone.

Normal blood tests → Seek Other Causes

Abnormal blood tests with DRE, PSA normal → Hormonal Therapy Baseline: Hct, Hgb, LFT's, Lipids → Follow-up every 3 - 6 months TT, SHBG, PSA, DRE

Abnormal blood tests with DRE, PSA abnormal → Prostate needle biopsy
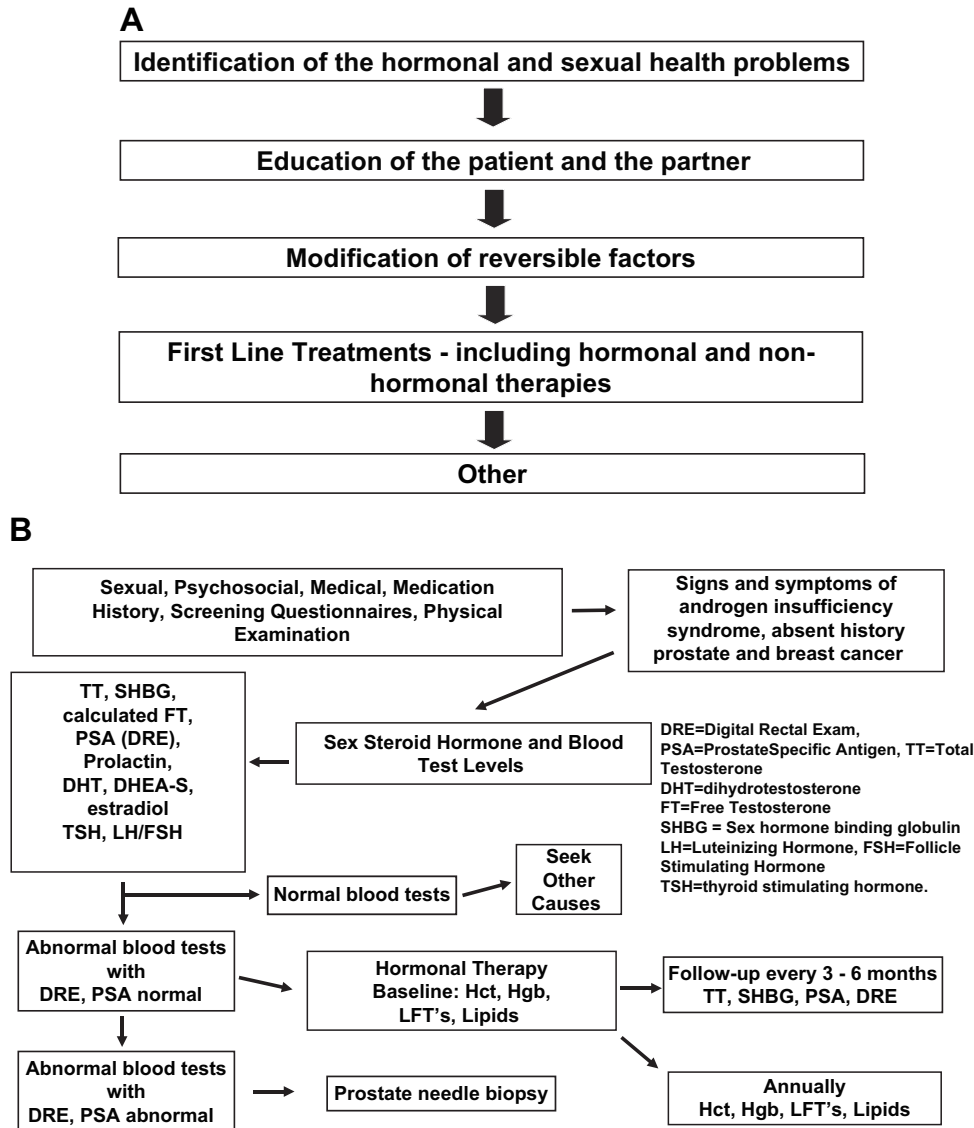
Annually Hct, Hgb, LFT's, Lipids

Fig. 1. Diagnosis and treatment algorithm for androgen insufficiency and ED. A rational, cost-effective, evidence-based clinical management paradigm that combines diagnosis and treatment of men who have androgen insufficiency and ED. This clinical paradigm is stepwise and advances from simple, low-cost, reversible, and minimally invasive strategies to more complicated invasiveness, costly, and irreversible strategies. The first step is critical and should include a careful clinical history, a focused physical examination, and select laboratory tests. Modification of reversible causes of androgen insufficiency and ED is recommended before initiation of therapeutic interventions. Mandatory blood tests include total testosterone, SHBG (albumen if the patient has a chronic medical condition), a calculated free testosterone based on the use of the free testosterone calculator (www.issam.ch/freetesto.htm), and PSA. Optional tests include DHEA-S, DHT, prolactin, LH, FSH, estradiol, and TSH. Mandatory follow-up at 3 months is a DRE and PSA, along with a calculated free testosterone value. Various treatments can be offered to the patient who has androgen insufficiency and ED. Safe and effective management requires a detailed follow-up strategy. (Fig. 1B *Adapted from* Morales A, Heaton JP, Carson CC III. Andropause: a misnomer for a true clinical entity. J Urol 2000;163:705–12; with permission.)
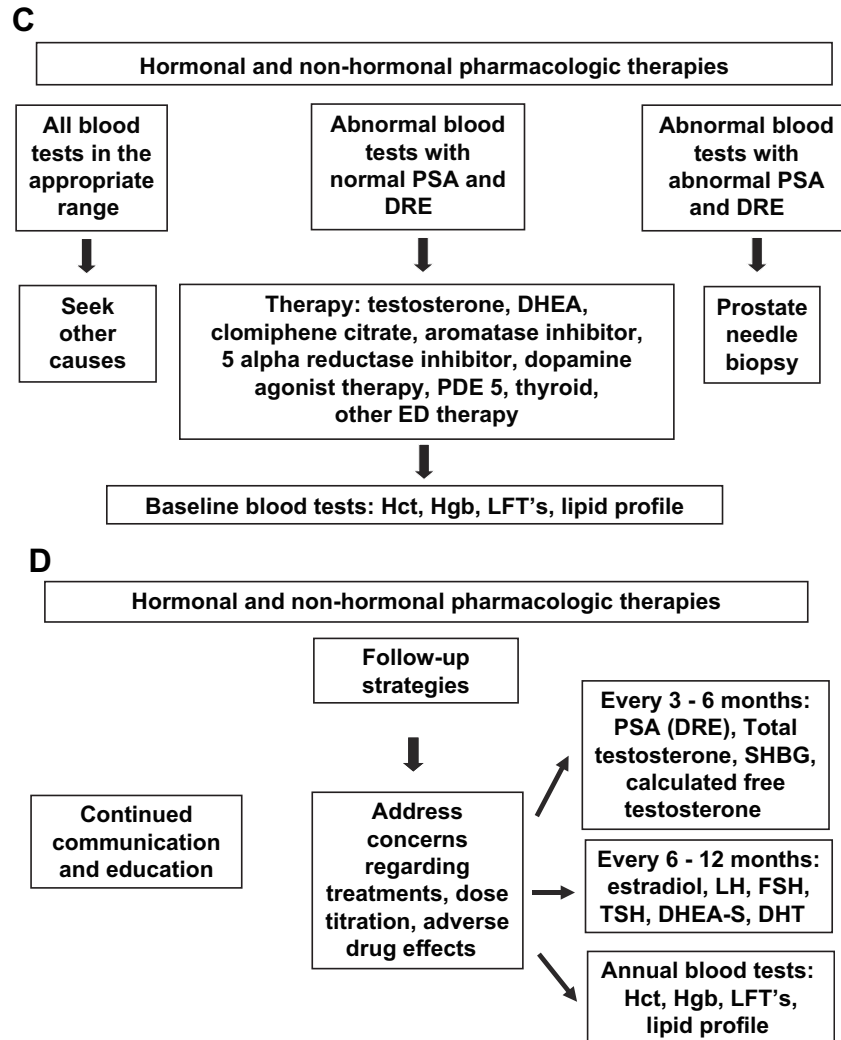
C

Hormonal and non-hormonal pharmacologic therapies

All blood tests in the appropriate range	Abnormal blood tests with normal PSA and DRE	Abnormal blood tests with abnormal PSA and DRE

Seek other causes

Therapy: testosterone, DHEA, clomiphene citrate, aromatase inhibitor, 5 alpha reductase inhibitor, dopamine agonist therapy, PDE 5, thyroid, other ED therapy

Prostate needle biopsy

Baseline blood tests: Hct, Hgb, LFT's, lipid profile

D

Hormonal and non-hormonal pharmacologic therapies

Follow-up strategies

Continued communication and education

Address concerns regarding treatments, dose titration, adverse drug effects

Every 3 - 6 months: PSA (DRE), Total testosterone, SHBG, calculated free testosterone

Every 6 - 12 months: estradiol, LH, FSH, TSH, DHEA-S, DHT

Annual blood tests: Hct, Hgb, LFT's, lipid profile

Fig. 1 (*continued*)

A psychosocial assessment is valuable because sexual dysfunction may affect the patient's self-esteem and coping ability. Androgen insufficiency is associated with changes in mood, diminished well-being, blunted motivation, changes in spatial orientation, reduced intellectual ability, fatigue, depression, and anger or irritability [32,33].

Medication use is relevant when the diagnosis of androgen insufficiency is suspected. Failure to respond to a maximum dose of oral phosphodiesterase type 5 (PDE5) inhibitor is a premonitory sign of androgen insufficiency [27,29]. Amar and colleagues reported that when patients who have ED cannot successfully benefit from PDE5 inhibitors, prescribing testosterone may improve the response [24]. Shabsigh stated that the combination of testosterone with PDE5 inhibitors may be considered for the treatment of ED in men who have low to low-normal testosterone levels and inadequate response to prior treatment with PDE5 inhibitors alone [26]. Greenstein

and colleagues noted that combined treatment with a PDE5 inhibitor and testosterone gel had a beneficial effect on patients who had ED and androgen insufficiency in whom treatment with testosterone supplement alone failed [37]. Rosenthal and colleagues showed successful use of testosterone gel with a PDE5 inhibitor in men who had low-normal serum testosterone levels in whom the PDE5 inhibitors alone failed [38]. They further stated that this underscores the large numbers of men with low to low-normal testosterone levels who would benefit from testosterone screening when evaluated for ED [38].

Aversa and colleagues were among the initial investigators to note the association between testosterone and androgen insufficiency and ED. They reported that aging men who have androgen insufficiency who fail first-line oral treatments should be considered for treatment with a combination of testosterone and PDE5 inhibitors to improve erectile function and quality of life, unless androgens are contraindicated [27,28]. In men who have ED, low free testosterone correlated independently of age with the impaired relaxation of the cavernous smooth muscle cells. These findings gave clinical support to the experimental knowledge of the importance of androgens in regulating smooth muscle function [28]. Androgen insufficiency seems to reduce the cavernosal expression of nitric oxide synthase (NOS) mRNA and protein and enzyme activity, whereas testosterone supplementation restores NOS expression and activity. The clinical responsiveness of PDE5 inhibitor seems to be strongly linked to NOS activity in vascular endothelial tissues [27,28].

The clinical diagnosis of androgen insufficiency may be aided by the use of screening questionnaires. These include the Androgen Deficiency of the Aging Male, which is widely used but has poor specificity in aging men [39]; the Aging Male Scale [40]; the low testosterone screener by Smith and colleagues, which reliably detects men at risk of androgen insufficiency [41]; and the ANDROTEST [42], which is a structured interview for the screening of androgen insufficiency in men who have sexual dysfunction. Although all of these questionnaires are useful to varying degrees, validated questionnaires cannot replace a detailed history and physical examination [23].

Physical examination

The physical examination may corroborate aspects of the medical history and may reveal unsuspected physical findings [23]. It should emphasize the endocrinologic examination, especially if the response to a PDE5 inhibitor is not robust. Androgen insufficiency is associated with small, less firm testes; a decrease in beard and body hair growth; skin thinning alterations; a decrease in lean body mass; an increase in body fat and a decrease in muscle mass and strength; and the development of breast tissue [32,33].

The diagnosis of androgen insufficiency in men should be based on a suggestive clinical picture and on the biochemical demonstration of androgen

deficiency [23,32,33]. Low androgen levels are not sufficient reason for instituting therapy. The most sophisticated biochemical measures of serum androgens can be at best an approximation of the androgen status. Such a measure does not take into account the intracrinologic role of the metabolism of androgens into bioactive metabolites or individual differences in androgen sensitivity based on endocrine disruptors. Based on these issues, there will be a variable response by the target organs to the levels of androgens in different individuals [23,32,33].

Laboratory testing

There is no universally accepted cut-off value of total testosterone that defines the state of androgen insufficiency [32,33]. Total testosterone values fall with age and at various times throughout the day. The ideal time to clinically measure total testosterone is in the early morning, except in aging men, in whom testosterone values can be measured at any time of the day because of the flattening of the circadian rhythm [23].

Total testosterone measurements can be misleading. Unbound testosterone is the major form entering the cells and initiating critical protein synthesis (growth factors, sex hormone receptors, enzymes, etc.) via genomic effects. In normal men, 2% of testosterone is free (unbound), 30% 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. Thus, the sex hormone binding protein, in part, regulates androgen function. Conditions associated with high values of SHBG lower the unbound, physiologically available form of testosterone [32].

Rather than relying on total testosterone exclusively, the health care provider has the option of assessing free testosterone values. The confusion arises on the methodologies used to measure free testosterone. Antibody-based, free testosterone assays using a testosterone analogue are not accurate. Reliable assays for free testosterone are based on equilibrium dialysis, a test that is usually difficult and time consuming to perform and not widely used clinically. Bioavailable testosterone measures free and albumin-bound fractions of testosterone and is more commonly accessible, more reliable, and less expensive than free testosterone values measured via equilibrium dialysis [30]. A contemporary management strategy for the health care provider is to record the total testosterone and the SHBG and to use the free testosterone calculator [23] from the International Society for the Study of the Aging Male (www.issam.ch/freetesto.htm). The calculated free testosterone, based on the total testosterone and SHBG values, has been shown to correlate to the free testosterone by equilibrium dialysis.

A calculated free testosterone value of less than 5 ng/dl is consistent with an abnormal calculated free testosterone. Morris and colleagues stated that when total testosterone is borderline, calculated free testosterone values are useful to help confirm androgen insufficiency [43]. The calculated free

testosterone is reliable in most clinical situations but should not be relied upon in situations with potential massive interference by steroids binding to SHBG, such as in men during treatment inducing high levels of dihydro-testosterone (DHT). Hwang and colleagues reported that calculated free testosterone declined and SHBG rose with age in normal patients and in patients who had ED [44]. Martinez-Jabaloyas and colleagues investigated the frequency of hypogonadism in men who had ED and the factors associated with low testosterone levels [45]. Using the calculated free testosterone levels, 17.6% of the men had criteria for androgen insufficiency. Hypertension, aging, absence of nocturnal erections, and a low erectile function score were associated with lower free testosterone levels.

Androgen administration is contraindicated in men who have been diagnosed with or are suspected of having carcinoma of the prostate [32,33]. Determination of serum PSA and digital rectal examination (DRE) are mandatory as baseline measurements of prostate health before therapy with androgens [46–48]. Many health care providers consider PSA levels of 0 to 2.5 ng/ml as low and values greater than 2.6 to 10 ng/ml as slightly to moderately elevated. PSA screening and DRE should be repeated every 3 to 6 months for the first 12 months and annually thereafter. When in doubt with the assessment of the prostate by PSA or DRE, the health care clinician should consider recommending a prostate biopsy [46]. If the PSA increases during androgen therapy and the biopsy is negative for prostate cancer, androgen therapy can continue with the PSA and DRE, repeated every 3 to 6 months. There is no evidence that androgen therapy causes prostate cancer. The risk that androgen therapy may accelerate an existing underlying prostate cancer must be clearly understood by the patient, and the regular and routine follow-up prostate check is thus particularly important.

Hyperprolactinemia is an uncommon cause of ED and androgen insufficiency [49,50]. If a patient presents with signs and symptoms of androgen insufficiency, such as diminished sexual interest by history and gynecomastia on physical examination, and has biochemical evidence of androgen insufficiency, determination of serum prolactin is recommended [50].

For some androgen-dependent functions, testosterone is a prohormone peripherally converted to DHT via the enzyme 5-alpha reductase. Physiologically, the most active androgen acting on the androgen receptors seems to be DHT [51].

Nonphysiologically high levels of DHT may be observed after topical testosterone gel administration, presumably 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 [52]. These high values of DHT may be associated with the side effects of acne and scalp hair loss [53]. Successful management of elevated DHT-associated side effects may be achieved with low doses of 5-alpha reductase enzyme inhibitors [51].

Nonphysiologically low levels of DHT may occur with the medical treatment for lower urinary tract symptoms (LUTS) using 5-alpha reductase inhibitors that block the conversion of testosterone to DHT. This results in a circulating level of DHT that can be reduced by as much as 70% [51]. The 5-alpha reductase inhibitors finasteride and dutasteride have been associated with a greater risk of ED, ejaculatory dysfunction, and decreased libido compared with placebo [54,55].

Animals treated with finasteride had significantly lower DHT levels and had significant ultrastructural changes, including marked irregularities in the tunica albuginea consistent with thick and irregular-arranged collagenous fibers and in the trabeculae of the corpus cavernosum [56]. Mantzoros and colleagues found serum DHT to be an independent hormonal predictor of increased frequency of orgasms [57].

Estradiol is synthesized in men peripherally by metabolism of testosterone via the enzyme aromatase. In aging men, estradiol values increase over time [58,59]. Elevated estradiol increases the liver synthesis of SHBG, which lowers unbound physiologically available testosterone. Mancini and colleagues found that estradiol values were significantly higher in patients who had venous leak compared with control subjects, supporting the hypothesis that estradiol level can influence penile smooth muscle function [60]. Estradiol levels were greater in the men who had aging male symptoms [61].

Dihydroepiandrosterone (DHEA) is an androgen precursor produced by the adrenal glands that has been shown to exert its effects via downstream conversion to testosterone and estradiol. DHEA values steadily decrease from age 40 [62]. It may be involved in multiple biologic effects, including cognitive, memory, metabolic, vascular, immune, and sexual functions [63]. Deficiencies of DHEA in men have been reported to be associated with various drugs and with endocrine, nonhormonal, and age-related disorders.

Dihydroepiandrosterone sulfate (DHEA-S) levels were significantly lower in the men who had aging male symptoms and in men who had sexual dysfunction as determined by the International Index of Erectile Function score [61]. Alexopoulou and colleagues reported that patients who had ED and type 1 diabetes had lower levels of DHEA and DHEA-S compared with men who had diabetes but no ED [64]. DHEA-S showed an inverse correlation with age and a positive correlation with testosterone [65].

No well designed clinical trials have definitively substantiated the role of DHEA in these functions in humans or the safety and efficacy of DHEA therapy [66]. In a small study, Reiter and colleagues evaluated the efficacy of DHEA replacement in the treatment of ED and determined that it was associated with higher mean scores for all five domains of the International Index of Erectile Function but had no impact on PSA and testosterone [67].

The thyroid gland promotes tissue growth and development, regulates energy metabolism, and indirectly plays a role in sexual health. Bodie and

colleagues evaluated the prevalence of laboratory abnormalities in men presenting for initial evaluation and therapy of ED and found that a total of 4% had increased thyroid-stimulating hormone [68].

Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) determination may be of value in men who have ED and androgen insufficiency, especially in those who are being considered for therapy by clomiphene citrate because this agent is effective only in hypogonadotropic hypogonadism [69]. In patients who have ED and androgen insufficiency, hypogonadotropic hypogonadism, and a LH level of less than 13 mIU/ml, Bunch and colleagues found that 10% had hypothalamic-pituitary structural abnormalities [70].

Patient/partner education

An essential component in the management of androgen insufficiency and erectile dysfunction is patient and partner education (Fig. 1) that is uniquely matched to individual needs [23]. 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 his partner, if possible. The education process is ongoing through regular follow-up visits. During the education process, patient's and partner's preferences for management should be respected and taken into consideration [23].

Modifying reversible causes

ED and androgen insufficiency are potentially reversible if specific etiologic factors can be addressed (Fig. 1). This may apply to altering or modifying prescription or nonprescription drug use, such as LUTS treatment with a 5-alpha reductase inhibitor, or altering psychosocial factors, such as stress and anger from poor partner relationship and communication.

Many patients have a history of prescription or nonprescription drug use. Of the drugs that may induce sexual dysfunction or androgen insufficiency, the most common are antihypertensives, antiarrhythmics, antidepressant agents, and antipsychotic agents. Drugs commonly used in the treatment of prostate disease typically lead to ED and diminished sexual interest. Recreational drug use should be considered as a potential negative influence.

Partner relationship factors should be appropriately addressed by a certified trained mental health care professional who provides psychosexual or couples therapy. Therapy can be conducted with the patient alone, but it is preferable to include the partner. For patients being treated concomitantly with medical therapy, a modified sex therapy approach can address psychologic reactions to the medical treatment. If there has been an

extended period of abstinence, brief sex therapy may facilitate resumption of sexual activity for the couple [71,72].

First-line therapies

Pharmacologic treatment (Fig. 1C) is delivered with reference to ease of medication administration and cost. Hormonal agents include testosterone, DHEA, clomiphene citrate, aromatase inhibitors, 5-alpha reductase inhibitors, dopamine agonists, and thyroid therapies. Nonhormonal treatments include vasodilators, such as PDE5 inhibitors, and intracavernosal agents. Before testosterone, DHEA, clomiphene citrate, or aromatase inhibitor therapy is considered, a patient should have 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 [32,33].

Hormonal pharmacologic treatment

Although testosterone has a recognized physiologic role in erections, its importance in ED treatment has been controversial. Relative contraindications include elevated hematocrit, abnormal liver function studies, LUTS, and sleep apnea. Testosterone therapy used selectively and carefully may be administered by topical (gel, patch, or cream) or parenteral (intramuscular) administration. Oral administration with methyltestosterone is discouraged due to limited efficacy data and potential associated hepatic side effects. There is a critical need for large-scale, long-term, randomized controlled trials to investigate the efficacy of testosterone therapy in men who have androgen insufficiency and ED [32,33].

Isidori and colleagues conducted a systematic review and meta-analysis of randomized, placebo-controlled studies to assess the effects of testosterone on the different domains of the sexual response. In men who had an average testosterone level at baseline below 12 nmol/l, testosterone treatment improved the number of nocturnal erections and successful intercourses, sexual thoughts, scores of erectile function, and overall sexual satisfaction but had no effect on in eugonadal men. The effect of testosterone tended to decline over time and was progressively smaller with increasing baseline T levels. Long-term safety data were not available [73].

Because DHEA is available over the counter, men can take it without physician supervision. Saad and colleagues reviewed clinical studies evaluating DHEA treatment for decreased DHEA values [62]. 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 when the diagnosis is based on the clinical picture and biochemical evidence, when there are periodic evaluations, and when individual dose adjustments are performed to maintain serum concentrations in the physiologic range [74].

Exogenous testosterone suppresses gonadotropins from the hypothalamic-pituitary axis as a result of elevation of the circulating values of testosterone. This may be deleterious in men who have relative infertility [32,33]. An alternative treatment is clomiphene citrate, particularly when the androgen insufficiency is due to hypogonadotropic hypogonadism, because this therapy increases gonadotropins [69]. Guay and colleagues found significant increases in LH and free testosterone and improved sexual function. Erectile improvement was lower in aging men and in men who had diabetes, hypertension, coronary artery disease, and multiple medication use [75]. In another study, results showed a significant increase in LH, FSH, and total and free testosterone levels versus placebo. Sexual function improved in limited parameters in younger and healthier men [76].

Because androgens are the precursors of estrogens, the administration of exogenous testosterone results in a suspicion of an increase in estradiol values by virtue of aromatization. Anastrozole is a potent and highly selective aromatase inhibitor, with no intrinsic estrogenic, antiestrogenic, androgenic, antiandrogenic, progestogenic, glucocorticoid, antiglucocorticoid, or mineralocorticoid activities [77]. Leder and colleagues investigated anastrozole's ability to increase endogenous testosterone production in men who had hypogonadism. Aromatase inhibition increased serum bioavailable and total testosterone levels in older men who had mild hypogonadism [78]. Serum estradiol levels decreased modestly but remained within the normal male range. The sexual benefits of aromatase inhibitor therapy were reported in a case report [79]. The use of an aromatase inhibitor normalized the testosterone level and improved sexual functioning. Greco and colleagues showed that sustained improvement in sexual function after 12 months of PDE5 inhibitor administration is associated with increased testosterone to estradiol ratio mainly related to reduction of estradiol levels. These investigators hypothesized that androgen–estrogen cross-talk and possible inhibition of aromatase activity during chronic exposure to PDE5 inhibitor use might play a role in the regulation of erectile function [80].

Hirsutism and acne are common and can be distressing complaints in individuals who have high values of androgens, in particular DHT. The most efficacious pharmacologic therapy to reduce DHT is by 5-alpha reductase inhibitors [81]. Mechanical therapies for hirsutism include laser photothermolysis and electrolysis. Other acne therapies include topical and systemic retinoids and antibiotics and topical antibacterial agents.

Nonhormonal pharmacologic treatment

Clinical use of dopamine agonists has been reported to improve sexual function based on research showing that sexual motivation is modulated by a number of central nervous system neurotransmitter and receptor changes [82]. These changes are induced, in part, by the action of sex steroids and by the central neurotransmitter dopamine, which may play

a critical intermediary role in the central regulation of sexual arousal and excitation, mood, and incentive-related sexual behavior and, in particular, in the motivational responses to conditioned external stimuli [83–85]. Androgens may be central in this by allowing more estradiol to be distributed to central nervous system target tissues via aromatase.

Treatment with a dopamine agonist such as bromocriptine or with cabergoline, a more potent and long-lasting ergoline-derived dopamine agonist, is beneficial in the presence of documented hyperprolactinemia. Six months of treatment with cabergoline normalized testosterone levels in most cases, thus restoring and maintaining during treatment the capability of normal sexual activity in hyperprolactinemic men [86]. In another study, De Rosa and colleagues compared the effects of chronic treatment with cabergoline and bromocriptine on sexual function in hyperprolactinemic men and found that in men who had prolactinomas, cabergoline normalized prolactin levels and improved sexual function earlier than bromocriptine treatment [87]. In men who had psychogenic ED and no prolactinoma, cabergoline treatment resulted in improvement in erectile function, sexual desire, orgasmic function, and in the patient's and the partner's sexual satisfaction [82]. Safarinejad reported that cabergoline is effective in salvage therapy for sildenafil nonresponders [88].

Bupropion is a dopamine agonist antidepressant with fewer reported adverse sexual effects than traditional selective serotonin reuptake inhibitors and therefore is clinically useful as an antidote to antidepressant-associated sexual dysfunction. Taylor and colleagues assessed the effectiveness of management strategies for sexual dysfunction caused by antidepressant medication [89]. Compared with serotonin reuptake inhibitors, the dopamine agonist bupropion revealed less desire dysfunction and less orgasm dysfunction and superior overall satisfaction with sexual functioning. No differences were found in self-reported sexual function, number of erections, total erection time, or penile rigidity in healthy subjects taking bupropion compared with those taking placebo or baseline [89,90].

In summary, dopamine agonist pharmacologic agents such as bupropion, bromocriptine, cabergoline, apomorphine, and Parkinson-type drugs such as L-dopa, pergolide, pramipexole, and ropinirole may be helpful in men who have sexual dysfunction [91,92].

If a patient who has androgen insufficiency and ED has a concomitant thyroid abnormality, it is likely that androgen therapy would not be successful until the thyroid status has been normalized. Carani and colleagues studied 34 men who had hyperthyroidism treated with methimazole and 14 who had hypothyroidism treated with thyroxine [93]. A total of 50% and 64%, respectively, had some abnormality in sexual function (decreased sexual desire, ED, or premature or delayed ejaculation) that improved with thyroid treatment without concomitant PDE5-inhibitor therapy. Based on an animal model of hypothyroidism, Kilicarslan and colleagues concluded that hypothyroidism results in an autonomic neuropathy and endothelial

dysfunction adversely influencing the release or synthesis of NO from nitrergic nerves and endothelium [94].

Follow-up strategies

Patients undergoing hormonal treatment for androgen insufficiency and ED should undergo reassessment and follow-up at regular and routine intervals (Fig. 1D). The major goals of reassessment and follow-up are to ensure optimum patient–physician communication and to assess the progress of therapy and the sexual, general medical, and psychosocial status of the patient and partner [23].

Strategies for safe blood test monitoring during testosterone therapy should include blood tests every 3 to 6 months for total testosterone, SHBG (albumin if appropriate), PSA screening, and DRE. Strategies for medical health monitoring during testosterone therapy should engage hematocrit and hemoglobulin, liver function tests, and lipid profile evaluations annually. Follow-up blood tests for LH, FSH, thyroid-stimulating hormone, DHEA-S, prolactin, DHT, and estradiol should be obtained as indicated in each individual [32,33].

During follow-up visits, the health care provider may address any relevant patient concerns regarding the treatments. There may be a need for dosage titration or substitution of another treatment intervention. Patients may change treatment preferences, seek new information, or wish to re-evaluate their current treatment choices. Patients may change medication strategies for these and other health problems. Adverse drug reactions or drug interaction effects should be carefully monitored [23].

Other treatments

Men who have androgen insufficiency and ED may not respond to the interventions described in this article and may need to consider such options as a vacuum erection device, intraurethral or intracavernosal administration of alprostadil or other vasoactive agents, surgical intervention with penile prostheses, or reconstructive surgery, such as penile revascularization [23] (Fig. 1).

Summary

Androgen insufficiency and ED are highly prevalent medical disorders in aging men who have associated multiple risk factors. Good clinical practice requires the use of appropriate strategies for patient- and goal-directed diagnosis and treatment. In the future, we will likely see new basic science investigations that may lead to new treatment strategies. In this fashion, management can be delivered in a more safe and effective manner for the majority of afflicted patients (and partners). New basic science laboratory and clinical research studies will provide a new awareness of the significance

of sexual health medicine because sexual health is an important element in the physical health and psychologic well-being of most patients. The contemporary health care provider must be aware of these issues to provide good medical practice.

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