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Androgens and erectile dysfunction
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·*Review*·

Hypogonadism and erectile dysfunction: an overview

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Abstract

In humans androgen decline is presented as a clinical picture which includes decreased sexual interest, diminished erectile capasity, delayed or absent orgasms and reduced sexual pleasure. Additionally, changes in mood, diminished well being, fatigue, depression and irritability are also associated with androgen insufficiency. The critical role of androgens on the development, growth, and maintanence of the penis has been widely accepted. Although, the exact effect of androgens on erectile physiology still remains undetermined, recent experimental studies have broaden our understanding about the relationship between androgens and erectile function. Preclinical studies showed that androgen deprivation leads to penile tissue atrophy and alterations in the nerve structures of the penis. Furthermore, androgen deprivation caused to accumulation of fat containing cells and decreased protein expression of endothelial and neuronal nitric oxide synthases (eNOS and nNOS), and phosphodiesterase type-5 (PDE-5), which play crucial role in normal erectile physiology. On the light of the recent literature, we aimed to present the direct effect of androgens on the structures, development and maintanence of penile tissue and erectile physiology as well. Furhermore, according to the clinical studies we conclude the aetiology, pathophysiology, prevalance, diagnosis and treatment options of hypogonadism in aging men. *(Asian J Androl 2008 Jan; 10: 36–43)*

Keywords: testosterone; erectile physiology; symptomatic late onset hypogonadism

1 Introduction

The gradual decline of reproductive and erectile functions in the aging male has become the focus of experimental and clinical researchs in several countries [1, 2]. The aim of this communication is to discuss the etiology, pathophysiology, prevalance, diagnosis and current treatment options for hypogonadism in aging men. Recently, the importance of androgens in the regulation of erectile physiology has been investigated in experimental animal models. The results of these studies has expanded our understanding of the cellular, molecular, and physiological mechanisms regulated by androgens, which play critical roles in the modulation of erectile physiology. This paper details much of the recent data.

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2 Hypogonadism: definition and etiology

Men with low sexual desire have been treated with testosterone for over 70 years, however, the issue of low sexual desire has recently re-emerged as an important topic in the field of male sexual dysfunction [2, 3]. This condition has been labelled the male climacteric or andropause, which is biologically incorrect. The recent literature has adopted new terms such as androgen decline in aging male (ADAM) and symptomatic late onset hypogonadism (SLOH). ADAM or SLOH is depicted as emotional and physical changes related to the aging process which parallel the hormonal changes associated with aging [2]. A significant decrease in testosterone levels is the most widely accepted change observed in the aging process, but changes in various other hormones are also observed and may be involved in age-related sexual dysfunction. While currently vascular-endothelial dysfunction is considered to be the most important cause of aging related erectile dysfunction (ARED), other pathological factors like hormonal alterations need to be considered in ARED [2–4]. Furthermore there are interac-

tions between the penis and the central nervous system which are also influenced by androgens [2].

In numerous studies the incidence of erectile dysfunction (ED) increases with age, concurrent with a progressive decline in androgen levels [5, 6]. The results of the Baltimore Longitudinal Study on Aging documented total serum testosterone levels decreasing approximately 1% per year in men from their 30s on [7]. In addition to the gradual decline of testosterone, there are similar age related decreases in production of several other hormones including dehydroepiandrosterone, thyroxine, melatonin and growth hormone [8].

A decrease in sexual interest and impaired quality of erectile function is commonly encountered in men with hypogonadism. Additionally, the testosterone decline is associated with parallel declines in bone mass, muscle mass/strength and physical function/fraility [9]. Furthermore, the potential metabolic consequences of hypogonadism, such as abdominal obesity, diabetes and markers of diabetes (insulin resistance, impaired glucose tolerance, and metabolic syndrome) have also been reported. Investigating the association between hypogonadism and metabolic syndrome, Makhsida *et al.* [10] reviewed the English literature from 1998 to 2004 focused on testosterone therapy. They concluded that metabolic syndrome is strongly associated with hypogonadism and testosterone therapy improves body mass, insulin secretion and sensitivity, lipid profile and blood pressure [10]. Researchers from Austria evaluated the impact of age, body mass index (BMI) and serum testosterone levels on erectile function in 675 workers. The results of detailed statistical analyses suggested that while BMI contributes strongly to ED, low total testosterone (TT) and bioavailable testosterone (BT) were related to International Index of Erectile Dysfunction (IIEF)-5 scores and specifically severe ED [11]. In another study Kaplan *et al.* [12] evaluated the association between total serum testosterone levels, obesity and the metabolic syndrome in aging males and showed that total serum testosterone levels in obese and severely obese aging men with the metabolic syndrome registered approximately 150 ng/dL and 300 ng/dL, respectivily, much lower than in a cohort of aging men without metabolic syndrome. Based on statistical analyses of this study, the presence of diabetes, BMI greater than 30 kg/m^2, and triglycerides greater than 150 mg/dL all have a clinical relevant association with low testosterone levels. The authors suggested a possible association between ED and pre-diabetes/diabetes involving a low hormonal influence [12]. Similarly, in a more recent paper Guay *et al.* [13] reported that metabolic syndrome and insulin reistance are strongly associated with hypogonadism. They recommended that men with ED should not only be evaluated for cardiovascular risk factors but should also be screened for hypogonadism [13]. Zohdy *et al.* [14] investigated the penile hemodynamic parameters in hypogonadal men with metabolic syndrome and showed that obesity was associated with lower testosterne levels and disturbances in penile hemodynamic parameters.

3 Hypogonadism: pathophysiology-preclinical and clinical evidences

The hypothalamic-pituitary gonadal system is a closed loop feedback mechanism, controling normal reproductive function. Gonadal hormones including testosterone, estrogens and other androgen precursors have inhibitory effects on the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretions. While testosterone is the major inhibitor of LH, the aromatized and nonaromatized forms of testosterone, namely estradiol and dihydrotestosterone (DHT), also inhibit LH [2]. Normally, 1%–2% of testosterone is free, about 30% is bound to sex-hormone-binding-globulin (SHBG) with high affinity, and the remainder is bound with low affinity to albumin.

The amount of testosterone not bound to SHBG is referred to as BT. Alterations in SHBG caused by estrogens, thyroid hormone and healty aging leads to increased or reduced testosterone levels [2].

Montorsi and Oettel [15] reported that between the ages of 40 to 70 years, TT decreases annually by approximately 1.6%, free testosterone decreases by 2%, and BT decreases by 2%–3%, whereas SHBG increases annually by 1.6%. Of note, aging related decreases of serum testosterone cause concomitant increases of LH and FSH levels [15].

3.1 The role of androgens in erectile physiology: lessons learned from basic science

Erectile function is a complex neurovascular phenomenon modulated by several biochemical and physiological factors [16]. Normal erections need healthy penile vascular tissues and intact neural innervation of the penis [17]. Although some researchers believe that androgens have a passive and negligible impact on erectile function, there is a growing body of data implicating androgens as of importance in normal erectile physiology. Many authors have published that testosterone is necessary for normal sexual desire, ejaculation and spontaneous erections [2–5, 15, 16].

This section summarizes results from animal studies documenting the role of androgens in cellular, molecular and physiologic mechanisms associated with erectile physiology. Attention is focused on the relationship between testosterone and a number of recognized structures/molecules associated with erectile physiology [17].

3.1.1 Testosterone-nerve structure and function

Researchers have investigated the potential role of androgens in the structure and normal function of the pelvic ganglion neurons, specifically how testosterone has a critical role for the maturation and maintenance of terminal axon density and neuropeptide content in the vas deferens [17, 18]. Further the effects of testosterone on erectile function via the spinal cord [17, 19]. Moreover, researchers have revealed the impact of castration on loss of erectile function, penile dorsal nerve ultrastructure and decreases in structural integrity and function of the cavernosal nerve [17, 20]. These significant structural changes in the cavernosal nerve were reversed when castrated animals were treated with testosterone [17]. Centrally in rodents, the medial preoptic area which can induce erections is testosterone dependent [17, 21].

3.1.2 Testosterone-nNOS expression and activity

The importance of the NOS/cyclic guanosine monophosphate pathway (c-GMP) is well documented. Nitric oxide (NO) causes relaxation of the vascular smooth muscle, which ultimately leads to penile erection [17]. The role of androgens on the expression of NOS isoforms in the penile tissue has been demonstrated [17, 22, 23]. In castrated animals, replacement with testosterone and 5α-DHT restored erectile function as well as NOS expression in the corpora cavernosa [17, 24].

3.1.3 Testosterone-phosphodiesterase type-5 (PDE-5) activity

The role of PDE-5 in normal erectile physiology is well recognized. PDE-5 catalyzes c-GMP which causes vascular smooth muscle contraction and penile detumescence. Regulation of PDE-5 is essential to normal erectile physiology. Expression and activity of PDE-5 is significantly decreased in castrated animals and restored with androgen replacement [17, 25–27].

3.1.4 Testosterone-cellular growth and differentiation

The impact of castration on trabecular smooth muscle and extracellular matrix proteins is well established. While there was a significant reduction in smooth muscle content, connective tissue deposition was markedly increased in castrated animals and the structure of the tunica albuginea was altered [17, 28]. With time (4 weeks) the tunica became thinner with fewer elastic fibers and disorganizations of collagen [17, 29]. Additionally, fat-containing cells have been encountered in the subtunical area of the penis in castrated animals. This finding was interesting and lead researchers to speculate that hypogonadism contribute to venous leakage in castrated animals [17, 30]. These results cumulatively suggest that androgens play an important role in the overall structure of the corpora cavernosa.

The regulatory effect of androgens on growth and differentiation of vascular smooth muscle cells has been shown where androgens induce pluripotent stem cells along a muscle lineage and inhibit the differentiation of the same cells into an adipocyte lineage [17, 31, 32]. Inhibition of 5α-reductase activity causes stromal remodeling and smooth muscle dedifferentiation in the prostate [17, 33]. Some researchers claim that 5α-DHT deficiency induces smooth muscle dedifferentiation in the penis. However this hypothesis needs further study.

3.1.5 Testosterone-diabetes related ED

In a recent study diabetes induced in both rabbits and rats caused decreased testosterone levels. Administration of testosterone improved erectile function and increased PDE-5, eNOS and nNOS expression. The researchers also showed that testosterone replacement restored sildenafil responsiveness in these animals [34].

3.2 The role of androgens in erectile physiology: clinical inferrences

Clinical evaluation is important to further understand the role of androgens in erectile physiology. Some believe that the role of androgens on erectile physiology is predominantly through effects in the central neural system via effects on libido and sexual drive rather than the function of the corpus cavernosum [15, 35]. Studies have shown that serum levels of testosterone and free testosterone were significantly lower in patients with ED when compared to normal individuals [15, 36]. Others have shown that there is a concomitant increase in cavernous and peripheral testosterone levels during penile erection, inferring a peripheral effect of testosterone [15, 37]. Carani *et al*. [38] found increased penile rigidity in hypogonadal men who underwent testosterone therapy, implying a possible direct end-organ effect. In support of this finding, Aversa *et al*. [6] described that in men with ED, low free testosterone levels correlated with diminished relaxation of cavernosal, endothelial and smooth muscle cells in response to vasoactive agents, which was independent of men's age. Chronic antiandrogen therapy significantly reduces PDE-5 mRNA protein levels and impairs erectile function [15, 26]. Hence it has been suggested that concomitant testosterone therapy may improve the efficacy of PDE-5 inhibitors in hypogonadal men [39]. Some clinicians now suggest a combination of PDE-5 inhibitor and testosterone supplementation as the treatment of choice in older men with SLOH who previously were unresponsive to PDE-5 inhibitor therapy [15].

The action of testosterone most probably acts through its conversion to 5α-DHT [22]. This hypothesis is supported by the observation that a selective type-2 5α-reductase inhibitor (namely finasteride) did not suppress sleep-related erections. Since type-1 5α-reductase en-

zyme is predominantly localized to the central nervous system and not inhibited by finasteride, 5α-DHT should be the major androgen responsible of libido [40]. Some investigations have stated that finasteride does not cause ED in men being treated for benign prostatic hyperplasia (BPH) [41]. In contrast, Rosen *et al.* [42] reported that both finasteride and dutasteride had similar deleterious side effects on erectile function, ejaculation and sexual desire. These findings further support the concept that 5α-DHT plays a crucial role in normal erectile physiology. It is well recognized that surgical or medical castration impairs libido and sexual function. Peters and Walsh [43] investigated the effect of nafarelin, a potent LH-releasing hormone (LH-RH) agonist, in patients with BPH. While ED occurred in the majority of patients, almost 50% of these men recovered their erectile function with cessation of LH-RH agonist [43]. Similarly, the effect of the competitive nonsteroidal antiandrogen bicalutamide in men treated for BPH showed that about 50% experienced ED. Surprisingly, sexual desire was not affected compared to the control group [44]. These observations support the hypothesis that androgen deprivation contributes to ED and androgens help to maintain normal erectile physiology.

Another interesting consideration is the role of androgens in sleep related erections (SREs). There is a recognized age-related decrease in the frequency and duration of nocturnal erections [45]. Researchers have speculated about a possible relationship between testosterone and nocturnal erections. Cunningham *et al.* [46] reported that in men with ED there is an association between decreased serum testosterone levels and abnormal SREs. Erections associated with visual stimulation are not affected by hypogonadism, suggesting that these types of erections are androgen independent versus centrally regulated SREs which are testosterone dependent [47]. Researchers now recognize that androgen insufficiency in aging men is related to insomnia and some sleep disturbances [15]. Schiavi *et al.* [48] showed that there is a clear relationship between low levels of testosterone and sleep efficiency, decreased latency to onset of rapid eye movement (REM) activity, and number of REM episodes. Of interest, supraphysiologic administration of testosterone reduced the total time slept, increased the duration of hypoxemia and disrupted breathing during sleep in men older than 60 years of age [49]. In summary, SREs are an indicator of the quality of sleep and are associated with age-related hypogonadism [15].

4 Hypogonadism: prevalence

The prevalence of SLOH can be estimated from population based studies. Numerous cross-sectional and longitudinal studies have shown that there is an age-related decline in androgen production in adult men [7, 8]. Studies suggest a prevalence of SLOH varying from 2% to 70% [2, 16], with most trials reporting a prevalence rate of 15–20%, while it is general higher in referral biased studies [51]. Recently Araujo *et al.* [9] investigated the prevalence of SLOH in men between the ages of 30 to 79 through the Boston Area Community Health (BACH) survey. SLOH was defined as low total (< 300 ng/dL) and free (< 5 ng/dL) testosterone and decreased libido, ED, osteoporosis or fracture, or two or more following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance. Results of that study showed that low testosterone and free testosterone levels were present in 24% and 11% men respectively. The prevalence of SLOH symptoms were: decreased libido (12%), ED (16%), osteoporosis/fracture (1%) and two or more of the non-specific symptoms (20%). The prevalence of SLOH was 5.6%, independent of race, and increased markedly with age [9].

5 Diagnosis of hypogonadism

The diagnosis of hypogonadism in men should based on both the suggestive clinical picture and the biochemical findings of low androgens. Initially a sexual, psychosocial and medical history should be obtained. Following this a focused physical examination should be performed on all aging men. Patients with SLOH may present with characteristic symptoms including decreased sexual desire, impaired erections, poor sleep related erections, reduced sexual pleasure, muscle atrophy, and delayed or absent orgasm. Additionally, changes in mood, diminished feelings of well being, loss of motivation, fatigue, depression, anger, decrease in body hair, osteoporosis due to decreased bone mineral density, an increase in visceral fat are frequently observed in patients with SLOH [2, 17]. Small and less firm testes are usually consistent with hypogonadotrophic hypogonadism. Of note, these findings need not all be present for the diagnosis of SLOH. Furthermore, using screening questionnaires as an adjunctive tool for the diagnosis of hypogonadism can be helpful. The ADAM scale is commonly used, its specificity is very low in the aging male. The Aging Male Scale (AMS) and ANDROTEST are also both reliable in detecting the presence or absence of androgen deficiency symptoms [51–53]. However, these validated questionnaires should not be considered alternative instruments, but a useful supplement to a detailed history and proper physical examination [2, 17].

As mentioned, the diagnosis of SLOH in men is based on the clinical picture and biochemical documentation of androgen deficiency. Low testosterone level alone is not an indication for administration of hormonal therapy. Several laboratory ranges for androgens are not always

reliable and sometimes at best are a rough approximation of the androgen status [2, 17]. Furthermore there is no absolute threshold value of testosterone which exactly defines the state of androgen deficiency. Because only unbound testosterone can act within cells, it is possible that TT measurements may be misleading. In normal men, 2% of testosterone is free and 30–60% is bound to SHBG with high affinity. In contrast the remaining amount of testosterone is bound to albumin and other serum proteins with a much lower affinity. Changes in SHBG can increase or reduce the effective testosterone milieu, which suggest that SHBG at least in part regulates androgen function. Therefore in patients who are suspected for androgen deficiency, SHBG levels need to be evaluated. On the other hand, some authorities suggest that, determination of free testosterone levels delivers a more reliable assessment about the androgen status of adult men [2]. There are a number of biases inherent in the methods used to determine free testosterone values. Direct free testosterone measures using a testosterone analogue assay do not provide reliable free testosterone results. Although, equilibrium dialysis and ultracentrifugation are reliable, they are not widely available and are technically difficult. BT using ammonium sulphate precipitation is generally used, reliable and less expensive [2].

The following provides a summary of biochemical assessments for SLOH:

1) Measure serum TT between 8.00 and 11.00 a.m.

2) If testosterone levels are below the normal limit (350 ng/dL) confirm the results with a second determination together with measurement of LH, FSH and prolactin. In the younger (< 40 years) men, low testosterone levels concomitant with elevated gonadotrophins indicates the presence of primary hypogonadism. In this circumstance prolactin levels are needed to rule out hyperprolactinemia.

3) In patients with a total testosterone level less than 200 ng/dL with accompanying signs and symptoms of hypogonadism, further calculation of free and/or BT is not necessary. On the other hand free testosterone or BT are required in men with SLOH who have a borderline (200–400 ng/dL) testosterone value. In the first step, TT (ng/dL), SHBG (nmol/L) and albumin (g/dL) concentrations are measured. Calculation of the free testosterone or BT levels can be performed with the help of the International Society for the Study of the Aging Male (ISSAM) Web page (www.issam.ch). Calculated values of free testosterone less than 5 ng/dL is considered abnormal, whereas values less than 110 ng/dL for BT suggests androgen deficiency [2, 17].

6 Treatment of hypogonadism

The general goals of hormone replacement therapy are to substitute the deficient hormone in a dose arrangement that mimics the normal diurnal variation [2]. For hypogonadism, androgen delivery systems include oral testosterone, intramuscular depot injections, scrotal transdermal patch systems, nongenital skin transdermal patch systems, hydroalcholic testosterone gels, adhesive buccal tablets, and more recently developed long acting intramuscular depot injections [17, 54–60].

According to the suggestion of the Sexual Medicine Society of North America (Annual meeting 2003): 'Testosterone supplementation should only be considered for men who have signs and symptoms of hypogonadism accompanied by abnormal serum testosterone levels' [2, 17]. Furthermore, a normal prostate specific androgen (PSA) and digital rectal examination (DRE) are required at baseline [2].

Several clinical trials have demonstrated the benefits of testosterone monotherapy on erectile function. In a meta-analysis, 57% response rate for all testosterone therapies has been reported, ranging from 64% for primary to 44% for secondary hypogonadism [61]. Testosterone treatment in hypogonadal men with ED improved sexual attitudes and performance in 61% of patients [62]. In another study testosterone replacement improved erectile function and penile vascular parameters in 36% and 42% of patients, respectively [63].

Testosterone monotherapy with transdermal gel formulation has been shown to improve sexual performance, desire and motivation in men with hypogonadism. Maximal effects were observed at approximately the 30th day of a 6-month treatment [64]. A comprehensive meta-analysis was performed using the data obtained from 17 randomized placebo-controlled trials to compare the effects of testosterone replacement on the different domains of sexual function. The results showed that testosterone improved the number of nocturnal erections and successful sexual intercourses, sexual thoughts, scores of erectile function, and overall sexual satisfaction in men with hypogonadism. Importantly, they reported that, the beneficial effect of testosterone appeared to attenuate over time and that long-term safety data were still not available [65]. Elevated hematocrit, abnormal liver function studies, lower urinary tract symptoms (LUTS) and sleep apnea are contraindications for testosterone replacement therapy. Enlargement of the prostate size was a rarely encountered adverse event related to testosterone replacement, which can be negated by the concomitant use of finasteride [65]. In a recent report Yassin *et al.* [66] investigate the effect of long-acting testosterone undeconate on men with hypogonadism. Briefly, sexual function was assessed by IIEF at baseline and after 24 weeks of testosterone treatment. All patients had serum testosterone levels restored to normal within 6 to 8 weeks with concomittant improvement in

libido, erectile function in more than 50%, and no changes in serum PSA or prostate volumes [66].

Combination treatment with oral PDE-5 inhibitors and testosterone in hypogonadal men may ensure improvement in erectile function. In a study by Kalinchenko *et al.* [67], 120 men with type-2 diabetes related ED were evaluated to investigate the cause of failure to respond to treatment with sildenafil. At baseline that patients had a low sexual desire and low testosterone levels when compared to age matched controls (patients with diabetes who respond to sildenafil). After a two-week oral testosterone undeconate course, testosterone levels were restored to physiological levels and libido was normalized. Subsequently, 70% of previous sildenafil nonresponders regained adequate erectile ability [67]. Similarly, in a placebo-controlled study Shabsigh *et al.* [68] have investigated the effect of testosterone gel in combination with sildenafil in men with ED and hypogonadism, who were previously unresponsive to sildenafil alone. These patients were evaluated at baseline, and 4, 8 and 12 weeks during the treatment period. Serum TT and free testosterone values significantly increased in the testosterone gel group compared to the placebo group. Furthermore, erectile function improved significantly in the group receiving testosterone and sildenafil combination whereas there was no significant change in erectile function in the group treated with placebo and sildenafil. Additionally, the group treated with testosterone gel and sildenafil showed significant improvements from baseline in orgasmic function, overall satisfaction, and in total scores of sexual function questionnaires [68]. In another study, the synergistic effect for testosterone therapy and efficacy of PDE-5 inhibitor therapy in hypogonadal men with ED showed that when testosterone treatment alone failed, combination therapy with a PDE-5 inhibitor and testosterone gel improved sexual function [69]. Vascular studies revealed that testosterone administration improved erectile response to both sildenafil and tadalafil by increasing arterial inflow to the penis [40, 70].

6.1 Monitoring strategies in patient with SLOH undergoing testosterone replacement therapy

Hypogonadal patients with ED undergoing testosterone treatment, need to be evaluated at regular periods to assess the efficacy of the treatment and the sexual, medical, and psychosocial status of the patient. Additionally, treatment related adverse events and drug interaction effects need to be carefully monitored.

Recently, recommendations related to the monitorization of hypogonadal men who are receiving testosterone replacement therapy were reported by Morales *et al.* [2]. According to their recommendations:

1) Liver function studies are suggested at baseline. Although most of the current testosterone preparations are free of hepatic toxicity, periodic assessment during testosterone therapy may be considered.

2) A fasting lipid profile at baseline and re-assessment at 3 or 6 months during the testosterone treatment period is recommended.

3) Recent studies suggest that the levels of PSA do not change with 1-year testosterone therapy, and testosterone therapy does not increase the risk of prostate cancer [71, 72]. However, it is the standard practice in men over 40 years of age to have DRE and PSA measurement at baseline, and after 3 to 6 months of therapy, and yearly thereafter. Transrectal ultrasound guided biopsy of the prostate is indicated if the DRE or PSA values become abnormal.

4) Testosterone replacement therapy is contraindicated in men suspected of having prostate or breast cancer. Hypogonadal men previously treated for prostate cancer and currently cancer-free may be considered for testosterone replacement therapy.

5) Androgen replacement therapy is contraindicated in men with severe bladder outlet obstruction, whereas mild and moderate obstructions represents a relative contraindication.

6) Normally, androgen replacement therapy improves mood and well-being. However, if adverse behavioral patterns such as aggressiveness and hypersexuality develop, therapy needs to discontinued.

7) Periodic hematologic evaluations are suggested to rule out polycythemia development during testosterone treatment.

8) Exacerbation of sleep apnea has been reported to may occur during testosterone treatment. Therefore detailed assessment is necessary before and during androgen replacement therapy

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