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Is Hypogonadism a Risk Factor for Sexual Dysfunction?

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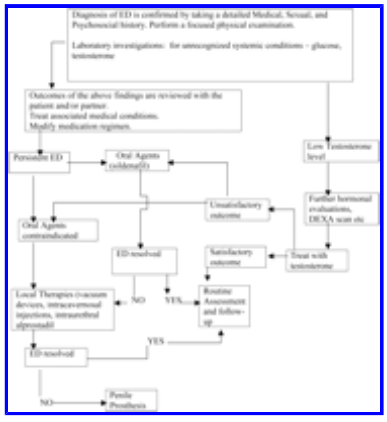
There has been an upsurge of research activities focusing on men's health. One such area that has attracted much research attention is erectile dysfunction (ED). The advent of new, potent, noninvasive therapies has led to improvement in the management of this condition. ED is the most common sexual problem affecting men. It affects the individual's physical and psychosocial well-being, including his quality of life, self-worth, and self-confidence. Although a relatively small number of men with ED are found to have hypogonadism, sexual dysfunction is a common finding among all men with low testosterone. Administration of testosterone to men with hypogonadism and ED has been shown to bring about a significant improvement in their sexual function, energy, mood, and body composition.



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Algorithm for the evaluation and management of erectile dysfunction.

The increased incidence of decreased libido and ED in the population because of advancing age and improved diagnoses, demands a better understanding of ED's predisposing risk factors. ED is a source of significant mental stress and emotional trauma, which affect relationships and quality of life.

The importance of low-serum testosterone to ED is still unclear. ED and hypogonadism both constitute a common problem affecting the aging male population worldwide. Although both male hypogonadism and ED are frequent disorders in older men, this does not necessarily imply causality.

Many advances have been made since the NIH Consensus Conference (1992) on ED. ED may be classified based on severity, etiology, or onset. It can be mild, moderate, or severe (in terms of severity). When classified based on etiology, it can be either psychogenic or organic; however, these 2 often coexist. Finally, ED can be classified either as primary or secondary, based on onset. This article will attempt to review the data on whether male hypogonadism is a risk factor for the presence of ED.

Epidemiology of ED

ED is the most common sexual function disorder in men, second only to premature ejaculation (Feldman et al, 1994). Over 20 million men are affected in the United States (Nehra, 2000). The Baltimore Longitudinal Study of aging reported that the prevalence of ED is nearly 70% in elderly men compared with 7% in younger men. In the Massachusetts Male Aging Study (MMAS), which was a regional survey, more than half of the participants reported ED. Of those who reported ED, about 10% had complete ED, about 25% had moderate ED, and about 5% had mild ED. In the MMAS, the prevalence of complete ED among 70-year-old men was 3 times that of the 40-year-old men, whereas the prevalence of moderate ED in 70-year-old men was twice that of the 40-year-old men. Mild ED was comparable across both ages. In follow-up data from the MMAS, the incidence rate of ED was about 26 per 1000 man-years (Johannes et al, 2000).

Risk Factors for ED

Nonhormonal— ED is often assumed to be one of the processes associated with aging, with the incidence of ED increasing with every decade. However, ED is also associated with specific disease conditions or medical procedures. Because the male erectile response is a vascular event initiated by neuronal action, any disorder that affects the blood flow to the penis may cause ED. Consequently, disease conditions such as vascular diseases, diabetes, multiple sclerosis, spinal cord injury, other endocrine problems, and postradical surgery have all been implicated in ED.

After adjusting for age, the prevalence of ED was directly correlated with diseases (hypertension, diabetes mellitus, and heart disease); medications (vasodilators, cardiac drugs, antihypertensives, and hypoglycemic agents); cigarette smoking in association with treated heart disease and treated hypertension; excessive alcohol consumption; suppression or expression of anger; and depression (Thomas, 2000).

Drugs and Modifiable Factors Associated With ED— Some of the risk factors associated with ED may be amenable to prevention strategies. These include cigarette smoking; alcohol consumption; drugs like antihypertensives (eg, thiazide diuretics); antidepressants (eg, tricyclic antidepressants, monoamine oxidase inhibitors, lithium, serotonin reuptake inhibitors); hormones (eg, estrogens, progestins, corticosteroids, gonadotropins-releasing hormone [GnRH] agonists); and tranquilizers (eg, phenothiazines, butyrophenones). These medications can affect ED by their effect on vascular tone, by direct action on the central nervous system, or by inducing hyperprolactinemia.

Hormonal Factors Associated With ED— (a) Gonadal Hormones in Normal Male. Testosterone and dihydrotestosterone are vital to the development of the male genitalia. Testosterone is synthesized within the Leydig cells under the control of luteinizing hormone (LH), secreted by the anterior lobe of the pituitary gland. About 1% of plasma testosterone is free, whereas 11% to 59% is weakly bound to albumin, and about 40% to 88% is bound tightly to sex hormone binding globulin (Klee and Hesser,

2000). In the central nervous system, testosterone undergoes aromatization to estradiol, and it is reduced to dihydrotestosterone in the prostate, penis, hair follicles, sebaceous gland, and seminal vesicles. The production of testosterone is mediated via the hypothalamic-pituitary-gonadal axis. The biologically active free testosterone causes a negative feedback inhibition of GnRH and LH secretion. The effect of testosterone in erotically mediated erections is unclear, but it is known to enhance sleep-related erections and frequency of sexual acts (Fahmy et al, 1999).

(b) Gonadal Hormones in Aging. In contrast to the decline in estradiol levels in the female, the process of aging in the male is gradual and characterized by large variations among individuals. About 50% of men 80 years or older still maintain their fertility (Schill, 2001). There is a progressive decline in the production of testosterone in the aging male, although the prevalence of older men with low testosterone levels is not well established. This decline in testosterone production is a result of both functional disturbances at the level of the hypothalamic/pituitary system and a gradual peripheral decline in the number of testicular Leydig cells (Wespes and Schulman, 2002). Other factors, such as an impaired feedback mechanism of the pituitary-gonadal axis or reduced bioavailability of sex hormones, may play a role. After men reach 70 years of age, there is an increase in sex hormone binding globulin levels (Baker et al, 1983), which may result in a decrease in the serum-free testosterone, although this is subject to interindividual variability.

Total testosterone (T) decreases at the rate of 0.11 nmol/L (3.2 ng/dL) per year (Harman et al, 2001). Both the total and the free testosterone decline with aging. A fixed lower reference limit of testosterone, 10.4 nmol/L (300ng/dL), is used in most studies. There is also the loss of the circadian rhythm of testosterone secretion with aging (Basaria and Dobs, 1999). The prevalence of hypogonadism is estimated to be 20% for men 65 years and older (Feldman et al, 1994) and may be as high as 92% for men older than 80 years if the free testosterone is used as the diagnostic test (Harman et al, 2001). The significance of this hypogonadism is hotly debated, with many health care professionals treating older men to attain serum testosterone levels similar to those of a middle-aged man (mean serum total T in a 40-year-old man is 500 ng/dL), whereas other health care professionals propose that age-adjusted values should be used to estimate the prevalence of hypogonadism (Schatzl et al, 2003). One drawback in the interpretation of the data from the various literatures is that the available data on the comorbidity of ED are predominantly for a white population. Data available for other races are inadequate for any meaningful analysis to be made. However, there is no evidence to suggest any racial or ethnic differences in the incidence of sexual dysfunction.

(c) Testosterone Use in Men With Hypogonadism and ED. Although the relationship between serum testosterone and ED can be variable in the population of all men with ED, sexually dysfunction is common in the subset of men with hypogonadism and can generally be remedied with testosterone replacement therapy. Several studies of men with hypogonadism and ED have shown that this population responds to testosterone replacement with an improvement in sexual function, mood, and energy. Although many questions remain about the relationship between serum testosterone and male sexual behavior, an association between hypogonadism in men and ED is likely (Cunningham et al, 1990).

In their study of 15 men with hypogonadism, Salmimies et al (1982) concluded that the men with ED responded to intramuscular injection of testosterone. They noted an improvement of sexual behavior, as defined by increase sexual desires, frequency of erections, and ejaculations, and concluded that male sexual behavior is in fact dependent upon testosterone. They obtained data which indicated the individual serum testosterone levels below which impairment of sexual function begins to manifest. In a double-blind experiment, Davidson et al (1979) found that testosterone has a rapid stimulatory effect on sexual function. Nocturnal penile tumescence and spontaneous daytime erections were found

to be reduced in untreated men with hypogonadism and significantly increased after treatment with testosterone (Kwan et al, 1983).

Carani et al (1990) corroborated these findings 8 years later in a separate study of 9 men with hypogonadism and 12 men with eugonodism. They observed an enhancement of performance of the sexual act and penile rigidity by administration of injectable testosterone. Libido was also improved in men with hypogonadism. Androgen treatment is said to increase both nocturnal and spontaneous erections, sexual interest, and mood (Burris et al, 1992).

Transdermal testosterone delivery as a patch (Androderm; Watson Laboratories Inc, Corona, Calif) is both safe and effective in producing circadian variations in the levels of total T, bioavailable T, dihydrotestosterone, and estradiol within normal physiological ranges (Dobs et al, 1999). Arver et al (1996) noted a significant improvement in sexual function of men with hypogonadism treated with the patches, as measured by the Rigiscan (Dacomed, Minneapolis, Minn) procedures to document nocturnal penile tumescence. The patches restored normal erectile activity with an increased frequency of ejaculation and positive effect on mood and energy in men with hypogonadism and ED (McClure et al, 1991). McNicholas et al (2003) observed that testosterone gel formulation (Testim, Auxilium Pharmaceuticals, Norristown, Pa) produced significant improvement in sexual performance in men with hypogonadism. In their study conducted on 406 men with hypogonadism, Steidle et al (2003) found significant improvements in sexual desire, sexual motivation, and spontaneous erections by using Testim. Wang et al (2000) concluded that a normal level of testosterone is vital for the maintenance of sexual characteristics, sexual behavior, mood, energy, and muscle development. Testosterone was also found to improve the quality of erections and level of libido in men with hypogonadism and ED (Monga et al, 2002).

Contrary evidence suggests that testosterone may be unrelated to ED. For example, erectile capacity may not be totally lost even in cases of surgical or pharmacological castration, suggesting that hypogonadism occurs independently of ED (Kubin et al, 2003). Mills and Lewis (1999) corroborated this in noting that erectile function is not always lost in cases of severe hypogonadism and that testosterone treatment does not necessarily correct ED. In studies of testosterone replacement therapy, approximately 50% of men reported adequate erections while still in the hypogonadal state. This would suggest that some level of testosterone concentration is necessary but not sufficient for adequate erectile function.

(d) Testosterone Use in Men With ED. The relationship between ED and testosterone levels, when all men are taken as a whole, is not clear. The prevalence of hypogonadism in men and ED varies greatly depending upon the population studied. Studies have shown that up to 25% of ED cases have below-normal serum testosterone levels (Nehra, 2000), whereas others report low-serum testosterone infrequently as a cause of ED (Morales and Heaton, 2001). In normal aging men, there is a clear association between ED and aging, but no such correlation exists between ED and total testosterone; a statistically significant relationship was not found between the testosterone levels and ED (Rhoden et al, 2002). In routine measurements of testosterone and prolactin, Maatman and Montague (1986) discovered that only a few men in a population of men with ED had endocrinopathy. Johnson and Jarow (1992) obtained similar results and found the prevalence of endocrinopathy to be low in a population of impotent men whose endocrine status was routinely screened. Although the frequency of erection in untreated cases of hypogonadism is reduced, several studies have not found evidence to support the fact that testosterone affects the erectile mechanism. Its role may be in the stimulation of the libidinal factors, which consequently leads to the stimulation of other aspects of sexual functioning (Davidson et al, 1982).

In a controlled study by O'Carroll and Bancroft (1984), an increase in sexual interest was produced by testosterone in a group of men with normal circulating levels of testosterone and with loss of sexual interest. No such increase was observed in erectile function in men who complained of ED and had normal testosterone levels.

(e) Mechanism of Testosterone Effect on ED. The mechanism of testosterone effect on ED in men is not clear, but several animal studies have suggested this may be through stimulation of nitric oxide (NO). Endocrine causes are responsible for a significant number of all sexual dysfunctions in men (Manieri et al, 1997). Voluntary erection depends upon normal androgen levels and also upon influences from the higher centers.

In castrated rats, neural NO synthase mRNA was found to be diminished (Chamness et al, 1995). Reilly et al (1997) observed a reduction in the nerve fibers containing NO synthase, which innervate the corpus cavernosum, in castrated rats. They also noted an enhanced nonadrenergic noncholinergic nerve-mediated relaxation in isolated corpus cavernosum strips with increased reactivity to α-adrenergic stimulation.

Low or inadequate circulating testosterone may lead to apoptosis of smooth muscle cells, with an increase in connective tissue content and consequent impaired relaxation of erectile smooth muscle. Aversa et al (2000) found that low free T correlates independently of age with impaired relaxation of the cavernous endothelial and corporeal smooth muscle. Other neurotransmitters that have been implicated in ED include prostaglandins, vasoactive intestinal peptide, serotonin, and dopamine (Nehra, 2000).

Evaluation of ED

Several schools of thought propose the most effective and cost-efficient way to evaluate the patient with ED. Some believe that the cost of ED evaluation can be reduced by performing endocrine screening only in patients with clinical signs of hypogonadism (Johnson and Jarow, 1992; Ansong and Punwaney, 1999). Lehman et al (1994) proposed that the first time a patient with ED is evaluated, the measurement of testosterone as a single endocrine test is adequate. Also, a multidisciplinary panel of experts has proposed the "process of care model" for the evaluation and treatment of ED by primary care physicians. This model creates a step-wise protocol for the diagnosis, assessment, and treatment of ED. Initial assessment includes a careful clinical history, focused physical examination, and selected laboratory tests. After this initial assessment, further management is individualized and goal oriented, depending upon the needs and preferences of patients and partners. According to this model, treatment is divided into first-, second-, and third-line therapy.

ED Treatment Options

Androgen replacement should be the first-line treatment option for men with hypogonadism and ED. It is reasonable to begin treatment in men with symptoms of hypogonadism and total testosterone lower than 300 ng/dL (Basaria and Dobs, 1999). Testosterone is available in the form of intramuscular injections of testosterone enanthate or cypionate. In the United States, testosterone is also available in form of a trandermal patch or a transdermal gel; outside the United States, testosterone pellets and oral administration of T-undecanoate are available (Schill, 2001). The beneficial effects of testosterone supplementation for sexual function are much more pronounced in young men with hypogonadism than in elderly men (Vermuelen, 2001), but the additional benefits on bone density, body composition, and quality of life necessitate its use.

For men with normal-serum testosterone and ED, or for men who are still symptomatic even after

testosterone therapy, there are a variety of very specific effective treatment options from which they can benefit. The first line of therapy is the use of oral erectogenic agents (sildenafil, or apomorphine). In situations when oral medication is ineffective or contraindicated, the second line of treatment is either intracavernous or intraurethral injection. The third line of treatment is either surgical prosthesis or penile revascularization.

Testosterone Treatment Side Effects

Some of the possible side effects of testosterone therapy include acne, migraine, sleep apnea, polycythemia, or fluid overload. These are usually mild but do require monitoring. In elderly men, the most important side effect is the exacerbation of prostatic disease, which necessitates regular digital rectal exam measurements of prostate serum antigen concentrations. Gynecomastia has been reported more frequently in elderly obese men than in young men with hypogonadism (Behre et al, 1994). Testosterone may also alter the low- or high-density lipoprotein (Schill, 2001), but this is rarely a problem with transdermal testosterone treatments.

Conclusion

Among all men with ED, hypogonadism as a sole cause is rare. However, among men with hypogonadism, ED is a frequent finding. Testosterone replacement has resulted in improved sexual response in men with hypogonadism. The response to testosterone replacement is decreased in the presence of comorbidities. Younger men with hypogonadism and without comorbidities have the best response to testosterone administration. Also, there may be an individual limit of plasma testosterone below which sexual behavior is impaired, and below this limit the response to testosterone may be more pronounced.

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