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Testosterone and Erectile Dysfunction

Review

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ABSTRACT: Aging is associated with a decline in several important health factors in men, including libido. Serum testosterone concentrations also decrease with age, and many age-related clinical features are closely associated with androgen deficiency, including erectile function (ED). Approximately 70% of ED is of organic origin, with the major risk factors being diabetes mellitus, hypercholesterolemia, smoking and chronic medical illnesses. These are also established risk factors for atherosclerosis, which is the predominant predisposing factor of vasculogenic ED. The introduction of phosphodiasterase-5 (PDE-5) inhibitors for the treatment of ED made a significant impact both in terms of clinical efficacy, and increasing the awareness of the condition. In spite of this, some patients fail to respond to PDE-5 inhibitors alone. Both animal and clinical studies indicate that testosterone therapy improves both erectile function and the response to PDE-5 inhibitors in patients with ED and hypogonadism. Indeed, interventional studies demonstrate that testosterone replacement therapy improves erectile function in hypogonadal men who have previously failed to respond to PDE-5 inhibitors alone. Furthermore, it has been demonstrated that the full therapeutic potential of PDE5 inhibitors will only become manifest in a eugonadal state. Recent studies have demonstrated a close relationship between testosterone and ED and suggest that testosterone therapy may be a valuable option for an increasing number of affected men. European guidelines recommend that all men presenting with ED should have their testosterone concentrations measured.

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Aging is associated with a decline in several important health factors in men, such as decreased muscle mass, muscle strength, physical performance, bone mineral density, blood formation, and libido (Davidson et al, 1983; Santavirta et al, 1992; Nguyen et al, 1996; Liu et al, 2004). An age-related decline in serum testosterone (T) levels is also observed (Pirke and Doerr, 1975; Purifoy et al, 1981; Tenover et al, 1987; Harman et al, 2001), and many age-related clinical features are closely associated with androgen deficiency, including erectile function. Not surprisingly, many men are reluctant to discuss erectile dysfunction with their physicians; thus, the condition remains underdiagnosed. Nevertheless, albeit a likely underestimation of the condition, experts have estimated that approximately 30 million men in the United States and 0.5 million men in the United Kingdom between the ages of 40 and 70 years suffer from varying forms of erectile dysfunction (ED) (Agarwal et al, 2006). The introduction of phosphodiasterase-5 (PDE-5) inhibitors for the treatment of ED made a significant impact both in terms of clinical efficacy and increasing the awareness of the condition. Some men however, fail to respond to PDE-5 inhibitors alone. Interventional studies have demonstrated that testosterone replacement therapy in men with subphysiological concentrations of testosterone improves erectile function in men who have previously failed to respond to PDE-5 inhibitors alone (Aversa et al, 2003; Kalinchenko et al, 2003; Shabsigh et al, 2004). Furthermore, it has been demonstrated that the full therapeutic potential of PDE-5 inhibitors will only become manifest in a eugonadal state (Gooren, 2006). Indeed, recent studies have demonstrated a close relationship between testosterone and ED (Yassin and Saad, 2006, 2007) and suggest that testosterone therapy might be a valuable option for an increasing number of affected men. Furthermore, European guidelines suggest that all men presenting with ED should have their testosterone levels measured (Wespes et al, 2006).

Erectile Dysfunction

ED is defined as the inability to achieve or maintain erections sufficient for satisfactory sexual intercourse (National Institutes of Health Consensus Development Panel on Impotence, 1993). Formerly dismissed as a psychological condition, ED is now known as a treatable disorder and an important risk marker for cardiovascular disease (Montorsi et al, 2004; Yassin and Saad, 2007). The physiological mechanism of normal

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penile erection is dependent on trapping incoming blood within the cavernosal bodies to increase pressure and volume. This physiological process, namely the veno-occlusive mechanism, depends on the integrity of endocrine, hormonal, neurological, and vascular components, as well as the fibroelastic properties of the cavernosal tissue. The penile corpus cavernosum is a vascular bed, and any alterations to its structure can produce vascular dysfunction (Krane et al, 1989). Cavernosal tissues from men with erectile dysfunction have been demonstrated to exhibit reduced lacunar spaces, reduced smooth muscle content, and a concomitant increase in connective tissue deposition (Mersdorf et al, 1991; Karadeniz et al, 1996). Indeed, changes in penile tissue structural integrity is thought to contribute to veno-occlusive dysfunction. Recent research has identified a number of the key mediators of normal erectile function, with nitric oxide (NO) being one of the most important (Rosenberg, 2007). However, many of the pathophysiological mechanisms of ED remain to be determined. It has been estimated that approximately 70% of ED is of organic origin, with the major risk factors being diabetes mellitus, hypercholesterolemia, smoking, and chronic medical illnesses (Lawless and Cree, 1998), which are also established risk factors for atherosclerosis, the predominant predisposing factor of vasculogenic ED (Kaiser et al, 1988).

The Role of Nitric Oxide Synthase and Nitric Oxide in Erectile Dysfunction—NO is produced from L-arginine by the NO synthases (NOSs), of which 3 isoforms are known: the calcium-dependent endothelium and neuronal NOSs (eNOS and nNOS, respectively) and the calcium-independent inducible NOS (iNOS). NO produced by NOS regulates several important physiological events, including smooth muscle relaxation, neurotransmission, and modulation of inflammation (Moncada et al, 1991). NO acts as a neurotransmitter in the genitourinary tract and is involved in nonadrenergic, noncholinergic neurotransmission (Ignarro et al, 1990), which mediates its effects by activating soluble guanylyl cyclase to produce cyclic guanosine monophosphate (cGMP) or by NO-based chemical modification of proteins via *S*-nitrosylation of cysteine residues (Iwakiri et al, 2006).

NO plays a key role in penile erection by initiating smooth muscle relaxation after sexual stimulation (Burnett, 1997). The penile erectile tissue is formed by 2 dorsal corporal bodies known as corpora cavernosa, composed of sinusoidal spaces and lined with endothelium. An erection is a coordinated process involving psychoneurogenic stimulation, arterial and cavernosal vasodilatation, smooth muscle relaxation, increased blood flow, and venous occlusion. Vasodilation results in increased blood flow, elevated intracavernosal blood pressure, and occlusion of the subtunical venous plexus and emissary veins (Watts et al, 2007). As a result, penile engorgement occurs and shear stress activates phosphoinositide-3-kinase/AKT signaling pathways, leading to further NO release by eNOS, which sustains the erection (Hurt et al, 2002). Endothelial dysfunction because of an abnormality in the release or action of NO, or both, is characterized by vasoconstriction, coagulation, elevated leukocyte adhesion and stimulation of smooth muscle cell growth and is, therefore, central to atherogenesis and ED (Bonetti et al, 2003).

However, although NO-dependent signaling is the conduit to the creation of an erection, excessive production of NO has been implicated as a possible cause of cavernosal damage (Agarwal et al, 2006). Under certain conditions (eg, inflammation from Peyronie disease), excessive NO can be generated in the corpora cavernosa, which consequently leads to an increased production of peroxynitrite and to cytotoxic effects on the cavernosal muscle (Wink et al, 1998).

Phosphodiesterase Inhibitors—The discovery of phosphodiesterase (PDE) inhibitors and their introduction as therapeutic agents for the treatment of ED revolutionized the management of the condition. The first PDE-5 inhibitor to become available commercially was sildenafil, more commonly known as Viagra, followed by vardenafil (Levitra) and tadalafil (Cialis). Preclinical studies in healthy individuals have demonstrated that sildenafil has a mild hypotensive effect, and also improves arterial stiffness (Jackson et al, 1999). Studies have also shown that PDE-5 inhibitors have a beneficial effect on coronary endothelial function in patients with ischemic heart failure (Katz et al, 2000; Halcox et al, 2002). Sommer and Engelmann (2004), studied the effects of daily sildenafil in 76 patients with ED for 6 months with a 12-month follow-up period. They observed that more men from the group who received daily sildenafil recovered normal erectile function than men who received placebo. The beneficial effects of regular use of PDE-5 inhibitors on erectile function have also been confirmed by other studies (Aliaev et al, 2007). The use of PDE-5 inhibitors is generally considered a safe option for the treatment of ED. The most commonly reported adverse effects include headaches, flushing, dyspepsia, rhinitis, transient abnormal vision, dizziness, and slight lowering of blood pressure (Corbin and Francis, 2003; Rosenberg, 2007), although these are attributed to actions outside the penile corpus cavernosum. Sildenafil and vardenafil present some slight cross-reactivity with PDE-6, which might account for reports of visual disturbances in some patients (Corbin and Francis, 2003). However, clinical trials with sildenafil showed no additional risks for myocardial infarction (Mittleman et al, 2005) or adverse effects on cardiac

ischemia (DeBusk, 2005). Nevertheless, patients with angina pectoris are advised to use alternative PDE-5 inhibitors because interaction between PDE-5 inhibitors and nitrates has a potential high risk for causing hypotension (Mittleman et al, 2005). The American Urological Association recommends that PDE-5 inhibitors should be offered to patients with ED as a first-line treatment option, unless contraindicated. However, men who do not experience first dose success with PDE-5 inhibitor therapy often do not respond well to continued treatment (McCullough et al, 2002). Similarly, subsets of patients who have undergone radical prostatectomy do not respond to sildenafil, even after nerve-sparing radical prostatectomy (Raina et al, 2004). For such individuals, alternative therapy is required.

Testosterone Deficiency

Male hypogonadism is defined as a clinical syndrome which results from failure of the testes to produce physiological concentrations of testosterone and the normal number of spermatozoa after discordances of 1 or more levels of the hypothalamic-pituitary-gonadal axis. The definition of hypogonadism remains a controversial issue. Traditionally hypogonadism is classified as either primary, testicular failure with elevated luteinizing hormone (LH), or secondary, hypothalamic-pituitary failure together with decreased LH. However, hypogonadism can occur with gonadotropin levels within the normal range. Clinical assessment of the testosterone deficiency syndrome includes symptoms and biochemical confirmation with low circulating serum testosterone concentrations to determine a diagnosis (American Society of Andrology, 2006). Symptoms of hypogonadism include sexual symptoms such as loss of libido, erectile dysfunction, difficulty achieving orgasm, diminished sexual penile sensation as well as other symptoms such as fatigue, lack of physical strength, impaired cognitive function, and depressed mood (Wald et al, 2006). Indeed, hypogonadism is often not easy to diagnose because of the nonspecific nature of the physical symptoms, coupled with the lack of consensus with regard to the concentration of testosterone that constitutes eugonadal, hypogonadal, or indeed a borderline diagnosis. Recent guidelines by the International Society for Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), and the European Association for Urology (EAU) (Nieschlag et al, 2005) have, however, provided some clarity when making a diagnosis. These guidelines suggest that testosterone therapy is required with a total testosterone of less than 8 nmol/L in the presence of symptoms and that testosterone concentrations of more than 12 nmol/L do not require therapy. Symptomatic men, however, with total testosterone concentration between 8 and 12 nmol/L, could be considered for a trial of testosterone therapy. Serum testosterone analysis should be undertaken between 0700 and 1100 h because the hormone exhibits diurnal variation and, as such, should not be taken in an afternoon clinic because this will lead to misdiagnosis. Patient testosterone levels can also be low, as we would expect in evolutionary terms, in the presence of intercurrent infection, infarction, and injury, including the post surgical period, and could also be increased following sexual intercourse the morning after.

The Relationship Between Low Testosterone and the Metabolic Syndrome—Prevalence of the metabolic syndrome is significantly higher in men with erectile dysfunction than in healthy controls (26.7% vs 13%; Esposito et al, 2005). Furthermore, metabolic syndrome is associated with a more severe erectile dysfunction, which is further exacerbated by the coexistence of hypogonadism (Corona et al, 2006). Both clinical observations and experimental data suggest that the metabolic syndrome and its components are associated with low serum concentrations of testosterone in men. The metabolic syndrome defined as a cluster of comorbidities, which is associated with an increased cardiovascular risk, is often found together in viscerally obese patients and has insulin resistance as the common denominator. Indeed, insulin resistance plays a key role in the pathogenesis of the metabolic syndrome. According to the International Diabetes Federation (IDF) definition (Scheen et al, 2006), for an individual to be defined as having the metabolic syndrome, they must have central obesity (defined as a waist circumference of 94 cm or more for Europid men and 80 cm or more for Europid women) and any 2 of the following factors: hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, and raised fasting blood glucose or previously diagnosed type 2 diabetes mellitus.

It is well established that erectile dysfunction is very common in diabetic men, with prevalence reports of between 30% and 90% (Cho et al, 2005; Kapoor et al, 2007). A recent study has shown that levels of both bioavailable and free testosterone (but not total testosterone) were significantly lower in diabetic men with erectile dysfunction as opposed to those without (Kapoor et al, 2007). However, the severity of erectile dysfunction as assessed by International Index of Erectile Function (IIEF) scores did correlate with total testosterone as well as the bioavailable and free fraction of testosterone (Kapoor et al, 2007).

Evidence suggests that insulin sensitivity, obesity, and testosterone are interlinked, with testosterone having beneficial effects on obesity and insulin resistance. Indeed, low levels of total and bioavailable testosterone

in men have been associated with type 2 diabetes, visceral obesity, insulin resistance, hyperinsulinemia, and dyslipidemia in cross-sectional studies. In the study of Stellato et al (2000), total and free testosterone levels were significantly lower among men who later developed diabetes, as determined in prospective analyses of individuals within the Massachusetts Male Aging Study. Similarly, analysis of the participants in the Multiple Risk Factor Intervention Trial demonstrated that the nondiabetic men who subsequently developed diabetes during 5 years of follow-up had significantly lower levels of bioavailable testosterone at baseline (Haffner et al, 1996). Elevated insulin levels were also reported in nondiabetic men undergoing androgen ablation therapy (Smith et al, 2001; Xu et al, 2002; Dockery et al, 2003). In addition, testosterone replacement therapy in hypogonadal men with diabetes has been reported to improve insulin sensitivity (Kapoor et al, 2006). Low testosterone levels have also been demonstrated to predict insulin resistance and future development of type 2 diabetes in men (Haffner et al, 1996; Stellato et al, 2000; Oh et al, 2002), and observational studies have reported an increased prevalence of hypogonadism in diabetic men compared with nondiabetic men (Barrett-Connor et al, 1990; Barrett-Connor et al, 1992; Anderson et al, 1995; Dhindsa et al, 2004).

Low circulating levels of total and bioavailable testosterone in men have been associated not only with components of the metabolic syndrome but also with the metabolic syndrome per se, independently of body mass index (BMI; Laaksonen et al, 2003). The hypogonadal-obesity cycle described by Cohen (1999) and Kapoor et al (2005) suggests that during the hypogonadal state, there is an increase in deposition of abdominal adipose tissue, which results in increased aromatase activity, leading to a greater formation of 17-β-estradiol from testosterone. As a consequence, this leads to further reduction in serum and tissue concentrations of testosterone and increased deposition of abdominal fat and progressive hypogonadism.

Abdominal, or central obesity, is reported to be inversely related to total and free testosterone concentrations (Seidell et al, 1990; Haffner et al, 1993; Phillips, 1993). Abate et al (2002) reported that subcutaneous fat accumulation in the truncal area is highly predictive of low concentrations of free testosterone. Indeed, hypogonadal men are recognized to exhibit a reduced lean body mass and an increased fat mass. Vermeulen et al (1999) reported that testosterone levels correlated negatively with percent body fat, abdominal fat, and insulin levels. After gastroplasty in morbidly obese men, and hence significant weight loss, a significant increase in testosterone is reported (Bastounis et al, 1998). Furthermore, Strain et al (1988) also demonstrated that weight loss in obese men produced a significant increase in both total and free testosterone in proportion to the degree of weight loss. Similarly, correction of testosterone levels in obese men has been demonstrated to reduce BMI and visceral fat mass (Rebuffe-Scrive et al, 1991; Marin et al, 1992a,b, 1995), and testosterone therapy is reported to produce in a significant reduction in body weight, body fat, and blood glucose in men with type 2 diabetes (Boyanov et al, 2003).

Androgens and Erectile Function

Animal Studies—A variety of experimental animal models (rat, dog, rabbit) have been used to assess the role of androgens in erectile function, and androgen receptors have been identified in the cavernosal tissue in most of them (Horwitz and Horwitz, 1982; Takane et al, 1991). A large body of evidence from experimental animal models suggests that androgens beneficially modulate numerous multiple cellular components in the corpus cavernosum, leading to the structural and functional integrity of penile erection. Indeed, androgen deprivation experiments have been demonstrated to induce smooth muscle cell apoptosis (Shabsigh, 1997; Marin et al, 1999), reduce the expression of endothelial and neuronal NO (eNOS and nNOS; Marin et al, 1999; Lue, 2000; Bivalacqua et al, 2004), promote accumulation of adipocytes in corpus cavernosum (Traish et al, 2005; Kovanecz et al, 2006), produce pathogenic alterations in the corpus cavernosum architecture including the arrangement of elastic fibers and connective tissue contributing to ED (Traish et al, 2007), and reduce PDE-5 gene and protein expression (Zhang et al, 2005).

It is thought that the primary action of androgens in erectile function in the rat model is via stimulation of NO synthesis. Numerous animal studies suggest that testosterone acts as a vasodilator in the penis (Mills et al, 1992; Chammness et al, 1995; Garban et al, 1995; Lugg et al, 1995; Zvara et al, 1995; Reilly et al, 1997) and in other vascular beds (Chou et al, 1996), in part by activation of NOS. Indeed, testosterone has been demonstrated to restore erectile response and normalize NOS protein expression and activity (Lugg et al, 1995; Park et al, 1999; Baba, 2000b). Chammness et al (1995) demonstrated that penile NOS activity was reduced by 45% in the castrated rat and that, after testosterone therapy, this reduction was prevented. Similarly, Lugg et al (1995) reported a decrease in NOS in castrated animals compared with either castrated animals receiving testosterone treatment or intact animals. Furthermore, Reilly et al (1997) noted a reduced intracavernosal pressure in castrated rats in response to electrical field stimulation of the cavernosal nerve. After testosterone administration, however, this response was restored,

suggesting that the NO-mediated mechanism of erectile function is androgen dependant.

Intracellular levels of cGMP and GMP are primarily regulated by NO and PDE-5 in penile tissue, and PDE-5 inhibitors are known to enhance smooth muscle cell relaxation by maintaining greater cGMP levels after sexual stimulation, leading to improved erectile function in men with ED. It is not surprising then that any disruption in this balance could lead to pathophysiology. Several studies in animal models of androgen deprivation have been demonstrated to reduce both protein expression and activity of PDE-5 (Traish et al, 1999; Morelli et al, 2004; Zhang et al, 2005). Indeed, PDE-5 expression is also shown to be reduced in hypogonadal rabbits (Morelli et al, 2004). Several studies, however, demonstrate that expression and activity of PDE-5 is up-regulated after androgen administration (Traish et al, 1999; Zhang et al, 2005; Morelli et al, 2004; Armagan et al, 2006). Furthermore, expression of PDE-5 and NO in penile tissue has been shown to be up-regulated by androgens (Burnett, 2004).

Androgen deprivation alters penile blood outflow in rats, resulting in reduced veno-occlusion, the basis of penile erection (Mills et al, 1998). Studies suggest that veno-occlusion is modulated by the balance between the smooth muscle and connective tissue content of the corpus cavernosum (Nehra et al, 1996, 1998; Moreland, 1998). It is thought that androgen deprivation might initiate tissue degeneration and trabecular smooth muscle apoptosis, thus causing an imbalance in the ratio of smooth muscle to extracellular matrix, leading to veno-occlusive dysfunction. Traish et al (1999) have previously reported that androgen deprivation by surgical castration resulted in a significant decrease in trabecular smooth muscle content. However, after testosterone treatment, smooth muscle content and erectile function were restored (Traish et al, 1999). Traish et al (2003) provided further evidence to support these data in a later study with New Zealand White male rabbits to study the effects of surgical or chemical castration on erectile function. The study confirmed that androgen ablation, by either medical or surgical castration, results in changes in smooth muscle content and tissue atrophy compared with controls. This research led to further mechanistic investigation by the study investigators. The objective of this study was to investigate whether androgen deprivation resulted in accumulation of adipocytes in the corpus cavernosum. Mature, New Zealand white male rabbits underwent either sham operation (control) or surgical orchiectomy. At 2-week after the procedure, cross sections from the medial region of the penile shaft were stained with hematoxylin and eosin or Masson's trichrome, allowing examination of the architecture of smooth muscle cells and connective tissue, and toluidine blue for lipid-containing cells. Interestingly, the results demonstrated that, orchiectomy was not only associated with reduced trabecular smooth muscle and increased connective tissue content but also that tissue from orchiectomized animals exhibited accumulation of adipocytes in the subtunical region of the corpus cavernosum. The authors hypothesize that androgen deprivation promotes differentiation of progenitor stroma cells into an adipogenic lineage, producing fat-containing cells, thus altering erectile function (Traish et al, 2005). Similarly, accumulation of adipocytes in the corpus cavernosum has been demonstrated in the diabetic rat (Kovanecz et al, 2006) and canine models (Traish et al, 2006).

Other structural and biochemical components of erectile function have also shown to be modulated by testosterone. Testosterone deprivation has been demonstrated to produce profound ultrastructural changes in the dorsal nerve of the penis. Shen et al (2003) examined the ultrastructural changes of penile corpus cavernosum and tunica albuginea in castrated rats compared with controls. They reported that the tunica albuginea was significantly thinner in the castrated group compared with controls and that elastic fibers in the tunica albuginea of controls were very rich, were arranged regularly, and undulated, whereas much of the elastic fibers in the castrated group were replaced by collagenous fibers. They concluded that androgens are essential for maintenance of normal structure of penile tunica albuginea and corpus cavernosum (Shen et al, 2003). Rogers et al (2003) also demonstrated that testosterone deprivation in castrated rats could alter the dorsal nerve ultrastructure, in that the diameter of both myelinated and unmyelinated axons appear smaller by transmission electron microscopy. Furthermore, Baba et al (2000a,b) reported that the integrity of nerve fibers in the rat corpus cavernosum and dorsal nerve is dependent on androgens.

Clinical Studies—In addition to the wealth of information we have from animal studies, an increasing body of evidence from human studies suggests that testosterone therapy is associated with significant efficacy in the treatment of hypogonadism and ED. Indeed, recent meta-analysis has provided data demonstrating that approximately one-third of men with erectile dysfunction have androgen deficiency (Isidori et al, 2005). The pathophysiology of erectile dysfunction is complex and multifactorial, with vascular disease probably being the most common component.

The effects of testosterone on the vasculature were first reported in 1939 by Edwards and coworkers, who observed that testosterone treatment in castrated men was associated with an increased arterialization of the cutaneous vasculature. Edwards et al (1939) also reported a marked improvement in mobility and

intermittent claudication in men with peripheral arterial disease and thromboangiitis obliterans. Some of the strongest evidence of the potential role of testosterone in erectile dysfunction perhaps comes from studies in castrated men. Early studies by McCullagh and Renshaw (1934) reported that of 12 castrated men, complete loss of erection was reported in 50% of patients, and sexual potency was diminished in all patients. Another early study observed elderly men who underwent bilateral castration or estrogen therapy for treatment of prostate cancer and who had normal erectile function before castration. After androgen ablation via either surgical or chemical methods, 58% of this cohort reported ED (Ellis and Grayhack, 1963). The effects of testosterone on erectile function have further been assessed in more recent studies that have induced profound hypogonadism by means of gonadotropin-releasing hormone (GnRH) antagonists (Bagatell et al, 1994) or long-acting GnRH agonists (Buena et al, 1993; Hirshkowitz et al, 1997; Bhasin et al, 2001). Indeed, Bagatell and colleagues report that in healthy young men receiving the GnRH antagonist, a decrease in libido and frequency of spontaneous erections and a trend toward impairment of maintenance of erection during intercourse was observed. However, after withdrawal of the GnRH antagonist and on restoration of normal serum testosterone concentrations, these abnormalities were reversed (Bagatell et al, 1994). For decades, it has been known that loss of erectile function and decrease in sexual interest and activity are important outcomes of either surgical or chemical castration and a concomitant decrease in testosterone levels (Ellis and Grayhack, 1963; Greenstein et al, 1995; Peters and Walsh, 1987). Hirshkowitz and co-workers (1997) investigated the effects of luteinizing hormone–releasing hormone (LHRH) agonists (leuprolide) in a small placebo-controlled trial of 10 healthy young males. The authors demonstrated that duration of episodes of nocturnal erection were decreased by week 4 in those receiving LHRH agonist compared with those receiving placebo and that this effect was maintained for the duration of the study period at 12 weeks. Further studies in patients undergoing treatment for prostate cancer through androgen ablation therapy also demonstrated that reduction in serum testosterone concentrations resulted in suppression of sexual desire, sexual interest, and sexual intercourse, with significant reduction also in frequency, magnitude, duration, and rigidity of nocturnal erections (Rousseau et al, 1988; Marumo et al, 1999). These studies clearly demonstrate that testosterone concentrations are closely associated with erectile function, sexual interest, and activity and demonstrate the potential for testosterone therapy on treatment of ED.

Data suggest that testosterone administration at physiological concentrations induces coronary vasodilatation and increases blood flow in men with coronary artery disease (Webb et al, 1999). Furthermore, Aversa et al (2000) report a direct relationship between bioavailable testosterone and cavernous vasodilatation in men with ED. In a retrospective, double-blind correlation analysis by Aversa and colleagues, 52 impotent men without any confounding risk factors for ED were studied to investigate the role of androgens in regulating trabecular smooth muscle relaxation in the corpus cavernosum in response to vasoactive challenge in men with ED. Patients had dynamic color duplex ultrasound and hormonal evaluation for LH, total and free testosterone, sex hormone–binding globulin (SHBG), and estradiol. On the basis of duplex ultrasound, 31 patients were diagnosed as having arteriogenic ($n = 18$; mean age 51 years) or corporeal veno-occlusive ($n = 13$; mean age 49 years) ED. A diagnosis of psychogenic ED was confirmed in all other patients. Interestingly, in patients diagnosed with arteriogenic and corporeal veno-occlusive ED, a 20%–25% lower resistive index of cavernous arteries were observed, compared with patients with psychogenic ED, and lower free testosterone levels than psychogenic patients. Importantly, a strong direct correlation between low free testosterone levels and impaired relaxation of cavernous endothelial and corporeal smooth muscle cells (demonstrated by the resistive index values) were observed. Furthermore, this relationship was maintained after adjustment for age, SHBG, and estradiol (Aversa et al, 2000). These data suggest that androgens have a profound effect on both the functional and structural integrity of the corpus cavernosum. Moreover, these clinical data support the experimental knowledge of the importance of androgens in regulating smooth muscle function and the regulation of the veno-occlusive mechanism in the penis.

Diabetes mellitus and smoking are well-known risk factors in men with ED (Corona et al, 2006; Mittawae et al, 2006). Furthermore, an increasing body of evidence suggests that these risk factors are also associated with a low serum testosterone concentration (Simon et al, 1997; Guay et al, 2001; Corona et al, 2004; Kapoor et al, 2007).

Yaman et al (2003) investigated the alterations of intracorporeal structures in patients with ED to quantify intracavernosal smooth muscle cell content (SMC), endothelial cells (EC), and elastic fibers (EF) from penile biopsies in both impotent and nonimpotent men. The data from impotent patients were analyzed with regard to patient age, etiology of impotence, presence or absence of diabetes mellitus, and smoking. Yaman et al (2003) observed statistically significant

differences in the amounts of corporeal SMC, EC, and EF with regard to the following subgroups: potent compared with impotent men, men with arterial etiology compared with veno-occlusive etiology, men under the age of 45 compared with men over the age of 45, patients with diabetes mellitus compared with non–diabetes mellitus, and smokers compared with nonsmokers. These data also suggest that changes in intracavernosal structures appear to be important for understanding the mechanism of impotence. Several other studies have shown a strong correlation between serum levels of testosterone and nocturnal penile tumescence, as well as subjective improvement in sexual function in hypogonadal patients (Murray et al, 1987; Kumamoto et al, 1990; Schiavi et al, 1993; Horita and Kumamoto, 1994; Carani et al, 1995; Foresta et al, 2004). Furthermore, hypogonadal men often benefit from testosterone therapy, with treatment being shown to improve parameters of well-being, bone density, muscle mass, physical strength, sexual function, and libido (Behre et al, 1997; Snyder et al, 2000). Evidence is increasing that a close relationship exists between androgen deficiency and ED (Yassin et al, 2006c; Yassin and Saad, 2007). Lazarou and Morgentaler (2005) suggested that testosterone therapy might be the best treatment for men with hypogonadism and ED, especially when the presentation includes diminished libido or other sexual symptoms or when nonsexual symptoms such as depressed mood, decreased sense of vitality, and increased fatigue also exist.

Since the introduction of PDE-5 inhibitors for the treatment of ED, testosterone has been largely ignored as a treatment option for the condition. However, as many as 50% of men discontinue treatment with PDE-5 inhibitors, and an inability of these agents to address the underlying testosterone deficiency present in ED is one of the potential causative factors for this high failure rate (Park et al, 2005). This has prompted a renewal in the interest in the treatment of ED with testosterone therapy (Harle et al, 2005; Yassin et al, 2006c; Yassin and Saad, 2007). Indeed, interventional studies in men with low serum testosterone levels and erectile dysfunction have demonstrated clearly that testosterone therapy facilitates the effect of PDE-5 inhibitors and is said to be beneficial as an additional treatment for patients in whom PDE-5 inhibitors alone have failed (Aversa et al, 2003; Kalinchenko et al, 2003; Shabsigh et al, 2004; Yassin et al, 2006b). Indeed, the administration of PDE-5-inhibitors is not always sufficient to restore erectile potency in men, and administration of testosterone has been demonstrated to improve the therapeutic response to PDE-5-inhibitors considerably. Shabsigh et al (2004) have shown that within 4 weeks, testosterone therapy converts sildenafil nonresponders to responders in men with hypogonadism and ED, and testosterone also improves response to sildenafil in patients with arteriogenic ED (Aversa et al, 2003). In a randomized, placebo-controlled, double-blind, parallel group, multicenter study, 75 hypogonadal or borderline hypogonadal men with confirmed lack of response to sildenafil and subphysiological serum total testosterone concentrations (400 ng/dL or less), were randomized to receive a daily dose of 1% testosterone gel or a 5-g placebo gel in combination with 100 mg of sildenafil during a 12-week period. At the end of the trial period, testosterone-treated subjects had significant improvement in erectile function compared with those who received placebo (Shabsigh et al, 2004). We have recently examined the role of testosterone therapy in 12 patients with ED presenting with comorbidities such as diabetes mellitus, metabolic syndrome, dyslipidemia, obesity, or a combination of conditions, in which oral PDE-5 inhibitor therapy had failed to improve erectile function. Each patient underwent baseline dynamic infusion pharmaco-cavernosometry and cavernosography to determine the degree of corporal veno-occlusive dysfunction. Patients received testosterone undecanoate (TU) for at least 3 months, and the dynamic infusion pharmaco-cavernosography was repeated in all patients. The results reveal that 5 of the 12 patients reported significant improvement in erectile function within 12–20 weeks of androgen treatment. In addition, after testosterone therapy, pharmaco-cavernosometry also demonstrated that venous leakage was abolished in the patients who reported improvement in erectile function compared with baseline measurements. Furthermore, improvements in sexual desire were even noted in the individuals who were not responsive to testosterone alone (Yassin and Saad, 2006, 2007b).

We have previously investigated the effects of long-acting TU on the normalization of testosterone levels in 22 hypogonadal men (mean age, 58 years) with complaints of low sexual desire and ED (Yassin et al, 2006a,c). Twelve patients reported significant improvement in sexual desire and erectile function. In 9 of 12 patients, this occurred after 12–24 weeks, indicating a latency before the beneficial effects of TU occur. Furthermore, no changes in serum prostate-specific antigen (PSA) or prostate volume were noted in patients receiving this long-acting TU. These data suggest that restoring serum testosterone levels to normal had a positive effect on libido as well as erectile function in more than 50% of the study subjects. This study has since been extended to a larger number of men, demonstrating a similar efficacy (Yassin et al, 2006b). Furthermore, cavernosography X-rays obtained from hypogonadal men with ED show clear signs of venous

leakage. After 12 weeks of testosterone treatment with Nebido (Indevus Pharmaceuticals Inc, Lexington, Massachusetts); however, all signs of venous leakage had disappeared in 5 of the 12 subjects (Yassin et al, 2006c). Greenstein et al (2003), also demonstrated that 63% of hypogonadal men with erectile dysfunction given testosterone therapy alone regained normal function and increases in sexual desire.

Results from an increasing number of studies indicate that testosterone treatment is not only a viable but also safe therapy to treat ED in hypogonadal men. Prostate safety parameters such as PSA, total prostate gland volume, and transition zone volume have all been assessed and shown to remain unchanged during treatment with TU (Yassin and Saad, 2007; Zitzmann and Nieschlag, 2007). New insights into the role of testosterone in erectile function have led to recommendations to measure serum testosterone as a standard procedure in men with erectile problems (Morales et al, 2004). The most recent guidelines of the European Association of Urology recommend treating testosterone deficiency before initiation of treatment with PDE-5 inhibitors (Wespes et al, 2006).

Conclusion

The risk of developing ED increases with age. It is expected that at least 26% of men between the ages of 50 and 69 years and 40% of men between the ages of 60 and 69 years will develop some form of ED (Rosenberg, 2007). However, it is estimated that as many as 70% of men with ED remain undiagnosed (Rosenberg, 2007). The recent shift in the management and evaluation of ED, with primary care physicians replacing urologists in the forefront of ED diagnosis and therapy, has been a welcome and timely change. It is likely to improve ED management and benefit a large number of men, particularly in terms of recognizing ED as a sentinel of vascular disease (Jackson et al, 2006). Approximately 20% of ED patients have low serum testosterone levels (Yassin and Saad, 2007). Serum levels of testosterone are closely related to manifestations of other etiologic factors in ED, such as atherosclerotic disease, diabetes mellitus, and metabolic syndrome, and an inverse relationship exists between serum testosterone and the severity of these symptoms (Kaufman and Vermeulen, 2005). Consequently, testosterone is becoming recognized as an important factor in ED.

Both animal and clinical studies indicate that testosterone therapy improves both erectile function and the response to PDE-5 inhibitors in patients with ED and hypogonadism. Among the benefits, we can name a positive effect on several aspects related to male health. Aging male symptom scores (psychological and sexual as well as somatic) improve in men treated with TU (Behre and Elliesen, unpublished data). Penetration, maintenance of erection, and desire all improve with treatment, as observed from IIEF scores (Kalinchenko et al, 2003; Shabsigh et al, 2004; Yassin and Saad, 2006, 2007). Testosterone also improves body composition in elderly men, including increase in lean body mass and decrease in fat tissue (Page et al, 2005).

Testosterone therapy alone can restore erectile function in the majority of hypogonadal patients and could be considered a first line of therapy in patients with hypogonadal ED. The recent evolution from monotherapies to combinational therapies employing T-treatment and PDE-5 inhibitors means that nonresponders to testosterone or PDE-5 inhibitors alone, as well as patients with ED-associated comorbidities such as diabetes mellitus and metabolic syndrome, can now be treated successfully.

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