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## TESTOSTERONE THERAPY IN MEN WITH SEXUAL DYSFUNCTION: REVIEW

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# The Impact of Testosterone on Erectile Function

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### Abstract

Erectile function is dependent on the correct balance of vasoactive substances, neurotransmitters, endocrine factors, and tissue fibroelastic properties. Erectile dysfunction (ED) is a multifactorial condition that results from an imbalance of any of the factors that contribute to maintaining proper erectile function. In animal and human studies, hypogonadism has been found to interfere with the proper synthesis and/or release of enzymes as well as the tissue structure and function in the corpora cavernosa leading to ED. Restoring testosterone levels can improve erectile function for hypogonadal men with ED. Combination therapy with testosterone and phosphodiesterase-5 inhibitors has the potential to improve parameters for a greater number of patients struggling with ED who have comorbidities and do not respond to either treatment alone. When used in the appropriate clinical scenario, testosterone therapy can be a safe and effective treatment option for ED.

**Keywords:** erectile dysfunction; erectile function; hypogonadism; testosterone; testosterone replacement therapy

### Introduction

An erection is a neuropsychological and hormone-mediated vascular event triggered by sensorial or direct stimulation.<sup>1</sup> The process is dependent on the correct balance of vasoactive substances, neurotransmitters, endocrine factors, and tissue fibroelastic properties.<sup>2</sup> The vascular reaction is achieved by increased blood flow in the paired corpora and decreased outflow that leads to increased intracavernosal pressure and volume.<sup>3</sup>

Nitric oxide (NO) is the major mediator of smooth muscle relaxation in the cavernosal arteries and trabecular muscle that leads to an increase in cyclic guanosine

monophosphate (cGMP) levels, which is ultimately degraded by phosphodiesterase-5 (PDE-5).<sup>4</sup> Sexual desire may precede and encourage sexual activity, or it may be in response to sexual stimulation, with the downstream effects described. Those who have a desire to engage in sexual acts are more likely to be distressed when there is impairment in erectile function and pursue treatment.

Erectile dysfunction (ED) occurs when a man is unable to attain or maintain a sufficient erection for sexual intercourse.<sup>5</sup> The International Index of Erectile Function (IIEF) is a standardized questionnaire that assesses a man's ability to initiate, maintain, or complete sexual

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intercourse.<sup>6</sup> Specifically, the IIEF-erectile function (IIEF-EF) domain includes six questions that evaluate the frequency and hardness of erections, penetration during intercourse, maintenance of an erection during intercourse, ability to maintain an erection to completion of intercourse, and a man's confidence in their ability to get and maintain an erection to determine the severity of ED from mild to severe.<sup>6</sup>

The ED more commonly affects men of increasing age with ~10% of men 20–30 years old and as many as 70% of men older than 70 years being diagnosed with ED.<sup>7–9</sup> The etiology is related to aging and vascular, neurogenic, psychological, and hormonal components.<sup>10</sup> Medications can also impact sexual functioning and erectile response. The pathogenesis, while multifactorial, has been linked to poor psychological status, arterial endothelial damage, and low testosterone.<sup>11,12</sup>

Hypogonadism is generally defined as low testosterone with symptoms and/or signs, including weakness, fatigue, decreased energy, low libido, reduced muscle and bone mass, and increased abdominal fat.<sup>13</sup> In general, proposed cutoffs used to define hypogonadism are <300–400 ng/dL or <8–12 nmol/L.<sup>13</sup> Based on varying definitions, the prevalence of hypogonadism in men with ED ranges from 1.7% to 35%.<sup>14–17</sup> The American Urology Association (AUA) guidelines recommend evaluation of testosterone in men with ED to determine whether hypogonadism could be influencing the disease process.<sup>18</sup>

The ED in patients with low testosterone may be due to low libido and/or changes in corpora cavernosa structure and function at the cellular level from hypogonadism.<sup>19</sup> Hypogonadism can be associated with aging and medical conditions such as obesity, hyperlipidemia, metabolic syndrome, diabetes, hypertension, and coronary artery disease (CAD).<sup>1</sup> Testosterone replacement therapy with or without PDE-5 inhibitors is an option to restore testosterone to normal levels and improve erectile function.

## Testosterone and Sexual Function

### Animal studies

The initial studies that established a connection between testosterone and ED were performed on castrated rats and rabbits. More recent studies applying a model of high-fat diet-induced hypogonadism have confirmed findings from castration studies. Overall, these studies have found that testosterone helps to preserve proper synthesis and/or release of enzymes as well as tissue structure and function of the corpora cavernosa. When

testosterone levels are below one-tenth the normal physiologic plasma concentration, erectile function is found to decline in a dose-dependent fashion.<sup>20</sup>

Animal models helped to link testosterone to erectile function at a biochemical and cellular level based on its ability to affect the production of both NO and nitric oxide synthase (NOS) as well as PDE-5, which are crucial to the erectile process. NO is important for erectile function, as it initiates smooth muscle relaxation after sexual stimulation through downstream effects of cGMP, and PDE-5 degrades cGMP at the end of the erection cycle.<sup>21,22</sup> Androgen deprivation in animals was found to lead to decreased expression and activity of NOS, with up to 45% decreased NOS activity after castration.<sup>2,23,24</sup> The decrease in NOS-containing fibers and NO leads to a loss of smooth muscle relaxation and vasodilation, a decrease in intracorporal pressure, and ultimately impaired erectile function in most orchietomized rats.<sup>2,24</sup> Testosterone replacement after castration was found to preserve NOS activity and erectile function in rats, even in a delayed fashion.<sup>25,26</sup>

Similarly, PDE-5 mRNA and protein levels have been found to be lower in the corpora cavernosa of hypogonadal rabbits and testosterone replacement has been found to restore these levels.<sup>2,21</sup> Since low testosterone has been found to decrease both NO and PDE-5, its overall effect on erections is influenced by the degree that each enzyme is decreased.<sup>1,27</sup> In hypogonadal conditions, the decrease in cGMP levels due to impaired NO production is likely counterbalanced by reduced PDE-5 activity and cGMP degradation so some erectile function may be preserved.<sup>1</sup> This association also explains the observation that some hypogonadal men have a lower level of erectile responsiveness to PDE-5 inhibitors and suggests that testosterone replacement may be necessary for full PDE-5 inhibitor responsiveness.<sup>21</sup>

Animal studies also demonstrated that testosterone is important for penile structure. Castration is associated with vascular smooth muscle cell atrophy or apoptosis, venous leakage, adipocytes in the subtunical space, loss of elastic fibers, and increase in collagen deposition.<sup>2,28</sup> A decrease in smooth muscle cells along with the presence of adipocytes in the subtunical space is hypothesized to interfere with the veno-occlusive process leading to venous leakage, decreased intracavernosal pressure, and ultimately inadequate erectile response seen in androgen-deprived animals.<sup>28</sup>

Elevated levels of extracellular matrix components in the corpora cavernosa with androgen deprivation not only interfere with venous occlusion, but also



lead to decreased cavernosal compliance that prevents penile engorgement.<sup>2,28</sup> Testosterone replacement has been found to help prevent smooth muscle changes in the corpora cavernosa, induce vascular smooth muscle growth, and restore erectile function to baseline.<sup>2,28</sup>

### Human studies

Testosterone has been implicated in all steps of the human sexual response cycle through the mediation of corpora cavernosa structure, function, and innervation in addition to the intercellular mechanisms involved in the regulation of erection and detumescence.<sup>29–33</sup> The second stage of the sexual response, the excitement phase, is a consequence of physical and/or mental erotic stimuli that results in sexual arousal. Testosterone can enhance sexual desire, leading to an increase in the frequency of sexual acts and an increase in the frequency of sleep related erections with little effect on fantasy or visually induced erections.<sup>34</sup>

In hypogonadal men, hypoactive sexual dysfunction, decreased nocturnal and morning erections, ED, delayed ejaculation, and reduced semen volume can all be presenting symptoms.<sup>35</sup> Of those, ED is usually the most common complaint and is considered to be the most closely related to testosterone levels.<sup>35</sup>

When comparing men with and without ED, Becker et al. found a significant difference in testosterone levels, with patients with ED having lower testosterone levels at all phases of the erection cycle.<sup>36</sup> In the flaccid phase, the difference between mean cavernous testosterone concentration and peripheral testosterone concentration in healthy subjects was 30% lower compared with 13% lower in patients with ED.<sup>36</sup> Although erections were accompanied by an increase in the cavernous and peripheral testosterone levels in both groups, in the men with ED, the mean increase in systemic and cavernous testosterone levels from flaccidity to tumescence was less pronounced than the levels observed in healthy controls.<sup>36</sup>

Although free testosterone was not measured in this study, the authors hypothesized that the difference between the peripheral and cavernous testosterone levels in the flaccid phase may be a future diagnostic tool to evaluate the amount of bioavailable testosterone and the activity of testosterone receptors in the smooth muscle of the corpora cavernosa.<sup>36</sup>

In a study by Aversa et al., free testosterone was found to be positively related to peak systolic velocity and resistance index and negatively related to end-

diastolic volume based on the assessment of 52 men with ED via dynamic color duplex ultrasound, suggesting a positive correlation between free testosterone with vessel dilation, penile elasticity, and cavernous artery compliance.<sup>4</sup> The link between free testosterone and resistance index also suggests that a threshold level of free testosterone is necessary for smooth muscle relaxation in an adequate erection.<sup>4</sup>

Although individual threshold levels for testosterone deficiency symptoms vary markedly from <100 to 450 ng/dL, they occur at reproducible levels for each patient.<sup>37</sup> In a study of hypogonadal men on long-acting testosterone depot injection, the majority of patients developed symptoms at a mean total testosterone level of 309 ng/dL, leading them to request reimplantation of the testosterone depot.<sup>37</sup> In a large cross-sectional study of 434 men between 50 and 86 years old, the incidence of low libido increased below a testosterone level of 15 nmol/L (433 ng/dL), obesity below 12 nmol/L (346 ng/dL), type 2 diabetes, depression, sleep disturbances and lack of concentration below 10 nmol/L (289 ng/dL), and hot flashes and erectile function below 8 nmol/L (231 ng/dL).<sup>11</sup>

A total testosterone level <150–200 ng/dL has been described as the level when sleep-related erections are usually affected.<sup>38</sup> Unlike reflexive and psychogenic erections, sleep-related erections are strongly androgen dependent and the least affected by external factors.<sup>38,39</sup> The association between testosterone and ED is more evident in studies that evaluate men with more severe hypogonadal states.<sup>40,41</sup>

In men with prostate cancer who undergo castration or androgen deprivation therapy (ADT), the effects of low testosterone on erectile function are clearly demonstrated. Castration results in ED in at least 50% of men.<sup>42,43</sup> Men on ADT with a gonadotropin-releasing hormone antagonist or luteinizing hormone-releasing hormone agonist similarly have a decrease in erectile function and sexual activity.<sup>44–48</sup> The frequency, magnitude, duration, and rigidity of nocturnal erections and libido are also decreased in patients on ADT.<sup>44–48</sup> After discontinuation of ADT and normalization of testosterone levels, there is a reproducible return of sexual function.<sup>46,49</sup>

### Special populations

Hypogonadism appears to be a common denominator in aging men with ED as well as in men with abdominal obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease (CVD) who have ED.<sup>10</sup>



**Aging.** As men age, there is generally a decrease in testosterone levels due to reduced gonadal function. Based on a gradual decline of systematic availability of testosterone in healthy men by 1% every year after the third decade of life, subphysiological values of 35–50% can be seen by the sixth decade of life.<sup>1,50</sup> The ratio of collagen to elastic fibers in the corpora cavernosa also increases with aging.<sup>51</sup> The association observed among age, testosterone deficiency, cavernosal fibrosis, and ED, suggests that this fibrotic process is a possible cause of ED in older men with decreasing levels of testosterone.<sup>52</sup>

The Massachusetts Male Aging Study (MMAS) provided the first major cross-sectional and longitudinal data on the epidemiology of ED.<sup>53</sup> In the study population of 1290 men between 40 and 70 years old, 52% of men had ED with 17.2% having minimal, 25.2% having moderate, and 9.6% having complete ED.<sup>53</sup> When considering age, the probability of complete ED tripled between 40 and 70 years old, from 5% to 15%.<sup>53</sup> Although this study did not find an association between testosterone and ED, the testosterone precursor dehydroepiandrosterone sulfate (DHEAS) was strongly correlated with ED.<sup>53</sup>

A reduction in DHEAS from 10 to 0.5  $\mu\text{g/mL}$  was associated with an increase in ED from 3.4% to 16% after adjustment for age.<sup>53</sup> The role of testosterone in sexual functioning may be less evident in epidemiologic studies such as this because of other factors, including organic, relational, and intrapsychic determinants that can influence the results.

**Obesity.** Among men with abdominal obesity, 74.7% have some degree of ED.<sup>54</sup> Men with a body mass index (BMI) <25 have a 30% lower risk of ED compared with those with a BMI >28.7.<sup>55</sup> The negative impact on vascular health and altered balance of endocrine factors seen with obesity are believed to be responsible for ED in this population.<sup>56</sup> Further, obesity-related comorbidities can lead to impaired NO synthesis in the vasculature, altered endothelial function, increased dyslipidemia, and further reduction of testosterone levels, all of which contribute to the pathophysiology of ED.<sup>56</sup>

Corona et al. showed that obese men with ED had lower testosterone levels even after adjusting for obesity-related factors, suggesting that low total testosterone may result from obesity in and of itself.<sup>57</sup> Since obese patients have abnormalities of sex hormone binding globulin (SHBG), free testosterone is an important consideration as well.<sup>58</sup> When compared with hypogonadal patients with normal free testosterone,

hypogonadal patients with low free testosterone appear to have worse sexual symptoms, including low desire, ED, and infrequent morning erections.<sup>58</sup>

Hypogonadal men who lose weight have an increased chance of recovering testosterone levels, which may improve their overall health and erectile function.<sup>59–61</sup> Longitudinal results from the European Male Ageing Study (EMAS) specifically show that a weight loss of at least 15% is necessary for significant increases in testosterone levels.<sup>59</sup>

**Metabolic syndrome and type 2 diabetes.** The prevalence of ED among men with metabolic syndrome increases based on the number of metabolic syndrome components with patients having three to five components exhibiting 20%, 30%, and 35% of ED, respectively.<sup>62</sup> In type 2 diabetes, ED affects 35–90% of men.<sup>63</sup> Since the early 1990s, an association between low testosterone and type 2 diabetes has been reported in the literature.<sup>64</sup> Up to 40% of men with type 2 diabetes have testosterone deficiency due to insulin resistance, hyperglycemia, increased visceral fat, poor nutritional status, and/or high triglyceride levels based on more recently published studies.<sup>64</sup>

Patients with decreasing testosterone levels in the presence of insulin resistance, hypercholesterolemia, and central obesity may have decreased sexual desire and fail to achieve adequate penile tumescence with sexual stimulation.<sup>64</sup>

**Cardiovascular disease.** In a study of 300 men with angiographically documented CAD, 147 men (49%) had ED.<sup>65</sup> In another study of 802 asymptomatic, intermediate cardiovascular risk patients, based on the Framingham Risk Score, between 40 and 80 years old who underwent ultrasound examination of brachial artery flow-mediated vasodilation (FMD), testosterone levels correlated with both FMD ( $r=0.85$ ;  $p<0.0001$ ) and IIEF-EF scores ( $r=0.65$ ;  $p<0.0001$ ).<sup>66</sup>

Multivariable logistic regression showed that lower testosterone levels were strongly associated ( $p<0.001$ ) with severe (odds ratio [OR] 0.78; 95% confidence interval [CI]: 0.62–0.86) and moderate ED (OR 0.85; 95% CI: 0.72–0.97) and impaired FMD percentages were strongly associated ( $p<0.001$ ) with severe (OR 0.68; 95% CI: 0.59–0.79), moderate (OR 0.76; 95% CI: 0.63–0.83), and mild to moderate ED (OR 0.8; 95% CI: 0.69–0.94).<sup>66</sup> Endothelial dysfunction seen in patients with CVD, hypogonadism, and ED is likely responsible for this observation.



## Testosterone Replacement

Testosterone replacement formulations include oral preparations, patches, gels, injections, and implants. Although the benefit of testosterone therapy in treating male sexual dysfunction has been questioned in the past, more recent literature is supportive of this treatment for hypogonadal men with ED. Historical studies were confounded by inclusion of patients without definite biochemical evidence of testosterone deficiency and/or lacking baseline sexual dysfunction, use of non-validated ED questionnaires, and overall weak study designs. More recent studies with improved study designs include hypogonadal men with documented ED based on standard definitions and questionnaires, such as IIEF. In studies that assess ED based on IIEF, a change of 2, 5, and 7 IIEF-EF domain points is used to determine clinical significance for men with mild, moderate, and severe ED, respectively.<sup>6,67</sup>

## Testosterone monotherapy

Testosterone monotherapy has been found to be an effective treatment for ED in hypogonadal men with no further contributing pathology, especially when there are signs and/or symptoms of testosterone deficiency, including decreased libido, depressed mood, and increased fatigue. Testosterone treatment in hypogonadal men with ED improves sexual attitudes and performance in 61% of patients.<sup>68</sup> Testosterone replacement improves erectile function and penile vascular parameters in 36% and 42% of patients, respectively.<sup>69</sup>

Lower baseline testosterone levels before the initiation of testosterone replacement correlate with good efficacy and a positive clinical outcome for men with ED, whereas eugonadal men have a few benefits.<sup>70</sup> The maximal effect of testosterone replacement on IIEF domains in hypogonadal men may not be observed until 6 months in some circumstances.<sup>71</sup>

The largest international, multicenter study on long-acting injectable testosterone involving 155 centers in 23 countries in Europe, Asia, Latin America, and Australia found that in 1438 hypogonadal men (mean age  $49.2 \pm 13.9$  years), testosterone replacement led to significant improvements in sexual desire and erectile function as well as improvements in quality of life at a follow-up of up to 12 months.<sup>72</sup> Specifically, the number of patients with moderate or severe ED decreased from 67% to 19% based on IIEF measurements.<sup>72</sup>

Other studies, with an even longer follow-up, essentially confirmed the earlier findings. In a study with an 8-year follow-up by Permpongkosol et al. on 428 men

treated with long-acting testosterone, there was a constant improvement in all IIEF-15 subdomains with testosterone replacement with the mean IIEF-EF ( $p < 0.05$ ) and IIEF-15 ( $p < 0.05$ ) scores improving significantly from  $12.72 \pm 6.87$  and  $36.18 \pm 19.80$  at baseline to  $15.16 \pm 5.38$  and  $44.18 \pm 16.21$ , respectively, at the end of the study period.<sup>73</sup> Another observational, prospective study of 805 hypogonadal men with different degrees of ED, based on IIEF-EF, found that among 412 patients on testosterone therapy, improvement in erectile function was observed each successive year until year 9, with stronger benefits seen for patients with moderate or severe ED than for patients with no or minor ED.<sup>74</sup> Despite their strengths, these observational studies have several limitations, including selection, information, and confounding biases.

In a randomized, double-blind, placebo-controlled trial evaluating the efficacy of transdermal testosterone gel in hypogonadal men, significant increases were observed in total testosterone at 1 month ( $p = 0.024$ ) and 2 months ( $p = 0.025$ ) along with a significant increase in IIEF scores at 3 months ( $p = 0.01$ ).<sup>75</sup> Another randomized controlled trial (RCT) found that when hypogonadal patients had normalization of testosterone levels on testosterone therapy, there was a significant improvement in IIEF scores after 1 month ( $p < 0.01$ ).<sup>76</sup>

In this study, however, the improvement was not maintained at 3- and 6-month follow-up visits, suggesting that the etiology of ED was influenced by other comorbidities that were not addressed in the study and the use of testosterone in the patient population as a sole treatment modality was questionable.<sup>76</sup>

All available meta-analyses have shown that testosterone replacement is effective in improving sexual function in hypogonadal men.<sup>77</sup> A mild to moderate effect was seen for ED in most meta-analyses.<sup>78</sup> In 2005, a comprehensive meta-analysis performed using data from 17 RCTs comparing the effects of testosterone replacement on different sexual function domains found that testosterone had a moderate improvement in the number of nocturnal erections and successful sexual intercourses, sexual thoughts, scores of erectile function, and overall sexual satisfaction in men with low baseline testosterone ( $<12$  nmol/L or  $<346$  ng/dL).<sup>79</sup>

The degree that erectile function was affected was inversely related to the baseline testosterone level, such that patients with lower levels of testosterone demonstrated more impressive results with testosterone replacement.<sup>79</sup> Another meta-analysis in 2007, including 17 RCTs, confirmed that a moderate effect on erectile



function was seen with testosterone replacement for patients with low baseline testosterone and a small effect was seen for patients with low-normal and normal baseline testosterone.<sup>80</sup> A meta-analysis conducted by Corona et al. in 2014 included a sub-analysis of studies that used IIEF to evaluate sexual function and found that testosterone treatment was associated with a mean difference of 3.7-points in the IIEF-EF score compared with placebo ( $p < 0.001$ ).<sup>81</sup>

In the more recent meta-analysis by Corona et al. in 2017, 14 studies enrolling 2298 participants were included while specifically looking at IIEF as the main outcome.<sup>82</sup> Testosterone treatment was found to significantly improve erectile function compared with placebo [mean difference = 2.31 (1.41; 3.22) IIEF-EF score,  $p < 0.0001$ ], and patients with more severe hypogonadism (total  $T < 8$  nmol/L or 231 ng/dL) reported even greater changes in IIEF scores compared with those with less severe hypogonadism [total  $T < 12$  nmol/L or 346 ng/dL; 1.47 (0.90; 2.03) and 2.95 (1.86; 4.03) for total  $T < 12$  nmol/L or 346 ng/dL and  $< 8$  nmol/L or 231 ng/dL, respectively,  $Q = 5.61$ ,  $p = 0.02$ ].<sup>82</sup>

The effect was less pronounced in the presence of comorbidities with metabolic derangements and vascular damage, such as metabolic disorder and type 2 diabetes, supporting the need for possible combination therapy in this group.<sup>82</sup>

### Combination therapy with testosterone replacement and PDE-5 inhibitors

Testosterone's role in the NO pathway explains how combination therapy with testosterone and PDE-5 inhibitors can be helpful in achieving erectile function in a broader range of hypogonadal men who have medical comorbidities.<sup>1,19</sup> In a small randomized, placebo-controlled crossover study of 24 men with hypogonadism, Rochira et al. found an improvement in sleep-related erections measured by nocturnal penile tumescence and rigidity monitoring for men taking both sildenafil and testosterone.<sup>83</sup>

A synergistic effect was suggested given that combination therapy was more effective than treatment with sildenafil or testosterone alone, which has been observed in other studies as well.<sup>83</sup>

Up to 50% of men will have no response to PDE-5 inhibitors alone.<sup>10</sup> For patients with a poor response to PDE-5 inhibitors, hypogonadism has been shown as an independent prognostic factor.<sup>84</sup> Testosterone replacement has been found to convert up to half of hypogonadal men unresponsive to PDE-5 inhibitor

monotherapy to responders.<sup>85,86</sup> The mean erectile function, as measured by IIEF, increases significantly in all patients on combination therapy who had minimal or no response to sildenafil monotherapy.<sup>87</sup> This finding was confirmed in a randomized, double-blinded, placebo-controlled multicenter study of 75 hypogonadal men who failed sildenafil monotherapy and received testosterone replacement.<sup>88</sup>

The study showed a mean change of 4.4 in IIEF scores from baseline in the testosterone group and 2.1 in the placebo group at 4 weeks ( $p = 0.029$ ), reflecting a 65.4% response rate for erectile improvement in the testosterone group compared with 16.7% in the placebo group.<sup>88</sup> In addition, orgasmic function, overall satisfaction, and quality-of-life scores were significantly better at 12 weeks for the testosterone group compared with the placebo group.<sup>88</sup>

Another small prospective RCT of patients with ED and low-normal testosterone showed that after 1 month of transdermal testosterone replacement, patients on sildenafil not only had a significant improvement in the erectile function domain of IIEF in the testosterone group, but also had a significant increase in arterial inflow to cavernous arteries as measured by penile dynamic color duplex ultrasound ( $32 \pm 3.6$  cm/sec vs.  $25.2 \pm 4$  cm/sec for the testosterone group vs the placebo group;  $p < 0.05$ ).<sup>89</sup> For hypogonadal men who do not respond to tadalafil monotherapy, combination therapy with transdermal testosterone and tadalafil has been found to be associated with a significant increase in the frequency of intercourse and mean IIEF scores, with an increase of seven points observed from baseline to the end of a 10-week treatment interval.<sup>90</sup>

Similarly, in men who do not respond to testosterone monotherapy, the addition of a PDE-5 inhibitor can help to improve erectile function. In a small prospective observational study, hypogonadal men who achieved normalized testosterone levels with testosterone replacement after 1 month still did not regain erectile function.<sup>91</sup> However, when started on combination therapy with testosterone and sildenafil, 92% of men reported at least some return of erectile function.<sup>91</sup> Another study of 49 hypogonadal men with ED found that after 3 months with testosterone monotherapy, 31 patients had significant improvement in erectile function, with the remaining men showing improvement in erectile function based on IIEF after the initiation of sildenafil.<sup>92</sup>

The one meta-analysis on combination therapy showed possible advantages using combination therapy



when placebo- and non-placebo-controlled trials were considered; however, when the analysis was restricted to only placebo-controlled RCTs, the significant effect was lost.<sup>81</sup> Of the five RCTs included in the analysis, three enrolled mixed eugonadal and hypogonadal patients, which may have contributed to the lack of significant results.<sup>81</sup>

### Special population considerations

Functional hypogonadism, also referred to as age-related or late onset hypogonadism, is a potentially reversible form of hypogonadism that is mainly associated with sexual symptoms.<sup>93</sup> Testosterone Trials (TTrials), funded by the U.S. National Institute on Aging, have been designed and performed as a coordinated set of seven 52-week randomized placebo-controlled, double-blind trials, including 788 men with hypogonadism ( $T < 271$  ng/dL or 9.4 nmol/L) older than 65 years randomly assigned to receive 1% testosterone gel or placebo.<sup>94</sup>

Results showed that compared with placebo, testosterone replacement increases erectile function as well as sexual interest and sexual activity, from flirting to sexual intercourse, proportionally to the increase in testosterone levels.<sup>94</sup> Specifically, in the testosterone group, sexual activity “moderately” increased to about four times per week.<sup>94</sup> The IIEF-EF score for men receiving testosterone improved 2.64 points (95% CI: 1.06–4.02) more than men who had been assigned to the placebo group.<sup>94</sup> This significant improvement in erectile function suggests that testosterone therapy can be a therapeutic option for elderly, hypogonadal men with ED.<sup>94</sup>

Although testosterone replacement may be beneficial in aging men, lifestyle changes and management of underlying conditions related to comorbidities, if present, is the recommended strategy to potentially improve vascular parameters and increase endogenous testosterone levels before initiating or in conjunction with testosterone therapy.<sup>93</sup>

For hypogonadal patients with metabolic syndrome, multiple interventional studies have shown that testosterone replacement has improving effects on central obesity, glucose regulation, serum lipid levels, and blood pressure in addition to sexual and erectile function.<sup>95–100</sup> In 1007 men at risk of type 2 diabetes, an RCT evaluating whether testosterone treatment prevented progression or reversed the diagnosis of early diabetes while they were enrolled in a community-based lifestyle program showed a reduction in the

number of patients with diabetes as well as improvements in sexual function scores, including erectile function scores, based on IIEF measures, for the men in the testosterone group.<sup>100</sup>

When considering erectile function specifically, the baseline levels for the placebo group and the testosterone group were 16.7 and 17.4, respectively, and the mean changes in the placebo group and testosterone group were  $-0.95$  and  $1.16$ , respectively.<sup>100</sup> Although the treatment effect was considered statistically significant, a mean increase of  $1.16$  is not clinically significant and it is worth considering whether the inclusion of men with testosterone levels  $<404$  ng/dL or  $14$  nmol/L, which is a higher threshold than that used for the diagnosis of low testosterone, limited the effect.<sup>100</sup>

When studying 199 hypogonadal men who already received a diagnosis of type 2 diabetes, a 30-week RCT showed a benefit in sexual symptoms for men treated with long-acting injectable testosterone, particularly when testosterone levels were  $<231$  ng/dL or  $8$  nmol/L.<sup>101</sup> Similar results were observed in other RCTs looking at hypogonadal men with metabolic syndrome or type 2 diabetes on testosterone replacement, suggesting that testosterone therapy can be used for the management of ED in these populations.<sup>102</sup>

Patients with metabolic syndrome, type 2 diabetes, and other chronic diseases, who are at a high risk of hypogonadism, may also benefit from combination therapy with testosterone if monotherapy with PDE-5 inhibitors is inadequate for the treatment of ED. In men with diabetes, combination therapy with testosterone and sildenafil has been shown to be effective in restoring erectile function in 70% of patients with hypogonadism who did not respond to sildenafil monotherapy after the normalization of testosterone levels.<sup>103</sup>

A systematic review and meta-analysis of six RCTs evaluating testosterone therapy for sexual dysfunction in 587 men with type 2 diabetes concluded that testosterone therapy improves erectile function (random-effects pooled effect size  $0.203$ ; 95% CI  $0.007$ – $0.399$ ) and could be considered for men with type 2 diabetes unresponsive to PDE-5 inhibitors when the risks and benefits of therapy are carefully considered.<sup>104</sup> Similarly, combination therapy with testosterone and sildenafil for 12 months results in a good response in erectile function and sexual performance as measured by IIEF for all hypogonadal patients with ED on renal dialysis or post-transplant.<sup>105</sup>



## Management

Shared decision making with the patient that takes into account the risks and benefits of testosterone treatment is essential to determine whether testosterone is an appropriate treatment option for ED. The combined use of PDE-5 inhibitors can be considered when a patient has multiple comorbidities and does not respond well to testosterone monotherapy. Every treatment plan must be individualized for each patient.

**Treatment initiation.** Although patients may exhibit symptoms of testosterone deficiency at varying testosterone levels, a total testosterone level of  $<300$  ng/dL on at least two early morning serum measurements is used as a reasonable cut-off for the diagnosis of low testosterone based on the AUA guidelines.<sup>18</sup> The clinical diagnosis of testosterone deficiency is made only when low testosterone is accompanied by signs and/or symptoms.<sup>18</sup> Erectile function is usually not affected until even lower testosterone levels, with sleep-related erections being affected below 150–200 ng/dL, but libido may be affected at higher testosterone levels, which can influence the sexual response cycle.<sup>38</sup>

Therefore, although there is mixed literature regarding the treatment of men with low-normal testosterone levels, especially when ED is the indication, it is reasonable to consider treatment with testosterone at testosterone levels  $>300$  ng/dL if a patient endorses bothersome loss of libido and has difficulty with erections after a thorough discussion of risks and benefits and there is an understanding that testosterone will be discontinued after a short trial without improvement.

In men with low-normal testosterone levels as well as a condition known to affect SHBG, free testosterone levels may be helpful to guide whether to initiate testosterone therapy as symptomatic hypogonadism is more likely to be observed in patients with low free testosterone. Until there is better clinical evidence for the use of free testosterone, a total testosterone level of  $<300$  ng/dL in a patient with ED can be used as a threshold to initiate treatment. If the patient is not already on a PDE-5 inhibitor before the initiation of testosterone therapy, it can be considered as combination therapy may have better results.

Lifestyle modifications with dietary changes and exercise should be discussed before or in conjunction with testosterone treatment and/or combination therapy, as it is a low-risk intervention that has the potential to improve overall health and erectile function.

**Formulation selection.** As previously mentioned, testosterone replacement formulations include oral preparations, patches, gels, injections, and implants. The use of oral testosterone is not endorsed by the current AUA guidelines initially published in 2018 since the alkylated forms available at that time were associated with severe liver toxicity.<sup>18</sup> Oral testosterone formulations that are not alkylated have since been developed but have not been specifically studied in hypogonadal men with ED and are not yet indicated in this clinical scenario.

Topical testosterone, such as gels and creams, carry a black box warning regarding skin-to-skin transference and should be used cautiously in men where there is high potential for transfer to women or children.<sup>18</sup> Formulation selection should be decided after reviewing the risks and benefits, such as these, with the patient.

When selecting a PDE-5 inhibitor to be used in conjunction with testosterone replacement, sildenafil, tadalafil, vardenafil, and avanafil are all options, but RCTs assessing the combination therapy effect on ED only exists for sildenafil and tadalafil. Daily tadalafil, specifically, is associated with greater therapeutic benefit than on-demand medications with improvements in low desire and motivation and the efficacy increases with duration in meta-analyses.<sup>106</sup>

**Alternatives.** When lifestyle modifications are made before the initiation of testosterone therapy and result in improvements in erectile function, this is an appropriate alternative treatment to testosterone replacement.

In hypogonadal men interested in fertility, testosterone is contraindicated. Aromatase inhibitors, human chorionic gonadotropin, selective estrogen receptor modulators, or a combination of these medications may be used in men with testosterone deficiency desiring to maintain fertility; however, the impact on erectile function is unclear and it cannot currently be recommended for this indication.

**Monitoring.** For hypogonadal men on testosterone replacement, the AUA guidelines recommend dose adjustments to achieve a level of total testosterone in the middle tertile of the normal reference range.<sup>18</sup> Testosterone levels should be checked between 2 and 6 weeks after commencement of therapy, depending on the formulation, and then every 6–12 months once in the appropriate range.<sup>18</sup> If signs and symptoms do not improve within 6 months after the normalization of testosterone levels between 450 and 600 ng/dL, testosterone



treatment should be discontinued.<sup>18</sup> Although there are no specific guidelines regarding testosterone management for ED, a similar approach can be used in hypogonadal men with ED where dose adjustments in testosterone are made up to, but not beyond the upper limit of the middle tertile until there is improvement in erectile function.

If erectile function does not improve, a PDE-5 inhibitor can be considered before the discontinuation of testosterone as combination therapy may be necessary to get the desired response. The dose of the PDE-5 inhibitor can be titrated when testosterone levels are in the appropriate range. Patients' overall satisfaction with treatment, sexual activity frequency, and IIEF can all be used as ways to monitor symptom response.

**Limitations: Complications and side effects.** The role of testosterone in complicated vasculogenic ED is limited compared with patients with comorbidities that do not include significant vascular disease.<sup>77</sup> In terms of safety, testosterone therapy can be safe and effective if hypogonadism is properly diagnosed and testosterone therapy is appropriately managed; however, the risk of blood clots as well as the long-term cardiovascular risk and prostate cancer risk remain controversial topics that still need to be clarified with high-level evidence.<sup>77</sup>

Testosterone therapy may cause elevations in hemoglobin and hematocrit levels. Of the 788 men enrolled in the TTrials, 126 were anemic with hemoglobin levels <12.7 g/dL at baseline and testosterone treatment was able to correct the anemia in at least half of the patients compared with placebo.<sup>94</sup> For hypogonadal patients with anemia, this increase in hemoglobin and hematocrit may be of positive clinical value as it was associated with increases in patients' global impression of change in general health and vitality.<sup>94</sup>

In contrast, polycythemia can be associated with an increased risk of blood clots; however, there is no definitive evidence showing an association between testosterone therapy and blood clots. Hemoglobin and hematocrit levels should be measured to monitor for polycythemia with a hematocrit level of >54% as a threshold to consider for reducing the dose of testosterone or temporarily withholding testosterone treatment.<sup>18</sup>

Although untreated hypogonadism is a risk factor for cardiovascular events, it is unclear whether testosterone therapy increases or decreases cardiovascular risk since studies have shown conflicting results.<sup>18</sup>

Currently, there are no definitive data linking testosterone treatment to prostate cancer. A prostate-specific

antigen (PSA) level should be obtained in men older than 40 years old before the initiation of testosterone treatment to ensure it is not elevated and/or stable and further work-up is not needed to exclude prostate cancer.<sup>18</sup> In men with a history of prostate cancer, the decision to proceed with testosterone treatment should be based on a conversation of the potential risks and benefits.

The AUA guidelines support the consideration of treatment in men on active surveillance, post-radiation, as well as post-prostatectomy with favorable pathology and undetectable PSA, but they do not recommend therapy in high-risk patients or men with locally advanced or metastatic prostate cancer.<sup>18</sup> Rising PSA levels during monitoring require further evaluation.

## Conclusion

Both animal and human studies support an association between hypogonadism and ED. Animal studies first elucidated testosterone's role in maintaining the proper synthesis and/or release of enzymes as well as tissue structure and function in the corpora cavernosa. When low testosterone is present in both animals and humans, erectile function is compromised as a result, which can be improved with testosterone replacement.

Testosterone monotherapy in hypogonadal men without significant comorbidities can improve erectile function in those struggling with ED. Combination therapy with testosterone and PDE-5 inhibitors can lead to improvement in erectile function for hypogonadal men with medical comorbidities who do not respond to monotherapy. Based on the evidence, it is important to screen all men with ED for hypogonadism, especially those with a history of inadequate response to PDE-5 inhibitors, so that the appropriate treatment plan is implemented. Further studies are crucial to better understand the nuances of testosterone treatment for patients with different degrees of hypogonadism and to optimize sexual outcomes in hypogonadal men with ED.

## Authors' Contributions

Dr. Schardein and Dr. Hotaling each contributed to all aspects of this article.

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### Abbreviations Used

ADT = androgen deprivation therapy  
 AUA = American Urology Association  
 BMI = body mass index  
 CAD = coronary artery disease  
 cGMP = cyclic guanosine monophosphate  
 CI = confidence interval  
 CVD = cardiovascular disease  
 DHEAS = dehydroepiandrosterone sulfate  
 ED = erectile dysfunction  
 FMD = flow-mediated vasodilation  
 IIEF = International Index of Erectile Function  
 IIEF-EF = IIEF-erectile function  
 NO = nitric oxide  
 NOS = nitric oxide synthase  
 OR = odds ratio  
 PDE-5 = phosphodiesterase-5  
 PSA = prostate-specific antigen  
 RCT = randomized controlled trial  
 SHBG = sex hormone binding globulin  
 TTrial = Testosterone Trials

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