Current Sexual Health Reports (2019) 11:358–369
https://doi.org/10.1007/s11930-019-00216-9

FEMALE SEXUAL DYSFUNCTION AND DISORDERS (A PASTUSZAK AND N THIRUMAVALAVAN, SECTION EDITORS)

The Complex Relationship Between Erectile Dysfunction and Hypogonadism in Diabetes Mellitus

Levi C. Holland, B.S.[1,2] · Jonathan A. Beilan, M.D.[2] · Alexander J. Tatem, M.D.[2] · Larry I. Lipshultz, M.D.[2]

Published online: 6 November 2019

Abstract

Purpose of Review As the prevalence of diabetes mellitus grows worldwide, it is increasingly important to understand the commonly comorbid urologic conditions, hypogonadism and erectile dysfunction, in the setting of the diabetic man. The relationship between the diabetes, hypogonadism, and erectile dysfunction is complex with significant interplay among the disease processes and potential for unique management of the triad. The purpose of this review is to provide an update on the intertwined nature of these diseases in diabetics with special consideration for pathophysiology, diagnosis, and management.

Recent Findings There is a wide range of pathophysiologic mechanisms central to hypogonadism and erectile dysfunction in diabetes mellitus which continue to be identified and better elucidated; nevertheless, metabolic syndrome, composed of insulin resistance, dyslipidemia, hypertension, and obesity, appears to be the common thread between both. An increasing body of evidence suggests that low testosterone is an independent risk factor for cardiovascular disease and worsened overall survival in diabetic men with potential that testosterone therapy may reduce these risks. The treatment of either erectile dysfunction or hypogonadism in diabetic men may also improve the other condition; some evidence suggests that testosterone therapy in hypogonadal diabetics may improve erectile function while daily vardenafil, in addition to improving erectile function, appears to restore hypogonadal diabetics' testosterone to the eugonadal range.

Summary Metabolic syndrome appears to be the central connection between the increasingly common clinical picture of diabetic men with erectile dysfunction and hypogonadism. The overlapping pathophysiology of these conditions results in unique management considerations.

Keywords Diabetes mellitus · Erectile dysfunction · Hypogonadism · Testosterone · Sexual dysfunction · Metabolic syndrome · Pathophysiology · Management

This article is part of the Topical Collection on *Female Sexual Dysfunction and Disorders*

✉ Larry I. Lipshultz, M.D.
larryl@bcm.edu

Levi C. Holland, B.S.
levi.c.holland@uth.tmc.edu

Jonathan A. Beilan, M.D.
jonbeilan2@gmail.com

Alexander J. Tatem, M.D.
alex.tatem@gmail.com

[1] McGovern Medical School at the University of Texas Health Science Center at Houston, 6431 Fannin St, Houston, TX 77030, USA

[2] Scott Department of Urology, Baylor College of Medicine, 6624 Fannin St, #1700, Houston, TX 77030, USA

Introduction

Diabetes mellitus (DM) continues to be one of the most devastating diseases in the world despite innovative and evolving treatment options. In 1980, the worldwide prevalence of DM was estimated to be 4.7%. As of 2014, this number had almost doubled to 8.5% representing a total of 422 million adults globally [1]. The disease is known not only for its widespread prevalence, but also for its significant complications including cerebrovascular disease, coronary artery disease, renal failure, vision loss, and neuropathy. Of particular importance to sexual medicine, diabetes has also been strongly associated with both hypogonadism and erectile dysfunction (ED).

The prevalence of ED in DM patients is quite high, even when controlling for other comorbidities like hypertension [2, 3]. A recent, robust meta-analysis showed the prevalence of

impotence to be as high as 37%, 66%, and 58% in type 1, type 2, and in both types of DM respectively [2]. This is consistent with previous estimates that 51–71% of diabetic men have coexisting ED [3, 4] compared to a prevalence in the general population of 18% [4]. In regards to hypogonadism, studies have also shown a high prevalence of low testosterone in diabetic men with estimates ranging from 24 to 43% [5–8]. In particular, hypogonadotropic hypogonadism is predominately seen in these patients [5, 6]. Interestingly, young men with type 2 diabetes (DM2) were found to have significantly lower serum testosterone levels than their type 1 diabetic (DM1) counterparts with a strong correlation to increased body mass index (BMI) [9]. The significantly increased prevalence of both hypogonadism and ED in DM2 compared to DM1 suggest that the unique metabolic derangements that precipitate and coexist with DM2 may be particularly relevant.

DM2 is typically preceded by metabolic syndrome (MetS) which consists of insulin resistance, dyslipidemia, hypertension, and obesity with increased waist circumference. These derangements are intrinsically linked to DM2 and continue to be seen after progression from MetS to DM2 [10]. The interplay between diabetes, hypogonadism, and ED appears to be woven together by the different diseases that make up MetS. Dyslipidemia, hypertension, and hyperglycemia drive the endothelial dysfunction [11] that, in conjunction with neuropathy, appear to be central to the pathogenesis of diabetic ED [12–15]. By comparison, diabetic hypogonadism appears to primarily be the result of obesity and insulin resistance [16–19]. Together, these aspects of MetS produce the overlapping phenotype of DM, ED, and hypogonadism.

Not only do DM and MetS drive ED and reduce testosterone levels independently, but hypogonadism itself contributes to ED (Fig. 1). Sufficient levels of testosterone are essential for proper endothelial function, vasodilation, cavernosal smooth muscle relaxation, and maintenance of normal penile architecture [12, 20]. Each of these factors is important for erectogenesis and the maintenance of normal erectile function. Consequently, the American Urological Association now recommends that all patients complaining of ED have a serum testosterone drawn as part of their initial evaluation [21]. The interplay between low testosterone and ED also applies at the level of treatment. For example, testosterone supplementation has been shown to improve erectile function in men with both ED and DM2 [22•]. In a similar fashion, level one evidence has shown that daily vardenafil improves both symptoms of hypogonadism and markers of endothelial inflammation commonly seen in DM2 [23••]. Due to the intimate epidemiologic, pathophysiologic, and potentially therapeutic relationships between DM, ED, and hypogonadism, we present a review of diabetic hypogonadism and ED with special consideration for the clinical evaluation and management of these complex patients.

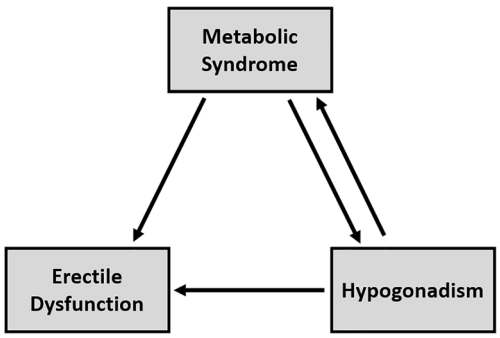

Fig. 1 The relationship between metabolic syndrome, hypogonadism, and erectile dysfunction

Erectile Dysfunction

ED can significantly impact diabetic men's quality of life (QoL), not only on specific measures related to sexual functioning and sexual satisfaction, but also in regards to their interpersonal relationships. Studies have shown that impotent diabetic men and their partners report significantly reduced sexual QoL [24] with patients themselves reporting poor emotional well-being that is inversely correlated with their International Index of Erectile Function (IIEF) score [25–27]. In fact, multiple studies have shown a higher prevalence of depressive symptoms with increased severity of diabetic ED [28, 29]. ED is also associated with a worsened psychological adaptation to diabetes and poorer control of blood sugar levels [25]. Consequently, recognition and proper management of diabetic ED can have significant benefits to the sexual, psychological, and overall well-being of diabetic men and their partners.

Poor erectile function is also medically important in its relationship to cardiovascular disease (CVD). After controlling for other factors, ED in diabetics is associated with an increased future risk of all CVD events, coronary artery disease, and cerebrovascular disease [30]. The relationship between ED and increased risk of CVD has been demonstrated in many large studies and is hypothesized to be the result of atherosclerosis and endothelial dysfunction first affecting the relatively small diameters of the penile arteries [31]. Interestingly, a recent study of impotent young men without traditional risk factors for CVD found an increased carotid artery intima-media thickness and reduced flow-mediated vasodilation [32]. This finding lends further evidence to poor erectile function being an early sign of systemic endothelial dysfunction and atherosclerosis. Importantly, a large prospective study published in 2013 found a direct relationship between ED severity and risk of future cardiovascular events which persists after adjusting for diabetes, BMI, and other possible confounders [33]. Compared with men with normal erectile function, men with severe ED had a significantly higher all-cause mortality (adjusted relative risk of 1.93 (1.52–2.44)) [33]. ED should be recognized for its

importance as a sign of poor systemic cardiovascular health. This may be particularly important to assess in diabetic patients who are at an already increased risk for CVD [1]. Conversely, all patients with diabetes or CVD should be screened for sexual and erectile dysfunction.

Pathophysiology

Obtaining and maintaining of an erection is dependent on a complex interplay of the central and peripheral nervous systems, penile vasculature, cavernosal structural integrity, and hormonal signaling. Endothelial dysfunction is believed to be one of the predominant pathophysiologic mechanisms of diabetic ED; with significant effects mediated through the action of advanced glycation end products (AGEs) and reactive oxygen species (ROS) [12, 13, 31, 34]. At the penile vascular endothelium, there is multifactorial dysfunction at the level of the vasodilatory molecule nitric oxide (NO) and its synthesizing enzyme, endothelial nitric oxide synthase (eNOS) [12, 14, 35, 36]. Molecular changes, including eNOS uncoupling and redox imbalance with resulting oxidative stress, occur early in the diabetic penile vasculature, being seen before systemic vascular function is affected [14]. Another molecular mechanism of endothelial dysfunction in diabetic impotence may be found in upregulation of the Rho-kinase pathway, activation of which results in smooth muscle contraction [34, 37]. Recent research has shown internal pudendal artery dysfunction in DM to be mediated, at least in part, by activation of Rho-kinase pathway from increased levels of ROS [38]. Increased expression of endothelin-1 (ET-1), a peptide vasoconstrictor whose effects are mediated by the Rho-kinase pathway [37], is also believed to be implicated in diabetic ED [34, 39]. A recent study in rats has shown that bosentan, an ET-1 receptor antagonist, results in a dose-dependent improvement in erectile response [40].

Abnormalities of the peripheral nervous system are also implicated in diabetic ED. There is a significant correlation between erectile dysfunction and both small and large fiber neuropathies in DM1 [41]. A positive association between severe ED and diabetic peripheral neuropathy has also been seen in DM2 [42]. Diabetic peripheral neuropathy can impede proper transmission of sensation from the penis, impairing the erectile reflex arc, while autonomic neuropathy can result in decreased parasympathetic output with reduced cavernosal smooth muscle relaxation, both of which may significantly impair erectile function [43]. The molecular basis of diabetic neurogenic ED is still under investigation but there appears to be reduced expression of neurotrophic factors at the level of the major pelvic ganglia in early T2DM [44]. This hypothesis is consistent with animal studies that have showed improvements in diabetic ED after supplementing with neurotrophic factors, such as brain-derived neurotrophic factor [45]. This is particularly relevant to the investigation of stem cell therapy and its ability to increase neurotrophic factors for the treatment of neurogenic ED [46].

Although the neurovascular changes of DM are likely the most significant factors in the resultant erectile dysfunction, the high prevalence of concomitant hypogonadism may also play a role. Normal endothelial function of the corpus cavernosum appears to be dependent on sufficient levels of testosterone [20, 47–50]. Testosterone acts via an androgen receptor (AR) dependent mechanism to activate eNOS which ultimately results in vasodilation and subsequent tumescence [48]. External to the epithelium, testosterone may also act directly on corpora cavernosa smooth muscle cells to open ATP-sensitive potassium channels thereby causing relaxation and dilation of the cavernosa [51]. Insufficient levels of testosterone, therefore, may worsen endothelial dysfunction and result in poor vasodilation. In fact, lack of testosterone results in p53-mediated apoptosis of the cavernosal epithelium [52]. Insufficient levels of testosterone may also result in a variety of adverse penile structure changes non-conducive to proper erectile function, including accumulation of adipocytes in corpora cavernosa [53], thinning and fibrosis of the tunica albuginea [54], loss of smooth muscle with resultant veno-occlusive dysfunction [55], and decreased cross-sectional area and hypotrophic vascular remodeling of the internal pudendal artery [50].

Evaluation

The evaluation of erectile dysfunction in the diabetic patient begins with a thorough history and physical examination. The details elicited serve as the foundation from which to better diagnose the patient. Studies have demonstrated that the relationship between diabetes and ED is multifactorial, including endocrine, vascular, neurologic, and psychosocial facets that must be addressed to successfully help the patient's sexual function [56, 57]. Therefore, the practitioner must obtain a comprehensive medical history, taking note of common risk factors for ED including cardiovascular disease, hypertension (and medical treatment thereof), obesity, the severity of diabetes, and its current management. The presence of dyslipidemia, frequent among diabetic patients, should also be noted. Hyperlipidemia, specifically a high low-density lipo-protein cholesterol (LDL-C), has been shown to be a risk factor for hypogonadism and ED [58, 59]. Social habits such as alcohol intake, tobacco use, and recreational drug use must be noted as they can negatively affect a man's sexual performance, both in the immediate and long-term. An often-overlooked part of the medical history revolves around the psychosocial aspects of the man's sexuality. Sleep deprivation, self-image and self-esteem, extrinsic stress such as work or financial problems, and unresolved relationship issues will play into the overall enjoyment of a couples' sexual encounters [60]. Finally, a complete hormone profile is paramount to exclude low testosterone or other

hormonal imbalances as contributing factors to ED. Per AUA guidelines, initial hormone testing includes serum testosterone (two morning draws) and LH (luteinizing hormone). Further adjuvant testing depends on the patient's clinical scenario, and may include estradiol if gynecomastia or breast symptoms are present, HgbA1c if the patient is at risk for diabetes, FSH (follicle stimulating hormone) if the patient interested in preserving fertility, DEXA scan there is a reported history of low trauma bone fracture, and HCT (hematocrit) if the patient is considering starting TTh (testosterone therapy). Additional tests may be obtained at the practioner's discretion, such as PSA (prostate-specific antigen), DHEA-S (dehydroepiandrosterone sulfate), Hgb (hemoglobin), SHBG (sex hormone binding globulin), and DHT (dihydrotestosterone).

Other testing, such as laboratory bloodwork, patient questionnaires, and clinical ultrasound can play a role in the diagnosis of ED in the diabetic patient. Aside from obtaining a hormone profile, metabolic and lipid panels, and hemoglobin A1c (HgbA1c) determination, the practitioner may also consider measuring platelet indices such as platelet count, mean platelet volume (MPV), and platelet distribution width (PDW) [61, 62]. El Taieb et al. demonstrated that measurement of platelet indices (PIs) may predict early erectile dysfunction in diabetic men [63•]. Their study evaluated 30 diabetic patients and found that PDW and MPV were significantly higher in diabetic patients than controls ($p < 0.001$). Of note, no significant relation was found between total platelet count and ED; however, PIs did significantly correlate with vasculogenic ED and levels of HgbA1c [63•].

Current Treatment Options

The treatment of erectile dysfunction in men with diabetes has some special considerations compared to those without diabetes or metabolic syndrome. While the advent of phosphodiesterase type 5 inhibitors (PDE5i's) revolutionized the treatment of erectile dysfunction, practitioners should be aware that certain types of PDE5i's may be more effective than others in the diabetic population. A recent meta-analysis evaluated 15 randomized clinical trials with 5274 patients to determine the most effective PDE5i regimen in diabetic men [64•]. The studies included eight kinds of PDE5i administration: avanafil PRN, mirodenafil PRN, sildenafil PRN, tadalafil PRN, tadalafil daily, udenafil PRN, udenafil daily, vardenafil PRN, and placebo. The authors found that vardenafil PRN ranked first, third and first, and mirodenafil PRN ranked second, first and second in the Global Assessment Question (GAQ), Erectile Function Domain of International Index of Erectile Function (IIEF-EF), and treatment-related adverse events (TRAEs), respectively. Their study demonstrated no significant difference between regular and on-demand regimens of PDE5i's [64•]. Practitioners in the USA may thus wish to consider vardenafil as a first-line PDE5i when treating diabetic men for ED.

Further evidence exists to support vardenafil as a first-line treatment for diabetic males. In 2016, Santi et al. performed a prospective, randomized, placebo-controlled, double-blind, clinical trial which included 54 male patients affected by type 2 diabetes mellitus and long-term ED [23••]. Patients were randomized to either vardenafil/placebo 10 mg twice daily for a treatment period of 24 weeks. By the end of the treatment phase, the authors found that the vardenafil group had significantly improved IIEF-15 scores ($p < 0.0019$), higher flow-mediated dilation (FMD) on penile Doppler ($p = 0.04$), and lower serum interleukin 6 (IL6) levels ($p = 0.019$). The increase in FMD correlated with an increase in serum testosterone levels with vardenafil treatment, and returned to the eugonadal range only in hypogonadal men [23••]. The improvement in FMD and testosterone, and the decrease in serum IL6 suggest that vardenafil may play a role in DM2 that addresses the pathophysiology of ED and hypogonadism itself, rather than just improving the symptoms. It is unclear if other daily PDE5i's result in similar findings.

Relevant to the discussion of treating erectile dysfunction in the diabetic patient is the topic of hormone replacement. As previously mentioned, the triad of diabetes, erectile dysfunction, and hypogonadism are often painted from the same clinical "brush." Buvat et al. demonstrated that the addition of testosterone replacement therapy (TTh) to daily tadalafil 10 mg improves erectile function in hypogonadal men with baseline T levels ≤ 300 ng/dL [65]. The authors performed a multicenter, multinational, double-blind, placebo-controlled study of 173 men, aged 45–80 years. These patients were nonresponders to PDE5i treatment and had baseline total T levels ≤ 400 ng/dL or bioavailable T ≤ 100 ng/dL. Men underwent a 4-week treatment period with daily 10 mg tadalafil; if unsatisfied with the effect, they were randomized to receive placebo or a 1% hydroalcoholic T gel. Patients in the TTh arm, once stratified to have a baseline T ≤ 300 ng/dL, demonstrated higher rates of sexual desire, IIEF scores, and occurrences of successful intercourse [65].

Hackett and colleagues performed the BLAST study in the UK (acronym derived from patient recruiting in the Midlands cities and towns of Birmingham, Lichfield, Atherstone, Sutton Coldfield, and Tamworth, UK), considered to be the first double-blind placebo-controlled study conducted exclusively in the male type 2 diabetic population to assess the metabolic changes with testosterone replacement [66, 67]. This study utilized type 2 diabetes registers of seven general practices to include 211 patients for a 30-week double-blind, placebo-controlled study of long-acting testosterone undecanoate (TU) 1000 mg followed by 52 weeks of open-label use [66]. The authors concluded that overall, TTh significantly improved HgbA1c, total cholesterol, and waist circumference in men with type 2 diabetes and without depression [66]. Further

review of their results shows that these metabolic improvements are not seen in men with severe testosterone deficiency syndrome (total T of ≤ 231 ng/dL or free T ≤ 52 pg/mL); however, this subset of patients did experience significantly improved sexual parameters and scores on the Ageing Male Symptom questionnaire. Men with mild testosterone deficiency syndrome (total T 234–346 ng/dL or free T 52–72 pg/mL) had significant improvements in metabolic but not sexual parameters [67]. These findings suggest that the degree of baseline hypogonadism affects the level of response to TTh in regards to its sexual benefits.

Emerging Therapies

There are a handful of restorative therapies that may prove beneficial to men with both diabetes and ED. Of these interventions, low-intensity shock wave therapy (LiSWT) has been the subject of the most human trials. A recent meta-analysis of 9 studies containing 637 patients found significantly improved IIEF scores (mean difference 2.54, p = .004) and Erection Hardness Scores (EHS) (mean difference 0.16, p = .01) but the strength of this analysis is limited by the heterogeneity of the included studies and the lack of high quality randomized controlled trials with long-term follow-up [68]. While LiSWT is most studied in primarily vasculogenic ED, diabetic ED has both neurogenic and vasculogenic components. Nevertheless, there does appear to be a role for this therapy in both PDE5i responder and nonresponder diabetics [69]. Other emerging interventions include intracavernous stem cell therapy (SCT) and intracavernous platelet rich plasma (PRP), but current human trials are significantly limited, particularly in regards to the latter [70, 71]. Stem cell therapy, which has been studied in combination with neurotrophic growth factors, has shown promise in rat models of cavernous nerve injuries [46]. Utilizing this therapy to address the neurogenic aspect of diabetic ED is a particularly interesting area that should be studied. Nevertheless, each of these investigational therapies, including LiSWT are largely considered experimental. Vigorous clinical trials are necessary prior to the widespread adoption of these treatment modalities [72].

Hypogonadism

In diabetic men, low testosterone has several significant adverse effects and untoward associations. One of the most well-known consequences of low testosterone is its negative effect on body composition. In 2003, Singh et al. demonstrated that androgenic stimulation of pluripotent stem cells results in increased myogenic differentiation and decreased adipogenesis [73]. Over the last two decades, multiple human studies have confirmed that supplementing testosterone significantly improves lean body mass, increases muscle strength, and decreases fat mass [74–76]. In fact, the adverse effect of low testosterone on adiposity has been demonstrated in diabetic patients specifically. Hypogonadal men with DM2 have both higher subcutaneous and visceral fat than their eugonadal counterparts [77•]. Many studies have also shown an association between low levels of testosterone and reduced insulin sensitivity [78, 79]. Among a cohort of type 2 diabetic men specifically, Dhindsa et al. found that men with low testosterone had higher insulin resistance when compared to those with normal testosterone levels [77•]. Furthermore, there is evidence that non-diabetic individuals with low-normal range testosterone are at a higher risk of later developing diabetes than those with higher-normal range testosterone, regardless of adiposity [80], supporting the idea that testosterone has some relationship with insulin resistance. Hypogonadism may act to perpetuate both MetS and DM2 through worsening insulin resistance and increased adiposity. Consequently, its importance in this area continues to be the subject of much investigation.

Much like ED, hypogonadism has also been associated with poor cardiovascular outcomes. Anemia, which is an independent risk factor for CVD [81], has been associated with comorbid hypogonadism and DM2 by multiple studies [16, 82, 83]. Anemia may be an important additional consequence of diabetic hypogonadism. Of note, a recent clinical trial has confirmed that TTh in older men significantly improves anemia of both known and unknown causes [84]. This finding is consistent with the well-established effect of testosterone on erythrocytosis via stimulation of erythropoietin (EPO); in fact, TTh appears to not only result in increased levels of hemoglobin but it also appears to recalibrate the EPO/hemoglobin set point [85]. Reduced testosterone levels have also been more directly associated with CVD risk; hypogonadism is associated with higher serum concentrations of CVD biomarkers independent of BMI, HbA1c, HDL, and hs-CRP [86]. In middle-aged type 2 diabetics, hypogonadism was found to be associated with more advanced atherosclerotic disease markers including increased carotid intima-media thickness and an increased presence of atherosclerotic plaques [87•]. Furthermore, Daka et al. found that lower testosterone levels predicted an increased risk of acute myocardial infarction in DM2, independent of other risk factors such as waist-to-hip ratio, total cholesterol, smoking status, and systolic blood pressure [88].

Beyond an increased risk of CVD, decreased testosterone has also been associated with increased mortality. Low testosterone has been independently associated with worse survival over the ensuing 20 years in elderly men [89]. This finding also held true in hypogonadal type 2 diabetics who have increased all-cause mortality compared to eugonadal type 2 diabetics when controlling for other variables (HR 2.02, p = 0.009) [90].

Pathophysiology

The pathogenesis of hypogonadism in the setting of diabetes is complex and not yet fully understood. It is clear, however, that low testosterone is much more common in type 2 diabetics than in men with type 1 diabetes [9, 91]. This finding is hypothesized to be a result of the effects of metabolic syndrome, obesity, insulin resistance, and their linked derangements. All appear to play key roles in the complex interplay seen among these overlapping conditions [8, 9, 16, 18]. Of note, any method of weight loss, whether from a low-calorie diet or bariatric surgery, has been shown to increase both total and free testosterone, with the degree of weight loss best predicting a patient's rise in total testosterone [92]. This finding supports the conclusion that obesity is an independent risk factor for low testosterone. But the relationship between DM2 and low testosterone cannot simply be explained by obesity, as there is a higher incidence of hypogonadism in patients with both DM2 and obesity compared to either disease alone [5, 17, 18, 93].

It was previously believed that the hypogonadotropic hypogonadism seen in DM2 and obesity was principally caused by hypothalamic suppression secondary to increased estrogen levels from aromatization of testosterone by adipose tissue [13, 18]. This idea has not been validated by the literature; in fact, multiple studies have actually shown decreased estradiol in these hypogonadal patients with DM2 and/or obesity [16, 93–96]. Specifically, in DM2, estradiol was directly related to free testosterone but had no association with BMI [95]. Furthermore, no difference in adipose aromatase expression has been seen between men of normal weight versus obese men with or without diabetes [93]. Therefore, the notion that the low gonadotropin levels seen in hypogonadal type 2 diabetics is secondary to increased aromatization of testosterone is unfounded. The mechanism remains to be precisely elucidated but appears to be multifactorial in etiology.

Chronic inflammation, which is seen throughout obesity, metS, and DM2 [97], may also decrease testosterone [16, 18]. Lower testosterone levels are associated with increased inflammatory markers such as macrophage inflammatory protein 1-alpha and 1-beta, tumor necrosis factor-alpha, and C-reactive protein (CRP) [82, 94, 98]. Inflammatory mediators including cytokines and adipokines are released by adipose tissue in obese patients and there is some evidence that these circulating inflammatory mediators can act centrally on the hypothalamus [99]. One such adipokine, leptin, is most well-known for decreasing appetite but is also necessary for GnRH production at the hypothalamus [99, 100]. Obese individuals tend to be leptin resistant [100, 101]; some postulate that this leptin resistance may therefore suppress the hypothalamic-pituitary-gonadal (HPG) axis [16, 79, 100], but more exploration must be done prior to reaching this conclusion.

Insulin resistance is strongly associated with hypogonadism. An inverse relationship between measures of insulin resistance and testosterone has been demonstrated in multiple studies [93, 94]. Peripherally, increased insulin resistance was associated with decreased hCG-induced testosterone secretion by Leydig cells [19]. Centrally, neuronal insulin resistance may also be a factor; insulin sensitivity appears to be necessary for normal central HPG axis function [16, 18]. This idea is built on the observation that neuronal insulin receptor knockout male mice had significantly lower LH levels [102] and also that GnRH neurons have been shown to be activated by insulin [103]. Insulin resistance, which appears to affect brain receptors in type 2 diabetic and obese patients [104], may therefore contribute to central hypogonadism in this population.

A functional eugonadal state is dependent not only on sufficient free testosterone levels but also on proper androgen receptor expression and function. Quite interestingly, Ghanim et al. recently showed that hypogonadal diabetic men not only have low serum concentration of testosterone, but also have reduced expression of both androgen receptors (AR) and estrogen receptors (ER); further, the poor AR expression was reversed by testosterone replacement [105••]. The authors note that this was surprising as they had hypothesized that these hypogonadal men would actually have a compensatory increase in AR expression. Diminished AR expression is a previously unknown factor that may be important to the complex pathophysiology of type 2 diabetic hypogonadism.

Diagnosis

The diagnosis of hypogonadism can be challenging given the non-specific nature of patients' symptomology. Although lack of libido, fatigue, increased abdominal adiposity, irritability, loss of muscle mass, and decreased mental acuity are all classic for low testosterone, these symptoms are far from exclusive to low T. Consequently, an accurate diagnosis of hypogonadism requires at least two separate low serum morning testosterone levels in addition to the aforementioned clinical symptoms [106]. In addition to being measured in the morning, the serum testosterone levels should ideally be obtained while the patient is fasting to improve accuracy. Once a diagnosis has been made, providers should be mindful that low testosterone can often be the result of other underlying pathology and seek to rule out conditions such as prolactinomas, chronic narcotic use, male infertility secondary to testis function, and chronic corticosteroid use among others.

The exact serum concentration of what constitutes a "low" serum testosterone is controversial even among experts and several different values have been proposed by various professional societies. The American Urological Association recommends two serum lab values below 300 ng/dL while the International Society of Sexual Medicine utilizes a threshold of 346 ng/dL [106, 107]. The European Urological

Association and the British Society for Sexual Medicine take a different approach and stratify their cutoffs based on symptomology with values ranging from 231 ng/dL to 375 ng/dL and 231 ng/dL to 346 ng/dL, respectively. Although some authors advocate the use of free testosterone when establishing a diagnosis of low testosterone, significant inter-assay variability with both direct and calculated measurements prevent this from becoming a widely accepted standard.

Risks and Benefits of Testosterone Replacement Therapy

Testosterone therapy has been shown with the highest levels of evidence to convey significant benefits including: increased bone mineral density, improved strength, increased lean muscle mass, fat loss, improved lipid metabolism, improved libido, and improved erectile function. In diabetic men, specifically, multiple studies have demonstrated improved survival with TTh [90, 108•, 109••]. For the majority of patients, testosterone therapy has been shown to be remarkably safe with a favorable risk/benefit profile. However, testosterone therapy does carry some risks that warrant discussion.

Testosterone supplementation disrupts the natural body's natural hypothalamic-pituitary-gonadal axis and subsequently inhibits the release of gonadotropins from the pituitary. This suppresses the native functions of the testis and can significantly impair sperm production. A 1990 study by the WHO Task Force found that 65% of men treated with 200 mg of testosterone enanthate once weekly became azoospermic at 6 months [110]. A more recent 2009 study found that 95.2% of men treated with monthly doses of 500 mg testosterone undecanoate became either azoospermic or severely oligospermic within the 24-month treatment period [111]. As a result, there has been great interest in the potential use of testosterone as a male contraceptive agent but there does not appear to be consistent sterility with TTh. Fortunately, once testosterone therapy is stopped, the vast majority of these men can see return of sperm to the ejaculate within a year [112]. This recovery can often be expedited through the use of adjuvant hCG or clomiphene citrate [113]. Still, testosterone therapy can have a significant deleterious effect on men desiring future fertility and caution should be used when treating this population.

Testosterone replacement has also been proven to contribute to polycythemia in some men. Defined as a hematocrit greater that 52%, one multi-institutional retrospective case series showed the rate of polycythemia was found to be highest in men receiving injectable testosterone (19%) followed by testosterone pellets (13%) and then topical gels/creams (5%) [114]. The 2018 AUA Guidelines recommend intervention in men with a hematocrit greater than 54%. A decrease in testosterone dose has been recommended by some as an initial intervention, but this runs the risk of worsening hypogonadal symptoms with a significant delay until normalization of hematocrit. Therapeutic phlebotomy, on the other hand, offers immediate relief of an elevated hematocrit without running the risk of disrupting an otherwise effective testosterone therapy regimen.

There has been much discussion about the potential risk of testosterone therapy, specifically in regards to prostate cancer, cardiac disease, and venous thromboembolism (VTE). In regards to testosterone therapy and prostate cancer, there has been a compendium of literature published showing no causality between testosterone therapy and the development of prostate cancer [115, 116]. Although there has been extensive debate regarding testosterone and cardiac disease, current evidence actually appears to suggest that testosterone has a cardioprotective effect and acts as a plaque stabilizer while hypogonadism is an independent risk factor for future cardiac events [117]. Lastly, although there has been some concern that TTh may increase risk of VTE, most evidence shows no association between TTh and risk of deep venous thrombosis or pulmonary embolism [118, 119].

Treatment Options

Overall, the evidence remains inconclusive as to whether testosterone supplementation improves insulin resistance, body composition, and other measures of diabetes. Therefore, the chief indication for treating hypogonadism in DM remains to be symptomatic hypogonadism. The primary goal of TTh is amelioration of hypogonadal symptoms and restoration of serum testosterone levels to the eugonadal range. Both the American Urological Association and Endocrine Society guidelines recommend treating to reach the middle-normal range at roughly 400–600 ng/dL [106, 120]. There have been very few studies comparing specific TTh formulations in diabetic hypogonadism; thus, at this time, management should be approached in a similar fashion to non-diabetic hypogonadism. The testosterone formulation chosen is largely individualized to the patient after discussion of the risks and benefits of each option.

In patients for whom testosterone supplementation should be avoided, such as those actively attempting to conceive or planning to conceive in the near future, other options may be useful for restoration of the eugonadal state such as clomiphene citrate (CC), human chorionic gonadotropin (hCG), and/or aromatase inhibitors. In fact, these agents may also be used concurrently with TTh or post-TTh to maintain or restore fertility, respectively [121]. Selective estrogen receptor modulators like CC have been used off-label for many years in men to increase serum testosterone and spermatogenesis via increased gonadotropin release. These are an enticing option in men wishing to preserve fertility and may also even be valuable in patients in whom there is higher concern for potential development of secondary polycythemia as there is a far lower prevalence of polycythemia patients treated with CC

compared to TTh at a similar mean change in serum testosterone [114]. A study in obese men with either impaired glucose tolerance or overt DM2 did find a substantial improvement in testosterone levels with low-dose CC (25 mg/day) compared to placebo [122]. However, there has been conflicting data regarding the ability of CC to reduce hypogonadal symptoms [123, 124]; thus, it may not be the best option. hCG, an LH analog, is another option for men who wish to preserve their fertility and is the only one of these three medications which is FDA approved in men for this indication. While both hCG and CC result in similar increases of testosterone concentration, a greater degree of improvement of hypogonadal symptoms has been seen when the two medications are combined [125]. Finally, in limited studies, aromatase inhibitors have been shown to increase testosterone and semen parameters of infertile men, particularly in those with low testosterone:estradiol ratios [126]. It is unclear if use of this medication class alone would result in any meaningful benefit for hypogonadal diabetics who have been shown to have paradoxically decreased serum estrogen levels [16, 95]. Unfortunately, there is a paucity of data for these TTh alternatives in DM; most patients should therefore be treated with their preferred testosterone formulation.

Conclusion

Both ED and hypogonadism are significantly more common in diabetic patients than in the general population. Although the etiology of each appears to be complex and multifactorial, the underlying connection between the two appears to be metabolic syndrome, which consists of insulin resistance, obesity, dyslipidemia, and hypertension. Hypogonadism may also worsen erectile function, compounding the issue. Management of diabetic hypogonadism and ED can overlap and begins with lifestyle modifications such as improving dietary/exercise behaviors. Certain treatment regimens such as testosterone supplementation may improve both conditions simultaneously. There are still many unanswered questions surrounding the pathogenesis and management of ED and hypogonadism in these patients. Future studies will no doubt increase our understanding of the complex interplay of these disease processes and direct us toward more targeted and successful therapies.

Compliance with Ethical Standards

Conflict of interest Dr. Tatem, Dr. Holland, and Dr. Beilan each declare no conflicts of interest. Dr. Lipshultz reports roles with AbbVie as consultant, American Medical Systems as speaker, Aytu Bioscience as consultant, Endo Pharmaceuticals as speaker and consultant, and Lipocine as consultant.

Research Involving Human Participants and/or Animals This article does not contain any studies with human or animal subjects performed by the author.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. World Health Organization. Global Report on Diabetes. Geneva: WHO Press; 2016.
2. Kouidrat Y, Pizzol D, Cosco T, Thompson T, Carnaghi M, Bertoldo A, et al. High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. Diabet Med. 2017;34(9):1185–92. https://doi.org/10.1111/dme.13403.
3. Giuliano FA, Leriche A, Jaudinot EO, de Gendre AS. Prevalence of erectile dysfunction among 7689 patients with diabetes or hypertension, or both. Urology. 2004;64(6):1196–201. https://doi.org/10.1016/j.urology.2004.08.059.
4. Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med. 2007;120(2):151–7. https://doi.org/10.1016/j.amjmed.2006.06.010.
5. Dhindsa S, Prabhakar S, Sethi M, Bandyopadhyay A, Chaudhuri A, Dandona P. Frequent occurrence of hypogonadotropic hypogonadism in type 2 Diabetes. J Clin Endocrinol Metab. 2004;89(11):5462–8. https://doi.org/10.1210/jc.2004-0804.
6. Corona G, Mannucci E, Petrone L, Ricca V, Balercia G, Mansani R, et al. Association of hypogonadism and type II diabetes in men attending an outpatient erectile dysfunction clinic. Int J Impot Res. 2006;18(2):190–7. https://doi.org/10.1038/sj.ijir.3901391.
7. Hamilton EJ, Davis WA, Makepeace A, et al. Prevalence and prognosis of a low serum testosterone in men with type 2 diabetes: the Fremantle Diabetes Study Phase II. Clin Endocrinol. 2016;85(3):444–52. https://doi.org/10.1111/cen.13087.
8. Grossmann M, Thomas MC, Panagiotopoulos S, Sharpe K, Macisaac RJ, Clarke S, et al. Low testosterone levels are common and associated with insulin resistance in men with diabetes. J Clin Endocrinol Metab. 2008;93(5):1834–40. https://doi.org/10.1210/jc.2007-2177.
9. Chandel A, Dhindsa S, Topiwala S, Chaudhuri A, Dandona P. Testosterone concentration in young patients with Diabetes. Diabetes Care. 2008;31(10):2013–7. https://doi.org/10.2337/dc08-0851.
10. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.
11. Hadi HA, Carr CS, Al SJ. Endothelial dysfunction: cardiovascular risk factors, therapy, and outcome. Vasc Health Risk Manag. 2005;1(3):183–98.
12. Castela Â, Costa C. Molecular mechanisms associated with diabetic endothelial–erectile dysfunction. Nat Rev Urol. 2016;13(5):266–74. https://doi.org/10.1038/nrurol.2016.23.

13. Gandhi J, Dagur G, Warren K, et al. The role of diabetes mellitus in sexual and reproductive health: an overview of pathogenesis, evaluation, and management. Curr Diabetes Rev. 2017;13(6). https://doi.org/10.2174/1573399813666161122124017.
14. Musicki B, Hannan JL, Lagoda G, Bivalacqua TJ, Burnett AL. Mechanistic link between erectile dysfunction and systemic endothelial dysfunction in type 2 diabetic rats. Andrology. 2016;4(5):977–83. https://doi.org/10.1111/andr.12218.
15. Moore CR, Wang R. Pathophysiology and treatment of diabetic erectile dysfunction. Asian J Androl. 2006;8(6):675–84. https://doi.org/10.1111/j.1745-7262.2006.00223.x.
16. Dhindsa S, Ghanim H, Batra M, Dandona P. Hypogonadotropic hypogonadism in men with diabesity. Diabetes Care. 2018;41(7):1516–25. https://doi.org/10.2337/dc17-2510.
17. Dhindsa S, Miller MG, McWhirter CL, Mager DE, Ghanim H, Chaudhuri A, et al. Testosterone concentrations in diabetic and nondiabetic obese men. Diabetes Care. 2010;33(6):1186–92. https://doi.org/10.2337/dc09-1649.
18. Saboor Aftab SA, Kumar S, Barber TM. The role of obesity and type 2 diabetes mellitus in the development of male obesity-associated secondary hypogonadism. Clin Endocrinol. 2013;78(3):330–7. https://doi.org/10.1111/cen.12092.
19. Pitteloud N, Hardin M, Dwyer AA, et al. Increasing insulin resistance is associated with a decrease in Leydig cell testosterone secretion in men. J Clin Endocrinol Metab. 2005;90(5):2636–41. https://doi.org/10.1210/jc.2004-2190.
20. Traish A, Kim N. The physiological role of androgens in penile erection: regulation of corpus cavernosum structure and function. J Sex Med. 2005;2(6):759–70. https://doi.org/10.1111/j.1743-6109.2005.00094.x.
21. Burnett AL, Nehra A, Breau RH, Culkin DJ, Faraday MM, Hakim LS, et al. Erectile dysfunction: AUA guideline. J Urol. 2018;200(3):633–41. https://doi.org/10.1016/j.juro.2018.05.004.
22.• Algeffari M, Jayasena CN, MacKeith P, Thapar A, Dhillo WS, Oliver N. Testosterone therapy for sexual dysfunction in men with Type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabet Med. 2018;35(2):195–202. https://doi.org/10.1111/dme.13553 **A meta-analysis of randomized controlled trials which shows that testosterone therapy may moderately improve erectile function and sexual desire in hypogonadal type 2 diabetics.**
23.•• Santi D, Granata ARM, Guidi A, et al. Six months of daily treatment with vardenafil improves parameters of endothelial inflammation and of hypogonadism in male patients with type 2 diabetes and erectile dysfunction: a randomized, double-blind, prospective trial. Eur J Endocrinol. 2016;174(4):513–22. https://doi.org/10.1530/EJE-15-1100 **High-quality trial demonstrating that daily vardenafil improves inflammatory parameters in addition to hypogonadism.**
24. Owiredu WKBA, Alidu H, Amidu N, Obirikorang C, Gyasi-Sarpong CK, Bawah AT, et al. Sexual dysfunction among diabetics and its impact on the SQoL of their partners. Int J Impot Res. 2017;29(6):250–7. https://doi.org/10.1038/ijir.2017.32.
25. Berardis GD, Franciosi M, Belfiglio M, et al. Erectile dysfunction and quality of life in type 2 Diabetic patients: a serious problem too often overlooked. Diabetes Care. 2002;25(2):284–91. https://doi.org/10.2337/diacare.25.2.284.
26. Malavige LS, Jayaratne SD, Kathriarachchi ST, Sivayogan S, Ranasinghe P, Levy JC. Erectile dysfunction is a strong predictor of poor quality of life in men with Type 2 diabetes mellitus. Diabet Med. 2014;31(6):699–706. https://doi.org/10.1111/dme.12412.
27. Chen S, Peng D, Xu X, Gao J, Dai F, Zuo C, et al. Assessment of erectile dysfunction and associated psychological distress in Chinese men with type 2 diabetes mellitus. Int J Impot Res. 2017;29(5):210–4. https://doi.org/10.1038/ijir.2017.25.
28. Furukawa S, Sakai T, Niiya T, Miyaoka H, Miyake T, Yamamoto S, et al. Depressive symptoms and prevalence of erectile dysfunction in Japanese patients with type 2 diabetes mellitus: the Dogo Study. Int J Impot Res. 2017;29(2):57–60. https://doi.org/10.1038/ijir.2016.45.
29. Maiorino MI, Bellastella G, Volpe ED, et al. Erectile dysfunction in young men with type 1 diabetes. Int J Impot Res. 2017;29(1):17–22. https://doi.org/10.1038/ijir.2016.38.
30. Batty GD, Li Q, Czernichow S, Neal B, Zoungas S, Huxley R, et al. Erectile dysfunction and later cardiovascular disease in men with type 2 diabetes: prospective cohort study based on the ADVANCE trial. J Am Coll Cardiol. 2010;56(23):1908–13. https://doi.org/10.1016/j.jacc.2010.04.067.
31. Gandaglia G, Briganti A, Jackson G, Kloner RA, Montorsi F, Montorsi P, et al. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014;65(5):968–78. https://doi.org/10.1016/j.eururo.2013.08.023.
32. Yao F-J, Zhang Y-D, Wan Z, Li W, Lin H, Deng CH, et al. Erectile dysfunction is associated with subclinical carotid vascular disease in young men lacking widely-known risk factors. Asian J Androl. 2018;20(4):400–4. https://doi.org/10.4103/aja.aja_73_17.
33. Banks E, Joshy G, Abhayaratna WP, et al. Erectile dysfunction severity as a risk marker for cardiovascular disease hospitalisation and all-cause mortality: a prospective cohort study. PLoS Med. 2013;10(1):e1001372. https://doi.org/10.1371/journal.pmed.1001372.
34. Thorve VS, Kshirsagar AD, Vyawahare NS, Joshi VS, Ingale KG, Mohite RJ. Diabetes-induced erectile dysfunction: epidemiology, pathophysiology and management. J Diabetes Complicat. 2011;25(2):129–36. https://doi.org/10.1016/j.jdiacomp.2010.03.003.
35. Ben Khedher MR, Abid M, Jamoussi K, Hammami M. Comprehensive insight into functional interaction between GNB3 C825T and eNOS T-786C, G894T gene polymorphisms and association with susceptibility to diabetic erectile dysfunction. Andrology. 2018. https://doi.org/10.1111/andr.12543.
36. Castela A, Gomes P, Domingues VF, Paíga P, Costa R, Vendeira P, et al. Role of oxidative stress-induced systemic and cavernosal molecular alterations in the progression of diabetic erectile dysfunction. J Diabetes. 2015;7(3):393–401. https://doi.org/10.1111/1753-0407.12181.
37. Miao L, Dai Y, Zhang J. Mechanism of RhoA/Rho kinase activation in endothelin-1- induced contraction in rabbit basilar artery. Am J Physiol Heart Circ Physiol. 2002;283(3):H983–9. https://doi.org/10.1152/ajpheart.00141.2002.
38. Alves-Lopes R, Neves KB, Montezano AC, Harvey A, Carneiro FS, Touyz RM, et al. Internal pudental artery dysfunction in Diabetes mellitus is mediated by NOX1-Derived ROS-, Nrf2-, and rho kinase-dependent mechanisms. Hypertension. 2016;68(4):1056–64. https://doi.org/10.1161/HYPERTENSIONAHA.116.07518.
39. Takahashi K, Ghatei MA, Lam HC, O'Halloran DJ, Bloom SR. Elevated plasma endothelin in patients with diabetes mellitus. Diabetologia. 1990;33(5):306–10.
40. Alkan E, Ugan RA, Basar MM, et al. Role of endothelin receptors and relationship with nitric oxide synthase in impaired erectile response in diabetic rats. Andrologia. 2017;49(2). https://doi.org/10.1111/and.12607.
41. Azmi S, Ferdousi M, Alam U, Petropoulos IN, Ponirakis G, Marshall A, et al. Small-fibre neuropathy in men with type 1 diabetes and erectile dysfunction: a cross-sectional study. Diabetologia. 2017;60(6):1094–101. https://doi.org/10.1007/s00125-017-4245-z.
42. Furukawa S, Sakai T, Niiya T, Miyaoka H, Miyake T, Yamamoto S, et al. Diabetic peripheral neuropathy and prevalence of erectile

dysfunction in Japanese patients aged <65 years with type 2 diabetes mellitus: The Dogo Study. Int J Impot Res. 2017;29(1):30–4. https://doi.org/10.1038/ijir.2016.40.
43. Malavige LS, Levy JC. Erectile dysfunction in Diabetes mellitus. J Sex Med. 2009;6(5):1232–47. https://doi.org/10.1111/j.1743-6109.2008.01168.x.
44. Matsui H, Musicki B, Sopko NA, et al. Early-stage type 2 diabetes mellitus impairs erectile function and neurite outgrowth from the major pelvic ganglion and downregulates the gene expression of neurotrophic factors. Urology. 2017;99:287.e1–7. https://doi.org/10.1016/j.urology.2016.08.045.
45. Hu L, Qi S, Zhang K, Fu Q. Essential role of brain-derived neurotrophic factor (bdnf) in diabetic erectile dysfunction. Andrologia. 2018;50(3). https://doi.org/10.1111/and.12924.
46. Shan H, Chen F, Zhang T, He S, Xu L, Wei A. Stem cell therapy for erectile dysfunction of cavernous nerve injury rats: a systematic review and meta-analysis. PLoS ONE. 2015;10(4):e0121428. https://doi.org/10.1371/journal.pone.0121428.
47. Aversa A, Isidori AM, De Martino MU, et al. Androgens and penile erection: evidence for a direct relationship between free testosterone and cavernous vasodilation in men with erectile dysfunction. Clin Endocrinol. 2000;53(4):517–22.
48. Yu J, Akishita M, Eto M, Ogawa S, Son BK, Kato S, et al. Androgen receptor-dependent activation of endothelial nitric oxide synthase in vascular endothelial cells: role of phosphatidylinositol 3-kinase/akt pathway. Endocrinology. 2010;151(4):1822–8. https://doi.org/10.1210/en.2009-1048.
49. Cui K, Li R, Liu K, Wang T, Liu J, Rao K. Testosterone preserves endothelial function through regulation of S1P1/Akt/FOXO3a signalling pathway in the rat corpus cavernosum. Andrologia. 2018:e13173. https://doi.org/10.1111/and.13173.
50. Alves-Lopes RU, Neves KB, Silva MA, Olivon VC, Ruginsk SG, Antunes-Rodrigues J, et al. Functional and structural changes in internal pudendal arteries underlie erectile dysfunction induced by androgen deprivation. Asian J Androl. 2017;19(5):526–32. https://doi.org/10.4103/1008-682X.173935.
51. Yildiz O, Seyrek M, Irkilata HC, Yildirim I, Tahmaz L, Dayanc M. Testosterone might cause relaxation of human corpus cavernosum by potassium channel opening action. Urology. 2009;74(1):229–32. https://doi.org/10.1016/j.urology.2008.12.022.
52. Yamamoto H, Sasaki S, Tatsura H, Umemoto Y, Kubota H, Kamiya H, et al. Penile apoptosis in association with p53 under lack of testosterone. Urol Res. 2004;32(1):9–13. https://doi.org/10.1007/s00240-003-0358-6.
53. Traish AM, Toselli P, Jeong S-J, Kim NN. Adipocyte accumulation in penile corpus cavernosum of the orchiectomized rabbit: a potential mechanism for veno-occlusive dysfunction in androgen deficiency. J Androl. 2005;26(2):242–8.
54. Shen Z-J, Zhou X-L, Lu Y-L, Chen Z-D. Effect of androgen deprivation on penile ultrastructure. Asian J Androl. 2003;5(1):33–6.
55. Traish AM, Munarriz R, O'Connell L, et al. Effects of medical or surgical castration on erectile function in an animal model. J Androl. 2003;24(3):381–7.
56. Corona G, Mannucci E, Mansani R, Petrone L, Bartolini M, Giommi R, et al. Organic, relational and psychological factors in erectile dysfunction in men with diabetes mellitus. Eur Urol. 2004;46(2):222–8. https://doi.org/10.1016/j.eururo.2004.03.010.
57. Bhasin S, Enzlin P, Coviello A, Basson R. Sexual dysfunction in men and women with endocrine disorders. Lancet Lond Engl. 2007;369(9561):597–611. https://doi.org/10.1016/S0140-6736(07)60280-3.
58. Zamorano-Leon JJ, Segura A, Lahera V, et al. Relationship between erectile dysfunction, diabetes and dyslipidemia in hypertensive-treated men. Urol J. 2018;15(6):370–5. https://doi.org/10.22037/uj.v0i0.4068.
59. Chen C, Zhai H, Huang G, Cheng J, Xia F, Zhao L, et al. Is lower low-density lipoprotein cholesterol associated with lower androgen and erectile dysfunction in men? Nutr Metab Cardiovasc Dis NMCD. 2018;28(12):1304–10. https://doi.org/10.1016/j.numecd.2018.08.006.
60. Cho JW, Duffy JF. Sleep, sleep disorders, and sexual dysfunction. World J Mens Health. 2018. https://doi.org/10.5534/wjmh.180045.
61. Yang G, Muzepper M. Platelet indices and erectile dysfunction: a systematic review and meta-analysis. Andrologia. 2019;51(5):e13248. https://doi.org/10.1111/and.13248.
62. Tangal S, Ozayar A, Ener K, Gokçe MI, Haliloglu AH. Does mean platelet volume (MPV) have a role in evaluation of erectile dysfunction and its severity? Rev Int Androl. 2018. https://doi.org/10.1016/j.androl.2018.07.007.
63.• El Taieb MA, Hegazy EM, Maklad SM, Khairy R. Platelet Indices as a marker for early prediction of erectile dysfunction in diabetic patients. Andrologia. 2019;51(1):e13163. https://doi.org/10.1111/and.13163 **Platelet indices may be used to predict diabetic vasculogenic ED**.
64.• Liao X, Qiu S, Bao Y, Wang W, Yang L, Wei Q. Comparative efficacy and safety of phosphodiesterase type 5 inhibitors for erectile dysfunction in diabetic men: a Bayesian network meta-analysis of randomized controlled trials. World J Urol. 2018. https://doi.org/10.1007/s00345-018-2583-1 **On-demand vardenafil and mirodenafil may have higher efficacy with lower adverse events in diabetic men than other PDE5i's.**
65. Buvat J, Montorsi F, Maggi M, Porst H, Kaipia A, Colson MH, et al. Hypogonadal men nonresponders to the PDE5 inhibitor tadalafil benefit from normalization of testosterone levels with a 1% hydroalcoholic testosterone gel in the treatment of erectile dysfunction (TADTEST Study). J Sex Med. 2011;8(1):284–93. https://doi.org/10.1111/j.1743-6109.2010.01956.x.
66. Hackett G, Cole N, Bhartia M, et al. Testosterone replacement therapy improves metabolic parameters in hypogonadal men with type 2 diabetes but not in men with coexisting depression: the BLAST study. J Sex Med. 2014;11(3):840–56. https://doi.org/10.1111/jsm.12404.
67. Hackett G, Cole N, Bhartia M, Kennedy D, Raju J, Wilkinson P, et al. The response to testosterone undecanoate in men with type 2 diabetes is dependent on achieving threshold serum levels (the BLAST study). Int J Clin Pract. 2014;68(2):203–15. https://doi.org/10.1111/ijcp.12235.
68. Man L, Li G. Low-intensity extracorporeal shock wave therapy for erectile dysfunction: a systematic review and meta-analysis. Urology. 2018;119:97–103. https://doi.org/10.1016/j.urology.2017.09.011.
69. Spivak L, Shultz T, Appel B, Verze P, Yagudaev D, Vinarov A. Low-intensity extracorporeal shockwave therapy for erectile dysfunction in diabetic patients. Sex Med Rev. 2019. https://doi.org/10.1016/j.sxmr.2019.06.007.
70. Matz EL, Terlecki R, Zhang Y, Jackson J, Atala A. Stem Cell Therapy for erectile dysfunction. Sex Med Rev. 2019;7(2):321–8. https://doi.org/10.1016/j.sxmr.2017.12.008.
71. Scott S, Roberts M, Chung E. Platelet-rich plasma and treatment of erectile dysfunction: critical review of literature and global trends in platelet-rich plasma clinics. Sex Med Rev. 2019;7(2):306–12. https://doi.org/10.1016/j.sxmr.2018.12.006.
72. SMSNA Position statement on restorative therapies for ED. http://www.smsna.org/V1/about/position-statements. Accessed December 24, 2018.
73. Singh R, Artaza JN, Taylor WE, Gonzalez-Cadavid NF, Bhasin S. Androgens stimulate myogenic differentiation and inhibit adipogenesis in C3H 10T1/2 pluripotent cells through an androgen receptor-mediated pathway. Endocrinology. 2003;144(11):5081–8. https://doi.org/10.1210/en.2003-0741.

74. Bhasin S, Storer TW, Berman N, et al. Testosterone replacement increases fat-free mass and muscle size in hypogonadal men. J Clin Endocrinol Metab. 1997;82(2):407–13. https://doi.org/10.1210/jcem.82.2.3733.
75. Wang C, Swerdloff RS, Iranmanesh A, et al. Transdermal testosterone gel improves sexual function, mood, muscle strength, and body composition parameters in hypogonadal men. J Clin Endocrinol Metab. 2000;85(8):2839–53. https://doi.org/10.1210/jcem.85.8.6747.
76. Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A, et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. Clin Endocrinol. 2005;63(3):280–93. https://doi.org/10.1111/j.1365-2265.2005.02339.x.
77.• Dhindsa S, Ghanim H, Batra M, et al. Insulin resistance and inflammation in hypogonadotropic hypogonadism and their reduction after testosterone replacement in men with type 2 diabetes. Diabetes Care. 2016;39(1):82–91. https://doi.org/10.2337/dc15-1518 **After 24 weeks of testosterone therapy, hypogonadal diabetic men had improved insulin sensitivity and body composition.**
78. Osuna JA, Gómez-Pérez R, Arata-Bellabarba G, Villaroel V. Relationship between BMI, total testosterone, sex hormone-binding-globulin, leptin, insulin and insulin resistance in obese men. Arch Androl. 2006;52(5):355–61. https://doi.org/10.1080/01485010600692017.
79. Traish AM, Saad F, Guay A. The dark side of testosterone deficiency: II. type 2 diabetes and insulin resistance. J Androl. 2008;30(1):23–32. https://doi.org/10.2164/jandrol.108.005751.
80. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the Third National Health and Nutrition Examination Survey (NHANES III). Diabetes Care. 2007;30(2):234–8. https://doi.org/10.2337/dc06-1579.
81. Sarnak MJ, Tighiouart H, Manjunath G, et al. Anemia as a risk factor for cardiovascular disease in the atherosclerosis risk in communities (aric) study. J Am Coll Cardiol. 2002;40(1):27–33. https://doi.org/10.1016/S0735-1097(02)01938-1.
82. Bhatia V, Chaudhuri A, Tomar R, Dhindsa S, Ghanim H, Dandona P. Low testosterone and high C-reactive protein concentrations predict low hematocrit in type 2 diabetes. Diabetes Care. 2006;29(10):2289–94. https://doi.org/10.2337/dc06-0637.
83. Grossmann M, Panagiotopolous S, Sharpe K, MacIsaac R, Clarke S, Zajac JD, et al. Low testosterone and anaemia in men with type 2 diabetes. Clin Endocrinol. 2009;70(4):547–53. https://doi.org/10.1111/j.1365-2265.2008.03357.x.
84. Roy CN, Snyder PJ, Stephens-Shields AJ, Artz AS, Bhasin S, Cohen HJ, et al. Association of testosterone levels with anemia in older men: a controlled clinical trial. JAMA Intern Med. 2017;177(4):480–90. https://doi.org/10.1001/jamainternmed.2016.9540.
85. Bachman E, Travison TG, Basaria S, Davda MN, Guo W, Li M, et al. Testosterone induces erythrocytosis via increased erythropoietin and suppressed hepcidin: evidence for a new erythropoietin/hemoglobin set point. J Gerontol A Biol Sci Med Sci. 2014;69(6):725–35. https://doi.org/10.1093/gerona/glt154.
86. Pastuszak AW, Kohn TP, Estis J, Lipshultz LI. Low plasma testosterone is associated with elevated cardiovascular disease biomarkers. J Sex Med. 2017;14(9):1095–103. https://doi.org/10.1016/j.jsxm.2017.06.015.
87.• Farias JM, Tinetti M, Khoury M, Umpierrez GE, et al. J Clin Endocrinol Metab. 2014;99(12):4698–703. https://doi.org/10.1210/jc.2014-2585 **In middle-aged diabetic men, low testosterone associated with increased levels of atherosclerotic disease parameters.**
88. Daka B, Langer RD, Larsson CA, Rosén T, Jansson PA, Råstam L, et al. Low concentrations of serum testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus. BMC Endocr Disord. 2015;15:35–7. https://doi.org/10.1186/s12902-015-0034-1.
89. Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab. 2008;93(1):68–75. https://doi.org/10.1210/jc.2007-1792.
90. Muraleedharan V, Marsh H, Kapoor D, Channer KS, Jones TH. Testosterone deficiency is associated with increased risk of mortality and testosterone replacement improves survival in men with type 2 diabetes. Eur J Endocrinol. 2013;169(6):725–33. https://doi.org/10.1530/EJE-13-0321.
91. Tomar R, Dhindsa S, Chaudhuri A, Mohanty P, Garg R, Dandona P. Contrasting testosterone concentrations in type 1 and type 2 diabetes. Diabetes Care. 2006;29(5):1120–2. https://doi.org/10.2337/dc06-0197.
92. Corona G, Rastrelli G, Monami M, Saad F, Luconi M, Lucchese M, et al. Body weight loss reverts obesity-associated hypogonadotropic hypogonadism: a systematic review and meta-analysis. Eur J Endocrinol. 2013;168(6):829–43. https://doi.org/10.1530/EJE-12-0955.
93. Bekaert M, Van Nieuwenhove Y, Calders P, et al. Determinants of testosterone levels in human male obesity. Endocrine. 2015;50(1):202–11. https://doi.org/10.1007/s12020-015-0563-4.
94. Mogri M, Dhindsa S, Quattrin T, Ghanim H, Dandona P. Testosterone concentrations in young pubertal and post-pubertal obese males. Clin Endocrinol. 2013;78(4):593–9. https://doi.org/10.1111/cen.12018.
95. Dhindsa S, Furlanetto R, Vora M, Ghanim H, Chaudhuri A, Dandona P. Low estradiol concentrations in men with subnormal testosterone concentrations and type 2 diabetes. Diabetes Care. 2011;34(8):1854–9. https://doi.org/10.2337/dc11-0208.
96. Tajar A, Forti G, O'Neill TW, et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab. 2010;95(4):1810–8. https://doi.org/10.1210/jc.2009-1796.
97. Esser N, Legrand-Poels S, Piette J, Scheen AJ, Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. Diabetes Res Clin Pract. 2014;105(2):141–50. https://doi.org/10.1016/j.diabres.2014.04.006.
98. Bobjer J, Katrinaki M, Tsatsanis C, Lundberg Giwercman Y, Giwercman A. Negative association between testosterone concentration and inflammatory markers in young men: a nested cross-sectional study. PLoS One. 2013;8(4):e61466. https://doi.org/10.1371/journal.pone.0061466.
99. Tsatsanis C, Dermitzaki E, Avgoustinaki P, Malliaraki N, Mytaras V, Margioris AN. The impact of adipose tissue-derived factors on the hypothalamic-pituitary-gonadal (HPG) axis. Hormones. 2015;14(4):549–62. https://doi.org/10.14310/horm.2002.1649.
100. Landry D, Cloutier F, Martin LJ. Implications of leptin in neuroendocrine regulation of male reproduction. Reprod Biol. 2013;13(1):1–14. https://doi.org/10.1016/j.repbio.2012.12.001.
101. Sáinz N, Barrenetxe J, Moreno-Aliaga MJ, Martínez JA. Leptin resistance and diet-induced obesity: central and peripheral actions of leptin. Metabolism. 2015;64(1):35–46. https://doi.org/10.1016/j.metabol.2014.10.015.
102. Brüning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, et al. Role of brain insulin receptor in control of body weight and reproduction. Science. 2000;289(5487):2122–5.
103. Salvi R, Castillo E, Voirol M-J, et al. Gonadotropin-releasing hormone-expressing neurons immortalized conditionally are activated by insulin: implication of the mitogen-activated protein kinase pathway. Endocrinology. 2006;147(2):816–26. https://doi.org/10.1210/en.2005-0728.
104. Kullmann S, Heni M, Hallschmid M, Fritsche A, Preissl H, Häring H-U. Brain insulin resistance at the crossroads of metabolic and

cognitive disorders in humans. Physiol Rev. 2016;96(4):1169–209. https://doi.org/10.1152/physrev.00032.2015.

105.•• Ghanim H, Dhindsa S, Abuaysheh S, et al. Diminished androgen and estrogen receptors and aromatase levels in hypogonadal diabetic men: reversal with testosterone. Eur J Endocrinol. 2018;178(3):277–83. https://doi.org/10.1530/EJE-17-0673 **Randomized double-blind placebo-controlled trial demonstrating that hypogonadal diabetics have decreased aromatase, androgen receptor, and estrogen receptor expression rather than the hypothesized compensatory increased expression. This was reversed with testosterone therapy.**

106. Mulhall JP, Trost LW, Brannigan RE, et al. Evaluation and management of testosterone deficiency: AUA guideline. J Urol. 2018;200(2):423–32. https://doi.org/10.1016/j.juro.2018.03.115.

107. Dean JD, McMahon CG, Guay AT, Morgentaler A, Althof SE, Becher EF, et al. The International Society for Sexual Medicine's process of care for the assessment and management of testosterone deficiency in adult men. J Sex Med. 2015;12(8):1660–86. https://doi.org/10.1111/jsm.12952.

108.• Hackett G, Heald AH, Sinclair A, Jones PW, Strange RC, Ramachandran S. Serum testosterone, testosterone replacement therapy and all-cause mortality in men with type 2 diabetes: retrospective consideration of the impact of PDE5 inhibitors and statins. Int J Clin Pract. 2016;70(3):244–53. https://doi.org/10.1111/ijcp.12779 **Retrospective analysis demonstrating that testosterone therapy was independently associated with decreased mortality in diabetic men. In addition, PDE5i usage was independently associated with reduced mortality regardless of testosterone therapy usage.**

109.•• Hackett G, Cole N, Mulay A, Strange RC, Ramachandran S. Long-term testosterone therapy in type 2 diabetes is associated with reduced mortality without improvement in conventional cardiovascular risk factors. BJU Int. 2019;123(3):519–29. https://doi.org/10.1111/bju.14536 **Analysis of men in the BLAST trial demonstrating that long-term testosterone therapy in men with DM2 associated with reduced mortality unrelated to improvement in traditional CVD risk factors.**

110. Contraceptive efficacy of testosterone-induced azoospermia in normal men. World Health Organization Task Force on methods for the regulation of male fertility. Lancet Lond Engl. 1990;336(8721):955–9.

111. Gui Y-L, He C-H, Amory JK, et al. Male hormonal contraception: suppression of spermatogenesis by injectable testosterone undecanoate alone or with levonorgestrel implants in chinese men. J Androl. 2004;25(5):720–7.

112. McBride JA, Coward RM. Recovery of spermatogenesis following testosterone replacement therapy or anabolic-androgenic steroid use. Asian J Androl. 2016;18(3):373–80. https://doi.org/10.4103/1008-682X.173938.

113. Wenker EP, Dupree JM, Langille GM, et al. The use of HCG-based combination therapy for recovery of spermatogenesis after testosterone use. J Sex Med. 2015;12(6):1334–7. https://doi.org/10.1111/jsm.12890.

114. Wheeler KM, Smith RP, Kumar RA, Setia S, Costabile RA, Kavoussi PK. A comparison of secondary polycythemia in hypogonadal men treated with clomiphene citrate versus testosterone replacement: a multi-institutional study. J Urol. 2017;197(4):1127–31. https://doi.org/10.1016/j.juro.2016.10.068.

115. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Effects of testosterone treatment in older men. N Engl J Med. 2016;374(7):611–24. https://doi.org/10.1056/NEJMoa1506119.

116. Snyder PJ, Bhasin S, Cunningham GR, Matsumoto AM, Stephens-Shields AJ, Cauley JA, et al. Lessons from the testosterone trials. Endocr Rev. 2018;39(3):369–86. https://doi.org/10.1210/er.2017-00234.

117. Morgentaler A, Miner MM, Caliber M, Guay AT, Khera M, Traish AM. Testosterone therapy and cardiovascular risk: advances and controversies. Mayo Clin Proc. 2015;90(2):224–51. https://doi.org/10.1016/j.mayocp.2014.10.011.

118. Sharma R, Oni OA, Chen G, Sharma M, Dawn B, Sharma R, et al. Association between testosterone replacement therapy and the incidence of DVT and pulmonary embolism: a retrospective cohort study of the Veterans Administration Database. Chest. 2016;150(3):563–71. https://doi.org/10.1016/j.chest.2016.05.007.

119. Kavoussi PK, Machen GL, Wenzel JL, Ellis AM, Kavoussi M, Kavoussi KM, et al. Medical treatments for hypogonadism do not significantly increase the risk of deep vein thrombosis over general population risk. Urology. 2019;124:127–30. https://doi.org/10.1016/j.urology.2018.11.009.

120. Bhasin S, Brito JP, Cunningham GR, Hayes FJ, Hodis HN, Matsumoto AM, et al. Testosterone therapy in men with hypogonadism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2018;103(5):1715–44. https://doi.org/10.1210/jc.2018-00229.

121. Tatem AJ, Beilan J, Kovac JR, Lipshultz LI. Management of anabolic steroid-induced infertility: novel strategies for fertility maintenance and recovery. World J Mens Health. 2019. https://doi.org/10.5534/wjmh.190002.

122. Pelusi C, Giagulli VA, Baccini M, Fanelli F, Mezzullo M, Fazzini A, et al. Clomiphene citrate effect in obese men with low serum testosterone treated with metformin due to dysmetabolic disorders: a randomized, double-blind, placebo-controlled study. PLoS One. 2017;12(9):e0183369. https://doi.org/10.1371/journal.pone.0183369.

123. Scovell JM, Khera M. Testosterone replacement therapy versus clomiphene citrate in the young hypogonadal male. Eur Urol Focus. 2018;4(3):321–3. https://doi.org/10.1016/j.euf.2018.07.033.

124. Dadhich P, Ramasamy R, Scovell J, Wilken N, Lipshultz L. Testosterone versus clomiphene citrate in managing symptoms of hypogonadism in men. Indian J Urol IJU J Urol Soc India. 2017;33(3):236–40. https://doi.org/10.4103/iju.IJU_372_16.

125. Habous M, Giona S, Tealab A, Aziz M, Williamson B, Nassar M, et al. Clomiphene citrate and human chorionic gonadotropin are both effective in restoring testosterone in hypogonadism: a short-course randomized study. BJU Int. 2018;122(5):889–97. https://doi.org/10.1111/bju.14401.

126. Raman JD, Schlegel PN. Aromatase inhibitors for male infertility. J Urol. 2002;167(2 Pt 1):624–9.