REVIEW

Type 2 Diabetes Mellitus and Erectile Dysfunction

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A B S T R A C T

Introduction. Diabetes mellitus (DM) is a major risk factor for the development of erectile dysfunction (ED). Although most diabetic ED cases are in patients with type 2 diabetes (T2DM), the majority of basic science studies examining mechanisms of diabetic ED have been conducted in animal models of type 1 diabetes.
Aim. Recently, however, clinical and laboratory-based studies have uncovered some key underlying factors of T2DM-associated ED, which we have compiled in this review of T2DM ED.
Main Outcome Measures. The outcomes discussed in this review include major mechanisms underlying T2DM, discussing both clinical and basic science studies.
Methods. We conducted an extensive search of pertinent clinical and basic science literature using PUBMED.
Results. Mechanisms causing ED in T2DM are multifactorial and often lead to resistance to current therapy. Systemic effects of hyperglycemia and hypogonadism contribute to the development of impaired vasodilatory signaling, smooth muscle cell hypercontractility, and veno-occlusive disorder in T2DM ED.
Conclusions. Understanding the different causes for ED in T2DM patients may allow targeted therapy for improved erectile function. **Hidalgo-Tamola J, and Chitaley K. Type 2 diabetes mellitus and erectile dysfunction. J Sex Med 2009;6:916–926.**

Key Words. Erectile Dysfunction; Type 2 Diabetes Mellitus; Endothelial Dysfunction; Oxidative Stress; Neuropathy; Smooth Muscle Dysfunction; Hypogonadism; Epidemiology; Diabetes

Introduction

Erectile dysfunction (ED) affects 30 million men in the United States [1]. Diabetes mellitus (DM) is a significant risk factor for the development of ED. According to the Massachusetts Male Aging Study, men with diabetes have a 28% prevalence of ED compared with 9.6% in the general population [2]. Diabetics have a 75% lifetime risk of developing ED and earlier onset of ED compared with nondiabetics [3,4].

With the advent of new pharmacological treatments for ED such as phosphodiesterase 5 inhibitors (PDE5), men are more likely to seek treatment. In 2002, Viagra use increased from 1.5% to 2.9% in 1998. If all men with ED were to seek treatment, the cost would reach a staggering $15 billion [5]. However, certain subsets of

patients with ED respond poorly to PDE5 such as patients with type 2 diabetes mellitus (T2DM). Compared with 87% response in normal patients, only 56% of T2DM patients respond to PDE5 [6]. Furthermore, Penson et al. showed that although T2DM patients initially respond to pharmacological treatments, the effects are not sustainable over time. After 12 months of ED treatment, mean International Index of Erectile Function (IIEF) scores for T2DM patients reverted to baseline values [7].

Although type 1 (T1DM) and T2DM both entail abnormal carbohydrate metabolism and hyperglycemia, these diseases differ in many characteristics including insulin and body mass index (BMI) status as well as cytokine and lipid profiles. Further, T2DM is responsible for 90–95% of cases of diabetes and occurs in the setting of insulin

resistance and obesity [8]. Despite this knowledge, clinical and epidemiology studies seldom separate T1DM and T2DM, and the vast majority of basic science studies examining mechanisms of diabetic ED utilize animal models of T1DM. Despite the rising cases of T2DM ED, no comprehensive review specific to ED in this context has been written. This review particularly discusses findings from clinical and basic science studies, which have begun to shed light on mechanisms underlying ED associated explicitly with T2DM.

Erectile Physiology

Sexual stimulation leads to the release of nitric oxide (NO) from non-adrenergic non-cholinergic (NANC) nerves through activation of neuronal nitric oxide synthase (nNOS) [9,10]. Binding of NO to soluble guanylate cyclase increases cyclic guanosine monophosphate (cGMP) levels and cGMP-dependent protein kinase activity, leading to smooth muscle cell (SMC) relaxation and cavernosal dilation [11]. Subsequent hemodynamic changes such as increased arteriolar shear flow stimulate the phosphatidylinositol-3-kinase/protein kinase B (Akt) pathway leading to activation of endothelial nitric oxide synthase (eNOS) in penile endothelium and further NO release [12–14]. Occlusion of venous outflow is also required for sinusoidal filling and the maintenance of high intracavernosal pressure and erection. This venous occlusion is achieved by the compression of the emissary veins that lie between the tunica albuginea and the expanding sinusoidal tissue.

In the absence of sexual stimulation, the penis is maintained in a flaccid state by continuous smooth muscle tone. Sympathetic innervation to the penis leads to the release of norepinephrine and activation of α-adrenergic receptors on SMC in the cavernosum [9,15,16]. An increase in intracellular calcium activates myosin light chain (MLC) kinase and phosphorylation of MLC to generate SMC contraction. Additional pathways such as RhoA/Rho-kinase lead to the sensitization of the SMC contractile apparatus to calcium, promoting contraction. Activation of Rho-kinase results in inhibition of MLC phosphatase and continued expression of phosphorylated MLC [17]. Data have shown that RhoA/Rho-kinase pathway is a predominant calcium-sensitizing pathway to mediate continuous smooth muscle tone in the penis. Protein kinase C (PKC) is also calcium sensitizing and acts to inhibit MLC phosphatase, also promoting the contractile response [18].

T2DM Animal Models Used to Study ED

In contrast to T1DM ED, less than 10 basic science studies examining the mechanisms of ED have been published utilizing animal models of T2DM. The obese diabetic Zucker rat (ZDF) is a model for T2DM with glucose intolerance and an autosomal recessive mutation in the leptin gene. It develops hyperinsulinemia, insulin resistance, and hyperlipidemia at an early age with progression to proteinuria and glomerular injury [19]. Similar characteristics exist between the ZDF rat and patients with T2DM including obesity, hypertension, and impaired vasodilation. The BBZ/WOR rat is a cross between the BB/WOR rat—a model for autoimmune diabetes—and a Zucker rat. Obese BBZ/WOR rats develop insulin resistance, are hyperinsulinemic, develop hyperglycemia earlier with higher mean serum glucose levels compared with lean T1DM rats [20,21]. Otsuka Long-Evans Tokushima Fatty (OLETF) rats are spontaneously diabetic rats developed by selective breeding. Male rats exhibit late onset of hyperglycemia, hypercholesterolemia, and mild obesity. Changes within the pancreatic islet cells mirror changes in humans with T2DM [22].

Recently, mouse models of T2DM have been utilized to study ED. The high-fat diet fed mouse model was first described by Surwit et al. and was used for a model of ED by Xie et al. [23,24]. C57BL6 mice were fed a high-fat, high-simple carbohydrate, and low-fiber diet for 22 weeks, and developed obesity with a mean body weight of 39 g, and developed diabetes with a mean fasting serum glucose of 223.6 mg/dL. An additional mouse model of T2DM is the *db/db* mouse [25]. The *db/db* mouse has a mutation in the leptin receptor, and develops spontaneous obesity, hyperglycemia, hyperphagia, hyperinsulinemia, and diabetic neuropathy, occurring from 10 days to 8 weeks of age.

Other animal models of T2DM and insulin resistance exist but have not been used to date to study mechanisms of T2DM ED. Spontaneous diabetic animal models have single or multiple gene mutations, predisposing them to develop T2DM and to occur in both obese and non-obese animals. Some examples of obese diabetic animal models include the *ob/ob* mouse (leptin-deficient), Tsumara Suzuki Obese Diabetes mouse, KK mouse, the New Zealand obese mouse, and the obese rhesus monkey. Spontaneous non-obese T2DM animal models include the Cohen diabetic rat, GK rat, Torri rat, and Akita mouse. T2DM
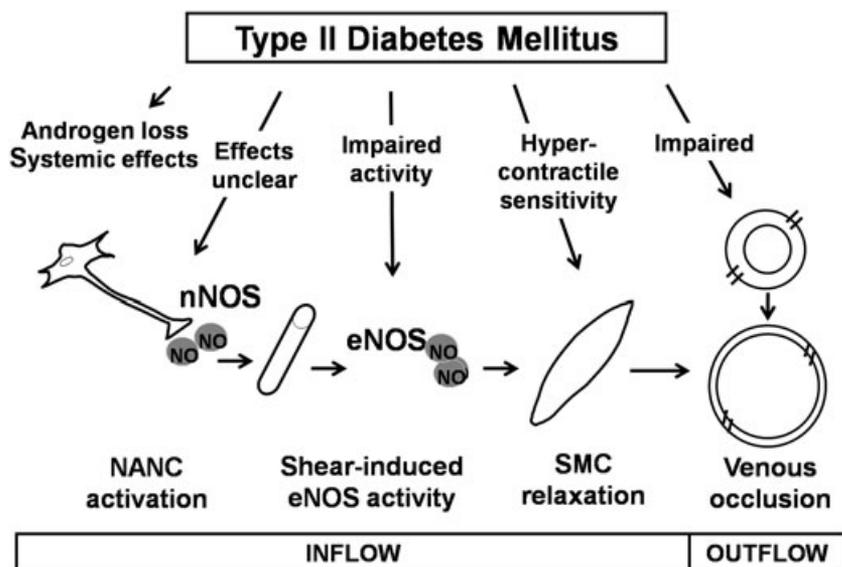
Figure 1 Mechanisms of Type II Diabetes-Associated Erectile Dysfunction. NANC = Non-adrenergic non-cholinergic nerves; nNOS = neuronal nitric oxide synthase; eNOS = endothelial nitric oxide synthase; SMC = smooth muscle cell.

can also be induced in certain animal models with diet such as the sand rat (*Psammomys obesus*) [26]. Future studies utilizing these additional valid animal models of T2DM in the study of ED should enhance our understanding of this pathologic disease complication.

Findings gained from the study of some of these T2DM animal models have shed light on mechanisms underlying the cause of T2DM ED. These factors include impaired vasodilatory signaling, cavernosal hypercontractility, and veno-occlusion, and will be discussed in more detail in the remainder of this review (Figure 1).

Impaired Vasodilatory Signaling

In the context of ED, impaired vasodilatory signaling often results from NANC nerve dysfunction and/or endothelial dysfunction. NO release from nNOS activation at NANC nerve terminals initiates the vasodilatory response. Maintenance of cavernosal vasodilation has been hypothesized to occur through the activation of eNOS in endothelial cells, presumably in response to shear stress. De Angelis et al. performed an age-matched case controlled study of 30 T2DM ED patients and found impaired cavernosal vasodilation in T2DM ED [27]. Injections of L-arginine (a known precursor to NO) were used to evaluate endothelial function. When injected, L-arginine normally leads to vasodilation and blood pressure changes, as well as antiplatelet activity. T2DM patients exhibited a reduced response to the L-arginine test, suggesting abnormalities in vasodilation such

as impaired nNOS activity or downstream endothelial dysfunction. This study, however, cannot rule out the possibility of attenuated downstream dilator signaling in the SMC as a cause for the impaired vasodilation seen with L-arginine.

Data from animal models of T2DM support these findings of impaired vasodilation in T2DM humans. Accompanying the impaired vasodilatory response, total penile NOS activity was found to be decreased in the BBZ/WOR rat model [21]. Gonzalez-Cadavid and colleagues showed that the BBZ/WOR rats had a 55% decrease in total NOS expression in penile cytosol compared with nondiabetic mice. Outlined below are studies examining specific mechanisms for cavernosal vasodilatory impairment in T2DM.

NANC Dysfunction

Decreased nNOS activity and expression from NANC dysfunction can contribute to the physiological alteration in corporal relaxation. Although NANC dysfunction is established to play a key underlying role in T1DM ED, the contribution of impaired nerve signaling to ED in the context of T2DM is unclear. In the BBZ/WOR mice, T2DM penile tissue demonstrate decreased soluble nNOS content; however, the difference compared with control mice was not statistically significant [21]. In contrast, OLETF rats showed decreased immunofluorescent staining for nNOS in dorsal nerves compared with controls, and showed 40% decrease in nNOS protein expression. Xie et al. evaluated total NOS activity in

high-fat diet mice using nicotinamide adenine dinucleotide (NADPH)-diaphorase staining of corporal tissue [24]. NADPH-diaphorase specifically stains NOS activity in penile nerve fibers and is an indicator for nNOS expression. Compared with control mice, the high-fat diet fed mice demonstrated decreased nNOS expression. In vitro myography studies with the *db/db* mice provide some support for the notion of NANC dysfunction, showing significantly decreased electrical field stimulation (EFS)-induced relaxation of cavernosum in the presence of bretylium tonsylate, a norepinephrine reuptake inhibitor. However, the extent of the impaired dilation response was strikingly small and the true pathophysiologic relevance of this dysfunction to the ED phenotype is unclear. Impairment in activation of vasoreactive signaling may also result from disorders with the endothelium. Indeed, studies suggest that endothelial dysfunction may play a significant role in T2DM ED.

Endothelial Dysfunction

Clinical- and laboratory-based studies demonstrate endothelial dysfunction as an important mechanism for the development of T2DM ED. Endothelial dysfunction is most often described as a decrease in NO bioavailability resulting from decreased eNOS expression or activity, or increased NO scavenging. Impaired endothelium-dependent vasoreactivity is demonstrated in several animal modes of T2DM. In vitro myography studies from both high-fat fed diet mice, *db/db* mice, and ZDF rats have demonstrated reduced muscle relaxation of cavernosal tissue to endothelium-dependent dilation with acetylcholine [24,28,29]. Jesmin et al. observed decreased eNOS immunofluorescent staining and protein expression in penile tissues of OLETF rats compared with controls [30]. A corresponding decrease in eNOS mRNA expression suggests that reduced eNOS expression begins at the transcriptional level.

Impaired eNOS activation is another mechanism that contributes to a decreased NO bioavailability. Activation of eNOS can occur through phosphorylation at Ser-1177 by serine-threonine protein kinase Akt [13]. The Akt-dependent pathway mediates both shear stress and vascular endothelial growth factor (VEGF) phosphorylation of eNOS [31]. Effects of VEGF include endothelial cell proliferation, migration, angiogenesis, and anti-apoptosis. VEGF increases eNOS phosphorylation and expression of anti-apoptotic proteins. The OLETF rat model showed decreased VEGF expression and mRNA transcription in penile tissues [30]. Diminished eNOS expression in the OLETF rats were found, corresponding to decreased VEGF expression. In addition to decreased eNOS activity, increased NO scavenging by free radicals and oxidants has been shown to play a role in cavernosal endothelial dysfunction in T2DM models of ED.

Oxidative Stress

Chronic hyperglycemia leads to inflammation and contributes to the formation of reactive oxygen species (ROS), resulting in increased NO scavenging. Inflammation and ROS are linked to the development of endothelial dysfunction in both atherosclerosis and diabetes. ROS are produced in aerobic metabolism through the single electron reduction of oxygen and are balanced by antioxidants that scavenge ROS. Elevated oxidative stress is a pathological state that results from the imbalance in favor of ROS, leading to detrimental effects on cellular and tissue function. Chronic hyperglycemia induces free radical production through formation of advance glycation end-products (AGE), lipid peroxidation, polyol pathway activation, superoxide production, and activation of protein kinase C [32]. Interaction between AGE and endothelial cells up-regulates adhesion molecules that mediate vascular damage. AGE also stimulates cytokine expression on monocytes and macrophages [33].

Increased oxidative activity and expression of inflammatory markers are seen in patients with T2DM ED. Circulating monocyte activity and expressions of inflammatory markers such as endothelin-1 (ET-1) and intracellular adhesion molecule-1 (ICAM-1) are used as markers for ROS and inflammation. Morano et al. evaluated circulating monocytes in T2DM patients with and without ED and without prior history of cardiovascular disease. Circulating monocytes showed increased oxidative activity in patients with T2DM ED compared with T2DM without ED. Circulating levels of ET-1 and ICAM-1 negatively correlated with IIEF scores [34]. Increased circulating monocyte activity supports the evidence that early endothelial damage may be present in T2DM patients with ED even before the development of cardiovascular disease.

Reduced levels of antioxidants may also contribute to elevated ROS and oxidative stress in

T2DM patients. Glutathione (GSH) is an important cell antioxidant that acts as an electron donor to reduce ROS and acts as a cofactor for NO synthesis from L-arginine. Depressed GSH levels contribute to decreased NO synthesis. Hyperglycemic states also deplete the NADPH necessary for GSH regeneration, leading to increased oxidative stress. Tagliabue et al. found that T2DM ED patients exhibited lower GSH red blood cell concentration compared with nondiabetic ED patients [35]. Furthermore, GSH levels in T2DM ED were even lower compared with controls without ED or T2DM. Negative correlation was seen between GSH levels and fasting glucose concentration and DM duration.

Elevated plasma homocysteine levels are also thought to contribute to the development of T2DM ED. Elevations in plasma homocysteine has been identified to be an independent predictor of cardiovascular disease and confers a 1.9-fold risk of death in men with T2DM [36]. Multiple mechanisms lead to homocysteine-induced vascular injury such as direct endothelial damage, impaired nitric oxide production, free radical formation, and platelet activation [37]. Hyperhomocysteinemia is associated with increased superoxide production. Mutations in the methylenetetrahydrofolate reductase (MTHFR) gene cause increases in the plasma levels of homocysteine by approximately 20%. In this population, lowering of homocysteine levels by 3 μmol/L decreases the risk of developing ischemic heart disease by 16% [38]. Using penile ultrasound Doppler evaluation, Demir et al. found that elevated homocysteine levels negatively correlate with peak systolic velocity [39]. Al-Hunayan and colleagues confirmed that mean plasma total homocysteine levels were statistically higher in patients with T2DM ED compared with nondiabetics with ED. T2DM ED men had an increased incidence of hyperhomocysteinemia leading to a 5.8-fold increased risk of developing ED [40,41]. The exact mechanism in which hyperhomocysteinemia contributes to ED is unclear but appears to involve oxidative stress and superoxide formation.

A small randomized controlled trial evaluated the effects of combined antioxidant and sildenafil treatment for patients with T2DM ED. Propionyl L-carnitine (PLC) is an intracellular superoxide scavenger, shown to have beneficial effects in decreasing diabetic complications and improving vascular function [42]. Morano et al. randomized 32 men with T2DM and ED to oral PLC alone, PLC plus sildenafil, sildenafil alone, or placebo

in a double-blinded study for 12 weeks. Markers of ROS and inflammation, such as circulating monocyte activity, ICAM, and P-selectin levels, decreased in patients treated with sildenafil and PLC compared with sildenafil alone, PLC only, or placebo [43]. For PDE5 nonresponders, this study suggests that combined PDE5 and antioxidant treatment can provide an added benefit. Several limitations exist in this study including small sample sizes, use of IIEF to assess improvement in erectile function, and variability in baseline values in the groups.

Experiments with the ZDF rats support evidence from clinical studies regarding the role of elevated oxidative stress in T2DM ED. GSH/ glutathione disulphide (GSSH) ratio estimates oxidative stress levels. Low-dose pioglitazone treatment for 22 weeks decreased markers of oxidative stress in ZDF rats [44]. Peroxisome proliferator-activated receptor γ (PPARγ) agonists, such as pioglitazone, are oral hypoglycemic agents with anti-inflammatory effects. PPARγ is expressed in vascular and endothelial cells, and PPARγ agonists have been shown to decrease the risk of adverse cardiovascular events [45]. After 22 weeks of treatment, the GSH/GSSH ratio improved compared with pretreatment dose, but did not normalize to control values.

It is apparent that cavernosal vasodilatory dysfunction may thus occur through impairments in endothelial function as well as heightened oxidative stress (and perhaps less so due to abnormal NANC signaling). These vasodilatory impairments may also occur in combination with heightened cavernosal contractile sensitivity. Together, these result in impaired inflow of blood into the penis, preventing the initiation of erection.

Cavernosal Hypercontractility

Cavernosal hypercontractility may occur from exacerbated sympathetic activity and/or heightened smooth muscle signaling. The role of cavernosal SMC hypercontractility in T2DM ED is difficult to discern from clinical studies, as most studies combine both T1DM and T2DM patients into one cohort. However, several animal studies have suggested the importance of hypercontractility in T2DM ED. Hyperinsulinemia and insulin resistance is associated with sympathetic nervous system overactivity, which leads to increased smooth muscle tone and the maintenance of the penis in a flaccid state. Carneiro et al. evaluated the role of sympathetic overactiv-

ity in T2DM ED [46]. Contractility of *db/db* mouse penile tissue was measured in response to EFS with the addition of inhibitors of NANC and parasympathetic nerves or to phenylephrine (PE). Heightened contractility was measured in the *db/db* mouse in response to EFS but not PE, thus suggesting sympathetic overactivity as the cause. However, in vitro vasoreactivity studies in the *db/db* mice from our lab showed enhanced penile contraction with both PE and EFS when normalized to penile weight. Thus, it is unclear if sympathetic overactivity only causes increased contractility or if downstream smooth muscle signaling pathways play a predominant role.

Use of the ZDF rat model elucidates the role of enhanced smooth muscle tone in T2DM ED. Wingard et al. evaluated force generation of rat penile tissue in the presence of inhibitors of the Rho-kinase and PKC pathways of smooth muscle contraction [29]. Elevated force generation was seen in the ZDF rats compared with controls in response to PE and ET-1. Presence of PKC inhibitor, chelerythrine, resulted in a significant decrease in force generation from corporal tissue in response to PE and ET-1. Results from the ZDF rat model suggest that augmented smooth muscle tone is mediated by PKC and RhoA/Rho-kinase.

Other modulators of SMC tone may have a role in T2DM ED. Elevated levels of angiotensin II were expressed in the cavernosal tissue of T1DM rats and ED reversed after treatment with angiotensin II receptor blockers [47]; however, evidence supporting the importance of this pathway in T2DM models is lacking.

In addition to mechanisms of impaired vasodilatory stimulus and heightened cavernosal contractility limiting penile blood inflow, the inability to limit the outflow of blood because of a veno-occlusive disorder may also underlie ED in T2DM.

Veno-Occlusive Dysfunction

Compression of the emissary veins against the tunica albuginea prevents outflow of blood from the corpora cavernosa. No clinical studies address the role of veno-occlusion solely with T2DM ED. However, two studies separate T1DM from T2DM into two cohorts and evaluate the role of veno-occlusive dysfunction, which is defined as end diastolic velocity greater than 5 cm/s and peak systolic velocity greater than 35 cm/s on penile Doppler studies. Colakoglu et al. used penile Doppler studies and pharmacocavernosometry to determine the role of venous leakage in 26 T2DM and 8 T1DM men. Pharmacocavernosometry was performed with a continuous infusion of heparinized saline to achieve an intracavernosal pressure (ICP) of 150 mmHg. Maintenance of ICP with an infusion <30 mL/min was considered normal. Evidence of venous leakage was found in 67% of diabetic patients [48]. Another study from Broderick and colleagues using penile Doppler studies demonstrated veno-occlusive disease in 39% of the T2DM patients [49].

Evidence from animal studies have further defined the importance of veno-occlusive dysfunction in the development of T2DM ED. Kovanecz et al. performed an in vivo veno-occlusive study in ZDF rats consisting of intracavernosal saline infusion and ICP monitoring [44]. The study showed an inability to sustain an adequate ICP after cessation of penile saline infusion, suggesting veno-occlusive dysfunction. Using the *db/db* mouse model, we recently showed an inability to sustain maximal ICP in response to electrical stimulation and increased time to reach maximal ICP with electrical stimulation [28]. Impaired veno-occlusion in T2DM rats appeared to improve with prolonged treatment of PPARγ. Nine-week treatment of the ZDF rats with high dose pioglitazone showed maintenance of ICP and improved veno-occlusion [44].

Impaired veno-occlusion could be caused by changes in structure, cell and/or matrix content. VEGF expression has widespread implications in penile structure resulting from changes in rates of apoptosis. Decreased VEGF expression correlates with elevated levels of pro-apoptotic proteins such as caspase-3 and decreased expression of anti-apoptotic proteins such as Bcl-2. This suggests that decreased VEGF in T2DM penile tissue results in increased apoptosis and loss of erectile cells [30]. The high-fat fed diet mouse model of T2DM manifests increased apoptosis in the cavernosal tissue. This is accompanied by decreased endothelial cell content and decreased smooth muscle cell/collagen ratio [24].

Previous studies with T2DM animal models demonstrated altered collagen expression and smooth muscle/collagen ratio in penile cavernosal tissue [24,28,44]. We previously found elastin, an extracellular matrix component in sinusoids and the tunica albuginea, to be decreased in the cavernosum of *db/db* mice. Specifically decreased expression of tropoelastin mRNA, a precursor of elastin, and fibrillin-1, a scaffold protein, was

seen as well in the *db/db* mouse compared with control mice [28]. These structural alterations in the tunica albuginea caused by T2DM may lead to an altered distensibility of the corpora required for veno-occlusion and maintenance of ICP.

Hypogonadism

Androgen deficiency can also contribute to the pathogenesis of T2DM ED. Well-known sexual symptoms of androgen deficiency and hypogonadism include decreased sexual desire and ED. Hypogonadism also promotes insulin resistance and places patients at higher risk for cardiovascular events [50]. Corona et al. showed that patients with ED and T2DM have a higher prevalence of hypogonadism [51]. T2DM ED patients demonstrated a decreased amount of total testosterone (TT) and free testosterone (FT) compared with nondiabetics despite adjusting for age. A second study demonstrated a significant association between low TT levels and poor diabetic control [52]. Thirty seven percent of T2DM patients with hemoglobin A1c (HbA1c) greater than 7% had TT levels less than 2.8 ng/mL vs. 22% of patients with normal TT. Low TT was correlated with worsening ED. Fifty six percent of patients with low TT complained of severe ED compared with only 27% of patients with normal TT. FT and bioavailable testosterone levels were found to be decreased in men with T2DM ED. Sixty to 80% of TT is bound to a sex hormone-binding globulin (SHBG) and is considered inactive. The remaining fraction exists as either FT or bioavailable testosterone which is bound to albumin. Kapoor et al. found that mean FT levels were 0.262 nmol/L in T2DM ED patients compared with 0.303 nmol/L in T2DM patients without ED [53]. Mean bioavailable testosterone was 3.83 nmol/L in T2DM ED vs. 4.46 nmol/L in non-ED patients. These studies were duplicated in the BBZ/WOR T2DM rat model, which showed 75% decreased serum testosterone levels in T2DM rats with impaired erections.

General obesity and visceral adiposity, common to T2DM, is associated with hypogonadism in two main ways. Visceral adipose tissue leads to an increased conversion of androgens to estrogens, leading to decreased testosterone levels. Aromatase is an enzyme elevated in adipose tissue and participates in the conversion of testosterone to estradiol. Various studies have shown an association between elevated BMI or waist circumference

and hypogonadism in patients with T2DM ED [52,54]. Maggi and colleagues found a significant association between elevated waist circumference and hypogonadism in T2DM ED patients after adjusting for age [54]. El-Sakka et al. found elevated mean BMI (31.3 ± 3.9 vs. 28.9 ± 3.4) in patients with low testosterone levels [52]. Increased visceral adipose tissue is associated with decreased SHBG. Decreased SHBG contributes to decreased TT levels in T2DM ED patients [53].

Hypogonadism may also be associated with other components of the metabolic syndrome such as increased triglyceride levels and lower HDL. The metabolic syndrome is a collection of cardiovascular risk factors including obesity, diabetes and hyperlipidemia, which predispose patients to cardiovascular events. Hypogonadal T2DM ED patients are found to have elevated triglycerides and lower high-density lipoprotein (HDL) cholesterol levels [51]. Another study looked specifically at the association between metabolic syndrome and T2DM ED and demonstrated that ED patients with metabolic syndrome and T2DM had a higher prevalence of hypogonadism. Specifically, a significant association was seen in patients with elevated triglycerides [54]. Because hypogonadism plays an important role in T2DM, the use of testosterone supplementation has been suggested as part of the treatment regimen.

Combination therapy with testosterone and sildenafil improves erectile function in T2DM patients. PDE5 inhibitor function requires the presence of testosterone. Studies from castrated rats demonstrate depressed erectile function, which improved with testosterone replacement. In addition, castrated mice did not respond to PDE5 treatment but erectile function improved to normal uncastrated levels with the combination of testosterone and sildenafil [55]. Kalinchenko et al. studied T2DM ED patients and evaluated their response to a combination of therapy of oral testosterone undeconate and sildenafil [56]. All the T2DM ED patients were prior sildenafil non-responders. With the combination of sildenafil and oral testosterone, all patients reported increased libido and 70% reported restored sexual function. Interestingly, discontinuation of the oral testosterone treatment resulted in recurrence of ED after 2 weeks. Although oral testosterone is not available in the United States, this study suggests that other forms of testosterone can produce similar effects in this population.

Relationship between T2DM ED and Cardiovascular Disease

Glycemic control correlates with the development of ED, ED severity, and other DM complications. It is established that tight glycemic control decreases the progression of diabetic complications. In T2DM patients, a 1% decrease in HbA1c corresponded to a 37% decrease in microvascular complications and a 21% decrease in diabetes-related death [57]. Severity of ED is inversely associated with glycemic control. In a population of T2DM men with ED, mean IIEF scores worsened with increasing HbA1c, even after adjusting for peripheral neuropathy [58]. A prospective study by Yaman et al. looked at the effect of glucose control on IIEF scores and nocturnal penile tumescence. It showed improved HbA1c and fasting plasma glucose with the tight control, but showed no effect on nocturnal penile tumescence or IIEF scores [59]. This study suggests that damage caused by hyperglycemia has lasting effects that cannot be reversed by glycemic control. T2DM occurs in the setting of other comorbidities that compound the effects of hyperglycemia.

T2DM is closely associated with other cardiovascular risk factors such as obesity, hypertension, and hyperlipidemia. In the setting of T2DM and known coronary artery disease, ED is a powerful predictor for the development of major adverse cardiovascular events. A study by Garraruso et al. showed that patients with ED were twice as likely to develop major adverse cardiac events compared with patients without ED. (Hazard raio [HR] 2.1, 95% confidence interval [CI] 1.6–2.6, $P < 0.001$) [60]. Ma et al. further supported this cardiovascular risk association by demonstrating that T2DM ED is an independent risk factor for new onset of cardiovascular disease. (HR 1.58, 95% CI 1.08–2.30, $P = 0.018$) [61]. These findings argue that physicians should actively screen diabetic patients for silent coronary artery disease if they present with ED [62].

Conclusion

This review comprehensively outlines mechanisms contributing to the pathogenesis of T2DM ED. Characteristics of T1DM and T2DM differ and mechanisms that prevail in T1DM ED are not necessarily translatable to T2DM ED. Although endothelial dysfunction and oxidative stress are common factors in T1DM and T2DM, the role of NANC dysfunction in T2DM ED is still debated. Androgen deprivation and veno-occlusive disorder, however, may play a larger part in T2DM ED. T2DM is associated with components of the metabolic syndrome, proving a unique environment in which ED develops.

Several avenues for treating ED are necessary, as T2DM patients respond poorly to PDE5 inhibitors. Combination therapies with PDE5 inhibitors and antioxidants or androgen replacement appear promising. However, larger, randomized controlled trials are necessary to determine their efficacy. More clinical and basic science studies focusing on T2DM ED are essential, in order to understand the different mechanisms that specifically underlie ED in this cohort, and to develop targeted therapy for treatment.

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Conflict of Interest: None.

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