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2018 Clinical Practice Guidelines

Sexual Dysfunction and Hypogonadism in Men With Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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KEY MESSAGES REGARDING SEXUAL DYSFUNCTION IN MEN WITH DIABETES

- Erectile dysfunction affects approximately 34% to 45% of adult men with diabetes. It has been demonstrated to negatively impact quality of life among those affected across all age strata and may be an early clinical indication of cardiovascular disease.
- All adult men with diabetes should be regularly screened for erectile dysfunction with a sexual function history.
- The current mainstay of therapy for erectile dysfunction is phosphodiesterase type 5 inhibitors. They have been shown to have major impacts on erectile function and quality of life, with a low reported side effect profile, and should be offered as first-line therapy to men with diabetes wishing treatment for erectile dysfunction.

KEY MESSAGES REGARDING HYPOGONADISM IN MEN WITH DIABETES

- Hypogonadotropic hypogonadism is common in men with type 2 diabetes, with a prevalence of up to 40%.
- Hypogonadal men with diabetes have a higher risk for cardiovascular mortality than eugonadal men with diabetes.
- Screening for symptomatic hypogonadism in men with type 2 diabetes is recommended.
- Evidence is conflicted as to whether treatment of hypogonadism in men with diabetes can increase quality of life, improve body composition, weight loss and glycemic control.
- Observational studies assessing the impact of testosterone use on cardiovascular health in hypogonadal men have produced mixed results. Randomized, placebo-controlled studies have been too small or short in duration to adequately answer this question.

KEY MESSAGES FOR MEN WITH DIABETES

- Low testosterone is common in men with type 2 diabetes.
- Symptoms of low testosterone can include: diminished interest in sex, erectile dysfunction, reduced lean body mass, depressed mood and lack of energy.
- If you are experiencing symptoms of low testosterone, you should talk with your health-care provider.

Erectile Dysfunction

Erectile dysfunction (ED) affects approximately 34% to 45% of men with diabetes and has been demonstrated to negatively impact quality of life among those affected across all age strata (1), with a greater impact on those with permanent—rather than intermittent—ED (2,3). Recent reports describe up to one-third of newly diagnosed men with diabetes have ED at presentation (4), with upward of 50% of men 6 years after diagnosis (5,6). In addition, studies indicate that 40% of men with diabetes greater than 60 years of age have complete ED (7–15).

Recent studies have reported that alteration of the cyclic guanosine monophosphate (cGMP)/nitric oxide (NO) pathway among men with diabetes with impaired vascular relaxation is related to endothelial dysfunction (16–18). Among men with diabetes, risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia, androgen-deficiency states (19) and cardiovascular disease (CVD) (6,11,12,20–24).

ED as a marker of potential cardiovascular (CV) events has been reported by numerous investigators (25–34). In fact, ED has been shown to be significantly associated with all-cause mortality and CV events (35–37). Diabetic retinopathy has been shown to correlate with the presence of ED (11,13,38). Organic causes of ED include microvascular and CV disease, and neuropathy. In addition, psychological or situational factors may cause or contribute to ED. In spite of the overwhelming amount of data linking ED and diabetes, it is often neglected by clinicians treating men with diabetes (39).

Compared with the general population, multiple studies have reported that men with diabetes have higher rates of hypogonadism (19,40–44). One report described a correlation between glycemic control and testosterone levels (45). Importantly, phosphodiesterase type 5 (PDE5) inhibitors appear to be less effective in men with diabetes with hypogonadism (41,43,46,47). In this population, treatment of nonresponders to PDE5 inhibitors with testosterone replacement is successful in roughly 50% of individuals. In addition, ED is a side effect of many drugs commonly prescribed to men with diabetes, such as certain antihypertensives and antidepressants. Obstructive sleep apnea (OSA) is commonly associated with ED and, like diabetes, is an independent risk factor for the presence of ED (48). Screening for OSA in men with obesity with type 2 diabetes and ED should be considered.

Conflict of interest statements can be found on page S231.

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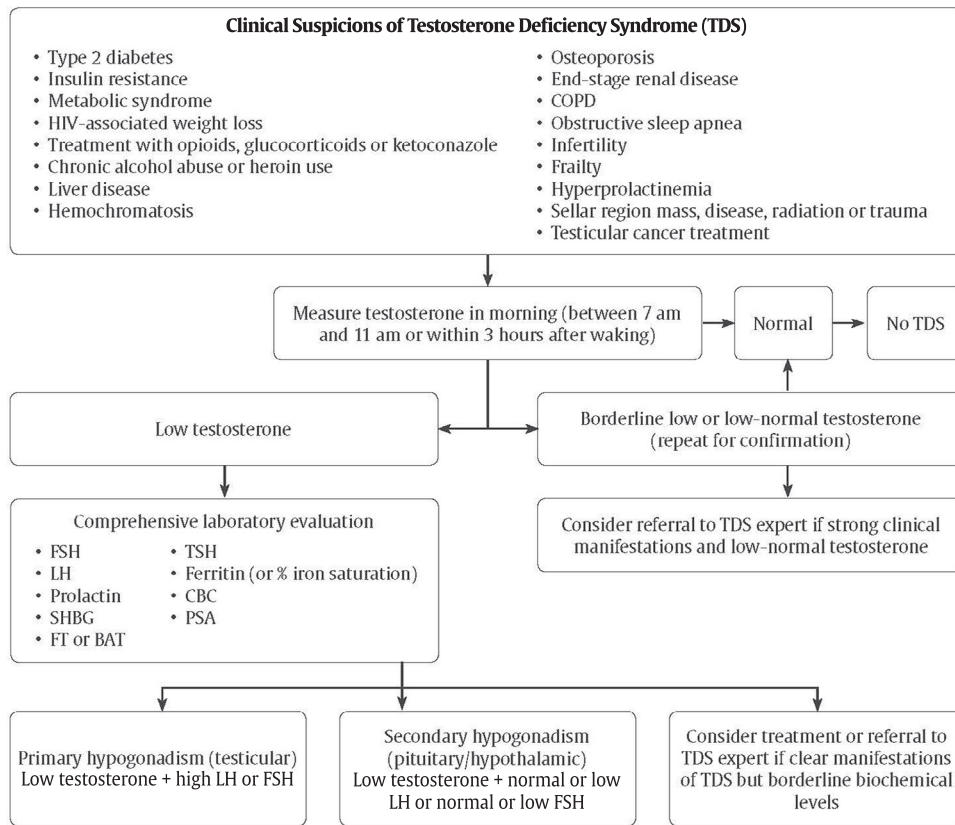


Figure 1. Diagnostic workup of hypogonadism (TDS) (modified from reference [91]).

BAT, calculated bioavailable testosterone; CBC, complete blood count; COPD, chronic obstructive pulmonary disease; FT, free testosterone; FSH, follicle stimulating hormone; LH, luteinizing hormone; PSA, prostate specific antigen; SHBG, sex hormone-binding globulin; TSH, thyroid stimulating hormone.

Screening for Erectile Dysfunction

All adult men with diabetes should be regularly screened for ED with a sexual function history. Screening for ED in men with type 2 diabetes should begin at diagnosis of diabetes. Validated questionnaires (e.g. International Index of Erectile Function (49,50) or Sexual Health Inventory for Men) (51) have been shown to be both sensitive and specific in determining the presence of ED and providing a means of assessing response to therapy (24). Men with diabetes and ED should be further investigated for hypogonadism (Figure 1).

Treatment of ED

While no randomized clinical trials have demonstrated that interventions that improve glycemic control also reduce the incidence and progression of ED, the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) showed that intensive glycemic control was effective for primary prevention of and secondary intervention for neuropathy, a condition that can impair sensory feedback from the penis, leading to reduced erectile function (52–54). The current data are controversial as they relate to diet, glycemic control and ED, with both positive and negative studies (36,55–57). Based on these conflicting data, a prudent clinician should encourage optimal glycemic control as a potential factor in maintaining erectile function (36,58,59).

Dyslipidemia and hypertension are also risk factors for ED. A meta-analysis of statin use in older men, many of whom had diabetes, suggests a benefit from statin treatment on erectile function. Diabetes-specific data are lacking (60). A small study of losartan in combination with tadalafil in men with type 2 diabetes showed an improved ED response rate compared to tadalafil monotherapy (61).

The current mainstay of treatment for ED in men with diabetes is therapy with PDE5 inhibitors (62–64). They have been reported to have a major impact on erectile function and quality of life, and should be offered as first-line therapy to men with diabetes wishing treatment for ED (65–70) (see Figure 2). There is evidence that scheduled daily therapy is effective within the population with diabetes and ED (71,72), and may improve efficacy with lower rates of side effects, may reduce lower urinary tract symptoms and has the potential for endothelial benefits (73). Additionally, among PDE5 inhibitor failure patients, use of a vacuum constriction device may salvage a significant percentage of men with erectile function and should be considered (74,75).

Contraindications for the use of PDE5 inhibitors include unstable angina or untreated cardiac ischemia and concomitant use of nitrates (5,76,77). Interestingly, men with diabetes appear to have lower rates of side effects with PDE5 inhibitors than the general population. This is believed to be a result of altered vasomotor tone or other factors (78).

Referral to a specialist in ED should be offered to men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated (see Figure 2). Second-line therapies (e.g. vacuum constriction devices [79], intracorporeal injection therapy with prostaglandin E1 [PGE1] alone or in combination with papaverine and phentolamine [triple therapy], or intraurethral therapy using PGE1) or third-line therapy (penile prosthesis) may be considered for these men (80,81).

Ejaculatory Disorders

Ejaculatory disorders are a common disorder of sexual function in men with diabetes, occurring in 32%–67% of that population

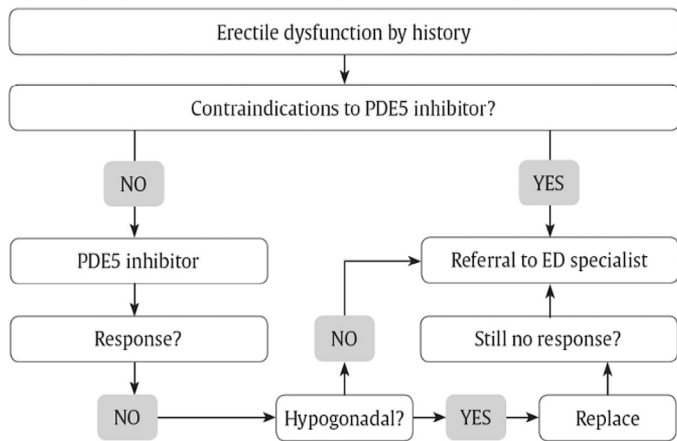


Figure 2. Management of erectile dysfunction in men with diabetes. PDE5, phosphodiesterase type 5.

(82,83). They range in scope from retrograde ejaculation, usually secondary to autonomic neuropathy with incomplete closure of the bladder neck during ejaculation, to premature or retarded ejaculation. Their recognition as an important component in sexual quality of life makes inquiry about ejaculatory function important.

Hypogonadism

Hypogonadotropic hypogonadism has a reported prevalence of 30% to 40% in men with type 2 diabetes (84–86). One study noted a prevalence of 30% in men with prediabetes, compared to 13.6% of age-matched controls (87). In contrast to type 2 diabetes, the prevalence of hypogonadism in men with type 1 diabetes is similar to the general male population (88,89). Although the pathophysiology may be related to numerous factors, including age, insulin resistance, glycemic control, concomitant sleep apnea and obesity, the most significant predictor is theorized to be the degree of central or visceral obesity (84,86,89,90). Insulin resistance is correlated with a reduction of sex hormone-binding globulin (SHBG). Measurement of total testosterone may be affected by low SHBG levels, giving the false impression of biochemical hypogonadism when bioavailable or free testosterone levels are still normal.

Biochemical testing should be by analysis of total testosterone levels drawn before 11 am or within 3 hours of awakening (91). Due to the natural variability of serum testosterone levels, repeat testing is often helpful to clarify the diagnosis. In men with diabetes with symptoms of hypogonadism but with total testosterone levels still in the lower normal range, measurement of bioavailable testosterone may be helpful.

Common symptoms of hypogonadism include fatigue, muscle weakness or muscle cramps, loss of sleep-related erections, low libido, night sweats or mood changes, such as depressive affect or irritability. A recent systematic review of male hypogonadism provides a more detailed discussion regarding diagnosis and treatment of testosterone deficiency (91).

Many men with type 2 diabetes and hypogonadism are asymptomatic, and treatment should be reserved for those who are biochemically hypogonadal and symptomatic. Some causes of secondary hypogonadism are potentially reversible, such as sleep apnea and obesity. Significant weight reduction is generally associated with an increase in testosterone in hypogonadal men with diabetes (92,93). In some instances, this can restore the eugonadal state without the need for testosterone replacement (92,93).

Conflicting evidence suggests that testosterone therapy in hypogonadal men with type 2 diabetes may increase quality of life

or improve sexual function (44,94–98). Studies assessing whether testosterone treatment in hypogonadal men with diabetes can reduce glycated hemoglobin (A1C) values have also produced mixed results (93,94,99–104). A nonrandomized, ongoing, observational study of testosterone-treated men with hypogonadism with (40%) or without diabetes showed reductions in weight, visceral obesity, abdominal circumference, as well as decreased hypertension and insulin resistance over a 5-year study interval (105,106).

Hypogonadism has been associated both with risk factors of CVD, including carotid intimal medial changes in men with type 2 diabetes (107), and an increased risk of myocardial infarction (MI) and increased CV mortality (108,109). A 3-year randomized, placebo-controlled study of testosterone use in men with hypogonadism age 60 years or older showed no significant change in either carotid artery intimal medial thickness or coronary artery calcium scores. However, only 15% of this cohort had diabetes (110). Hypogonadism also predicted an increased CV risk in men (27% of whom had type 2 diabetes) with known coronary artery disease (CAD) (111). Several nonrandomized, observational studies have produced conflicting results in regards to cardiac risk vs. benefit from testosterone replacement (101,109,112).

As men with type 2 diabetes are high risk for CV events, any positive or negative impact could, therefore, potentially have a very significant clinical impact due to the high CVD event rate in this population. Until future studies clarify the effect of testosterone on CVD, it is prudent to discuss the issue with men with diabetes prior to initiating testosterone treatment.

To date, no large, randomized, placebo-controlled study has shown an increased risk of prostate cancer in men treated with testosterone. Monitoring for prostate cancer both prior to initiation of testosterone therapy and while on therapy is recommended.

Evaluation of hypogonadal symptoms

Biochemical testing is recommended in men with diabetes who are symptomatic. In the absence of symptoms of hypogonadism, biochemical testing is not indicated. OSA is very common in people with type 2 diabetes and obesity (113). Increasing age and obesity are risk factors (113). When hypogonadotropic hypogonadism is diagnosed in men with type 2 diabetes, the presence of underlying OSA should be considered.

Treatment of hypogonadism

There is no evidence that 1 preparation of testosterone is superior to another in the relief of hypogonadal symptoms or the prevention of hypogonadism-related complications. The selection of a testosterone preparation should consider the benefits and risks of testosterone therapy in addition to patient preference. Monitoring the effects of testosterone should be done in accordance with national guidelines, such as those recommended by the Endocrine Society or the *Diagnosis and management of testosterone deficiency syndrome in men: Clinical Practice Guideline* (91).

RECOMMENDATIONS

1. All adult men with diabetes should be regularly screened for ED with a sexual function history [Grade D, Consensus].
2. A PDE5 inhibitor should be offered as first-line therapy to men with diabetes and ED in either an on-demand [Grade A, Level 1A (65–71)] or daily-use [Grade B, Level 2 (71,72)] dosing regimen.
3. Men with diabetes and ED who do not respond to PDE5 inhibitors should be investigated for hypogonadism with measurement of a morning serum total testosterone level drawn before 11 am [Grade D, Level 4 (19,40,41,43)].

4. Referral to a specialist in ED should be considered for eugonadal men who do not respond to PDE5 inhibitors or for whom the use of PDE5 inhibitors is contraindicated [Grade D, Consensus].
5. Men with diabetes and ejaculatory dysfunction who are interested in fertility should be referred to a health-care professional experienced in the treatment of ejaculatory dysfunction [Grade D, Consensus].

Abbreviations:

A1C, glycated hemoglobin; CV, cardiovascular; CVD, cardiovascular disease; CAD, coronary artery disease; ED, erectile dysfunction; NO, nitrous oxide; PDE5, phosphodiesterase type 5; OSA, obstructive sleep apnea; SHBG, sex hormone-binding globulin.

Other Relevant Guidelines

Cardiovascular Protection in People With Diabetes, p. S162
 Screening for the Presence of Cardiovascular Disease, p. S170
 Diabetes in Older People, p. S283

Author Disclosures

Dr. Brock reports personal fees from Lilly, Pfizer, Astellas, Ferring, Boston Scientific, and Paladin, outside the submitted work. No other author has anything to disclose.

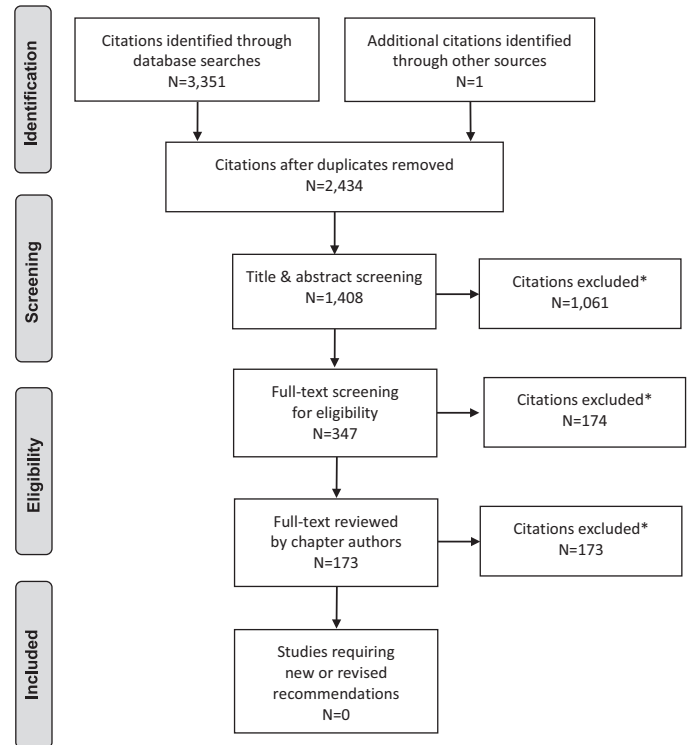
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Literature Review Flow Diagram for Chapter 33: Sexual Dysfunction and Hypogonadism in Men with Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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