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GUIDELINES

Chapter 29: Male sexual dysfunction in type 2 diabetes

The Society for Endocrinology, Metabolism and Diabetes of South Africa Type 2 Diabetes Guidelines Expert Committee.
**Chapter 29: Male sexual dysfunction in type 2 diabetes in 2017 SEMDSA Guideline for the Management of Type 2 Diabetes Guideline Committee. JEMDSA 2017; 21(1)(Supplement 1): S135-139.*

Refer to Appendix 29 for an overview of the approach to male sexual dysfunction.

29.1 Erectile Dysfunction

29.1.1 Epidemiology

Erectile dysfunction (ED), defined as the inability to sustain adequate penile erection for satisfactory sexual activity, is common in adult men with T2DM (50 to 75%)[1] and negatively impacts quality of life.[2,3] ED has also been described in up to 1/3 of *newly diagnosed* men with diabetes.[4] Additional risk factors for ED include diabetes duration, increasing age, poor glycaemic control, cigarette smoking, hypertension, dyslipidemia, androgen deficiency states and cardiovascular disease (CVD). ED occurs 10–15 years earlier in men with diabetes, is more severe and less responsive to oral drugs.[3]

29.1.2 Pathophysiology

An erection is a neurovascular event requiring intact neural pathways and normal endothelial function. Diabetes mellitus is frequently associated with micro and macrovascular complications which contribute to ED. Endothelial dysfunction is thought to play a major role and accounts for the consistent association between ED and cardiovascular disease risk and mortality.[5-7] Though there are no randomised clinical trials demonstrating reduced incidence or altered progression of ED with management of the hyperglycaemia, there is data from the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study indicating that better glycaemic control leads to reductions in peripheral neuropathy. Peripheral neuropathy impairs sensory feedback from the penis resulting in erectile dysfunction. Though there is conflicting data regarding diet, glycaemic control and ED, it is advisable to improve glycaemic control as a potential factor for maintaining erectile function in these individuals. In addition, psychological factors, such as depression, performance anxiety and relationship factors may contribute to ED e.g. depression was present in 28% of men with T2DM in a large meta-analysis of 51,331 patients from 10 controlled studies. [8]

Table I: Mechanisms associated with ED in type 2 diabetes[9]

Autonomic neuropathy
Peripheral neuropathy
Hypertension and therapies
Peripheral vascular disease
Hyperlipidaemia
Drug-related side effects
Cavernosal smooth muscle disorder
Hypogonadism with reduced sexual desire (double risk)
Psychological factors including depression
Ejaculatory disorders
Retrograde ejaculation /anejaculation
Reduced sensation

The multitude of factors contributing to ED in type 2 diabetes is listed in Table I.

29.1.3 Screening

Adult males with type 2 diabetes should be screened regularly for ED. A sexual function history may be sufficient, but a number of validated questionnaires exist and have been shown to be sensitive and specific for determining presence of ED and providing a means of assessing response to therapy.[10] The 5-item version of the International Index of Erectile Function (IIEF-5) is shown in Table II. A detailed history is the cornerstone of the evaluation of sexual dysfunction and ED but must be sensitive to the patient's personal, cultural and ethnic background. Having the partner attend and engage in the clinical interview assists in clarifying symptoms and refining the diagnosis. Identifying potentially reversible causes of ED is important (e.g. drugs, depression).

Recommended blood tests include HbA_{1c}, lipid profile and serum testosterone. An effort ECG is advised if there is a family history of premature cardiovascular disease.

29.1.4 Treatment

Treatment of ED should occur concurrently with lifestyle modification along with treatment of organic (e.g. neuropathy or vasculopathy) and psycho-sexual dysfunctions (e.g. depression and/or anxiety).

PDE 5 inhibitors are the cornerstone of therapy for ED, and if there are no contraindications, should be offered as first-line therapy to men with diabetes in the absence of hypogonadism.[12-14] PDE5 inhibitors are absolutely contraindicated with concurrent nitrate use. They are safe to use in men with stable ischaemic heart disease who are not using nitrates, and may actually be beneficial for ischaemic heart disease, peripheral neuropathy and nephropathy.[9] Men with diabetes generally need the higher dose PDE5 inhibitor, and about 50% will have an adequate response to therapy.

Patients who fail adequate on demand or daily dosing with a PDE 5 inhibitor therapy should be referred to a specialist (sexual medicine or urologist) for second-line therapies such as vacuum constriction devices, intracorporal injection therapy with prostaglandin E1 and/ or papaverine and phentolamine. In some cases a penile prosthesis may be considered. Treatment of hypogonadism prior to initiating therapy with

Table II: The International Index of Erectile Function (IIEF-5) Questionnaire[11]

			Over the past 6 months:		
1. How do you rate your **confidence** that you could get and keep an erection?	Very low 1	Low 2	Moderate 3	High 4	Very high 5
2. When you had erections with sexual stimulation, **how often** were your erections hard enough for penetration?	Almost never / never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
3. During sexual intercourse, **how often** were you able to maintain your erection after you had penetrated (entered) your partner?	Almost never/ never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5
4. During sexual intercourse, **how difficult** was it to maintain your erection to completion of intercourse?	Extremely difficult 1	Very difficult 2	Difficult 3	Slightly difficult 4	Not difficult 5
5. When you attempted sexual intercourse, **how often** was it satisfactory for you?	Almost never/never 1	A few times (much less than half the time) 2	Sometimes (about half the time) 3	Most times (much more than half the time) 4	Almost always/ always 5

IIEF-5 scoring:
The IIEF-5 score is the sum of the ordinal responses to the 5 items.
22-25: No erectile dysfunction
17-21: Mild erectile dysfunction
12-16: Mild to moderate erectile dysfunction
8-11: Moderate erectile dysfunction
5-7: Severe erectile dysfunction

phosphodiesterase type 5 (PDE5) inhibitors decreases the number of non-responders.[15,16]

29.2 Hypogonadism

29.2.1 Risk factors for hypogonadism

T2DM is a risk factor for hypogonadism.[17] While it is advisable to measure testosterone levels in all adult males with T2DM (it is estimated that up to 40% have hypogonadism),[9] it is mandatory to measure total and/or free testosterone levels in all individuals with symptoms of hypogonadism/low libido (decrease in sexual thoughts), poor morning erections as well as erectile dysfunction. The presence of non-sexual symptoms (low mood, fatigue, lack of vitality and cognitive impairment) should also necessitate measurement.[18] Additional considerations for measurement are all patients with obesity and features of the metabolic syndrome, osteopaenia or osteoporosis, vitamin D deficiency, hypertension and the use of glucocorticoids, opioids or antipsychotics.[19,20] The overlapping symptoms of hypogonadism with hypothyroidism necessitate the assessment of TSH.[21,22]A prolactin level is useful to exclude primary pituitary disorders.

Hypogonadism associated with metabolic disorders such as T2DM and obesity usually results from hypogonadotrophic hypogonadism; The LH and FSH levels are usually low or inappropriately normal in this situation and pituitary imaging is usually not necessary in the absence of other features of hypopituitarism. Addressing metabolic parameters and obesity may allow for recovery of the hypogonadism. This is unlike age-related hypogonadism or more permanent conditions, such as pituitary or testicular disease, which will necessitate lifelong testosterone therapy (TTh).

29.2.2 Diagnosis and laboratory testing

The diagnosis of hypogonadism requires the presence of symptoms and signs of androgen deficiency (impaired cognitive and sexual function, often in association with depressive symptoms) together with decreased serum testosterone concentration. The recommended laboratory tests for confirming the diagnosis are serum total testosterone (TT) and free testosterone. Equilibrium dialysis is the gold standard for measurement of free testosterone, but in South Africa a calculated free testosterone is widely used - this requires measurement of serum SHBG and TT and is considered acceptable for determining free testosterone levels.[23] Testosterone secretion shows diurnal variation so the preferred time for sampling for TT measurement is 7h00 -11h00, preferably after an overnight fast. Despite diurnal variation being substantially blunted in older men[24] and possibly in symptomatic hypogonadal men regardless of age, the same sampling time is recommended.[24] A serum prolactin measurement is indicated when TT level <5.2 nmol/L or secondary hypogonadism is suspected. Additional tests include LH, to differentiate between primary and secondary hypogonadism, TSH and vitamin D should also be measured as there is overlap of symptoms of hypothyroidism and hypogonadism, and vitamin D deficiency is a risk factor for hypogonadism.[19,20]

Though measurement of TT is widely accepted as a diagnostic test for hypogonadism, there is no consensus on the definition of testosterone deficiency based on the lower TT threshold. The International Society for the Study of the Ageing Male (ISSAM) Hypogonadism panel recommend a cut off of 12.1 nmol/L,[25] while the European Male Ageing Study (EMAS) recommended a threshold of 11 nmol/L.[26] Hypogonadal symptom prevalence increases with TT levels <12.1 nmol /L.[18] Testosterone receptor sensitivity varies between individuals which may account for differing degrees of hypogonadal symptoms and variable levels of TT.[27] The free testosterone should be evaluated In individuals with hypogonadal symptoms and normal TT and TSH levels. Differing lower thresholds for free testosterone have been recommended with 225 pmol/L being the lowest[28] and 347 pmol

/L being suggested by others.[29,30] Regardless of the level used, the diagnosis of hypogonadism is only confirmed if symptoms are present.

29.2.3 Treatment

Testosterone therapy (TTh) is approved for the treatment of hypogonadism. A trial of therapy for 3 to 6 months may be considered in patients with uncertain diagnostic levels of serum testosterone, though 12 months TTh may be required to fully assess response.[1] The patient should be given the opportunity to actively participate in the choice of testosterone formulation. Patients with inadequate therapeutic responses to TTh should be referred for further investigation of other causes for sexual dysfunction. T2DM men with hypogonadism who wish to maintain their fertility, now or in the future, should receive other forms of therapy (not TTh) and be referred to a healthcare professional with expertise in managing these men .

TTh options are oral and intramuscular and include:

Testosterone undecanoate

Oral, 3 to 4 capsules in divided doses daily. Absorption is through the lymphatic system, with consequent reduction of liver involvement.

Intramuscular injection is initiated after measurement of testosterone levels; depending on testosterone levels and severity of hypogonadal symptoms the interval to the 2nd injection may be reduced and given at 6 weeks with subsequent injections every 10-14 weeks. This allows for a more rapid achievement of the steady-state testosterone levels which are achieved with this form of testosterone without fluctuation.[34] Long-acting preparations cannot allow early drug withdrawal in case of side effects.[33]

Testosterone cypionate

One injection every 2-3 weeks. Short-acting preparation that allows drug withdrawal in case of onset of side-effects. Possible fluctuation of testosterone levels.[31,32]

Testosterone enanthate

One injection every 2-3 weeks. Short-acting preparation that allows drug withdrawal in case of onset of side-effects. Fluctuation of testosterone levels.[31,32]

29.2.4 Monitoring

Monitoring after initiation of TTh includes the assessment of symptom resolution, side-effects, serum testosterone levels, prostate specific antigen (PSA), haematocrit and regular digital rectal examination(DRE); the suggested monitoring interval is 3, 6 and then 12 months post-initiation and annually thereafter, and is also dependent on the formulation of TTh used.

Insufficient data exists for determination of the optimal target serum testosterone; hence the recommendation is for maintenance of levels within the normal range. Due to variability in laboratory values the same laboratory should be used for measurement.[25] Testosterone levels should be measured towards the end of the injection interval (trough level) regardless of the preparation and levels below the normal range should receive dosing at shorter injection intervals; for testosterone levels above the normal range extension of the injection interval or dose reduction must be considered.[34]

Concerns exist about a link between prostate cancer and testosterone therapy: recent evidence fails to support this concern or that TTh is associated with growth of subclinical prostatic lesions.[35,36] It is still recommended that patients undergo prostate assessment prior to commencement of therapy, including a PSA and digital rectal examination (DRE). The presence of abnormalities on DRE or elevated PSA may warrant ultrasound guided prostatic biopsy, and these patients should be referred to a urologist for further assessment.

Polycythaemia and haematocrit

Follow up should include haematological assessment with maintenance haematocrit levels below 54%. There does not appear to be an increase in cardiovascular events with the elevated haematocrit possibly on the basis of vasodilator and anti-atherosclerotic effects, but levels repeatedly in excess of 54% require therapeutic phlebotomy with or without discontinuation of TTh.[37]

29.2.5 Hypogonadism and cardiovascular disease

Numerous studies have shown an association between low testosterone levels and increased cardiovascular risk and mortality. An observational study from Italy which included 1687 patients managed for erectile dysfunction showed that the risk for major adverse cardiovascular events after adjustment for age and chronic diseases was 20% higher when testosterone levels were < 8 nmol/L.[38] The Copenhagen Heart Study showed that reductions of total testosterone below the 10th percentile increased risk of ischaemic stroke by 34% when compared to normal testosterone individuals.[39] There does appear to be an association between testosterone levels and glycaemic control in type 2 diabetes, suggesting that better glycaemic control is beneficial for maintaining testosterone levels.[40] TTh improves surrogates markers of cardio metabolic risk, including fasting plasma glucose, triglycerides and waist circumference.[41]

29.2.5 Therapy outcomes

Resolution of hypogonadal signs and symptoms occur at variable times for different organ systems.[42] Libido, vigor and depression as well as quality-of-life measures can expect to improve from 3 to 4 weeks following commencement of therapy, although erectile and ejaculatory function may require up to 12 months of TTh to improve.[1] Decreased fat mass and increased lean body mass and muscle strength and improvement in insulin sensitivity may be apparent about 3 to 4 months after initiation of TTh. Improvements in bone are detectable from 6 months, but the full beneficial effect may take between 2 and 6 years.[43]

29.3 Ejaculatory disorders

These are common as part of the spectrum of sexual dysfunction in men with diabetes occurring in 32 to 67% of the male diabetic cohort and require enquiry as recognition of these is an important component in sexual quality of life. Disorders

include retrograde ejaculation with incomplete closure of the bladder neck during ejaculation usually secondary to autonomic neuropathy, premature ejaculation and retarded ejaculation.[44]

29.4 Peyronies Disease

Peyronies disease presents with a fibrotic plaque within the tunica albuginea of the penis leading to penile shortening, curvature and sexual dysfunction in approximately 20% of diabetic males with ED. 15% of men with Peyronies disease have concomitant Duputyrens contracture. Surgery remains the gold standard for correcting erect penile deformity in men with stable disease.

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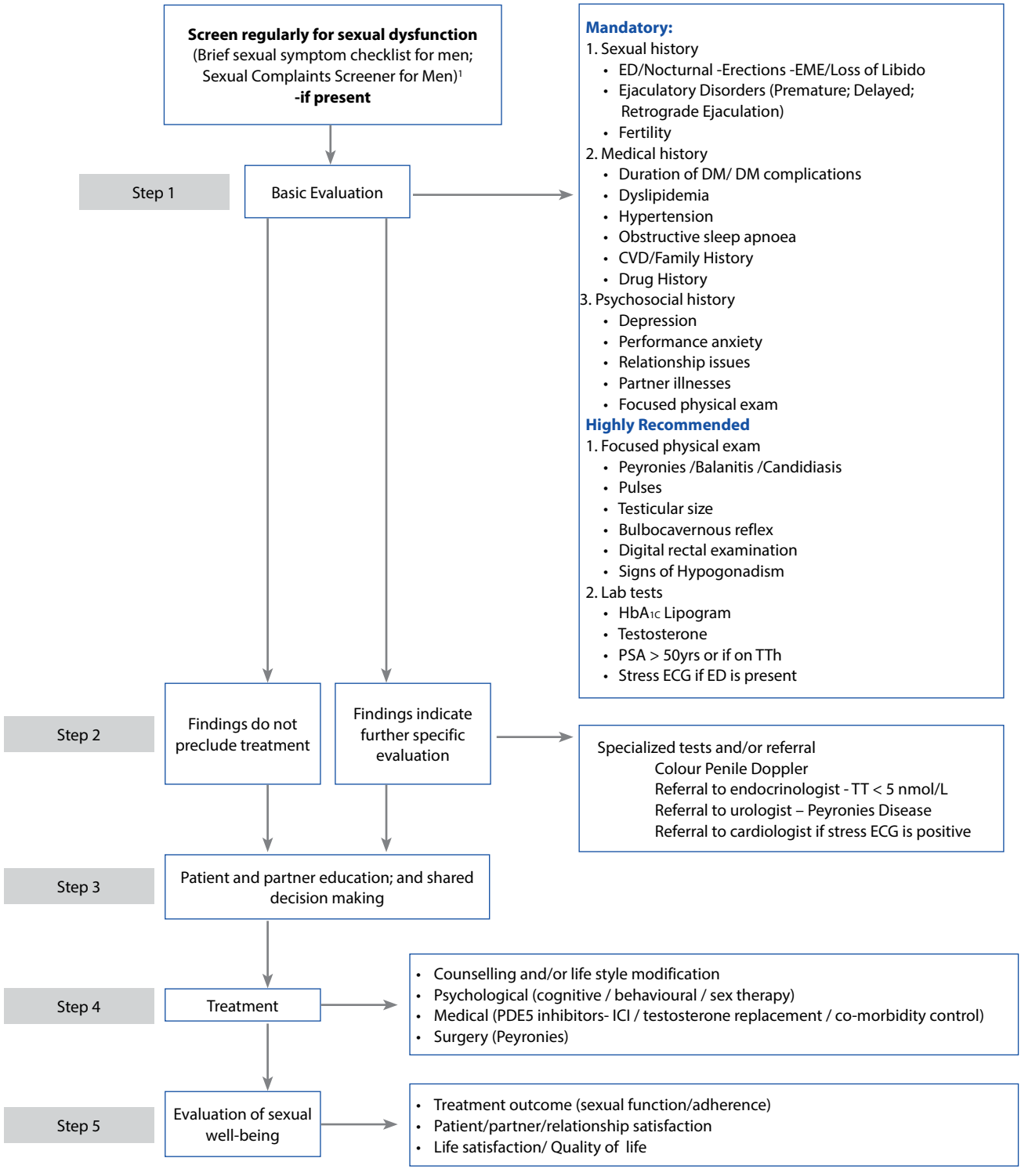
Appendix 29: The evaluation of male sexual dysfunction in type 2 diabetes

SEMDSA Type 2 Diabetes Guideline Expert Committee



DM: diabetes mellitus; EME: early morning erection; ED: erectile dysfunction ; PSA: prostate specific antigen; TT: total testosterone; PDE5i: Phosphodiesterase enzyme 5 inhibitors; TTh: testosterone therapy

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