Erectile dysfunction, diabetes and cardiovascular risk

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Abstract

Erectile dysfunction (ED) occurs in up to 75% of men with type 2 diabetes (T2DM) and has a complex pathogenesis owing to a combination of microvascular, macrovascular, endocrine and neuropathic disease. ED is established as an independent marker for the development of coronary artery disease (CAD) occurring on average 3–5 years before the onset of CAD. Thus, timely detection of ED offers an opportunity for early intervention, thereby reducing morbidity associated with CAD. The average UK male, however, suffers for 3 years before discussing symptoms of ED with a healthcare professional. The National Institute for Health and Care Excellence (NICE) recommends an annual review of ED symptoms in susceptible patients with T2DM with an appropriate discussion of management options. Screening questions regarding ED were introduced in the 2013 Quality Outcome Framework but were removed by NHS England in 2014 on grounds of 'simplification'. Response to treatment strategies for ED is poor in diabetes, and poor glycaemic control, long duration of disease and severity of complications is predictive of a poor treatment response. The concomitant presence of hypogonadism in over 40% of men with T2DM also makes ED difficult to treat in this group. Further, ED and severe hypogonadism have been shown to independently predict mortality in T2DM. Treatment for ED is more likely to be effective if given early, although complex regimens may be required.

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Key words: erectile dysfunction, coronary artery disease, type 2 diabetes

Background

Erectile dysfunction (ED) is the inability to obtain and maintain a penile erection that allows adequate sexual intercourse.[1] Data from a large community-based observational study found that 52% of non-institutionalised men between the age of 40 and 70 years reported ED.[2] Diabetes mellitus is strongly associated with the development of ED, with a reported prevalence of ED of 35–90% in those with diabetes in different populations.[3,4] The pathophysiology of ED in diabetes is multifactorial. Under normal circumstances, both biological and psychological factors work synchronously resulting in an erection.[5] Psychological arousal results in a biological cascade that involves parasympathetic activation and consequent nitric oxide (NO) release from local endothelial cells. NO mediates smooth muscle and vascular relaxation resulting in increased arterial flow to the penile corpora cavernosa. The increasing blood flow impedes venous return via compression of penile venules, thus maintaining an erection.[5] ED can therefore develop in diabetes owing to an interplay between neuropathy, vasculopathy, hypogonadism, endothelial dysfunction and psychological factors.

Depression is more common in people with diabetes than in those without, and a meta-analysis found twice the odds of depression in diabetes compared with controls (odds ratio (OR) 2.0, 95% CI 1.8 to 2.2).[6] Studies have shown that sexual function is more closely linked with depression than other diabetes complications both in men and women (Figure 1), yet antidepressant medications frequently adversely affect sexual function.[7] Recent work also increasingly recognises ED as an independent risk factor for coronary artery disease (CAD), which appears to be particularly significant in younger men and those with diabetes who are already at high risk of developing CAD.[8,9]

Here we will review the evidence linking ED to CAD and explore the relationship between diabetes control and development of ED and other sexual dysfunctions. Further, we will high-

Figure 1. Association of depression and diabetes complications: a meta-analysis

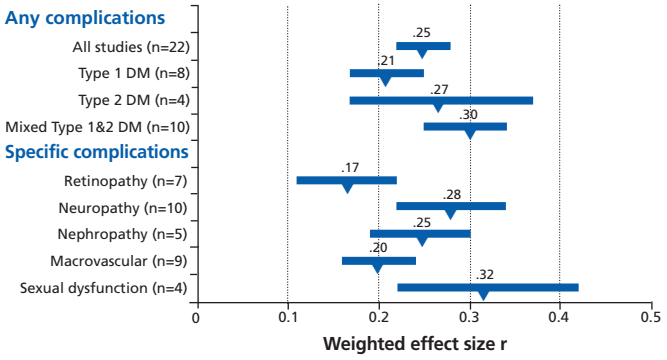

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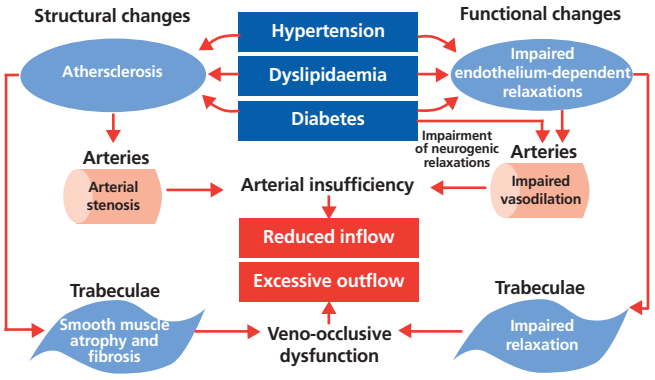
Figure 2. Interplay of cardiovascular risk factors, endothelial dysfunction and erectile dysfunction



Adapted from Saenz de Tejada *et al*.[10]

light the role of hypogonadism in the context of type 2 diabetes mellitus (T2DM) and its link with ED prior to discussing treatment strategies for ED with a focus on diabetes and cardiovascular disease (CVD) risk reduction.

ED as a risk factor for CAD

The development of ED is attributable to neural, vascular, hormonal, metabolic and psychogenic factors, all mediated through endothelial and smooth muscle dysfunction (Figure 2).[10] Early intervention at the stage of endothelial dysfunction may potentially reverse ED but, at the stage of fixed atherosclerosis, reversibility is unlikely.[11,13] The arterial size hypothesis explains why a 50% penile artery occlusion will manifest symptoms of ED 3–5 years before symptoms of CAD develop in the larger coronary arteries (Figure 3).[11,12,14] ED has been shown to be associated with the severity of ischaemic heart disease in terms of plaque burden and the number of coronary arteries affected.[12] Screening for ED offers an important window of opportunity for intervention to prevent coronary events, especially in younger men where the predictive value of ED is greatest.[13]

A large body of evidence suggests that the presence of ED increases the risk of CAD by 50%.[15] Ma *et al*.[16] found that the predictive value of ED is greater in men with T2DM and no known CAD (Figure 4). Indeed, the authors found that ED was an independent risk factor for new onset CAD events, equivalent to an established risk factor of incident hypertension and greater than microalbuminuria. Conventional (CVD) risk markers and scores, however, do not account for ED. Araujo *et al*.[17] aimed to test the hypothesis that ED improves CVD prediction beyond traditional risk factors. In a prospective study population, the authors found that ED was significantly associated with the incidence of CVD; however, ED detection does not confer any additional benefit in predicting future CVD compared with traditional risk factors. The Princeton III guidelines[18] reaffirmed ED as a risk factor for CVD, with the presence of ED increasing the relative risk of CAD by 1.46 (95% CI 1.31 to 1.63; p<0.01).

Figure 3. Erectile dysfunction (ED) occurs 3–5 years before coronary artery disease (CAD)

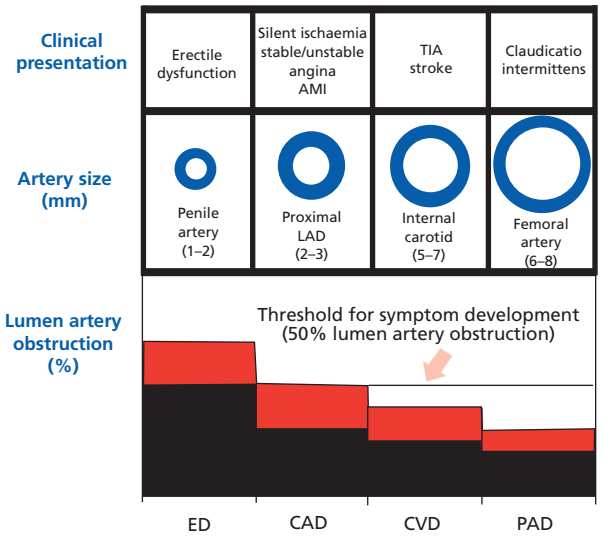


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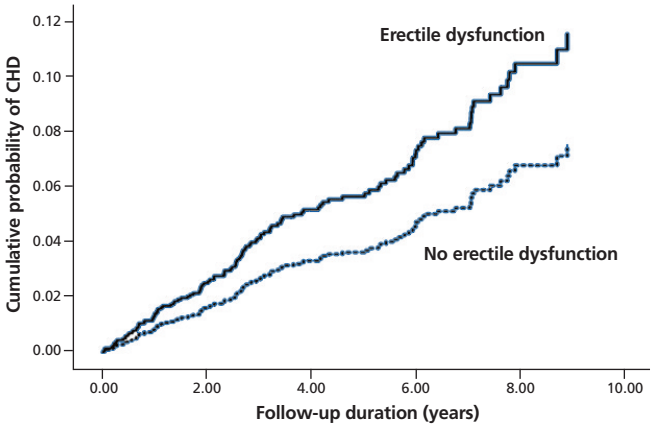
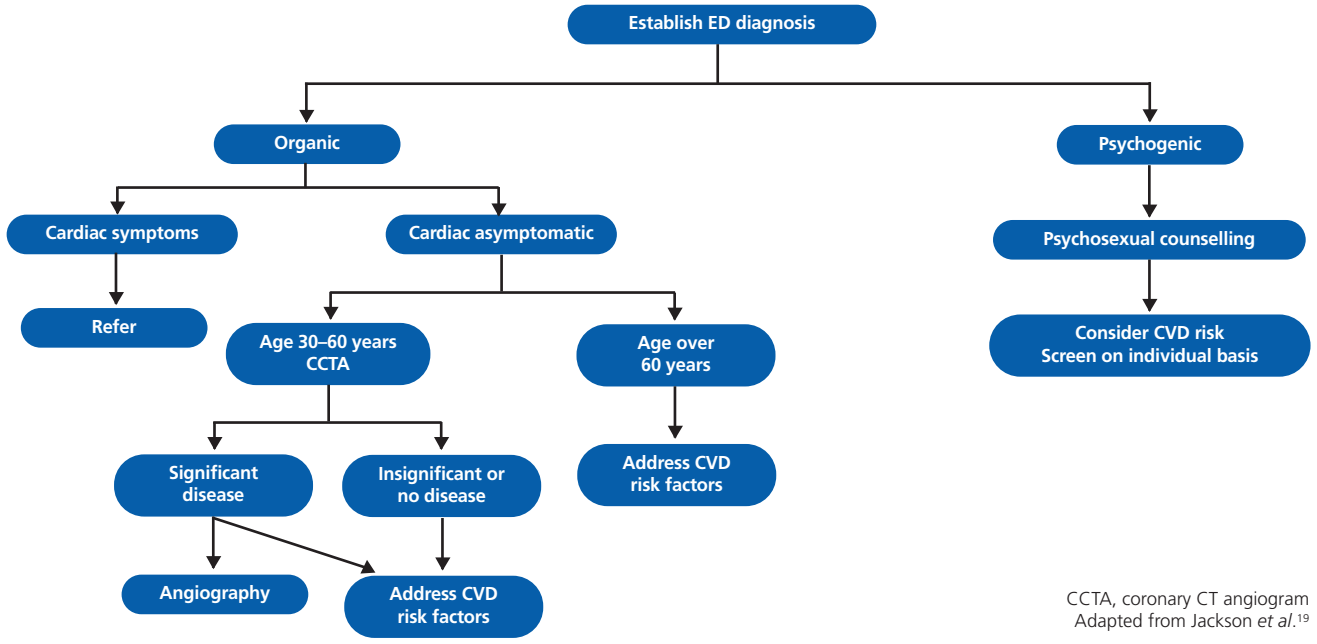
Figure 4. Cumulative hazard ratio of coronary heart disease (CHD) events stratified by erectile dysfunction



Reproduced with permission from Ma *et al*.[16]

Given a common pathophysiological link of endothelial dysfunction between ED and CAD in addition to a strong epidemiological association, Jackson *et al*.[19] recommended that ED should be considered a 'cardiac equivalent' and aggressive risk reduction therapy should be initiated for those with ED, specifically younger men. With regard to detecting the presence of silent CAD in men with ED, stress testing on exercise will only identify those lesions influencing flow (>50–70% stenosis). Jackson *et al*.[19] provide an algorithm for the cardiovascular assessment of the patient with ED, targeting aggressive intervention in the younger patient (Figure 5).

Figure 5. Algorithm for cardiovascular assessment of men with erectile dysfunction



CCTA, coronary CT angiogram
Adapted from Jackson *et al*.[19]

ED associated with diabetes control, complications and medications

Studies suggest a link between glycaemic control and ED.[19,20] Lu *et al*. conducted a study involving 792 men, of whom 83.6% had some degree of ED, including 43% with serious ED.[20] The study showed that, even after controlling for age and duration of diabetes, there was an association between glycated haemoglobin levels (HbA_{1c}) and ED (OR 1.12, 95% CI 1.01 to 1.25). The authors also performed subgroup analysis to investigate the association between age and severe ED. In patients aged <60 years, HbA_{1c}, age and duration of diabetes were independent predictors of severe ED. However, for patients aged >60 years, only age and duration of diabetes were independent predictors of severe ED.[20] In patients with diabetes, the severity of ED has been linked to the number of circulating endothelial microparticles.[21]

The medications that patients are receiving for treatment of diabetes and their complications may influence ED. In particular, ED has been associated with the use of β-blockers, thiazide diuretics, metformin, antidepressants, statins, fibrates and drugs used for neuropathic pain such as pregabalin, gabapentin and opiate analgesics.[22] Other drugs may have a beneficial effect. In patients with hypertension and diabetes, a study showed that initiation of an angiotensin receptor blocker (valsartan) in patients on no other antihypertensives (n=952) reduced the rate of ED from 65% to 45% (p<0.0001).[23]

Hypogonadism in type 2 diabetes

Hypogonadism is common in diabetes. Studies consistently show that, in patients with T2DM, 35% have total testosterone (TT) levels below 12 nmol/L and 15% have TT levels below 8 nmol/L.[24,25] In a study of 1,413 men, those in the first (lowest) tertile of low free testosterone (FT) and TT were four times more likely to have diabetes than those in the third tertile of low TT and FT.[26] Furthermore, low FT and sex hormone binding globulin (SHBG) have been shown to predict the onset of diabetes in men in up to 10 years of follow-up (OR 1.58 for a decrease of 4 ng/dL FT and OR 1.89 for a decrease of 16nmol/L SHBG).[27] Treatment of severe hypogonadism with testosterone replacement may help to improve both sexual function and quality of life. In a double-blind placebo-controlled study, patients with severe hypogonadism (TT<8 nmol/L or FT <180 pmol/L) receiving testosterone undecanoate reported improved sexual function at 30 weeks follow-up, although there was no significant improvement in sexual function in patients with mild hypogonadism at baseline (TT 8.1–12 nmol/L or FT 181–250 pmol/L).[28] Another study showed that, in patients with TT <9.54 nmol/L, treatment with testosterone gel was associated with improved responses to phosphodiesterase 5 (PDE5) inhibitors in comparison with placebo.[29]

In patients receiving testosterone replacement therapy (TRT), beneficial effects on reported quality of life and sexual interest may manifest as early as 3 weeks, although effects on erectile function may take up to 6 months.[30] Improvement in quality of life with TRT has been reported to be higher at 52 weeks than at 30 weeks in diabetic patients, with the best results in patients without obesity and co-existent depression. This suggests that treatment may need to be given for a prolonged time.[31]

In view of the association between hypogonadism and diabetes, researchers have postulated whether TRT can also improve metabolic parameters in diabetes. Studies have shown an association between TRT and reductions in HbA_{1c},[32] improvement in insulin resistance[33] and a reduction in body mass index.[34] A large Australian study (T4DM) is currently underway to assess whether

treatment of low testosterone in younger men can reduce the incidence of diabetes, and findings are due to be reported in 2017.

Diabetes and other sexual dysfunctions

In addition to ED, T2DM is associated with other sexual dysfunctions. Corona *et al*. conducted a prospective study of 499 patients with newly or recently diagnosed diabetes.[35] They reported that, around the time of diagnosis of diabetes, the prevalence of premature ejaculation, delayed ejaculation and low sexual desire was 28.3%, 32.9% and 58.4%, respectively. Sexual dysfunction preceded the diagnosis of diabetes in 30%, and 45.3% had never consulted about sexual dysfunction.[35]

T2DM has also been associated with diseases that can indirectly cause sexual dysfunction, such as balanitis and Peyronie's disease. In a study conducted in 1,137 Danish patients, a higher HbA_{1c} level was associated with an increased frequency of balanitis in patients with diabetes compared with those without (OR 1.25, CI 1.09 to 1.44), despite adjustment for age, sex, body mass index, blood pressure, complications and antihypertensive treatment.[36] The inflammation, pain and discharge related to fungal balanitis may adversely affect sexual function. Peyronie's disease, which may be associated with sexual dysfunction, is more common in diabetes, with a higher incidence related to a longer duration of diabetes and poor glycaemic control.[37]

Treatment of ED in T2DM

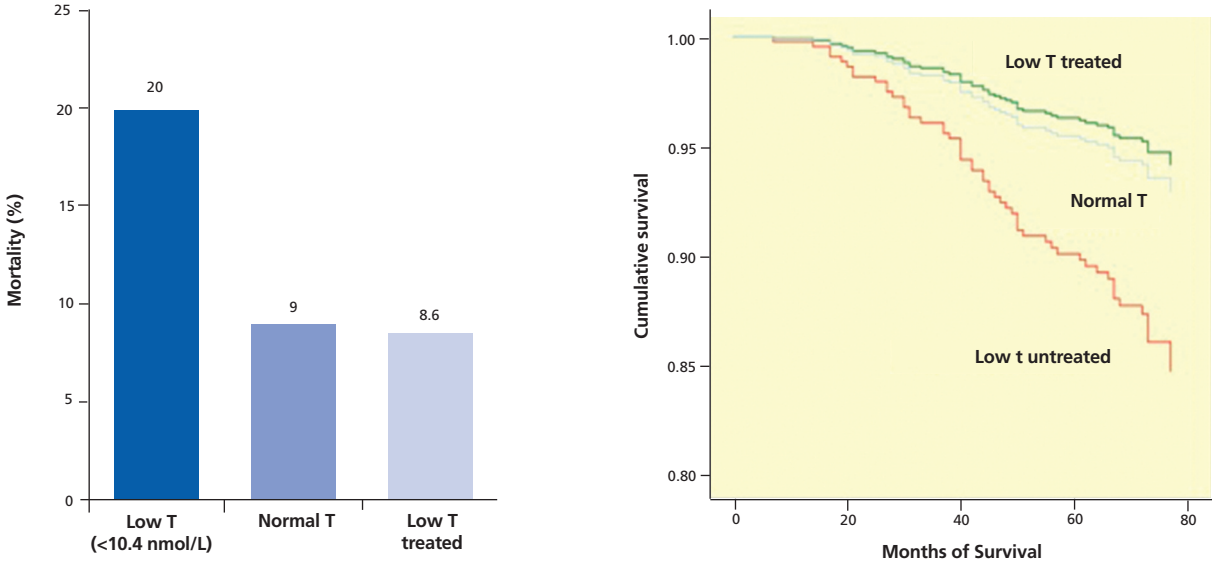
Treatment options for ED in T2DM include lifestyle changes and oral medications, amongst other treatments.

Wing *et al*. studied the effects of lifestyle interventions in obese patients with T2DM and ED.[38] A cohort of patients in the intensive lifestyle intervention group (ILI) had group and individual sessions focusing on weight loss and exercise, whilst the control group of patients received diabetes support and education only (DSE). At 1 year, 8% of men in the ILI group reported worsening of erectile function, 70% reported no significant change and 22% reported some improvement. In the DSE group, 20% reported worsening of ED at 1 year, 57% reported no significant change and 23% reported improvement (p=0.006). Thus, the effect of lifestyle intervention in ED is likely to be modest.[38]

For patients with hypogonadism, in the context of ED and diabetes, this should be treated as discussed previously. PDE5 inhibitors are generally considered first-line therapy for men with diabetes and ED in the absence of hypogonadism.[39] They work by reducing breakdown of cyclic guanosine monophosphate (cGMP), a crucial second messenger in NO-mediated smooth muscle relaxation that is responsible for erection. All four of the currently available PDE5 inhibitors (sildenafil, tardenafil, tadalafil and avanafil) are safe and effective in diabetes. However, studies suggest that the response rate to PDE5 inhibitors is lower in patients with diabetes than in those without diabetes (63% vs. 83%).[40,41] This may be because the response to PDE5 inhibitors relies on an intact neurogenic vascular response, whilst patients with diabetes commonly have endothelial and autonomic dysfunction.[40,41] A combination of folic acid and tadalafil has been shown to be more effective than tadalafil alone in restoring erectile function in diabetic patients.[42] Other strategies to improve the response to oral PDE5 inhibitors include addition of L-arginine or use of daily dosing of a combination of PDE5 inhibitors.[43]

In addition to improving ED, PDE5 inhibitors may reduce cardiovascular risk through a range of effects. They have been shown to reduce subclinical inflammation and thrombosis,[44]

Figure 6. Testosterone replacement therapy and mortality in UK men with type 2 diabetes mellitus



T, testosterone

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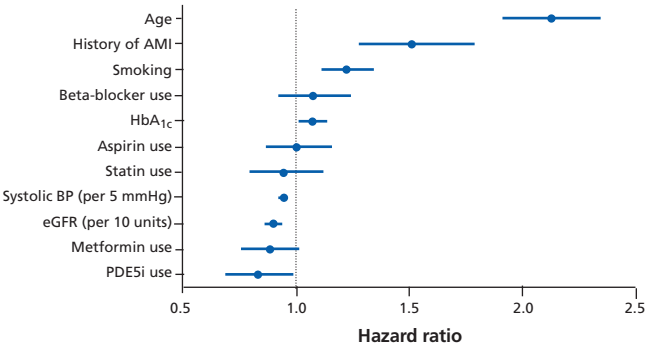
Figure 7. Multivariate regression model for risk of mortality



Reproduced with permission from Anderson *et al*.[49]

improve cardiac inotropism[45] and have anti-remodelling effects.[45] In patients with established CAD and T2DM, PDE5 inhibitors may help to reduce the incidence of major adverse cardiac events.[12,46] In a study of 7,680 men with T2DM, 432 had a myocardial infarction over a follow-up period of 6.4 years. In this group, patients who were using PDE5 inhibitors had a 50% lower mortality rate than those not on PDE5 inhibitors (hazard ratio 0.5 (95% CI 0.29 to 0.85, p=0.01).[46] Two recent studies have shown reduced all-cause mortality with TRT for low testosterone levels in US veterans[47] and a UK population of men with T2DM (Figure 6).[48] A recent study by Anderson *et al*. evaluated mortality data and events in terms of levels of TT achieved after treatment and demonstrated that TRT impacts more on the chances of surviving major events rather than reducing absolute numbers (Figure 7).[49]

There is relatively little research on non-oral treatments such as vacuum therapy and self-injection therapy for ED in diabetes, so these are usually reserved as second-line treatment options. Reported satisfaction rates for vacuum devices vary between 35% and 84%.[39] Long-term usage of vacuum devices is still higher than intracavernosal injections.[39]

Conclusions

ED is common and adversely affects patients psychologically and biologically. In particular, ED is an important predictor of prospective CVD in men. Anecdotal evidence suggests that current NICE guidance to assess ED annually and address contributory factors is not being comprehensively adhered to. Recent research, however, suggests that addressing low testosterone levels with TRT in the context of ED is associated with multiple small health benefits that may be equated to considerable benefit to patients. Furthermore, instituting therapy with TRT for low testosterone and treating ED with PDE5 inhibitors may be independently associated with a reduction in all-cause CVD mortality.

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Key messages

- The prevalence of ED in the primary care T2DM population is approximately 75%
- The development of ED is related to duration and control of diabetes plus the severity of complications
- Development of ED is a strong predictor of future cardiovascular events particularly in younger men
- NICE guidance suggests annual assessment and discussion of therapeutic options for ED in all men with T2DM.
- Hypogonadism is found in over 40% of men with T2DM. Treatment with lifestyle change and Testosterone replacement improves ED and salvages patients who otherwise fail to respond to PDE5Is
- Recent evidence suggests that testosterone replacement and PDE5Is may independently reduce all-cause mortality in T2DM

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