REVITALISE audit: Erectile dysfunction and testosterone review in primary care

Janine David, David Edwards, Patrick Wright

Type 2 diabetes is associated with metabolic and endocrine complications, including erectile dysfunction (ED) and low testosterone. Despite the well-documented relationship between type 2 diabetes, ED and low testosterone, a substantial number of men with type 2 diabetes are not assessed for either condition, missing a valuable opportunity to potentially improve their overall health and quality of life. The REVITALISE audit assessed the prevalence of men with type 2 diabetes and ED or who were potentially at risk of ED and/or testosterone deficiency across 13 practices in the UK. It also investigated how often ED and testosterone deficiency was discussed, based on recorded read codes in practice notes.

The prevalence of type 2 diabetes is increasing rapidly worldwide (World Health Organization, 2016). In England, over 3 million people are currently diagnosed with diabetes, with an estimated 90% of these having type 2 diabetes (NHS Digital, 2016). In recent years, the quality of services for patients with, or at risk of, diabetes in the UK has improved, with a corresponding overall benefit for long-term health outcomes and reduction in the risk of mortality. However, evidence shows that there are considerable differences across England and Wales in the provision of care for people with type 2 diabetes (Fleetcroft et al, 2017; NHS Digital, 2017). A service review conducted in 2012–13 found that as many as two-thirds of patients in some areas of England are not receiving optimal diabetes care (National Audit Office, 2015).

In men, type 2 diabetes is associated with various metabolic and endocrine complications including erectile dysfunction (ED) and testosterone deficiency (Sayyid and Fleshner, 2016). There are large differences in reported prevalence rates of ED in men with type 2 diabetes, ranging from 32% to 90%, which could be due to differences in study methodology and population characteristics, such as age and duration of diabetes (Malavige and Levy, 2009, Kamenov, 2015). ED may be a predictor of type 2 diabetes, and conversely, this condition is one of the most frequent organic causes of ED (Mazzilli et al, 2015). ED in men with type 2 diabetes shows a complex pathophysiology that may include neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, and hormonal changes (Hatzimouratidis and Hatzichristou, 2014). This complex pathogenesis, often combined with a reluctance from the patient and healthcare professional to discuss the condition, means that these patients represent a "difficult-to-treat" group that often presents a challenge for the primary care practitioner (Kamenov, 2015), as characteristically many patients fail to achieve an adequate response to oral phosphodiesterase type 5 inhibitor (PDE5i) therapy (Binmoammar et al, 2016).

Low testosterone levels occur in over 40% of men with type 2 diabetes and are associated with an increased risk of ED, more severe ED, increased adiposity, insulin resistance, poor glycaemic control, dyslipidaemia and increased mortality (Cheung et al, 2015; Chiles, 2016; Hackett et al, 2016a). Low testosterone may also impair response to PDE5i therapy in men with ED (Alhathal et al, 2012). Recent evidence suggests that low testosterone in these men may be a marker of type 2 diabetes, rather than a causal risk factor for the condition (Holmboe et al, 2016).

Men with type 2 diabetes also have an increased risk of cardiovascular disease, as well as having other metabolic and cardiovascular risk factors, such as obesity, hypertension and

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Article points

1. Type 2 diabetes is associated with metabolic and endocrine complications, including erectile dysfunction (ED) and low testosterone in men.
2. Screening for ED and low testosterone provides an opportunity to assess men's metabolic and cardiovascular health risks and improve quality of life if they are experiencing ED or low testosterone.
3. The REVITALISE audit demonstrated that men who had been diagnosed with ED or low testosterone were frequently not receiving optimal care in line with evidence-based guideline recommendations.

Key words

- Erectile dysfunction
- Hypogonadism
- Testosterone deficiency

Authors

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Box 1. Codes used to identify erectile dysfunction.

- **E2273** (impotence)
- **Eu522** (failure of genital response)
- **K27y1** (impotence of organic origin)
- **K27y7** (erectile dysfunction due to diabetes)
- **1D1B** (C/O erectile dysfunction)
- **8Htj** (referral to erectile dysfunction clinic)
- **7C25E** (treatment of erectile dysfunction NEC [not elsewhere classified])
- **1ABJ** (does not complain of erectile dysfunction)

hyperlipidaemia (Tamler and Deveney, 2010; Cheung et al, 2015). Screening for ED and low testosterone in men with type 2 diabetes and other at-risk groups provides an opportunity to assess their general metabolic and cardiovascular health, as men with type 2 diabetes also have an increased risk of cardiovascular disease (Miner and Seftel 2010). Primary care providers should be aware of the common cluster of type 2 diabetes, ED and low testosterone, and a diagnosis of one of these conditions should prompt inquiry about the others (Tamler and Deveney, 2010).

The aim of the REVITALISE audit was to assess the care of men with and without type 2 diabetes who may be at risk of testosterone deficiency and/or ED, and identify where the clinical management of these individuals could be improved.

Methods

The REVITALISE audit was conducted at 13 primary care practices across the UK (Birmingham, Bridgend, Corby, Coventry, Doncaster, Dudley, Durham, Gloucester, Heywood, Manchester and Sandwell). The average practice size was 7319 patients (smallest 2093 patients; largest 14 732). Information from patients at each centre was gathered between 13 October 2015 and 28 April 2016. Data for the previous 24 months from the date on which the audit was conducted were collected electronically from primary care clinical systems (EMIS Web, InPS Vision and SystmOne), with the same search criteria applied across all the systems in all practices. Data from all centres were collated and analysed centrally.

Men with and without ED were identified using the codes listed in *Box 1*. Data on the incidence of ED, testosterone testing, total testosterone levels and the use of testosterone therapy in men with or without type 2 diabetes were recorded in a stepwise manner. Serum total testosterone levels were stratified as follows (British Society for Sexual Medicine, 2010):

- Normal: >12 nmol/L
- Borderline: >8 and ≤12 nmol/L
- Low testosterone: ≤8 nmol/L

Data from all centres were collated and analysed centrally. In this article, the results will focus on the incidence of ED, testosterone testing, total

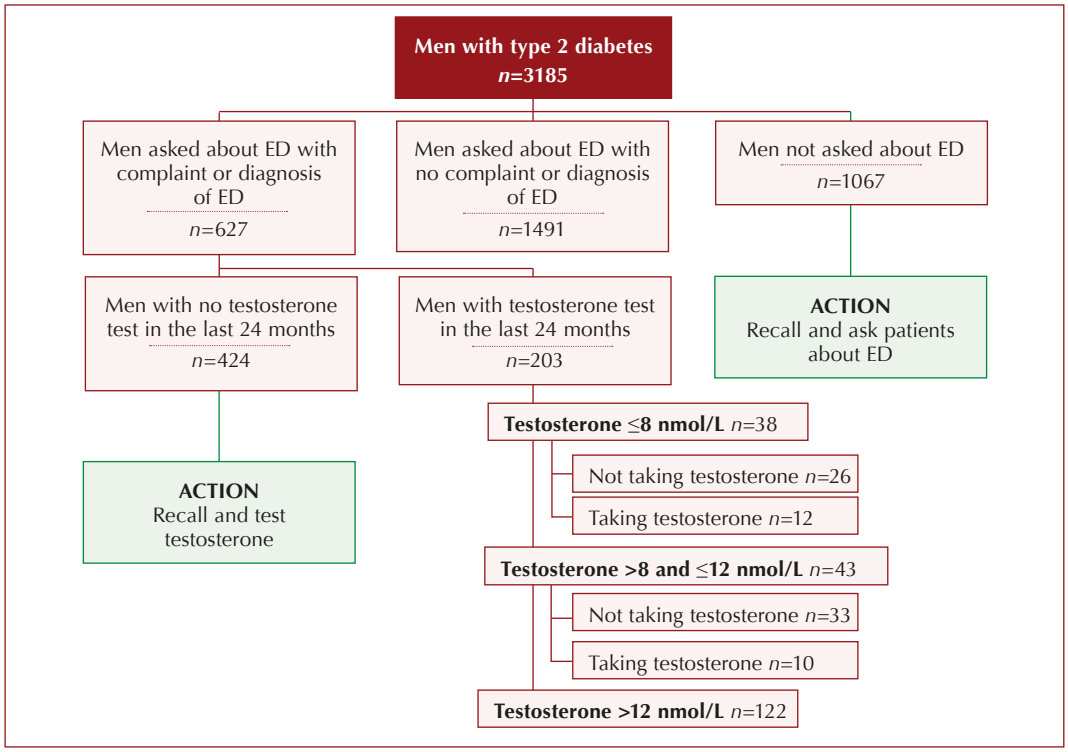

Figure 1. Disposition of men with type 2 diabetes from 13 GP practices. ED=erectile dysfunction.

testosterone levels and the use of testosterone therapy in men with type 2 diabetes.

Results

Study population

Data from 43 633 men from 13 practices were analysed. In total, 3185 men had type 2 diabetes, corresponding to a prevalence of 7.3%. *Figure 1* shows the disposition of men with diabetes in the audit.

Prevalence of ED and use of PDE5i therapy

The prevalence of erectile problems was considerably higher in men with type 2 diabetes than in those without. In total, 627 (19.7%) of men with type 2 diabetes had a complaint or diagnosis of ED compared to 470 (1.2%) of men without type 2 diabetes. Of the 627 men with type 2 diabetes and ED, 67.6% (*n*=424) had not had a testosterone test in the last 24 months. Approximately one third (*n*=1067) of men with type 2 diabetes had not discussed ED, or a discussion had not been recorded about ED. And of the men with type 2 diabetes with ED, over three quarters (78.0%; *n*=489) were not recorded as taking a PDE5i (*Figure 2*), which was similar to the men without diabetes.

Prevalence of low testosterone and use of testosterone replacement therapy

Data on testosterone levels assessed during the 24 months prior to the audit were available for approximately a third of men with and without type 2 diabetes who had ED. Of those with type 2 diabetes, 18.8% (38/203) had a testosterone level ≤8 nmol/L, compared to 5.9% (11/187) of men without type 2 diabetes.

There were 81 men with type 2 diabetes and ED who had a testosterone level ≤12 nmol/L and only a quarter (27.2%) were receiving testosterone replacement therapy (*Figure 3*).

Discussion

The aim of the REVITALISE audit was to assess the care of men with and without type 2 diabetes who may have ED, or be at risk of ED and/or low testosterone, and to identify where the clinical management of these individuals could be improved, particularly for those with diabetes.

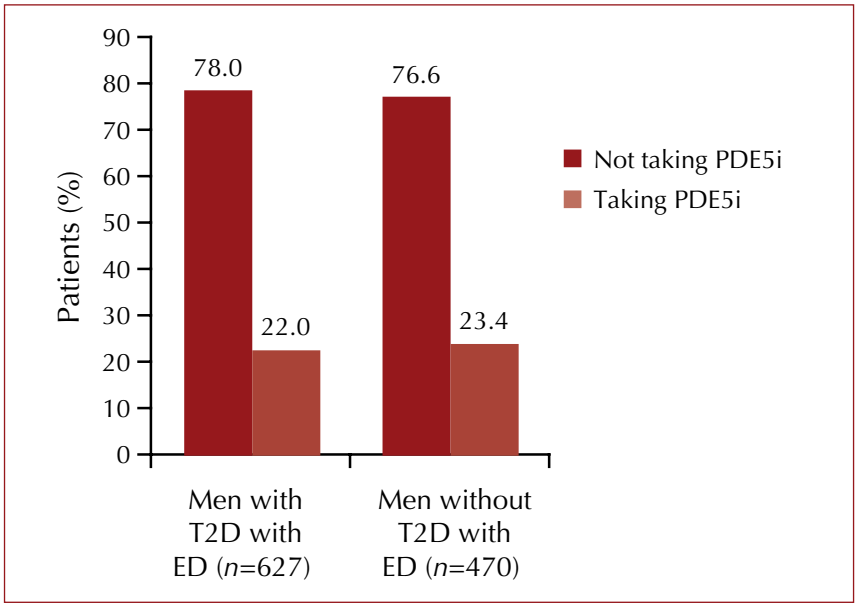

Figure 2. Use of phosphodiesterase type 5 inhibitors (PDE5i) in men with or without type 2 diabetes with erectile problems. ED=erectile dysfunction; T2D=type 2 diabetes.

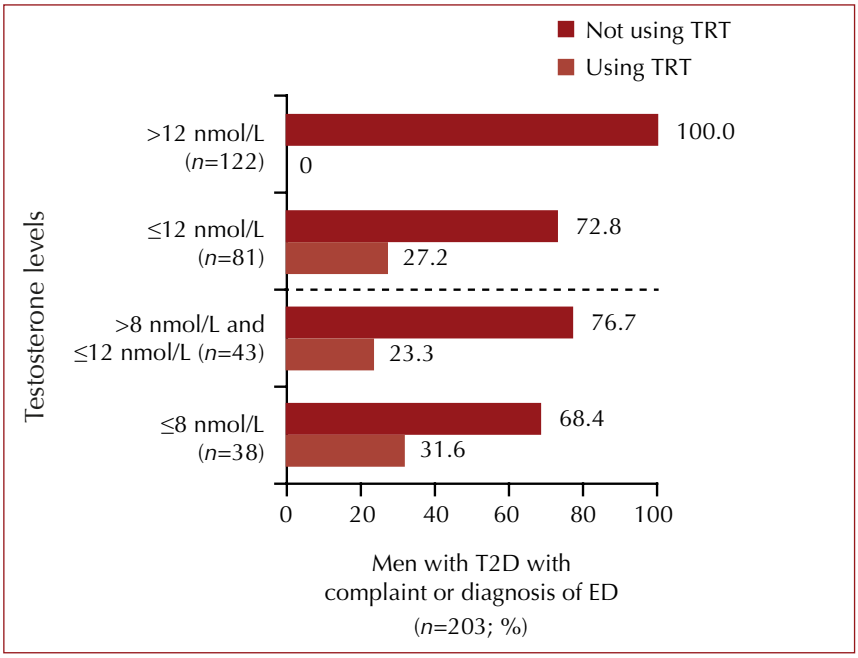

Figure 3. Testosterone levels and use of testosterone replacement therapy in men with type 2 diabetes with erectile problems. ED=erectile dysfunction; T2D=type 2 diabetes; TRT=testosterone replacement therapy.

The prevalence of recorded ED in men with type 2 diabetes (19.7%) was lower than that reported in previously published literature (Malavige and Levy, 2009). Approximately one third of men with type 2 diabetes in REVITALISE were not asked about erection problems, so it is possible that ED was

"NICE (2015) guidelines recommend that men with type 2 diabetes should be offered the opportunity to discuss erectile dysfunction as part of their annual review."

undetected in some patients, while in other cases ED or discussions about ED may not have been recorded in patient notes. With this in mind, the prevalence of recorded ED in men without type 2 diabetes (1.2%) is also likely to be underestimated.

Previous studies have shown that men with diabetes have an almost 3-fold higher probability of developing ED compared with men without diabetes (Feldman et al, 1994). Furthermore, the onset of ED is likely to occur 10–15 years earlier in men with diabetes (American Diabetes Association, 2001). ED in men with diabetes has also been shown to be more severe and associated with a poorer quality of life than men without diabetes (Penson et al, 2003). Various factors can increase the risk of ED in men with type 2 diabetes, including poor glycaemic control, age, duration of type 2 diabetes, BMI and peripheral neuropathy (Binmoammar et al, 2016). This emphasises the importance of early screening for ED and for effective HbA_{1c} control in men with type 2 diabetes (Binmoammar et al, 2016). Evidence suggests that from the onset of ED to subsequent cardiovascular events, there is a time span of approximately 3 to 5 years, and the early detection of ED presents an opportunity for intervention to reduce cardiovascular risk (Hackett et al, 2016b).

NICE (2015) guidelines recommend that men with type 2 diabetes should be offered the opportunity to discuss ED as part of their annual review. Although ED is one of the most frequent chronic health problems in men aged over 40 years (Brotons et al, 2004), particularly those with diabetes, ED is often missed during clinical evaluation or is not recorded, either because of a lack of consideration or awareness, or through embarrassment on the part of both the healthcare professional and patient to discuss or raise the topic (Grant et al, 2013). It is anticipated that the percentage of men identified with type 2 diabetes and ED will reduce considerably in future reviews because questioning is no longer part of the Quality and Outcomes Framework (QOF) Indicators for Diabetes (the current audit used a 24-month time scale and included data from QOF year 2013–14).

ED management

The management of ED in people with type 2 diabetes can be challenging because it may be less responsive to medical treatment than ED in men without diabetes as there are usually other comorbidities and contributing factors (Binmoammar et al, 2016). NICE (2015) guidelines recommend assessment, education and support for men with type 2 diabetes who have problematic ED, and that contributory factors, such as cardiovascular disease, are addressed. Despite PDE5i being the recommended first-line treatment (British Society for Sexual Medicine 2013), with demonstrated efficacy and safety in men with ED and diabetes (Phé and Roupret, 2012), less than a quarter of men with type 2 diabetes and ED in REVITALISE were using PDE5i therapy. Similarly, an earlier study in the United States found that only 25.4% of over 6 million men aged ≥30 years with ED identified from an insurance dataset were treated for ED, with PDE5i therapy being the most commonly prescribed medical therapy (Frederick et al, 2014). The reasons for the low rates of treatment in REVITALISE are unclear but are unlikely to be solely cost-driven as PDE5i therapy is available as low-cost generics. Other potential reasons may include patient preference (e.g. where men do not have a partner or have no desire to have sex), lack of efficacy or undesirable side effects (Raheem and Kell, 2009). Side effects are generally similar for the three PDE5i and include headache, flushing, dyspepsia and rhinitis. Sildenafil has been associated with visual disturbances and tadalafil has been associated with back pain. These side effects typically result in 1–2% drop-out rates.

British Society for Sexual Medicine (2013) and European Association of Urology (Hatzimouratidis, 2015) guidelines recommend that all men with ED are screened for low testosterone. However, over two-thirds of men with type 2 diabetes and ED in REVITALISE had not had a testosterone test in the last 24 months. Furthermore, a substantial proportion of men with type 2 diabetes and low testosterone were not receiving treatment. Among men with type 2 diabetes who had received a testosterone test, over two thirds of those with a testosterone

level ≤8 nmol/L were untreated, while just under three quarters of men with type 2 diabetes and ED who had a testosterone level <12 nmol/L were untreated. Testosterone replacement therapy can improve multiple aspects of sexual function, increase lean muscle mass and strength, and improve mood and cognitive function, with further potential benefits noted in reducing osteoporosis, frailty and mortality (Hackett, 2016; Hackett et al, 2016a). In men with type 2 diabetes, testosterone replacement therapy is also associated with improvements in glycaemic control, insulin resistance, cholesterol levels and visceral adiposity, which together may reduce cardiovascular risk (Kapoor et al, 2006). Many primary care practices would need to refer men requiring testosterone treatment either to a local GP colleague with a special interest in andrology, or to an endocrinologist in secondary care, for the initiation of testosterone replacement therapy.

All 13 practices are planning to re-audit following the actions implemented after the initial audit. One practice is assessing the impact of adding a testosterone blood test to the annual diabetic review, and plans to audit the results of this following a year-long trial.

Limitations

This study has several limitations. No information was gathered on the demographics of the study participants, which may limit the generalisability of the findings; however, the patient population at each participating practice was typical of most primary care practices in England and Wales. Information on the presence of ED was gathered using codes to document whether men had been asked about erectile problems, and a validated instrument was not used to confirm the presence of this condition. A lack of ED was assessed by code 1ABJ (does not complain of erectile dysfunction), which could have led to an underestimation of the number of men without ED as there are potentially many cases where it was not recorded. Also, the British Society for Sexual Medicine (2010) guidelines recommend that blood samples are taken between 9:00 and 11:00 am for the assessment of total testosterone and, in REVITALISE, information was not gathered on the time of day that samples were taken.

Conclusion

Findings from REVITALISE highlight the need to improve the clinical management of men with and without type 2 diabetes who are potentially at risk of ED or low testosterone or both. Despite the well-documented relationship between type 2 diabetes, ED and low testosterone, a substantial number of men with type 2 diabetes were not assessed for either condition, meaning a valuable opportunity to diagnose and to potentially improve the overall health of this group was missed. Furthermore, men who had been diagnosed with ED or low testosterone, or both, were often receiving care that was not in line with current evidence-based guideline recommendations. A proactive approach to the screening and management of ED and low testosterone is needed in men with type 2 diabetes. ■

Take-home messages on erectile dysfunction and diabetes for primary care healthcare professionals.

- Erectile dysfunction (ED) and low testosterone are under-diagnosed in men, especially so in men with diabetes.
- The relationship between ED, diabetes and low testosterone is complex. ED may be a marker of diabetes and diabetes may be a cause of ED.
- According to the British Society for Sexual Medicine (2010), the reference ranges for total serum testosterone are as follows:
  - **>12 nmol/L**: normal
  - **>8 to ≤12 nmol/L**: borderline
  - **<8 nmol/L**: low testosterone

  For borderline cases, repeat the test in line with the guideline recommendations.
- The treatment of ED and low testosterone includes phosphodiesterase type 5 inhibitors (PDE5is). There is evidence that PDE5is are under-used in men with ED.
- Treating ED and low testosterone can have a positive impact on quality of life and overall wellbeing.

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Disclosures

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