The clinical importance of testosterone in men with type 2 diabetes

GEOFF HACKETT

Although the association of low testosterone with type 2 diabetes is well established, testosterone levels are not routinely measured in diabetic patients.

Various studies have highlighted the high prevalence of low total and free testosterone (late-onset hypogonadism or testosterone deficiency syndrome) in men with type 2 diabetes and demonstrated links with visceral adiposity, insulin resistance, HbA1c, and symptoms of hypogonadism such as erectile dysfunction (ED) and low sexual desire. Insulin resistance and visceral obesity are important features of type 2 diabetes and are established markers of cardiovascular risk. An inverse relationship has been established between testosterone levels and insulin concentration in healthy men. Low testosterone has been found to predict insulin resistance and later appearance of metabolic syndrome and type 2 diabetes, as well as a significant increase in all-cause and cardiovascular mortality in long-term studies.

GUIDELINE RECOMMENDATIONS

Current expert guidelines recommend that patients with symptoms of overt hypogonadism and total testosterone levels below 8nmol/l (free testosterone 180pmol/l) should be treated with testosterone replacement therapy, but there is no UK policy for screening at-risk populations such as those with type 2 diabetes. The NICE guideline on

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**Figure 1. Investigation and treatment of testosterone deficiency syndrome**

<table>
<thead>
<tr>
<th>Signs and symptoms of testosterone deficiency</th>
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<tr>
<td>Take morning serum sample for determination of TT and SHBG (between 07.00 and 11.00, when testosterone is at its peak)</td>
</tr>
</tbody>
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**Overt hypogonadism**

- TT <8nmol/l

**Borderline hypogonadism**

- TT 8–12nmol/l

**Not hypogonadism**

- TT >12nmol/l

Retest TT

- LH/FSH, prolactin, SHBG, calculate free testosterone

Confirmed TT

- <8nmol/l or 8–12nmol/l with signs and symptoms, with normal LH/FSH and prolactin

Abnormal LH/FSH and prolactin

Refer

Other causes

Examine occult prostate cancer (DRE and PSA) and check baseline haematocrit

Initiate TRT

Monitor

TT, Total testosterone; SHBG, sex-hormone-binding globulin; LH, luteinising hormone; FSH, follicle-stimulating hormone; DRE, digital rectal examination; PSA, prostate-specific antigen; TRT, testosterone replacement therapy

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management of type 2 diabetes\textsuperscript{10} recommends annual assessment, appropriate investigation and treatment of all men with type 2 diabetes for ED.

ED is recognised as an independent predictor of coronary risk, especially in men with type 2 diabetes.\textsuperscript{11} The current guidelines of the British Society for Sexual Medicine and the European Association of Urology list diabetes as an independent predictor of ED, as it represents a potentially treatable risk factor.\textsuperscript{6,9} They recommend that men with a total testosterone of less than 8nmol/l should be treated and that those between 8 and 12nmol/l should be considered for treatment according to symptoms (Figure 1).

An Endocrine Society task force in 2006 recognised the link between hypogonadism and type 2 diabetes and recommended physicians to consider measuring testosterone in all men with type 2 diabetes.\textsuperscript{12} In their public health guidance 15,13 NICE also recommended that it should be a high priority to identify populations at risk of early death from coronary heart disease. Men with type 2 diabetes, ED and hypogonadism are surely an important group for active intervention. The current GP contract is associated with strict targets in type 2 diabetes linked with the Quality and Outcomes Framework (QOF) and GP performance and payment.

CONSEQUENCES OF LOW TESTOSTERONE
The association of low testosterone with type 2 diabetes has been established in many studies. Three large long-term studies, including the Massachusetts Male Ageing Study\textsuperscript{14} and the Multiple Risk Factor Intervention Trial,\textsuperscript{15} suggest that low total testosterone, free testosterone and sex-hormone-binding globulin (SHBG) are independent risk factors for later development of type 2 diabetes. The Third National Health and Nutrition Survey\textsuperscript{16} demonstrated that men in the lowest tertiles of free testosterone and bioavailable testosterone, but not total testosterone, were four times more likely to develop type 2 diabetes than those in the third tertile, after adjustment for adiposity, age, race and ethnicity.

Kapoor \textit{et al.}\textsuperscript{1} showed strong associations between symptoms and biochemical hypogonadism. Hackett \textit{et al.}\textsuperscript{17} showed clear links between low testosterone and increased body mass index (BMI), waist circumference, HbA\textsubscript{1c} and ED. ED is the most common symptom seen in men with type 2 diabetes (50–75 per cent)\textsuperscript{8,11} in most series, as assessed by the Sexual Health Inventory for Men.\textsuperscript{18} Other symptoms associated with low testosterone are listed in Box 1.\textsuperscript{1} Unfortunately, many press articles have chosen to concentrate on these issues under the guise of the non-existent ‘male menopause’, to the detriment of evidence-based patient care.

The current GP contract puts strong emphasis on type 2 diabetes as a target priority and rewards GPs financially for achieving quality targets in areas that include BMI, waist circumference, HbA\textsubscript{1c}, blood pressure, total cholesterol, prescribing of angiotensin-converting enzyme inhibitors, and eye and foot assessment.

Hackett \textit{et al.}\textsuperscript{19} suggest strong associations between total testosterone and BMI, waist circumference, HbA\textsubscript{1c} and SHBG (Figures 2 and 3). Patients with low total testosterone, free testosterone and bioavailable testosterone\textsuperscript{15} will not only be subject to the potentially greater risk associated with these levels, but are significantly more likely to fall outside QOF targets and result in underperformance. The current top HbA\textsubscript{1c} target of 7.5 per cent is not being achieved by 50 per cent of men in the low testosterone group versus 33 per cent in the normal group. As this target is to be reduced to 7.0 per cent for 2009/10 and possibly 6.5 per cent in line with NICE guidance,\textsuperscript{10,20} these new targets may be very difficult to achieve with current strategies, particularly as conversion to insulin therapy is associated with weight gain.

ERECTILE DYSFUNCTION: THE IMPORTANT DRIVER FOR TREATMENT
Testosterone is not measured routinely in UK and European diabetic practice, in spite of current guidelines suggesting that it should always be measured in the 75 per cent of men with type 2 diabetes who suffer from ED.\textsuperscript{8,10}

Wu \textit{et al.}\textsuperscript{21} highlighted the strong associations of late-onset hypogonadism with type 2 diabetes and the importance of ED, reduced libido and absence of spontaneous erections in making the diagnosis. Failure to measure testosterone results in considerable waste of resources, as response rates to phosphodiesterase type 5 inhibitors (PDE5Is) are low in men with type 2 diabetes and late-onset hypogonadism. Testosterone supplementation has been clearly shown to enhance responsiveness, and in 10–20 per cent of cases\textsuperscript{12} resolves the problem as sole therapy. Improvement of libido and orgasm can be equally important in men with type 2 diabetes.

Once testosterone deficiency syndrome is diagnosed in men presenting with ED, the patient expectation is that it should be treated, and this fact alone is the
The major reason for the significant increase in NHS prescriptions for testosterone over the past five years.

The usual explanation for not measuring testosterone stated in review articles is the presumption that low total testosterone is a consequence of visceral obesity and ageing, or that the fall in SHBG associated with obesity in type 2 diabetes will result in adequate levels of free testosterone, yet the studies suggest that prevalence of testosterone deficiency is even greater if assessed by free testosterone.\(^{14-16}\)

A more realistic explanation is that the target-based management of type 2 diabetes is already an onerous workload for clinicians and that routine questioning about ED and associated testosterone estimation will lead to considerable additional workload, without resources or remuneration.

When ED is detected, it will usually have to be managed, with associated prescribing costs and possible referral implications.

The prevalence of ED in type 2 diabetes is around 75 per cent and is strongly associated with low free testosterone. Romeo et al\(^ {22}\) and Rhoden et al\(^ {23}\) described a linear relationship with HbA1c in men with type 2 diabetes.

In the IPASS study\(^ {26}\), the largest published series of treatment of over 700 patient years with long-term depot testosterone undecanoate, there was a mean 5cm reduction in waist circumference, marked improvement in energy levels, mood, concentration, libido and erectile function. The rate of ED fell from 61 to 25 per cent and the response rate to PDE5Is increased from 37 to 60 per cent.\(^ {26}\) There was a minor normalisation of prostate-specific antigen, but no cases of prostate cancer in the treated group.

The metabolic effects of testosterone are enhanced by lifestyle change.\(^ {27}\) Recent meta-analyses have consistently shown no link between testosterone supplementation and prostate cancer.\(^ {28}\)

**CONCLUSIONS**

NICE guidance on type 2 diabetes recommends that men should be asked annually about ED, and the prevalence of ED in type 2 diabetes is clearly established as being around 75 per cent. There are important implications that arise from this
single recommendation. All ED guidelines recommend testosterone evaluation in all men with ED, and at least 40 per cent of men with type 2 diabetes will have testosterone levels that guidelines suggest should be treated. The Endocrine Society recommends measurement of testosterone in all men with type 2 diabetes. Low response rates to ED medication in men with low testosterone means considerable waste, as low testosterone has been shown to be a major reason for non-response.

Once men with type 2 diabetes are asked about ED, following evidence-based guidelines, many will be diagnosed with low testosterone and this will demand testosterone supplementation as optimal treatment for important troublesome symptoms. The current NHS care pathway of urologist management of ED and associated testosterone deficiency syndrome is not helpful, as the greatest benefits of testosterone supplementation will be seen by the diabetologist, cardiologist, GP and, most importantly, the patient.

Declarations of interests
Geoff Hackett is an occasional speaker for Lilly, Bayer and Boehringer Ingelheim.

REFERENCES
18 Cappelleri JC, Rosen RC. The Sexual Health Inventory for Men (SHIM): a 5-year review.

KEY POINTS
• Late-onset hypogonadism or testosterone deficiency syndrome is prevalent in men with type 2 diabetes.
• There are also links with visceral adiposity, insulin resistance, HbA1c, and symptoms of hypogonadism such as erectile dysfunction and low sexual desire.
• Insulin resistance and visceral obesity are established markers of cardiovascular risk.
• Guidelines recommend that patients with symptoms of overt hypogonadism and total testosterone levels below 8nmol/l should be treated with testosterone replacement therapy, but there is no UK policy for screening at-risk populations such as those with type 2 diabetes.
• Failure to measure testosterone results in considerable waste of resources, as response rates to phosphodiesterase type 5 inhibitors are low in men with type 2 diabetes and late-onset hypogonadism.


