



# 'Every obese male with type 2 diabetes should be screened for hypogonadism'

## FOR

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Hypogonadism is a clinical syndrome complex which consists of symptoms with or without signs and biochemical evidence of testosterone deficiency. The symptoms of testosterone deficiency are non-specific which can make the diagnosis difficult. Symptoms which are most commonly associated with testosterone deficiency are reduced or loss of libido, absent morning erections and erectile dysfunction.<sup>1</sup> Other common symptoms include tiredness, fatigue, impaired physical endurance, loss of vitality, lack of motivation and mood disturbance.

### Erectile dysfunction

Erectile dysfunction (ED) is a common complication in diabetic men with some reports finding up to 70% have the condition. The pathogenesis of ED in diabetic men is multi-factorial and can be due to a combination of these which include vasculopathy, neuropathy, psychological issues and testosterone deficiency. The presence of hypertension, smoking and higher waist circumference are associated with ED in diabetic men.<sup>2</sup> Lower testosterone positively correlates with worsening IIEF (International Index of Erectile Function) in diabetic men.<sup>2</sup> Not all diabetic men with ED have testosterone deficiency but evidence shows that it is present in a significant number. NICE guidelines recommendation is to 'review the issue of erectile dysfunction annually'.<sup>3</sup> The European Association of Urology (EAU) guidelines on ED state that measurement of testosterone is a minimum requirement in the diagnostic evaluation.<sup>4</sup>

Penile Doppler ultrasound has shown that basal systolic velocity and dynamic peak velocity after administration of a phosphodiesterase type 5 (PDE-5) inhibitor are significantly reduced in hypogonadal diabetic men when compared to eugonadal men with diabetes.<sup>5</sup> Failure to respond to sildenafil is associated with low testosterone in diabetes.<sup>6</sup> Animal work has found that castration leads to reduction in vascular smooth muscle content in the corpus cavernosum, reduced elastic fibres and increased collagen in the tunica albuginea, fat deposition between the tunica and corpus cavernosum and reduced nerve sheath thickness in the cavernosal nerve.<sup>7</sup>

### Prevalence of hypogonadism

Epidemiological studies consistently report that men with type 2 diabetes have lower testosterone and higher oestra-

diol levels than healthy controls.<sup>8</sup> Sex hormone binding globulin (SHBG) levels may be low or in the low normal range in some diabetic subjects. Testosterone bound to SHBG is considered to be biologically inactive. Importantly, studies have shown that the biologically active fractions of the total testosterone, i.e. measured free and bioavailable (free + albumen bound) testosterone which are independent of SHBG, are low. Furthermore, there is a high prevalence of hypogonadism in diabetes: 17% with total testosterone below the normal range <8nmol/L with symptoms, and a further 26% with testosterone levels between 8–12nmol/L (borderline low), again with symptoms.<sup>9</sup>

Full investigation is required to determine the underlying cause for hypogonadism; classical causes of hypogonadism include Klinefelter's syndrome, haemochromatosis, pituitary tumours and other causes of hypopituitarism. Registry studies have reported that only 25% of men with Klinefelter's are diagnosed in life and they may present with diabetes.<sup>10</sup> In the absence of a classical aetiology then the hypogonadal state may be due to obesity, a chronic inflammatory state or aging, or a combination of these. Central fat deposits metabolise testosterone to oestradiol as well as secreting adipocytokines which inhibit the hypothalamic-pituitary-testicular axis.<sup>10</sup> Gonadotrophin levels may be normal or low as a result of this mechanism.

Late-onset hypogonadism (LOH) is defined as: 'A clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and a deficiency in testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organ systems.'<sup>11</sup> The European Male Aging Study (EMAS) has reported that increasing BMI and the presence of one or more co-morbidities are two major factors which predict lower testosterone in aging.<sup>12</sup>

The importance of the association between hypogonadism and type 2 diabetes is now recognised, being included in international guidelines for LOH. The recommendation reads as follows: 'The metabolic syndrome and type 2 diabetes are associated with low plasma testosterone. Serum testosterone should be measured in men with type 2 diabetes mellitus with symptoms suggestive of testosterone deficiency.'<sup>11</sup>

### Cardiovascular risk factors

Several studies have shown that testosterone deficiency is associated with adverse cardiovascular risk factors which include insulin resistance, impaired glucose tolerance, dyslipidaemia, hypertension, central adiposity, and hypercoagulable and low-grade systemic inflammatory states.<sup>13</sup> Furthermore, low testosterone correlates with the degree of atherosclerosis as assessed by carotid intima media thickness (CIMT) and aortic calcification, and with the progression of CIMT over a four-year follow-up period.<sup>13</sup>

The majority of population studies report that a low

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testosterone at baseline is associated with an increased risk of death from all-cause mortality and, in some studies, cardiovascular, respiratory and cancer deaths.<sup>14</sup> Low testosterone levels in men with coronary artery disease,<sup>15</sup> and in diabetic men, have also shown poor survival.<sup>16</sup> Androgen deprivation therapy for prostate cancer leads to an increase in incident diabetes, cardiovascular disease and sudden cardiovascular death.<sup>17</sup>

**Testosterone replacement therapy**

Testosterone replacement therapy (TRT) alone can in some men correct erectile dysfunction and convert approximately 60% of sildenafil non-responders into responders.<sup>18</sup> A study in hypogonadal men with metabolic syndrome and/or type 2 diabetes observed that TRT led to an improvement in libido, intercourse and overall sexual satisfaction.<sup>19</sup>

Small studies of TRT in men with type 2 diabetes have beneficial effects on insulin resistance, glycaemic control, waist circumference, and total and LDL cholesterol. No changes in blood pressure were reported.<sup>20</sup> The TIMES2 (Testosterone In METabolic Syndrome and type 2 diabetes) study has confirmed these findings which were maintained for the 12-month study duration.<sup>19</sup> TRT suppresses serum inflammatory cytokines and increases levels of the anti-inflammatory and anti-atherogenic cytokine interleukin-10 in men with coronary artery disease.<sup>21</sup>

**Conclusion**

According to currently available guidelines, screening for hypogonadism consists of the clinician enquiring about symptoms of testosterone deficiency of which the sexual symptoms are the most specific. If symptoms are present, then testosterone levels should be assessed. Erectile dysfunction is a common complication which occurs in men with type 2 diabetes and is a symptom of hypogonadism. Guidelines recommend that all patients with ED as part of a minimum assessment should have testosterone measured. By adhering to NICE guidance recommending an annual enquiry in regard to sexual health, diabetologists are already screening for hypogonadism in the diabetic clinic. There is currently no recommendation that testosterone be checked in all diabetic men. The recently

updated clinical practice guideline of the American Endocrine Society does say that they suggest measurement of testosterone in men with type 2 diabetes.<sup>22</sup>

The benefits of TRT on sexual function and on body composition in hypogonadal men have been recognised for several years and this therapy is a recognised and established treatment for the condition. There is accumulating evidence that TRT may have specific benefits on metabolic and cardiovascular parameters in men with type 2 diabetes. When replacing testosterone the aim should be to try and achieve as near normal physiological replacement as possible. The importance of this is underlined by a recent publication of a study designed to determine the effects of the hormone on frailty where testosterone doses used in frail elderly men with established co-morbidities exceeded those used in normal clinical practice.<sup>23</sup> It is important to recognise that this study was not powered to detect a significant increase in cardiovascular events but did report more cardiovascular-related symptoms/events in the testosterone treatment group. The cardiovascular-related events were heterogeneous and included oedema, which would be expected in high testosterone dose therapy, and self-reported symptoms such as syncope. A similar study using normal testosterone gel dosing did not show an increase in cardiovascular events.<sup>24</sup> These findings, however, demonstrate that larger and longer-term studies are needed to verify the cardiovascular and metabolic action of testosterone replacement in men with diabetes. It also underlines the importance of making a correct diagnosis of hypogonadism and, if indicated, treating with testosterone replacement to attain serum testosterone levels usually in the mid-normal to upper normal range.<sup>25</sup>

**Conflict of interest statement**

THJ is a consultant for ProStrakan as a chief investigator of the TIMES2 study. He has also been a member of advisory boards and has received honoraria for educational lectures from Bayer-Schering Pharma, ProStrakan and Ferring. He has received no funding for the preparation of this article.

**References**

References are available online at [www.practicaldiabetes](http://www.practicaldiabetes)

**AGAINST**

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Screening asymptomatic individuals is worthwhile if the condition to be screened for has an appreciable morbidity, if the diagnostic test for the condition is reliable, with good sensitivity and specificity, and if, once diagnosed, there is safe, cost-effective and

evidence-based treatment.

**Age- and obesity-related decline in serum testosterone level**

The prevalence of type 2 diabetes increases with age and obesity. According to Diabetes UK, since 1996 the number of people diagnosed with diabetes has increased from 1.4 million to 2.6 million. By 2025 it is estimated that over four million people will have diabetes. According to WHO figures globally, there are more than one billion overweight adults, at least 300 million of them obese. There is also an age-related decline in the serum testosterone level, mediated by defects of both pituitary gonadotrophin secretion (central or secondary hypogonadism) and of testicular function itself (peripheral or primary hypogonadism). There is also loss of circadian rhythm of testosterone secre-



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tion and a rise in sex hormone binding globulin (SHBG), leading to a much steeper decline in measures of free or bioavailable testosterone.<sup>1</sup> The association between age-related testosterone decline and symptomatic late-onset hypogonadism remains controversial in the absence of large randomised controlled trials (RCTs). Moreover, the testosterone level below which symptoms of androgen deficiency emerge and adverse health outcomes potentially ensue in older men remains unclear.<sup>2</sup> Ill-health of any cause,<sup>3</sup> including obesity, is also associated with lower serum testosterone level, primarily mediated via an acquired central defect that is reversible with resolution of the underlying condition.<sup>4,5</sup> However, as with non-thyroidal illness ('sick euthyroid') syndrome, we have no definitive information as to whether low serum testosterone levels in this context of functional hypogonadism are maladaptive, neutral or even adaptive.

### What can we learn from postmenopausal sex hormone replacement in women?

An historic literature review stated that: 'We know that menopause is a deficiency state and oestrogen therapy restores the premenopausal endocrine milieu; oestrogen therapy reduces the risk of cardiovascular disease, osteoporosis and Alzheimer's disease. Although its immediate effect is to alleviate climacteric symptoms, the major therapeutic benefit of oestrogen seems to be cardiovascular disease prevention.'<sup>6</sup>

This statement resonates strongly with so many elements of Prof Jones' accompanying article, that we need to delve a bit more deeply into the literature from that period. Until around 1999, expert clinicians believed that available evidence pointed to the following:

- Protection against cardiovascular disease (CVD) is the major benefit of menopausal hormone replacement therapy (HRT).<sup>7</sup>
- Oestrogen replacement therapy reduces morbidity and mortality from coronary heart disease (CHD) by approximately 50% in normal postmenopausal women<sup>8-10</sup> and also in those with established CHD.<sup>11</sup>
- Oestrogen therapy is also associated with a reduction in the risk of death from stroke.<sup>12</sup>
- Angiographic studies have provided particularly strong evidence for the benefits of oestrogen.<sup>13-16</sup>
- Oestrogen therapy reduces coronary stenosis, as documented by a repeat coronary angiogram.<sup>14,15</sup>
- Oestrogen treatment also improves survival after coronary bypass surgery.<sup>17</sup>
- Women with risk factors for CVD, such as smoking, hypertension or history of myocardial infarction, seem to be those who have the most to gain from HRT.<sup>10</sup>
- Oestrogen therapy reduces serum total and LDL cholesterol.<sup>18,19</sup>

However, the Heart and Estrogen/progestin Replacement Study (HERS) randomised control trial ultimately showed no benefit of oestrogen and progesterone in the secondary prevention of CHD.<sup>20</sup> Moreover, the Women's Health Initiative (WHI) study was terminated early based on increased risk of:

- Breast cancer (from 30 to 38 cases per 10 000 women).
- CHD (from 30 to 37 cases per 10 000).

- Stroke (from 21 to 29 cases per 10 000 women).<sup>21</sup>

The Million Women Study (MWS) also revealed an increased risk of breast cancer, with current HRT users more likely to develop it than past users and, moreover, an increased risk of both incident and fatal ovarian cancer.<sup>22,23</sup>

Both of these studies were arguably flawed, with a large number of women randomised who were either obese, smokers or over 60 years of age (or all three), such that they would have been unlikely to have been offered HRT in normal clinical practice. Nevertheless, these studies serve to demonstrate the power of large RCTs over even the best case-controlled association studies. The Committee on Safety of Medicines subsequently recommended that: 'HRT should not be used to prevent coronary artery disease. For menopausal symptoms or osteoporosis it is important for women to discuss risks and benefits of HRT with their GP.'

Thus, although the data on testosterone deficiency and the potential benefits of replacement therapy in men with obesity and/or type 2 diabetes are fascinating (and, incidentally, comparable in quality and scope to that for vitamin D – e.g. higher vitamin D status is associated with decreased risk of type 2 diabetes),<sup>24</sup> it would be inadvisable to recapitulate the over-enthusiastic appraisals of postmenopausal female HRT that were promoted prior to the MWS and WHI era.<sup>25</sup> Until we have large studies available to change our practice, the primary focus for reducing mortality and morbidity in type 2 diabetic men must necessarily lie with reducing their HbA<sub>1c</sub>, blood pressure, lipids and weight.

### The beginning of the end for 'late-onset hypogonadism'?

Fred Wu and colleagues<sup>26</sup> studied 3369 men from the general population between the ages of 40 and 79 years in eight European centres, analysing cross-sectional data from questionnaires and a single serum testosterone measurement. The aim of the study was to examine the potential clinical symptoms associated with a low testosterone level, to identify the thresholds of testosterone below which such symptoms become increasingly prevalent, and to define essential criteria for the syndrome of late-onset hypogonadism on the basis of the presence of symptoms associated with a low testosterone level.

Out of 32 possible symptoms, only nine were confirmed to be related to the total or free testosterone level. These included three sexual symptoms (decreased frequency of morning erection, decreased frequency of sexual thoughts, and erectile dysfunction), three physical symptoms (an inability to engage in vigorous activity, an inability to walk more than 1km, and an inability to bend, kneel or stoop), and three psychological symptoms (loss of energy, sadness and fatigue).

The analysis suggested that late-onset hypogonadism is characterised by the presence of the three sexual symptoms in men with total testosterone levels <317ng/dl (11nmol/L) and free testosterone levels <64pg/ml (220pmol/L), but the results also highlighted the substantial overlap between late-onset hypogonadism and non-specific symptoms of aging.

Wu and colleagues found that the long list of non-

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specific symptoms that have a potential association with testosterone deficiency made it difficult to establish a clear diagnosis of late-onset hypogonadism. Moreover, even the most specific symptoms of 'androgen deficiency' were relatively common even among men with normal testosterone levels.

The study authors concluded that, in order to increase the probability of correctly diagnosing late-onset hypogonadism, all three 'sexual symptoms' (among the total of nine 'testosterone-related symptoms') had to be present. Thus, late-onset hypogonadism emerged from this analysis as something of a niche diagnosis – rather than the pandemic that industry might have us believe exists.

A study involving 1445 community dwelling US men, looking at the relationship between sex hormones, mobility limitations and physical performance, found that lower levels of baseline free testosterone were associated with a greater risk of incident or worsening mobility limitation. The question necessarily arose as to whether this risk could be reduced with testosterone therapy, something that could only be determined by large randomised trials.<sup>27</sup>

Recently published research data looked at adverse events associated with testosterone administration in 209 community-dwelling men, 65 years of age or older (mean age 74 years), with limitations in mobility and a total serum testosterone level of 100–350ng/dl (3.5–12.1nmol/L) or a free serum testosterone level of less than 50pg/ml (173pmol/L). At baseline there was a high prevalence of hypertension, diabetes, hyperlipidaemia and obesity. Subjects were randomly assigned to receive placebo gel or testosterone gel, to be applied daily for six months. The trial was discontinued early because there was a significantly higher rate of adverse cardiovascular events in the testosterone group (23 subjects) than in the placebo group (five subjects).<sup>28</sup>

The Endocrine Society recommends against a general policy of offering testosterone therapy to all older men with low testosterone levels, suggesting instead that clinicians consider offering testosterone therapy on an individualised basis to older men with low testosterone levels on more than one occasion and clinically significant symptoms of androgen deficiency, after explicit discussion of the uncertainty about the risks and benefits of testosterone therapy.<sup>2</sup>

However, only a minority of USA clinicians prescribing testosterone therapy are members of the Endocrine Society, possibly explaining the explosion of testosterone prescribing that has occurred in North America since the ready availability of transdermal preparations.<sup>29</sup> Our USA colleagues advise us anecdotally that something very similar may be happening in respect of testosterone prescribing in obesity and/or type 2 diabetes.

At the end we agree with Prof Jones' statement in a recent publication: 'A number of short-term studies support the notion that testosterone therapy improves independent cardiovascular risk factors, but there is no clear answer as to whether testosterone treatment reduces mortality.'<sup>30</sup>

The data from association studies and small-scale intervention studies look promising, but it would be imprudent to proceed to mass screening of men with type 2 diabetes in order to detect functional hypogonadism of chronic disease in the absence of data from large RCTs.

Nevertheless, we should remember that the prevalence of endocrine disturbance in the typical diabetes clinic may be of an order of magnitude greater than in the general population, specifically including patients with organic hypogonadism related to Cushing's disease, acromegaly, Klinefelter's syndrome and haemochromatosis. In the end, there is no substitute for careful case ascertainment arising from talking to and examining our patients with type 2 diabetes. It would be reasonable to measure a morning serum testosterone level in any patient with osteoporosis or other feature of hypogonadism, or in whom erectile dysfunction failed to respond to standard therapy with PDE-5 inhibitors.

**Conflict of interest statement**

The authors have received no funding for the preparation of this article. Over the past five years, RQ has received various small honoraria, unrestricted educational donations and consulting fees from all of the companies presently marketing testosterone replacement therapies in the UK, amounting to a total sum of under £2000.

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References are available online at [www.practicaldiabetes](http://www.practicaldiabetes)

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### AGAINST

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