ABCD position statement on the management of hypogonadal males with type 2 diabetes

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Introduction

Levels of testosterone drop slowly with ageing. Within any age group there is a wide spectrum of what may be considered 'normal' levels of testosterone. This, and the fact that testosterone deficiency may present with a wide variety of non-specific symptoms, makes the diagnosis of testosterone deficiency or hypogonadism difficult in any given individual. In addition, the prevalence of obesity and diabetes is increasing and both of these conditions are associated with reduced serum testosterone levels. This position statement addresses the diagnosis and management of hypogonadism in type 2 diabetes, and highlights areas of controversy.

Definition

Hypogonadism can be defined as a clinical syndrome of symptoms, with or without physical signs, in conjunction with biochemical evidence of testosterone deficiency. Classically, hypogonadism occurs due to either primary testicular failure or a disruption in the hypothalamic-pituitary-testicular pathway. The term late-onset hypogonadism (LOH) is now widely used for testosterone deficiency associated with ageing; however, this term should only be used once other causes of hypogonadism have been excluded. LOH is defined as a clinical and biochemical syndrome associated with advancing age and characterised by typical symptoms and signs of testosterone deficiency. LOH may significantly reduce quality of life and adversely affects the function of multiple organ systems.[1] The consensus of the International Society for Andrology, the International Society for the Study of the Aging Male, and the European Association of Urology, the European Academy of Andrology and the American Society of Andrology recommend that hypogonadism be defined as total serum testosterone (TT) of <8nmol/L.[1] The American Endocrine Society suggests that hypogonadism be defined as being symptoms and signs of androgen deficiency associated with a TT of less than 10.4nmol/L.[2] Furthermore, it should be borne in mind that these are general guidelines and that there are variations in testosterone assays between laboratories and suppliers. The wide reference ranges quoted by assay manufacturers can lead to practical difficulties when applying the arbitrary value for hypogonadism to an individual without access to their pre-morbid testosterone (T) level.

ABCD believes that the diagnosis of hypogonadism in men with type 2 diabetes should be based on clinical symptoms and, recognising the circadian rhythm of testosterone secretion, biochemically confirmed using a sample taken between 8am and 11am for total or free testosterone depending upon local arrangements and reference ranges. However, because evidence suggests that many patients with TT levels between 8 and 12nmol/L also benefit from testosterone replacement therapy (TRT), some international guidelines recommend a trial of TRT in patients with these intermediate TT levels.[1] ABCD generally favours a cut-off total testosterone level of <8nmol/L for a confirmed diagnosis of hypogonadism.

Free testosterone (fT) should not be measured using analogue assays because these still correlate with sex hormone binding globulin (SHBG). In addition, it is essential to validate local assays with their own reference ranges due to the variability in populations, as well as the coefficient of variations within the assay kits. However, calculating the fT using the Vermeulen equation (www.issam.ch/freetesto.htm) can be helpful in assessing the patient with borderline hypogonadism.[3]

Incidence and prevalence

Depending on the definitions used, it has been estimated that between a fifth to a half of all men with type 2 diabetes have hypogonadism.[4,5] However, in one study the high prevalence was based only on testosterone levels without recording concurrent symptoms.[4] It must also be remembered that other causes of hypogonadism, such as Klinefelter's syndrome and haemochromatosis, may present initially with diabetes. Thus, in a population of men with type 2 diabetes, the prevalence of hypogonadism based on symptoms and low T levels may be in the order of 20–30%. It may be a reasonable assumption to suggest that for 30–50% of these men it may not be appropriate to offer TRT

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either because they chose not to have treatment or due to other comorbidities. Thus, it may be necessary to treat 10–15% of diabetic men with TRT.

Several longitudinal observational studies suggest that the prevalence of hypogonadism increases as men get older.[6–8] This physiological age related decline in testosterone reduces levels by about 1–2% per year after the age of 40.[9,10] Ageing and obesity are both independently associated with increasing incidence of hypogonadism.[6] The low testosterone levels found with ageing and obesity have complex biochemical relationships. In a normal ageing population approximately 8% of men aged between 50–79 years develop hypogonadism.[11] The European Male Aging Study has reported that testosterone levels are lower with obesity and in the presence of one or more comorbidities.[12] Central adiposity is associated with lower testosterone levels, even in younger men. Testosterone directly influences insulin sensitivity. In healthy lean or obese men a low testosterone is associated with an increased risk of developing diabetes or the metabolic syndrome. Visceral adipose aromatase consumes testosterone converting it to oestradiol. These raised oestradiol and adipocytokine levels then inhibit the hypothalamic-pituitary-testicular response to lower testosterone levels.

Thus, although ageing alone lowers testosterone, if levels are already lowered due to other factors, e.g. obesity, then the fall in T with age may exacerbate this.

Hypogonadism in the general population may be under-diagnosed because of the multitude of non-specific symptoms (Table 1), embarrassment in discussing sexual function, and possibly a lack of awareness about the condition among some health care workers. Table 2 highlights who should have biochemical tests for hypogonadism.

Signs and symptoms

As outlined in Table 1, whilst the most common symptom of hypogonadism is erectile dysfunction, other symptoms are variable, non-specific and may vary with age. They therefore mimic other conditions. Two widely used tools to help determine the presence of androgen deficiency are available: the Androgen Deficiency in the Aging Male (ADAM) questionnaire,[13] and the more detailed Aging Male Symptom Scale (AMS).[14] With the ADAM questionnaire, if the patient answers yes to the erectile dysfunction question then the questionnaire becomes positive. The AMS may be used to judge the effects of treatment. However, these tools do not carry a high specificity for diagnosis and are currently not recommended for this purpose.

Table 1. List of signs and symptoms of male hypogonadism

- Reduced or loss of libido
- Reduced quality and frequency of erections
- Fatigue, reduced physical strength and endurance
- Changes in mood with depressed mood and irritability
- Sleep disturbances
- Reduced motivation
- Hot flushes and sweats
- Change in body composition, with less lean body mass and increased visceral fat
- Sarcopaenia
- Decreased body hair and skin alterations
- Gynaecomastia
- Subfertility
- Reduced bone mineral density
- Low haematocrit

Table 2. Who should have biochemical tests to confirm hypogonadism?

- All patient with type 2 diabetes who present with erectile dysfunction
- Patients with clear and unequivocal symptoms of hypogonadism
- Patients suspected of primary or central hypogonadism due to other clinical conditions

Biochemistry

Testosterone levels vary due to circadian rhythms. If androgen deficiency is suspected then a blood sample should be taken between 8am and 11am for testosterone. If this is above 12nmol/L then hypogonadism can be safely excluded. However, if it is lower than 12nmol/L then the level should be repeated, in addition to luteinising hormone (LH), follicle stimulating hormone (FSH), SHBG, ferritin, and prolactin. These additional tests help differentiate between primary or secondary testicular failure. In two-thirds of men, the LH is in the normal range but this does not exclude a diagnosis of hypogonadism. An inappropriately normal LH in the face of a low testosterone is still diagnostic of hypogonadotrophic hypogonadism.

In healthy men, about 60% of circulating testosterone is tightly bound to SHBG and is thus thought to be unavailable. About 38% is loosely bound to albumin with the remaining 2% being free in the circulation. The albumin bound and the fT are considered 'bioavailable'. There is a distinct relationship between type 2 diabetes and hypogonadism. However, the relationship between ageing, obesity and diabetes with SHBG is more complex. Ageing is associated with a rise in SHBG, and visceral obesity and insulin resistance may be associated with low SHBG levels, thus it is difficult to determine whether the associated low TT levels are due to ageing or to the diabetes *per se*. Furthermore, the aromatisation of testosterone to oestradiol further raises SHBG levels. In addition, the use of statins, a class of drugs widely advocated in type 2 diabetes, has been shown to lower SHBG (and hence TT), but had no effect on bioavailable T or calculated fT.[15] Therefore it is important to use a validated tool, such as the Vermeulen equation,[3] to determine the fT level.

As mentioned previously, evidence suggests that a low TT itself predicts the onset of the metabolic syndrome.[16–18] With low SHBG levels, TT levels may be low, but fT may be within the reference range. There is evidence to suggest that obesity is associated with low fT levels[5] and that these low levels may, in part, be responsible for the development of insulin resistance and impaired glucose regulation.[16] With the onset of glucose intolerance, TT drops further when compared with BMI and aged

matched controls. The potential mechanisms for this are complex and are outside the remit of this document. The use of the on-line equations, together with reported symptoms, will help to determine whether the hypogonadism is severe enough to warrant treatment. If SHBG levels are low and the patient is overweight, weight loss alone may improve symptoms without the need for testosterone therapy. Other potentially adverse effects of testosterone deficiency are listed in Table 3.

Treatment

The exact biochemical levels below which TRT should be started are unknown and the treatment should be guided clinically based on symptoms and a low fT. The current consensus for the goal of TRT is to restore circulating plasma levels into the reference range. If there is no appreciable clinical benefit, then the dose may be increased to get the levels into the upper half of the reference range (taking care not to exceed it). This 'clinical benefit' includes the alleviation of symptoms of androgen deficiency, the induction or restoration of androgen-dependent physiological functions and the prevention of long-term health risks of androgen deficiency (Table 3). Few of the currently available formulations are able to mimic the normal circadian rhythm of testosterone production; an exception to this are some of the topical gel preparations.

Prior to initiation

Prior to initiation men should have a thorough history taken to exclude the presence of breast or prostate cancer and to determine if any relative contraindications are present. A rectal examination of the prostate should be performed to exclude any pre-existing pathology in men over 45 years of age and if found to be abnormal an urgent referral made to the urologists.[1] A full blood count (for haematocrit) and prostate specific antigen (PSA) in men over 45 years of age should also be done prior to starting therapy.[1] Liver function tests may be performed if haemochromatosis is suspected as a cause of the hypogonadism.

Table 3. Potential risks of long-term androgen deficiency in men with diabetes

- Increased risk of premature cardiovascular morbidity and mortality
- Osteoporosis
- Increased incidence of respiratory disease
- Falls
- Sarcopaenia

Table 4. Potential benefits of treating hypogonadism in type 2 diabetes

- Improvement in erectile dysfunction and sexual function
- Relief of other symptoms of hypogonadism
- Decrease in truncal adiposity
- Increase in insulin sensitivity
- Improved glycaemic control
- Decrease in total cholesterol
- Improved quality of life
- Improved psychological wellbeing

Potential benefits of TRT

These are outlined in Table 4; however, a few are worthy of a little more discussion.

Sexual function

TRT in hypogonadal diabetic men can improve libido and sexual performance. In some instances, erectile function also improves. In addition, studies have shown that diabetic men who previously did not respond to sildenafil have lower levels of T than responders. When non-responders were treated with TRT this resulted in conversion of 60% of sildenafil non-responders to responders.[19,20]

Metabolic

Testosterone replacement for men with type 2 diabetes has been shown to improve glycaemic control as well as reducing waist circumference and insulin resistance, measured using the HOMA index.[21]

Cardiovascular

Low levels of testosterone have been shown to be associated with adverse cardiovascular risk profiles, in particular with greater rates of visceral adiposity, inflammatory markers, insulin resistance, and an adverse atherogenic profile. In addition, epidemiological work has shown that rates of all-cause mortality and cardiovascular disease are highest in the proportion of men with the lowest quartile of T,[22,23] although this was not a universal finding.[24,25] Whilst there have been a number of animal and small-scale human studies showing that TRT improves these markers of cardiovascular risk, there have been very few large, well-conducted studies looking at cardiovascular endpoints with TRT. Thus, long-term outcomes with TRT remain to be determined.

Table 5. Potential side effects of testosterone replacement

- Significant increase in haematocrit
- Increase in prostatic volume
- Increase in prostate specific antigen levels
- Dyslipidaemia
- Abnormalities of liver function tests associated with the use of oral preparations (not available in the UK or EU)
- Mood changes – aggression
- Gynaecomastia
- Acne and oily skin

Note. Supraphysiological levels can potentially aggravate latent or overt cardiac failure, stimulate appetite and cause weight gain, water and sodium retention, or priapism. The use of testosterone is contraindicated in male breast cancer and in most forms of prostate cancer

Table 6. Monitoring testosterone therapy (at three, six and 12 months and annually thereafter)

- Full blood count (haemoglobin and haematocrit)
- Liver function tests (especially with oral preparations)
- Fasting lipid profile
- Prostate specific antigen
- Testosterone level

Potential adverse effects

Despite TRT reversing the symptoms of testosterone deficiency it has also been shown to be associated with potential adverse effects. These are listed in Table 5. Ongoing monitoring

is mandatory in men on TRT. The PSA and full blood count to check the haematocrit should be done at three, six and 12 months after treatment initiation, and annually thereafter. It should be remembered, however, that with testosterone deficiency the PSA may go down, and that there may be an initial rise in PSA at the start of replacement therapy. The levels should, however, remain within the reference range. It is also important to remember that it is the speed at which the PSA rises (the 'PSA velocity') that needs to be assessed. If the total PSA rises above the reference range, the levels should be rechecked after three months. If the levels remain high, then an appropriate referral should be made.[26]

Other necessary tests that need monitoring are listed in Table 6.

Table 7. Stopping criteria for testosterone replacement therapy

Absolute contraindications:
- The development of a sex hormone dependent malignancy, e.g. prostate or breast cancer or a primary liver tumour
- Unexplained rise in prostate specific antigen
- Unexplained hypercalcaemia
- Nephrotic syndrome
- Untreated obstructive sleep apnoea

Stopping TRT should be considered if:
- No clinical benefit is seen after 3–6 months of replacement (many patients can take up to 6 months to respond to benefits in erectile function)
- There is persistent elevation of haematocrit (>0.54) which cannot be controlled by testosterone dose adjustment, change in testosterone formulation or regular venesection. Referral to haematologist should be considered in case of other disease entity
- There are symptoms of severe lower urinary tract outflow obstruction
- There are psychological problems, e.g. aggression, sexually inappropriate behaviour, depression or anxiety
- There is rising prostate specific antigen. TRT should be stopped until investigated by a urologist to exclude prostate carcinoma

Methods of replacement

The prime aim is to replace testosterone to physiological or as near physiological levels as possible. Testosterone levels need to be checked in men on TRT to be sure that they remain within or near the normal range depending on the preparation. Ideally, a testosterone level greater than 15nmol/L but less than 30nmol/L should be achieved. This is based on evidence from one study showing that there may be a threshold of 15nmol/L above which symptoms related to hypogonadism are unlikely to occur.[27] Some of the topical gel preparations – after careful titration – may make this possible, but most formulations of testosterone do not allow for this. In addition, the mode of testosterone replacement should be determined

Table 8. Key messages regarding hypogonadism in type 2 diabetes

- Low total testosterone levels are common in people with type 2 diabetes and the metabolic syndrome
- Several epidemiological studies have confirmed that there is relationship between obesity and low testosterone levels
- These is a complex interaction between diabetes, obesity and sex hormone binding globulin
- Many hypogonadal men have been shown to have features of the metabolic syndrome (obesity, hypertension, dyslipidaemia, impaired glucose regulation and reduced insulin sensitivity)
- ABCD believes that questionnaires such as AMS and ADAM should not be used for the diagnosis of hypogonadism. However, the AMS in particular is useful in assessing symptoms and provides a score and can be used to assess clinical improvement on TRT
- The effect of testosterone replacement on glycaemic control in type 2 diabetes at present remains uncertain
- ABCD at present believes that it is premature to recommend routine testosterone treatment in type 2 diabetes or for those with the metabolic syndrome
- Treatment in type 2 diabetes should be limited to those showing both clinical and laboratory evidence of hypogonadism. Treatment in this group of patients may have benefits on their metabolic status but the long-term metabolic outcome and impact on cardiovascular disease and prostate health need confirmation in intervention trials
- If androgen deficiency is suspected then at least two blood samples drawn between 8am and 11am should be taken for testosterone, and if the first sample is low or low normal then luteinising hormone, follicle stimulating hormone, sex hormone binding globulin, ferritin, and prolactin should be measured
- If the total testosterone level is between 8 and 12nmol/L in a symptomatic individual then a trial of testosterone replacement is warranted, with early review to monitor the effects
- As with other forms of hormone replacement, patients need to be assessed regularly (as per international guidelines) by an experienced clinician to see if they continue to need it or if they have developed any conditions where continued treatment may be detrimental
- If the man has tried a phosphodiesterase inhibitor without success and has a total testosterone of <12nmol/L, then a six-month trial of testosterone replacement is warranted
- Prior to starting testosterone, men should have a full blood count, liver function tests, lipid profile and prostate specific antigen, as well as a prostate examination
- Initiation of TRT should be undertaken under specialist supervision in secondary care

by the patient after discussion of the different options available. In some instances, patients may wish to change to an alternative preparation at a later date. The available options for starting testosterone have recently changed because of the withdrawal of the testosterone patch. This leaves the transdermal testosterone gels. The gels are either in fixed dose containers, or as actuated dose dispensers. An advantage of the graded, incremental approach offered by the actuated meter is that it allows symptoms and biochemical parameters to be assessed with less risk of developing the potential adverse effects of fixed, higher doses. Transdermal testosterone given using patches achieved physiological levels, but were not consistent in maintaining the levels within the normal range and had many local side effects, including skin irritation and ulceration. These patches have recently been withdrawn. Although oral and buccal preparations provide an alternative, these are now rarely used.

Short-acting injections are commonly used; however, these tend to result in large fluctuations in serum T levels over several weeks through variable absorption. If the patient prefers parenteral administration, there is a role for three- to four-monthly long-acting injections of testosterone undeconoate.

The criteria to consider stopping TRT are listed in Table 7.

Summary

Table 8 summarises the key messages regarding hypogonadism in type 2 diabetes. Hypogonadism and low testosterone levels are common in type 2 diabetes. There is a clear relationship between low testosterone levels and the metabolic syndrome. However, there are only a few small studies showing that testosterone replacement may be helpful in improving the metabolic control, wellbeing and quality of life of patients with type 2 diabetes. ABCD does not recommend that testosterone should be measured routinely in all male patients with type 2 diabetes. Long-term studies are needed to establish the benefits of treating low testosterone levels in people with type 2 diabetes.

Conflict of interest statement

KD has received honoraria for speaking, and travel grants from Pfizer, Bayer and Lilly.

THJ is a consultant for Prostrakan as a chief investigator of the TIMES2 study, has a research grant from Bayer-Schering Pharmacy and has received honoraria for educational lectures and advisory boards from Bayer-Schering, Prostrakan and Ferring.

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