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Review

Androgen deficiency and type 2 diabetes mellitus

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ABSTRACT

The rising incidence of T2DM is well recognised and associated with trends in obesity and ageing. It is estimated that 2.8% of the world population had a diagnosis of diabetes mellitus in 2000, which is projected to rise to 4.3% by 2030. Diabetes, obesity and ageing are also associated with an increased risk of isolated male hypogonadotropic hypogonadism, often labelled 'late onset hypogonadism' (LOH) to distinguish it from hypogonadism secondary to distinct hypothalamopituitary pathology. Whether the incidence of hypogonadism is increasing is open to question; the past decade, however, has witnessed a marked increase in the prescription of testosterone replacement therapy. Testosterone deficiency appears to be particularly common in type 2 diabetes with a prevalence of 33% observed in one cohort of 103 men (mean age 54.7). However, the diagnosis of androgen deficiency states is not necessarily straightforward, depending amongst other factors, upon whether a biochemical threshold or a syndromic approach (mandating the presence of certain key clinical features) is employed. The pathogenic mechanisms underlying obesity and diabetes related hypogonadism remain unclear with several competing theories, most of which are not mutually exclusive. Whilst a large body of epidemiological evidence associates testosterone deficiency with increased risk of cardiovascular disease and mortality, little evidence exists to support a protective effect of testosterone replacement. The benefits of androgen replacement in younger men with pituitary disease are well established, however, the potential benefits and safety of androgen replacement in older men is much less well developed. At present, replacement therapy in older men is advocated principally for the amelioration of sexual symptoms. This review will seek to explore issues around the pathogenesis, diagnosis, clinical consequences and management of male hypogonadism as it relates to T2DM.

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Introduction

The rising incidence of type 2 diabetes mellitus T2DM is well recognised and associated with trends in obesity and ageing. It is estimated that 2.8% of the world population had a diagnosis of diabetes mellitus in 2000, which is projected to rise to 4.3% by 2030 [101]. Diabetes, obesity and ageing are also associated with an increased risk of isolated male hypogonadotrophic hypogonadism, often labelled 'late onset hypogonadism' (LOH) to distinguish it from hypogonadism secondary to distinct hypothalamo-pituitary pathology. Whether the incidence of hypogonadism is increasing is open to question [79]; the past decade, however, has witnessed a marked increase in the prescription of testosterone replacement therapy [30]. Testosterone deficiency appears to be particularly common in type 2 diabetes with a prevalence of 33% observed in one cohort of 103 men (mean age 54.7) [19]. However, the diagnosis of androgen deficiency states is not necessarily straightforward, depending amongst other factors, upon whether a biochemical threshold or a syndromic approach (mandating the presence of certain key clinical features) is employed. The pathogenic mechanisms underlying obesity and diabetes related hypogonadism remain unclear with several competing theories, most of which are not mutually exclusive. Whilst a large body of epidemiological evidence associates testosterone deficiency with increased risk of cardiovascular disease and mortality [63,54], little evidence exists to support a protective effect of testosterone replacement. The benefits of androgen replacement in younger men with pituitary disease are well established, however, the potential benefits and safety of androgen replacement in older men are much less well developed. At present, replacement therapy in older men is advocated principally for the amelioration of sexual symptoms [3]. This review will seek to explore issues around the pathogenesis, diagnosis, clinical consequences and management of male hypogonadism as it relates to T2DM.

Diagnosis

Definition of androgen deficiency states

Androgen deficiency in the context of type 2 diabetes, conforms more to the entity described as 'late onset hypogonadism' than so-called 'pathological' or 'classical' hypogonadism. Whilst diagnosing pathological hypogonadism tends to be relatively straightforward, the criteria by which LOH is diagnosed remain controversial. An ideal diagnostic threshold would closely correspond with symptoms and ultimately help differentiate between individuals likely to benefit from replacement therapy and those who would not. Rather than adopting a straightforward biochemical diagnostic threshold, it has been suggested that a syndromic approach, combining testosterone levels and the most reproducible symptoms, is preferable. The European Male Ageing Study (EMAS) assessed over 3000 community dwelling men (mean age, 59.7 years), 7.5% of whom had a diagnosis of diabetes and 73.8% were either overweight or obese. EMAS identified decreased frequency of morning erections, erectile dysfunction and decreased frequency of sexual thoughts as the most discriminatory symptoms of testosterone deficiency; inflexion points for these symptoms occurred with testosterone levels below 11 nmol/L, 8.5 nmol/L and 8 nmol/L, respectively [104]. The proposed EMAS definition of LOH is, therefore, a total testosterone less than 11 nmol/L in association with at least 3 sexual symptoms. Adopting this syndromic diagnostic approach reduces the prevalence of LOH in men from 17%, when considering a simple biochemical threshold (<11 nmol/L), to 2.1%. What remains unresolved is the issue of identifying individuals, with testosterone levels below the normal range, likely to benefit symptomatically from testosterone replacement; it is conceivable that some individuals not fulfilling EMAS criteria may still obtain symptomatic benefit from normalisation of their testosterone levels.

The link between symptoms and plasma testosterone concentration is much clearer in classical androgen deficiency states than in diabetes related hypogonadism. A cohort of 355 men with T2DM reported reduced libido in 58% of men with subnormal total testosterone and in 48% of those with normal testosterone. Erectile dysfunction was almost as common in eugonadal men (68%) as those with low total testosterone (72%) [46]; this highlights the fact that the origin of sexual dysfunction is often multifactorial in men with T2DM and identifying those most likely to respond to testosterone replacement is problematic.

Longitudinal follow-up studies suggest that increasing adiposity, smoking cessation and the presence of comorbid conditions (including depression), are associated with declining levels of total testosterone [80] and largely account for the observed changes which accompany ageing. In the absence of significant comorbidity or development of obesity, total testosterone levels remain relatively stable with advancing age. However, from middle age, SHBG levels gradually increase with a resultant fall in free testosterone levels and a consistent upward trend in LH. [103]. As a consequence of apparent age-related changes in the hypothalamo–pituitary–gonadal axis, the advisability of age-adjusted reference ranges has been mooted, particularly as many clinicians are wary of medicalising a process that may represent normal ageing. In selected healthy community-dwelling men aged 70–89, the 2.5th centile for testosterone was 6.4 nmol/L and this has been advanced as possible diagnostic threshold in older men [105].

Investigation of androgen deficiency

Although Endocrine Society guidelines suggest measurement of testosterone in all men with T2DM, given the high prevalence of androgen deficiency [3], there is not a strong evidence base to support case finding in the absence of symptoms. However, the prevalence of erectile dysfunction is as high as 70% in men with T2DM [46] and enquiry into sexual symptoms is often neglected during diabetes clinic consultations. When measuring testosterone, it is important to consider factors that may result in transient suppression of testosterone, including acute reversible illness and numerous medication classes, including opioid analgesia and glucocorticoids. In a recent meta-analysis, statins were shown to reduce total testosterone by an average of 0.66 nmol/L in men [77]. In eugonadal men with T2DM, the thiazolidinedione pioglitazone was shown to reduce total testosterone by 1.1 nmol/L over a six month period [85]; although the opposite effect was observed in a small uncontrolled study of rosiglitazone [47]. Another small study in men with T2DM demonstrated a greater than 10% reduction in total testosterone following three months of treatment with metformin and a low calorie diet, despite beneficial effects upon weight [65]. Testosterone should be measured in the morning as it is subject to marked diurnal variation, although this is less pronounced in older men [9]. Recently recognition