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REVIEW

Male hypogonadism. Part I: Epidemiology of hypogonadism

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Male hypogonadism is a frequent and potentially undertreated condition. A number of longitudinal epidemiologic studies, including the Baltimore Longitudinal Study of Aging, the New Mexico Aging Process Study, and the Massachusetts Male Aging Study, have demonstrated age-related increases in the likelihood of developing hypogonadism. In addition to advancing age, increasing body mass index and/or type II diabetes mellitus may be associated with lower circulating androgen levels. Owing to the demographic trends toward increasing population age and life expectancy, together with the emerging pandemic of diabetes and recent trend toward an increasing prevalence of obesity in the United States, clinicians are likely to encounter increasing cases of hypogonadism in the near future.
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Introduction

Hypogonadism affects up to 4 million American men, yet only 5% of candidates receive treatment.[1] Evidence suggests that low testosterone (T) and the attendant symptoms and signs of hypogonadism can be effectively treated using testosterone replacement therapy (TRT). This article will review the epidemiology of male hypogonadism. Subsequent articles will review (1) the etiology, pathophysiology, and diagnosis of male hypogonadism; and (2) the pharmacokinetics, efficacy, tolerability, and safety profiles of different forms of TRT, as well as required screening and monitoring tests prior to and during TRT.

Epidemiology

Demographic trends and potential risk factors

Aging

Trend. The advancing median age, increased life expectancy, and rising prevalences of obesity and type II diabetes mellitus (DM2) in western industrialized societies may result in increasing numbers of male hypogonadism cases in the near future. According to US Census Bureau projections, the number of Americans ages 65 or older will rise from approximately 35 million (12.4% of all Americans) in 2000 to nearly 55 million (16.3% of total) by 2020 and nearly 87 million (20.7%) in 2050.[2] In addition to a two-fold increase in the number of elderly patients, octogenarians will comprise the fastest-growing population segment according to age.[3]

Effects of aging on circulating testosterone. In healthy, young eugonadal men, serum T levels range from 300 to 1050 ng/dl, but decline with advancing age, particularly after 50 years (Figure 1).[4–6] Using a serum T level <325 ng/dl, the Baltimore Longitudinal Study of Aging (BLSA) reported that approximately 12, 20, 30, and 50% of men in their 50s, 60s, 70s, and 80s, respectively, are hypogonadal.

Longitudinal and cross-sectional studies have demonstrated annual T decrements of 0.5–2% with advancing age.[5–9] The rate of decline in serum T in men appears to be largely dependent on their ages at study entry. In the BLSA, the average decline was 3.2 ng/dl per year among men age 53 years at entry.[5] On the other hand, the New Mexico Aging Process Study of men 66–80 years at entry showed a decrease in serum T of 110 ng/dl every 10 years.[6] Although serum T levels are generally measured in

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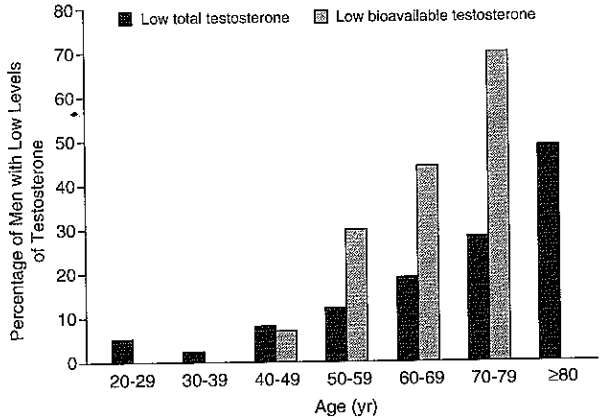

Figure 1 Percent of men with low levels of testosterone and bioavailable testosterone as a function of age. Reproduced with permission from Rhoden *et al.*[4] ©Copyright 2004 Massachusetts Medical Society. All rights reserved.

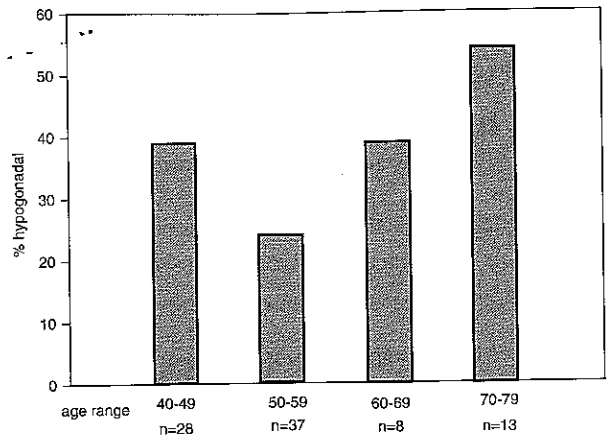

Figure 2 Percentage of hypogonadal (low free T or calculated free T index) patients with type II diabetes mellitus in age groups ranging from 40 to 79 years. Reproduced with permission from Dhindsa *et al.*[13]

the morning when at peak, this circadian rhythm is often abolished in elderly men.[10]

In healthy men, only 1–3% of biologically active steroids circulate free, with the balance being bound tightly to sex hormone binding globulin (SHBG) or loosely to albumin. The free T (FT) and the fraction bound loosely to albumin are readily available for entry into tissues. Unlike serum T, concentrations of SHBG, as well as luteinizing hormone (LH) and follicle-stimulating hormone (FSH), rise significantly with age[5,6] such that the SHBG level of a man in his 80s is about twice as high as in his 20-year-old male counterpart.[11] In the Massachusetts Male Aging Study, SHBG increased by 1.2% annually.[9] Owing to the differences in binding affinities of male and female hormones for SHBG, increases in circulating levels of this glycoprotein tend to generate a more estrogenic, rather than androgenic, milieu.[11]

Unlike the sharp, universal decreases in hormone levels observed in women with menopause, declines in circulating androgens in men with advancing age are gradual and variable. For this reason and others, the term *andropause* is misleading and should be avoided when discussing age-associated male hypogonadism;[12] the term *partial androgen deficiency of the aging male (PADAM)* is generally preferred. Waning T levels represent one facet of a larger endocrine decline in many elderly men, with frequent reductions in secretion of thyroid hormone, growth hormone, and/or insulin-like growth factor.

Advancing age independently lowers T levels even after controlling for chronic conditions associated with aging. Conditions associated with reduced T and/or higher SHBG levels include obesity; diabetes mellitus (DM);[13] use of certain medications; hyperthyroidism, which elevates hepatic SHBG output; as well as alcoholism (daily intake $>40\,g$[14]) and/or alcoholic liver disease.[11]

Diabetes mellitus

Trend. Approximately 5% of persons ages 20–79 years have DM, according to data from the International Diabetes Federation.[15] This includes 48 million Europeans and 43 million residents of the Western Pacific. Diabetes rates are highest in the United States (7.9%) and Europe (7.8%). With population aging, as well as unhealthful diets, sedentary lifestyles, and/or attendant obesity, the number of people with DM has increased from 30 million in 1985 to more than 150 million in 2000. The number is projected to escalate to nearly 333 million by the year 2025.[15]

Effects of DM on circulating testosterone. In a recent study, hypogonadism (low FT) was observed overall in 33% of men with DM2, who had a mean body mass index (BMI) of 33.4 kg/m^2 and a hemoglobin A1c of 8.4%.[13] Figure 2 shows the distribution of hypogonadism (defined as low FT or calculated FT (cFT)) across different age groups in men with DM2.[13] A total of 58% of massively obese individuals with DM2 (BMI $>40\,kg/m^2$) had hypogonadism as defined by low FT.[13] According to the authors, FT should be measured before designating any DM2 patient as hypogonadal. Using only a low T (<300 ng/dl) to define hypogonadism resulted in 36% false positives and 12% false negatives compared with low FT or cFT.[13]

Obesity

Trend. In the United States, visits to physicians for obesity-related maladies rose 90% from 1988 through 1994.[16] In addition, about one in four

American adults has metabolic syndrome, a condition indicative of insulin resistance that includes overweight, central (upper-body) adiposity, hypertension, low levels of high-density lipoprotein cholesterol, and high levels of small dense low-density lipoprotein cholesterol, which is considered to be highly atherogenic. According to the third National Health and Nutrition Examination Survey,[17] 47 million Americans have metabolic syndrome, including approximately 44% of those ages 60 years or more.[18]

Potential effects of obesity on circulating testosterone. In the aforementioned study on hypogonadism in men with DM2, values for T, FT, and cFT were all significantly lower in hypogonadal compared with eugonadal men, while SHBG was not significantly different between the two groups. Testosterone ($r=-0.327$; $P<0.01$) and FT ($r=-0.382$; $P<0.01$) were inversely correlated with BMI. The study demonstrated that BMI was an independent predictor of hypogonadism.[13]

On the other hand, 31.3% of lean men (normal BMI) with DM2 were also hypogonadal, suggesting that factors other than adiposity may play a role in the hypogonadism associated with insulin-resistant states.[13] A recent study involving men without DM showed that age-adjusted bioavailable T (BT), FT, and T correlated inversely with fasting insulin ($P\leqslant 0.03$ for each), and both SHBG and T correlated inversely with fasting glucose ($P\leqslant 0.003$ for each).[19]

Epidemiologic relationships between obesity and hypogonadism are complex. In a large-scale longitudinal study, T decreased by 10 ng/dl per 1 kg/m^2 increment in BMI.[5] Other studies have also shown reduced T and FT in men with increasing total or abdominal adiposity.[20,21] The direction of causality between abdominal adiposity and low T levels is not clear.[8]

In one cross-sectional study of 400 community-dwelling men ages 40–80 years, increases in both BMI and central adiposity (waist circumference) were associated with low levels of T, BT, and dehydroepiandrosterone sulfate, whereas both current smoking and greater physical activity were associated with higher T concentrations.[14]

Some grossly obese patients have reduced total T and SHBG levels, as well as diminished T-SHBG binding, such that FT levels remain normal.[11,22] Obesity may lower circulating androgens or reduce T-SHBG binding via (1) excessive metabolic clearance of androgens in adipose tissues;[11] (2) aromatization of androgens in adipose tissues; or (3) increased formation of inflammatory cytokines (eg tumor necrosis factor-α, interleukin-1β), which may also blunt secretion of LH and gonadotropin-releasing hormone (GnRH).[23,24] Conversely, T has potential anti-inflammatory (and antiatherogenic) properties in animal models and humans.[25]

Controversies in diagnosis

Diagnostic issues in hypogonadism will be covered at greater length in part II of this three-part review. The diagnosis of male hypogonadism, particularly PADAM, is fraught with controversy. Frequently debated topics include threshold hormone levels for determining PADAM; whether low T levels in the presence of normal LH levels warrant further work-up to detect underlying hypothalamic–pituitary axis disorders; the optimal manner in which to measure these hormone levels, particularly total testosterone (TT); and the ideal hormone fraction to identify patients with hypogonadism: TT, bioavailable testosterone (BT), or free testosterone (FT).

According to the preponderance of literature from the past 30 years based on traditional radioimmunoassay (RIA) methods with or without chromatography, the reference range for TT is 300–1000 ng/dl.[26,27] Another way to determine the threshold for 'low TT' is statistical, that is, 2.5 standard deviations (s.d.'s) below the mean for healthy young men. In a recent study on the clinical utility of GnRH testing in the differential diagnosis of PADAM and secondary hypogonadism, a Swiss group used a threshold TT of <337 ng/dl, which was 2.5 s.d.'s lower than the mean for a group of 13 young healthy controls (mean age = 33.9 years): approximately 625 ng/dl.[28]

One argument for using 300 ng/dl as the threshold for diagnosing male hypogonadism is that there is a functional correlation with erectile dysfunction (ED). Studying 162 elderly (mean age = 64.1 years) men with ED (mean duration = 45.6 months), a Korean group reported that hypogonadism (serum TT <300 ng/dl) was among the strongest independent predictors of a poor response to sildenafil 25–100 mg for 8 weeks. Only poor pretreatment erectile function (International Index of Erectile Function (IIEF) erectile function domain score <17) was a stronger independent prognostic factor (OR = 2.2; 95% CI = 1.45–7.33).[29]

Another consideration in the diagnosis of male hypogonadism is that measurements of TT may vary during different times of the day or year and from laboratory to laboratory. In a recent study, coefficients of variation between laboratories using the same methods/instruments ranged from 5.1 to 22.7%.[26] The median value of the quality control sample across all laboratories was 297 ng/dl, with results as low as 160 ng/dl (hypogonadal) and as high as 508 ng/dl (eugonadal). Certain manufacturers of automated assay platforms also provide normal male reference ranges that are much lower than the reference TT range of 300–1000 ng/dl cited above, with lower limits ranging from 170 to 200 ng/dl and upper limits ranging from 700 to 800 ng/dl.

Total T levels show marked circadian and circannual variation. Owing to the circadian variation,

the Second International Consultation on Erectile Dysfunction of the World Health Organization (WHO)[30] recommended that a blood sample for serum T determination should be obtained between 0800 and 1100, when T levels typically peak in healthy young men. This circadian rhythmicity may be abolished or blunted in men with advancing age[10] or during certain forms of TRT.

The method of choice for determining serum TT levels is liquid chromatography-tandem mass spectrometry (LC-MS-MS). However, this methodology is not available to many hospitals and office practices. A recent study determined that commercially available automated and manual methods are capable of discriminating eugonadal from hypogonadal TT values in the presence of adult male reference ranges established by each laboratory.[26] More than 60% of serum samples from men with TT within the adult male range were within ±20% of values determined by LC-MS-MS. Certain methods (eg DPC Immulite) were biased toward lower values, while others were biased toward higher values (eg Bayer ADVIA Centaur) across a wide range of serum TT concentrations.

The chief problem with the commercially available immunoassays was in determining very low serum TT (<100 ng/dl): in specimens with such low TT values typical of prepubertal males (and females), 56–90% of values generated by commercially available assays fell outside the ±20% window around LC-MS-MS values.[26] As mentioned above, values obtained with the DPC Immulite were systematically lower and those obtained by the Bayer ADVIA Centaur systematically higher than the values provided by LC-MS-MS. Other assays (DPC-RIA and Roche Elecys) exhibited large percent differences in both directions. None of these assays is considered reliable enough to investigate serum TT levels in children and women.[26,31]

A morning T level ⩽300 ng/dl should be confirmed by a repeated measurement at the same time of day. However, neither a low TT nor clinical symptoms are sufficient to discriminate PADAM from secondary, hypogonadotropic hypogonadism attributed to hypothalamic-pituitary axis disorders. In a recent study,[28] lack of libido was present in approximately 54% of men with PADAM and 67% of those with secondary hypogonadism; ED in 58 and 53%, respectively; fatigue in 38 and 58%; depressive mood in 25 and 21%; and osteopenia or osteoporosis in 17 and 29%.

According to guidelines from the American Association of Clinical Endocrinologists (AACE), exceedingly low T levels (⩽150 ng/dl) warrant pituitary imaging even in the absence of other signs or symptoms.[32] Others use a threshold of <200 ng/dl to trigger magnetic resonance imaging (MRI).[33,34] Some authorities recommend sellar MRI with thyroxine, cortisol, and prolactin assessments when secondary hypogonadism is considered likely.[33]

Based on extensive hormonal evaluation of elderly men with normal and low levels of T, as compared with those with primary and secondary hypogonadism and young, healthy volunteers, a Swiss group[28] recently developed an algorithm for the use of GnRH testing to discriminate secondary, hypogonadotropic hypogonadism from PADAM. First, if repeated serum TT levels are below <337 ng/dl in an elderly man, a GnRH stimulation test should be conducted. A peak LH following GnRH stimulation of >15 mU/l precludes costly imaging studies to rule out secondary (hypogonadotropic) hypogonadism. On the other hand, elderly men who have TT levels below <337 ng/dl in the presence of a blunted LH response to GnRH (<15 IU/l) should undergo MRI to rule out pituitary disease.[28] The most recent WHO guidelines recommend a confirmatory TT if a morning level is below the lower limit of 'the accepted normal values' as well as assessment of LH, FSH, and prolactin.[30]

Compared with men having PADAM, those with secondary hypogonadism were significantly younger (52.5 vs 62.3 years; $P<0.05$) and had significantly lower levels of basal TT (167 vs 271 ng/dl), as well as significantly lower levels of basal LH and FSH and LH and FSH responses to GnRH administration.[28]

Finally, there is ongoing debate as to which androgenic fraction is the most reliable indicator of hypogonadism. Approximately 50–70% of circulating T is bound tightly to SHBG and is hence physiologically inactive. A further 20–30% is bound loosely to albumin and 1–3% circulates free in the serum. Only these latter two fractions are available to tissues and are thus termed BT. Free testosterone can be calculated[35,36] or measured by equilibrium dialysis. One measure of FT is the free androgen index (FAI = TT/SHBG × 100).[37] Bioavailable T is measured using an ammonium sulphate precipitation method and may also be computed.

According to the most recent WHO guidelines,[30] TT assays may not indicate true androgenic status, particularly in elderly men. The WHO guidelines state that BT and cFT are the most reliable and accessible assays to establish male hypogonadism. Because, for example, serum TT may be normal in patients with primary testicular disorders (eg, Klinefelter syndrome) or increased SHBG, obtaining FT or BT may also be useful.[32] However, the validity and accessibility of a number of diagnostic tests (eg, equilibrium dialysis) and other, dynamic assessments are matters of ongoing debate.

A recent cross-sectional study of a cohort of 1072 men undergoing elective coronary angiography demonstrated that measures of TT were superior to computed FT or BT in the determination of hypogonadism. When TT levels were borderline, in the range of 216–346 ng/dl, estimates of FT proved superior to TT alone.[38]

Conclusion

Owing to demographic trends toward greater longevity, as well as increasing prevalences of obesity, metabolic syndrome, and DM, clinicians in western industrialized societies may be confronted with a burgeoning hypogonadism case burden in upcoming years. These trends merit enhanced vigilance for the problem in daily practice.

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