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Reproductive Endocrinology:

Late-onset hypogonadism: evidence for diagnostic criteria

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Abstract

Various symptoms are typical of severe testosterone deficiency in young men; in aging men, however, these symptoms are nonspecific and overlap with symptoms of other prevalent disorders. A new study offers evidence-based criteria for the identification of late-onset hypogonadism in the general population on the basis of an association between symptoms and a low testosterone level.

Serum testosterone concentrations fall as men age, such that almost 50% of men aged >80 years could be defined as hypogonadal on the basis of biochemical evidence alone.¹ Given the nonspecific nature of many of the symptoms associated with testosterone deficiency, uncertainty exists as to whom to consider as a candidate for testosterone replacement. The work of Wu *et al.*² provides some novel information regarding the epidemiology of the syndrome of late-onset hypogonadism.

In a recent issue of the *New England Journal of Medicine*, the investigators report the results of the European Male Aging study, a very large cross-sectional survey of 3,369 men, aged 40–79 years, from eight European centers. Employing a unique approach facilitated by their relatively large sample size, the investigators first randomly divided the cohort into a training group and a validation group. Any associations were initially examined in the training group and then independently evaluated in the validation group, thus enabling corroboration of their definitions and conclusions.

From questionnaire data, the researchers identified nine symptoms that were associated with low serum testosterone concentrations: three sexual symptoms (poor morning erection, erectile dysfunction or low sexual desire), three physical symptoms (difficulties in performing vigorous activity, walking >1 km or bending, kneeling or stooping) and three psychological symptoms (sadness, energy loss or fatigue). Using morning testosterone levels from the training group, the investigators defined thresholds of serum testosterone for each symptom below which the prevalence of these conditions increased significantly. Interestingly, the prevalence of each symptom increased at different threshold levels of testosterone; for example, low sexual desire (determined by a decreased frequency of sexual thoughts) was more frequently associated with testosterone concentrations <8.5 nmol/l, whereas diminished vigor was associated with testosterone levels <13.0 nmol/l.

In an effort to synthesize these data to define a syndrome of late-onset hypogonadism rather than a checklist of various symptoms, Wu *et al.* used rigorous and complex statistical analyses to determine whether any cluster of symptoms were, together, strongly associated

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Competing interests

The author declares associations with the following companies: BHR Pharma, GlaxosmithKline. See the article online for full details of the relationships.

with testosterone levels below a threshold concentration. With this approach, only the three sexual symptoms were significantly clustered with one another and with a low total testosterone level. Importantly, these associations were confirmed in the validation group. Wu and colleagues conclude that the presence of these three sexual symptoms and a morning total testosterone level <11 nmol/l can be considered an evidence-based, minimum criteria for the diagnosis of late-onset male hypogonadism.

One of the clear strengths of this study is the population-based study design, which included a sampling of men across ages, countries and ethnicities. However, the respondent population was relatively healthy compared with men one might encounter in clinical practice. For example, the average number of comorbidities among us veterans seeking ambulatory care was >5 , compared with roughly 1 in the cohort by Wu and co-workers.³ This discordance is of particular importance when analyzing syndrome prevalence. Using the criteria of Wu *et al.*, the overall prevalence of late-onset hypogonadism in the study cohort was only 3% and 5% in men aged 60–69 years and 70–79 years, respectively, and thus much lower than the prevalence reported elsewhere using similar definitions.⁴ The investigators' supplementary data is consistent with previous studies that report an increased incidence of late-onset hypogonadism with increasing BMI and comorbidities; however, an analysis of the data that combines these factors and syndrome prevalence is lacking. Moreover, men with primary testicular failure or pituitary disease were specifically excluded from the analysis. Such patients might present to a clinic with very low testosterone levels (<6.9 nmol/l) and may not have sexual complaints, but should nonetheless be considered for therapy. Providers should, therefore, not extrapolate the reported prevalence rates to patients who seek medical care and present with signs, symptoms or clear laboratory abnormalities that suggest hypogonadism.

The data presented by Wu and colleagues is indicative of the nonspecificity of many symptoms associated with hypogonadism. Sexual symptoms were present in $>25\%$ of middle-aged and older men with serum testosterone levels in the normal range for healthy, young men. The overlap of symptoms of hypogonadism with other aging-associated syndromes and diseases highlights the importance of using a combination of biochemical and symptomatic data for the diagnosis and potential treatment of male late-onset hypogonadism.⁵ However, the absolute values of serum testosterone that define late-onset hypogonadism, as suggested by the researchers, are difficult to translate into clinical practice. The study by Wu *et al.* utilized a central lab with state-of-the-art measurements for testosterone (gas chromatography–mass spectrometry). In practice, clinicians use clinical laboratories that employ a variety of analytical methods that are notoriously variable in the quantification of serum levels of sex steroids.⁶ Consistent with current clinical guidelines, clinicians should use the lower limit of the normal range of serum testosterone levels for healthy young men (as defined by their reference laboratory) when considering the diagnosis of late-onset hypogonadism.⁵ notably, the level of serum testosterone that defines late-onset hypogonadism in the study by Wu and colleagues is near the lower limit of the normal range for many reference laboratories.⁵

Finally, Wu *et al.* are very careful to point out that their findings should not be used to define which patients might benefit from testosterone therapy. The investigators did not observe a linear relationship between symptoms and testosterone levels beyond the observed threshold levels. This result is consistent with an intervention study that did not show any improvement in aspects of sexual function, cognition or mood with increasing doses of exogenous testosterone after serum levels in the mid-normal range had been achieved.⁷ Moreover, the low prevalence of hypogonadism in the study by Wu and co-workers and the high prevalence of symptoms associated with hypogonadism in men with normal testosterone levels is a reminder of the potential for 'over treatment' of age-associated

declines in testosterone. On the one hand, epidemiologic studies have found low testosterone levels to be associated with early mortality, and a meta-analysis of testosterone intervention trials suggests that the risk of adverse events with replacement therapy is low.⁸ However, in a report by Basaria *et al.*,⁹ the improvement of physical function observed in elderly men with mobility impairment and multiple comorbid conditions treated with exogenous testosterone therapy came at the expense of an increased risk of cardiovascular events.⁹ Although these findings should not be extrapolated to the general population, as the cohort of Basaria *et al.*⁹ included only a very select population of men treated with higher doses of testosterone than have been used in other studies, they serve as a reminder that strong evidence regarding the long-term risks and benefits of testosterone replacement is lacking.

Patients are clearly interested in androgen-based therapies, as evidenced by the marked increase in testosterone prescriptions over the last decade.¹⁰ The work of Wu *et al.* has demonstrated which symptoms of aging are most closely associated with reduced concentrations of circulating testosterone, and their results confirm a current guideline⁵ that recommends a combination of low testosterone levels and presence of symptoms, such as decreased libido and spontaneous erections, hot flashes, or mild anemia, as the best definition of late-onset hypogonadism. Ultimately, this study has important implications for the design of much needed, larger, randomized, placebo-controlled trials of testosterone therapy in older men that will provide a true understanding of its risks and benefits.

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Practice points

- Symptoms of late-onset hypogonadism overlap with many other age-related diseases
- The diagnosis of late-onset hypogonadism should include both symptoms and biochemical evidence of low serum testosterone levels
- Reference ranges for serum testosterone levels vary among clinical laboratories
- The long-term risks and benefits of testosterone therapy in older men are not known