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EXPERT OPINION

The diagnosis of late life hypogonadism

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Abstract
The diagnosis of late life hypogonadism is controversial. For the purposes of discussion, it is suggested that treatment of late life hypogonodism requires the presence of symptoms, a low level of circulating free or bioavailable testosterone level and a positive response to treatment. While this may appear to be a radical proposal, we believe it represents the most rigorous scientific approach to the diagnosis of late life hypogonadism at the present time.

Keywords: *Hypogonadism, testosterone, ADAM, aging male survey, androgen deficiency*

Introduction

Few areas have created as much controversy as the diagnosis of late life hypogonadism and its management. So while the condition was first mentioned in the Chinese *Text of Internal Medicine* and had a major, though controversial, role in the medicine of the late nineteenth and first half of the twentieth century [1], it was considered an invention of the pharmaceutical industry in the beginning of the twenty-first century [2]. Over time it has had many names including male menopause (a truly inappropriate name), male climacteric, adrenopause, androgen deficiency of the aging male (ADAM), partial androgen deficiency of the aging male (PADAM) and late-onset hypogonadism. Recently, a number of guidelines have been published in an attempt to define the condition and provide treatment guidelines [3,4]. Despite this, much confusion still exists regarding the appropriate approach to diagnosing late life hypogonadism.

There would appear to be some consensus that the appropriate diagnosis of late life hypogonadism requires a complex of symptoms as well as an arbitrary testosterone level. The first problem arises in determining which constellation of symptoms determines that a male has late life hypogonadism. Part of the problem is many of the symptoms of late life hypogonadism are similar to those of depression, protein energy undernutrition, fatigue and frailty [5–8] and some, such as muscle weakness (sarcopenia), are considered by some to be a characteristic of the aging process [9]. While attempts to create symptom complexes as questionnaires, such as the Saint Louis University Androgen Deficiency in Aging Males (ADAM) questionnaire and the Aging Male Survey are highly sensitive, they have suboptimal specificity [10–16]. There is also a pervasive viewpoint that a careful history and examination by a clinician would in some magical way perform better than either of these two questionnaires [17]. This viewpoint has not been tested, though an attempt to look at a variety of other symptoms failed to enhance the specificity [13, and unpublished observations].

A problem with symptoms is that recent studies have shown that there is marked inter-individual variation of the testosterone level at which symptoms occur, though within an individual the level appears to be relatively constant [18,19]. Using a single symptom, namely libido, as the gold standard for the diagnosis has also proved to be poorly associated with a given level of total or calculated bioavailable testosterone [20]. An attempt to improve the discriminate value of libido by using CAG repeats as a determinant of testosterone receptor efficacy also proved not to be successful [20]. Thus, while there is ample evidence that a low libido in the presence of some level of 'low testosterone' can be reversed by testosterone therapy [21], a low libido by itself is

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insufficient to allow the diagnosis of hypogonadism. Similar problems exist with determining the role of testosterone in producing poor quality erectile function [22–25]. There is even less ability to use other symptoms classically associated with hypogonadism as diagnostic markers. At a minimum it would appear that prior to using symptoms as a partial component of the diagnosis of late life hypogonadism, both depression and hypothyroidism should be excluded. Another conundrum is that many of the symptoms associated with hypogonadism are commonly seen in persons with illness and many of these diseases can produce low testosterone levels [26].

If symptoms perform poorly to diagnose late life hypogonadism then perhaps a biochemical measurement would be a better diagnostic tool? It is now well recognized that total testosterone, free testosterone and bioavailable testosterone all decline with aging [27–30]. Thus, a reasonable approach would be to create a normal range for young persons and use values below the normal range to make the diagnosis. This has stood endocrinologists in other conditions, e.g. hypothyroidism, in good stead over the years. Unfortunately, there are young persons with perfectly normal libido and sexual function, who spend a significant portion of the day with testosterone levels well below any arbitrary normal range [31]. While, in part, this is due to the circadian rhythm, in some individuals these ultra low levels occur at times when testosterone levels would be expected to be well within the normal range [31–33]. In addition, a significant week to week variation in testosterone levels occurs [34,35]. Further, classical testosterone measurements have been shown to be highly variable from assay to assay and often it appears that normal values for the assays have not been appropriately calculated [36–38]. Because most late-onset hypogonadism is due predominantly to hypothalamic-pituitary dysfunction, measurement of luteinizing hormone is not useful in aiding in the determination of gonadal status [39,40].

A second controversy in the measurement of testosterone in the diagnosis of hypogonadism revolves around whether total testosterone is sufficient or if some measure of unbound (free) or loosely bound (bioavailable) testosterone is a more appropriate measure [34,38,41–44]. Endocrinology has championed the measurement of free hormones and it seems strange that this principle is not championed when it comes to testosterone. While there are sex hormone binding globulin (SHBG) receptors and in some cases cellular effects may be due to testosterone bound to SHBG, this would appear to be a limited situation [44]. When it has been looked at, bioavailable testosterone appears to correlate better with potential hypogonadal symptoms than does total testosterone [45]. Salivary testosterone, a proxy for unbound testosterone, may also perform better than total testosterone [46–48]. Because of the increase in SHBG with aging and a possible alteration in binding kinetics, men with total testosterone as high as 17 nmol/L may have low bioavailable testosterone levels [42, and unpublished observations].

Since the original studies by Tenover [49], Morley et al. [50] and Sih et al. [51] demonstrating positive effects of testosterone replacement in older males with biochemical hypogonadism a number of other placebo controlled studies have been published. While numbers are not large, there is sufficient data to allow rigorous meta-analyses to demonstrate positive effects of testosterone replacement on sexuality and muscle mass and strength [21,52–54]. In addition, a well conducted three year study showed that testosterone increased function in older men [55]. It should be recognized that there is a significant placebo effect, and replacement doses of testosterone may need to be relatively elevated to produce a measurable effect [56]. Finally, evidence for serious side effects in carefully monitored males is minimal [57–59].

Based on the above, we would like to suggest that a combination of symptoms and testosterone measurement is inadequate to make the diagnosis of late life hypogonadism. An appropriate diagnosis of hypogonadism can only be made when an older person has symptoms of low testosterone (or possibly sarcopenia or osteopenia), for which other common causes have been excluded and has a relatively low testosterone (<12 nmol/L or a low free or bioavailable testosterone (measured or calculated) if the total testosterone is between 12 to 17 nmol/L) *and* responds to a treatment trial of 3 months duration with amelioration of symptoms. An adequate trial requires the testosterone level to be elevated at least above 15 nmol/L. We recognize that this will lead to a significant number of persons having their symptoms ameliorated because of the placebo effect. However, this is akin to the situation with antidepressants where there is also a significant placebo effect [60]. The role of the physician is to alleviate symptoms while doing a minimum of harm and we suggest that this modest proposal concerning the approach to the diagnosis of late life hypogonadism will improve the quality of life of many older men [61]. We also believe that while this may appear to be a radical proposal, it represents the most scientifically rigorous approach presently available for the management of late life hypogonadism.

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