

Society for Endocrinology Position Statement on Male Hypogonadism and Ageing

Testosterone is important for general as well as sexual health in men. Symptoms of testosterone deficiency commonly include decreased libido, loss of morning erections and erectile dysfunction, but may also involve tiredness (fatigue), reduced physical strength and endurance, loss of motivation and concentration, irritability, and low moods. As these symptoms may be caused by conditions other than testosterone deficiency, it is important that any diagnosis of hypogonadism is supported by biochemical evidence of low circulating testosterone levels.

Hypogonadism is defined as a clinical syndrome complex that comprises symptoms and signs as well as biochemical evidence of testosterone deficiency. It is increasingly recognised that older men with common medical conditions have a higher prevalence of borderline low serum testosterone levels; these conditions include obesity, metabolic syndrome, type 2 diabetes, osteoporosis, COPD, coronary heart disease, HIV, inflammatory conditions (e.g. arthritis), cardiac, renal and liver failure (1). These conditions have much stronger associations with the finding of borderline low testosterone than ageing *per se*.

Laboratory diagnosis

National and International guidelines, recommendations and position statements are available for the diagnosis of hypogonadism (2-5). To establish the diagnosis, serum total testosterone levels should be measured (a) before 11am as there is a circadian rhythm, (b) fasted as LH-stimulated testosterone levels are acutely lowered by oral carbohydrate intake and (c) not during episodes of non-gonadal illness or night shift work. Readings below the reference range on at least two different occasions support a diagnosis of hypogonadism, as do low bone density and haemoglobin or haematocrit below the adult male reference range - although there are multiple other causes for these findings. A diagnosis of hypogonadism is more secure if it can be framed in the context of a recognised clinical syndrome (e.g. primary gonadal insufficiency from past chemotherapy, or secondary hypogonadism due to opiate analgesia).

Additional investigations include measurement of gonadotrophins and prolactin, and the calculation of free testosterone when total testosterone is borderline and/or SHBG levels are unusually high or low. Methods for the calculation of free testosterone can be found at www.issam.ch.

In order to minimise false-positive diagnosis, it is important to consistently adhere to these sampling conditions, as the biochemical fingerprint of true secondary hypogonadism (low testosterone, with low or inappropriately normal LH and FSH levels) is not dissimilar to that of artefactual post-prandial or afternoon clinic pseudo-hypogonadism, and non-gonadal illness - the physiological hypothalamo-pituitary-testicular axis suppression observed with all forms of acute disease and chronic illness (1).

By contrast, the biochemical fingerprint of primary gonadal insufficiency is far more specific, (low testosterone and raised gonadotropins), although circulating LH concentrations do fluctuate in train with central GnRH pulses, consistently raised LH and FSH levels reliably identify gonadal insufficiency even under less-stringent sampling conditions.

Late onset hypogonadism

Late-onset hypogonadism (LoH) was originally characterised as a clinical and biochemical syndrome associated with ageing-related co-morbidities (especially obesity), characterised by symptoms suggestive of testosterone deficiency and consistently low testosterone levels, after exclusion of classical causes for hypogonadism (e.g. Klinefelter syndrome, Kallmann syndrome, pituitary tumours) (4). The number of men

with LoH by this original definition is small, with the European Male Ageing Study (EMAS) reporting a general population prevalence of only 2.1% in men aged greater than 40 years (6).

Moreover, EMAS recently found the age-related decline in gonadotropin-mediated serum testosterone concentrations to reside overwhelmingly in accumulating co-morbidities, including obesity, and only a minor direct association with ageing *per se* (7,8). The same investigators did, however, identify a small subset of men with genuine age-related (primary) hypogonadism, characterised by raised LH levels. Thus, the term LoH may be better reserved for older men with otherwise unexplained primary gonadal insufficiency. Although the incidence of primary hypogonadism in men is low (0.2%/year), it increases with both age and chronic illness (7, 8). An elevated luteinizing hormone level with a normal testosterone level is more frequent (5-6%), but this does not necessarily imply an inexorable progression towards frank primary gonadal insufficiency, as LH can spontaneously revert to normal particularly among younger men, possibly because the earlier blood sampling having coincided with an LH pulse (8).

Treatment of hypogonadism and its monitoring

Testosterone treatment in patients with a well-founded diagnosis of classical hypogonadism is effective and safe (2, 9). Whilst there are studies that suggest testosterone replacement in older men with low testosterone levels and low-normal gonadotropins may have some short term benefits, longer term studies of sufficient power to document clinical outcomes are lacking.

Although testosterone replacement therapy has been used effectively for many years in men of all ages with classical hypogonadism without major adverse effects, this experience and the risk-benefit balance cannot be extrapolated to older men whose low testosterone levels predominantly reflect frailty, obesity, or non-gonadal co-morbidity.

Occult prostate cancer is common in elderly men. In the absence of long-term, controlled studies, it is unclear whether testosterone therapy has adverse effects on the prostate. A history of prostatic symptoms should be taken and measurement of prostate-specific antigen (PSA) should be performed before commencing testosterone treatment in men over 40 yr. Currently, major International guidelines recommend continued surveillance with annual PSA measurement and, if abnormal, urological referral. Since testosterone replacement may cause secondary polycythaemia, the haematocrit should be assessed before and annually after therapy. The long-term effects of testosterone treatment on cardiovascular disease susceptibility are currently unknown (7); testosterone replacement therefore should be used cautiously in men with symptomatic cardiovascular disease.

Modern testosterone preparations allow delivery of physiological doses to achieve better replacement therapy. The aim of testosterone treatment is to achieve serum testosterone levels within the mid-reference range, subject to achieving a normal haemoglobin or haematocrit.

Treatment of LOH in the context of published guidance

Position statements and guidance on the use of testosterone have been recently published (10-12). It is the position of the society for Endocrinology that testosterone treatment in the context of LOH should be considered only when a clinical diagnosis has been made (including the use of laboratory measurements) and where there is a sound pathological basis to the diagnosis. We would not advocate the replacement of testosterone in those individuals where these criteria are not met.

This position statement has been revised and updated by Dr. Richard Quinton (University of Newcastle) and Prof. Jeremy Tomlinson (University of Oxford) in May 2018 and is based upon the original position statement published in October 2012. This information is provided and endorsed by the Society for Endocrinology's Clinical Committee.

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