
Current Guidelines for the Diagnosis of Testosterone Deficiency

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Abstract

Hypogonadism in males is a clinical syndrome complex which comprises symptoms with or without signs as well as biochemical evidence of testosterone deficiency. The diagnosis of hypogonadism thus includes both clinical history and examination as well as biochemical assessment of serum testosterone levels. Hypogonadal symptoms depend on the age at onset of hypogonadism, severity of the deficiency, its duration and sensitivity to androgen action. Prepubertal onset results in lack of virilization and pubertal development and produces features such as eunuchoid body proportions and undeveloped secondary sex characteristics. Development of hypogonadism in adult life is characterized by a loss of androgen-dependent functions such as reduction in muscle mass, a shift in body composition towards more adipose tissue, decreased sexual function with diminished libido, depressed mood, loss of psychological energy osteoporosis and several other possible symptoms. The majority of men who suffer from hypogonadism do not have classical endocrine disorders. These men present with concomitant disease such as metabolic syndrome or type 2 diabetes, chronic infections, inflammatory disease, COPD, or cardiovascular disease. All these conditions are associated with a high prevalence of hypogonadism. Pharmacological therapy with opiates and corticosteroids are also known to cause hypogonadism. Hypogonadal symptoms are precipitated at different testosterone levels. Total testosterone levels of less than 8 nmol/l highly support a diagnosis of hypogonadism whereas levels greater than 12 nmol/l are likely to be normal. The grey zone between 8 and 12 nmol/l requires further evaluation and assessment of free or non-sex hormone-binding globulin-bound (bioavailable) testosterone. A trial period of testosterone treatment may be required.

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Testosterone Deficiency – Terminology

Hypogonadism is a clinical syndrome complex which comprises symptoms with or without signs as well as biochemical evidence of testosterone deficiency.

Male hypogonadism is classically related to relatively rare disorders of the hypothalamic-pituitary-gonadal axis. Thus the classical diagnosis of hypogonadism involves disorders such as Kallmann's syndrome, pituitary tumors (secondary hypogonadism) and Klinefelter's syndrome, and XX male syndrome (primary hypogonadism). It is however

evident that hypogonadism is far more prevalent than these disorders and that men with symptoms related to testosterone deficiency are regularly seen in most clinical settings, though without being identified as potential candidates for testosterone replacement therapy. The classical underlying diseases causing hypogonadism are thus not responsible for the majority of testosterone deficiency in men. There is a need to make the diagnosis of hypogonadism less challenging and more familiar to physicians in a wide range of settings. Men with severe hypogonadism are easily diagnosed in a straightforward way, whilst men with less severe deficiency without a definite or clearly identifiable cause are more of a challenge. In these cases a combination of primary (testicular) and secondary (hypothalamic/pituitary) failure is often present.

The terminology regarding hypogonadism has not been very precise and in an effort to distinguish the more common forms of hypogonadism from the classical etiologies various nomenclatures have been put forward especially related to the increased prevalence of testosterone deficiency in elderly men, i.e. partial androgen deficiency in aging men, androgen deficiency in aging men and late-onset hypogonadism (LOH). These proposed names have also been prompted by the need to suppress the use of climacterium-related names (male climacterium, etc.) as they are misleading. In the current text the term testosterone deficiency or testosterone deficiency syndrome is used as a synonym for hypogonadism and includes the combination of low testosterone levels and the presence of clinical symptoms attributed to low testosterone levels. LOH has become a commonly used term and has been introduced to clearly identify hypogonadism occurring in aging men. The definition is similar to general hypogonadism but also includes the age aspect. In the recommendations for management of LOH [1] the definition reads: 'A clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels. It may result in significant detriment in the quality of life and adversely affect the function of multiple organs.' There is no clear definition of the age that defines advancing age, though taken from the context of the recommendations it may be interpreted as men over 60 years of age. The relevance of the age distinction is the increased prevalence of low testosterone levels in elderly men and that our knowledge and experience of risks and benefits of testosterone therapy in this group are limited. Most of our current knowledge and understanding of signs and symptoms of hypogonadism are based on experiences from clinical observations and substitution therapy in younger men. It remains to be clarified whether or not in the older men symptoms are precipitated by testosterone deficiency which do or do not regress with substitution therapy. An important contribution to this was the recent demonstration that the androgen-stimulated increment in lean body mass showed the same dose response relationship in young as well as elderly men [2]. Hypogonadism in aging men is often associated with obesity and/or concomitant medical disorders. The classification of hypogonadism into primary or secondary etiology is less clear. In many older men a low testosterone level occurs with LH levels within the normal range. This could be regarded as an insufficient

hypothalamic or pituitary response to a low circulating testosterone level and thus a secondary hypogonadism. At the same time the testicular response to LH stimulation may be weakened indicating a primary component. These cases may be referred to as a state of mixed hypogonadism with both a primary and a secondary component.

It is well documented that testosterone replacement therapy in hypogonadal men improves muscle mass and strength, bone mineral density, mood, sexual function (libido and erectile function) as well as giving generally a feeling of increased energy. Identifying eligible men for testosterone therapy is based on a combination of serum testosterone measurements and clinical assessment of hypogonadal symptoms.

Symptoms and Signs of Testosterone Deficiency

The clinical presentation of hypogonadism depends on four main factors: (1) age at onset of androgen deficiency, (2) duration of androgen deficiency, (3) the profoundness of the deficiency and (4) genetic factors controlling androgen receptor responsiveness reflecting androgen receptor polymorphism and mutations.

Prepubertal onset results in lack of virilization, sustained height increase without closure of the epiphysis, lack of pubertal growth spurt, incomplete sexual development and aspermia. Adult onset results in a loss of the function of androgen-dependent pathways and symptoms and signs are often nonspecific and subject to the influence of comorbidity, age and other factors. Androgen deficiency-related symptoms and signs in the adult include reduced libido and reduced sexual activity, loss of spontaneous erections and erectile dysfunction, loss of body hair, reduced need to shave, reduced muscle mass and strength, and also flushes and sweating. Gynecomastia signifies a decrease in testosterone levels as well as low-trauma fractures and very small testes (<5 ml). These symptoms are regarded as more specific to testosterone deficiency than other symptoms that are also reported to occur as a consequence of lowered testosterone levels. These symptoms include depressed mood and dysthymia, poor ability to concentrate and poor memory, decreased energy, initiative and self-confidence. Also irritability or aggressiveness is seen as a result of testosterone deficiency as well as a shift in body composition with increased body fat and BMI and diminished physical performance [3].

In the Endocrine Society Guidelines symptoms are separated into two groups, suggestive of hypogonadism (group A) and less specific symptoms (group B) [3] (table 1).

The selection of symptoms indicating androgen deficiency is based on clinical observations of hypogonadal men and from intervention studies with testosterone substitution therapy. There are no population-based symptom surveys relating symptoms to testosterone levels. There are few symptoms which are pathognomonic for hypogonadism, though lack of pubertal development (voice deepening, genital organ maturation, development of secondary hair and muscle accretion) is a strong indicator of hypogonadism in a person of postpubertal age. Whether loss of libido or spontaneous

Table 1. Classification of symptoms and signs of androgen deficiency according to the Endocrine Society's Clinical Guidelines

Group A: Symptoms and signs suggestive of androgen deficiency in men: incomplete sexual development, eunuchoidism, aspermia

- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillar and pubic) hair, reduced shaving
- Very small or shrinking testis (especially <5 ml)
- Inability to father children, low or zero sperm counts
- Height loss, low-trauma fracture, low bone mineral density
- Reduced muscle mass and strength
- Hot flushes, sweats

Group B: Symptoms and signs associated with androgen deficiency that are less specific than those in group A

- Decreased energy, motivation, initiative, aggressiveness, self confidence
 - Feeling sad or blue, depressed mood, dysthymia
 - Poor concentration and memory
 - Sleep disturbance, increased sleepiness
 - Mild anemia (normochromic, normocytic, in the female range)
 - Increased body fat, body mass index
 - Diminished physical or work performance
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erection is more suggestive than decreased energy or dysthymia of hypogonadism could be debated. The complete spectrum of symptoms potentially related to androgen deficiency needs to be assessed where hypogonadism is part of the differential diagnosis. Loss of body hair requires a long duration of hypogonadism and a beard may stay for decades in a severely hypogonadal man. Changes in hair growth and shaving frequency may be a more specific and sensitive indicator of testosterone deficiency.

The onset of symptoms seems to be related to prevailing testosterone levels [4]. There is evidence that the symptoms of hypogonadism are precipitated at different testosterone levels. This implies that there may be different thresholds for specific androgen-dependent pathways. Loss of libido and vigor becomes significant below a serum testosterone level of 15 nmol/l whilst erectile dysfunction and flushes are significantly related to a testosterone level below 8 nmol/l (see fig. 1 for further details).

Questionnaires and Interview Instruments for Hypogonadism Diagnosis

Questionnaires and a structured interview for the screening of male hypogonadism have been proposed and four different tools with some validation are currently available.