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Current topics in testosterone replacement of hypogonadal men

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All forms of hypogonadism – primary, secondary and late-onset – require testosterone substitution. The indication is given when the patient presents with symptoms of androgen deficiency and the serum testosterone levels are below normal. Several testosterone preparations and modes of application are available of which those producing physiologic serum levels should be preferred e.g. preferentially transdermal gels and long-acting intramuscular testosterone undecanoate. Testosterone substitution must be monitored at regular intervals, best at 3, 6 and 12 months after initiation and then annually. Parameters for surveillance include well-being, libido and sexual activity, measurement of serum testosterone levels, haemoglobin and haematocrit, PSA and digital rectal examination, and, biannually, bone mineral density. Testosterone has positive effects on comorbidities such as obesity, metabolic syndrome, diabetes type II, cardiovascular diseases and osteoporosis.

Introduction

The testes have the dual function of producing hormones and sperm. Hypogonadism, defined as impaired function of the testes is expressed either as testosterone deficiency or as infertility or as a combination of both. Its causes are so manifold that the reader is referred to relevant textbooks for pathophysiological details [1,2].

However, all forms of hypogonadism – primary, secondary and late-onset – are characterized by symptoms of testosterone deficiency. Hypogonadism with testosterone deficiency is the universally

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accepted indication for testosterone treatment. As practically all tissues and all organs have androgen receptors and/or may also show non-genomic response to testosterone, testosterone deficiency results in a broad spectrum of symptoms. Some of these symptoms such as fatigue, loss of libido, erectile dysfunction, depression and osteoporosis can also be caused by diseases other than hypogonadism and would not respond to testosterone treatment unless serum levels are below normal. Therefore, all current guidelines agree that the combination of symptoms of testosterone deficiency and subnormal testosterone levels are prerequisites for diagnosis and treatment ([3–5], for review [6]).

Disregarding these clear precepts, testosterone preparations appear to be increasingly prescribed and consumed for symptoms without documented testosterone deficiency. This seems to be more prevalent in the USA than in Europe as US sales of testosterone preparations have quadrupled from 2000 to 2011 although the number of low testosterone levels revealed in laboratory testing has remained constant [7]. In comparison, in the UK testosterone prescriptions have doubled within a decade [8], almost in pace with low testosterone levels detected in laboratory testing [7]. Prescribing testosterone at random without documented low testosterone levels and symptoms of testosterone deficiency is not in accordance with current good medical practice and borders on testosterone abuse, culminating in doping with androgens to enhance physical performance in sports and bodybuilding. Currently discussed unwanted side-effects of testosterone may, at least in part, be caused by improper prescribing (see below).

Normal testosterone levels: thresholds for substitution

As stated above, good clinical practice requires that testosterone is only to be administered if symptoms of testosterone deficiency are encountered and levels are below normal. But what is the lower limit of normal?

First, due to the diurnal rhythm of testosterone in serum [9] blood samples of testosterone should always be taken in the morning hours from men with a regular day–night rhythm in order to obtain results comparable to reference values.

While there is not one fixed lower limit of normal, symptom-specific threshold levels do exist [10,11]. Loss of libido and vigour may already occur below 15 nmol/L, but certainly is present below 12 nmol/L when obesity also begins; below 10 nmol/L depressive moods, sleep disturbance, lack of concentration and diabetes type II are found and erectile dysfunction and hot flushes are reported below 8 nmol/L. These symptom-specific threshold levels may explain why the lower limit of normal and the limits for starting testosterone substitution vary in different countries [12]. The perception of the physician rather than the patient's complaints may govern prescribing behaviour.

As loss of libido is the most frequent and an early symptom demanding treatment [13,14], mostly occurring below 12 nmol/L, this is a distinct signal for beginning testosterone therapy. Levels for younger men also serve as reference values for older men, and several recent large epidemiological studies from the USA [15], Australia [16] and Europe [17,18] show that 12 nmol/L is the lowest value for testosterone in the serum of healthy men.

While total testosterone remains the most important diagnostic parameter (assuming that it is determined with methods under strict quality control), free testosterone can be used as an additional parameter in borderline cases. However, many labs offer the “free androgen index” (FAI) as a pseudo-parameter for which total testosterone is simply divided by SHBG. This index correlates with the actual real free testosterone in women, but not in men and should therefore not be used. Free testosterone can easily be calculated from total testosterone and SHBG by using a generally available formula (http://issam.ch/freetesto.htm). Only free testosterone measured by this method can be helpful in male diagnosis [19,20]. Free testosterone values below 225 pmol/L (65 pg/ml) require testosterone treatment.

Mass spectrometric methods (LC-MS/MS) are the gold standard for measuring testosterone and provide the option of simultaneously determining a great spectrum of steroid hormones [21]. These methods continue to be reserved for large centres and have persevered only in connection with clinical studies relevant to licensing procedures. In addition, comparison of various methods for determining testosterone has shown that well-controlled immunoassays correlate very well with results from mass spectrometry, at least for diagnostic purposes [15,17,22]. The reliability of immunoassays becomes