Challenges in the Diagnosis of the Right Patient for Testosterone Replacement Therapy

Christina Wang*
Harbor-UCLA Medical Center, David Geffen School of Medicine at UCLA, Torrance, CA, USA

1. Introduction

The diagnosis of testosterone deficiency is important to identify patients who may benefit from testosterone replacement therapy. Numerous studies have shown that testosterone replacement can improve sexual function, muscle mass, bone density, body composition, mood, and energy in hypogonadal men [1,2]. A diagnosis of testosterone deficiency is based on a reproducibly low level of serum testosterone levels. However, marked variations in the reference ranges of serum testosterone levels among laboratories pose a challenge for physicians when interpreting the results. In addition, initial laboratory assessments usually determine total testosterone levels. About 1–2% of total testosterone is free and a further 30–50% is bound with low affinity to albumin; only these two components are bioavailable to the target tissues. In general, assuming the normal reference range for serum total testosterone in adult men is 300–1000 ng/dl (10–35 nmol/l), levels of < 250 ng/dl (8.7 nmol/l) suggest the patient is likely to be hypogonadal, whereas levels of > 350 ng/dl (12.7 nmol/l) suggest the symptoms may not be due to androgen deficiency. Values between 250 to 350 ng/dl warrant a repeat morning serum testosterone determination with assessment of free or bioavailable testosterone. In men with symptoms suggestive of androgen deficiency and borderline serum testosterone levels, where there are no contraindications to androgen therapy, a short therapeutic trial of testosterone may be justified.

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Abstract

Diagnosis of testosterone deficiency is important to identify patients who might benefit from testosterone replacement therapy. Unfortunately, the diagnosis of hypogonadism may be a challenge for many practicing physicians, including endocrinologists and urologists. Signs and symptoms, such as sexual dysfunction, change in body composition, lethargy, and mood changes, are nonspecific and the available questionnaires are generally not useful in clinical practice. The diagnosis of testosterone deficiency is ultimately based on measurement of serum testosterone levels. However, marked variations in the reference ranges of serum testosterone levels among laboratories pose a challenge for physicians when interpreting the results. In addition, initial laboratory assessments usually determine total testosterone levels. About 1–2% of total testosterone is free and a further 30–50% is bound with low affinity to albumin; only these two components are bioavailable to the target tissues. In general, assuming the normal reference range for serum total testosterone in adult men is 300–1000 ng/dl (10–35 nmol/l), levels of < 250 ng/dl (8.7 nmol/l) suggest the patient is likely to be hypogonadal, whereas levels of > 350 ng/dl (12.7 nmol/l) suggest the symptoms may not be due to androgen deficiency. Values between 250 to 350 ng/dl warrant a repeat morning serum testosterone determination with assessment of free or bioavailable testosterone. In men with symptoms suggestive of androgen deficiency and borderline serum testosterone levels, where there are no contraindications to androgen therapy, a short therapeutic trial of testosterone may be justified.

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* Harbor-UCLA Medical Center, Los Angeles Biomedical Research Institute, 1000 West Carson Street, Torrance, CA 90509, USA. Tel. +1 310 222 2503; Fax: +1 310 533 6972. E-mail address: wang@labiomed.org.

1. Introduction

The diagnosis of testosterone deficiency is important to identify patients who may benefit from testosterone replacement therapy. Numerous studies have shown that testosterone replacement can improve sexual function, muscle mass, bone density, body composition, mood, and energy in hypogonadal men [1,2]. A diagnosis of testosterone deficiency is based on a reproducibly low level of
serum testosterone, or its biologically active component, in association with signs and symptoms of androgen deficiency. In patients with severe testosterone deficiency, for example, due to diseases of the testes or pituitary, the diagnosis is usually straightforward. However, in the majority of hypogonadal patients with less severe testosterone deficiency without a definitive cause, the diagnosis remains a challenge [3].

2. Signs and symptoms of androgen deficiency

The common signs and symptoms of androgen deficiency include decreased libido and erectile dysfunction; reduced muscle strength and mass; back pain, low bone mass, and subsequent fractures (osteopenia); increased abdominal fat; loss of body hair and thinness of the skin; and an array of symptoms such as mood changes, lack of motivation, lethargy, decreased well-being, and poorer quality of life [4,5] (Table 1). At first glance, a diagnosis based on these signs and symptoms would appear to be relatively straightforward. However, closer examination reveals that they are all relatively nonspecific for testosterone deficiency. For example, as shown in Fig. 1, the pathogenesis of erectile dysfunction is multifactorial and, in addition to hypogonadism [6], it can be due to a combination of cardiovascular or neurologic problems or medication side effects leading to a defect in cavernosal release of nitric oxide. Thus, the presence of erectile dysfunction or decreased libido is not diagnostic for testosterone deficiency. Similarly, the changes in body composition that occur with testosterone deficiency, including an increase in body fat and a decrease in lean body mass, which may be associated with insulin resistance, are clearly not specific to androgen deficiency. Testosterone deficiency is a major cause of osteoporosis and deterioration of trabecular architecture in men [7]; around 5–30% of men with osteoporosis have no apparent cause other than hypogonadism. This lack of specificity for testosterone deficiency is even more obvious when considering symptoms such as depression or low vitality. Studies in older men suggest that depression was associated with lower bioavailable testosterone [8,9]. Randomized trials of testosterone replacement therapy have shown mixed results regarding efficacy in depression [10,11]. Testosterone deficiency is also associated with decreased vitality and quality of life. Epidemiologic studies have shown correlations between low testosterone and decreased energy, and energy is improved in most, although not all, studies of testosterone replacement therapy [12–14]. Nevertheless, symptoms such as depression and low vitality are associated with many conditions other than testosterone deficiency.

Transient suppression of testosterone, and associated symptoms, can also occur with stress, and more prolonged testosterone deficiency occurs in a range of severe medical conditions such as HIV infection, chronic kidney disease, chronic obstructive airway disease, and cardiovascular disease [15]. Recent reports show that a substantial proportion of patients with type 2 diabetes mellitus with insulin resistance and visceral obesity have low testosterone levels [16–20]. Thus, hypogonadism should be excluded in patients with these chronic medical conditions, especially if they have associated symptoms such as sexual dysfunction.

Table 1 – Signs and symptoms of androgen deficiency

| Decreased libido, erectile dysfunction |
| Decreased muscle strength and mass (frailty) |
| Decreased body hair and thinness of skin |
| Decreased general well-being and mood changes |
| Fractures and back pain (osteopenia) (frailty) |
| Increased abdominal fat |
| Decreased energy and work capacity (frailty) |
| Gynecomastia |

Fig. 1 – Pathogenesis of erectile dysfunction.
3. Questionnaires assessing androgen deficiency

There are no specific validated questionnaires to diagnose androgen deficiency in younger men. A number of questionnaires are available to assess testosterone deficiency in older men, such as the Androgen Deficiency in Ageing Males (ADAM), the Aging Males Survey (AMS), and the Massachusetts Male Aging Study (MMAS) scales [21–23]. The sensitivity and specificity of the ADAM, MMAS, and AMS scales for hypogonadism were compared in 148 men (aged 23–80 yr) with serum bioavailable testosterone of < 70 ng/dl [24]. As shown in Table 2, the sensitivity was relatively high, notably for the ADAM and AMS scales, but all three had low specificity. Unfortunately, because they have a low specificity, they are generally not very useful in clinical practice. A questionnaire that is more specific for hypogonadism has yet to be developed and may be helpful for the clinician, not only for diagnosis, but also for assessing the response to testosterone treatment. A recent study also found that an expanded modified version of the ADAM-AMS questionnaire did not improve the ability to identify patients with testosterone deficiency [3].

In addition to these questionnaires, a structured interview has been developed to screen for hypogonadism in men with sexual dysfunction. This 12-item interview, known as the ANDROTEST, has been shown to have a sensitivity of 68% and a specificity of 65% in detecting low total testosterone [25].

4. Measurement of serum testosterone

Ultimately, the diagnosis of testosterone deficiency, as the name implies, must be based on measurement of serum testosterone. Serum testosterone is relatively simple to measure, and most practicing physicians will determine total testosterone levels as the initial laboratory assessment. It should be noted that only about 1–2% of total testosterone is free, and a further 30–50% is bound with low affinity to albumin; therefore, only about 50% of total testosterone is bioavailable.

Many different methods are available also for measuring testosterone (eg, direct radioimmunoassay, enzyme-linked immunoassays, chemiluminescent assays, radioimmunoassay after column extraction, and tandem mass spectrometry after high-performance liquid chromatography or gas chromatography). All of these methods are generally adequate for the diagnosis of male hypogonadism, but marked variations can occur from one laboratory to another. For example, an external quality control program carried out by the College of American Pathologists compared the results from 891 laboratories using 11 different assay methods [26]. The median serum total testosterone level measured in a single quality control sample ranged from 215 to 378 ng/dl among the various methods used, with the results from individual laboratories ranging from 160 to 508 ng/dl (Table 3). These results span the range between eugonadal and hypogonadal levels. This illustrates the importance of each laboratory establishing its own individual reference testosterone range for adult men for the diagnosis of hypogonadism. Studies have compared serum testosterone measurements by non-isotopic immunoassays, radioimmunoassay, gas chromatography-mass spectrometry, and liquid chromatography-tandem mass spectrometry [17,19,26]. These three studies, conducted in France, Australia, and the United States, indicated large variations in measurement of serum testosterone by different non-isotopic platform methods commonly used in clinical chemistry laboratories. In some methods, systematic bias gave higher or lower testosterone results when compared

| Table 3 – Serum total testosterone in a College of American Pathologists quality control sample (Y-04) measured using various different instruments/assays [26] |
|----------------|----------------|----------------|
|                | No. of laboratories | Median, ng/dl | Range, ng/dl |
| Abbott Architect | 11              | 243            | 219–262     |
| Bayer ACS:180   | 83              | 314            | 227–410     |
| Bayer Centaur   | 231             | 319            | 234–454     |
| Bayer Immuno-1  | 43              | 300            | 254–335     |
| Beckman Access/2| 98              | 298            | 239–330     |
| Diagnostic Systems solid | 10          | 375            | 177–440     |
| DPC Coat-a-Count| 76              | 281            | 196–363     |
| DPC Immulite    | 86              | 228            | 160–330     |
| DPC Immulite 2000| 83             | 215            | 130–299     |
| Roche Elecsys/E170 | 87           | 348            | 299–408     |
| Ortho Vitros ECI| 54              | 280            | 254–324     |
| All instruments | 891             | 297            | 160–508     |

Adapted from Wang et al. J Clin Endocrinol Metab 2004;89:534–43.

| Table 2 – Sensitivity and specificity of screening questionnaires for hypogonadism (defined as bioavailable testosterone < 70 ng/dl) [24] |
|----------------|----------------|-------------|
|                | Sensitivity, % | Specificity, % |
| ADAM           | 97             | 30          |
| MMAS           | 60             | 59          |
| AMS            | 83             | 39          |

with methods using mass spectrometry. Most importantly, these studies showed that with the current methods commonly used in clinical laboratories, serum testosterone cannot be measured accurately and precisely in women and children. Most assays are adequate to distinguish eugonadal from hypogonadal men provided reference ranges are established in each individual laboratory. In a recent position statement by the Endocrine Society, it was concluded that “laboratory testing should be based on the ability to measure samples containing known levels of testosterone, not only on agreement with other laboratories using the same method” [27]. They also proposed that unified normative values should be established, if possible, for total and free testosterone. In the interim, before such uniform standards or methods can be implemented, the clinician should be aware of the type of assay the laboratory is using and the reference ranges. Based on the studies [17,19,26], the panel indicated that most of the current testosterone assays are adequate for the diagnosis of male hypogonadism.

Clinicians should optimize the determination of serum testosterone levels by drawing the blood sample in the morning (between 7 and 10 AM). Although circadian rhythms in serum testosterone are less marked as men age, the reference ranges are usually obtained in the morning in younger men. In addition, physicians should check the reference range for serum testosterone in the laboratory they use to help them interpret the results. They should ask the laboratory how the reference ranges were determined; these should be established for each laboratory based on healthy younger men.

In general, assuming that the normal reference range for serum total testosterone in adult men is 300–1000 ng/dl (10–35 nmol/l), levels of < 250 ng/dl (8.7 nmol/l) suggest that the patient is likely to be hypogonadal, whereas levels of > 350 ng/dl (12.7 nmol/l) suggest that the symptoms may not be due to androgen deficiency. Note that some recent publications suggest using cut-off values of 200 and 400 ng/dl [28]. The International Society of Andrology (ISA), International Society for the Study of the Aging Male (ISSAM), and European Association of Urology (EAU) guidelines recommend that levels < 231 ng/dl (8 nmol/l) are representative of hypogonadism and that testosterone replacement may therefore be appropriate, and levels above a threshold of 346 ng/dl (12 nmol/l) are normal [29]. Values between these limits warrant a repeat morning serum testosterone determination with direct measurement of free testosterone by equilibrium dialysis or calculated by measurements of sex hormone-binding globulin (SHBG) and total testosterone levels [30]. The guidelines from the Endocrine Society (United States) recommend that clinicians use the lower limit of the normal range for healthy young men that has been established in their reference laboratory [31]. In some laboratories, this is 300 ng/dl (10.4 nmol/l). Free testosterone assays performed by many laboratories using analogue displacement give no additional information over total testosterone levels. Alternatively, direct measurement or calculated free or non–SHBG-bound testosterone levels have been suggested to correlate better with symptoms of hypogonadism in elderly men.

5. Diagnosing the right patient for testosterone replacement therapy

Fig. 2 summarizes the proposed steps in identifying the right patient for testosterone replacement therapy.
therapy. If the patient has signs and symptoms of androgen deficiency, and morning serum total testosterone levels are <250 ng/dl, then he is a candidate for testosterone replacement therapy. At this stage, luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels should be checked; LH and FSH levels are elevated in primary hypogonadism but are normal or low in secondary hypogonadism. If testosterone, LH, and FSH levels are low, serum prolactin should be checked to exclude a prolactin-secreting pituitary tumor.

Borderline levels of total testosterone should be followed up by measurement of free or bioavailable testosterone. If these levels are low, then the patient is a candidate for testosterone replacement therapy. In men with borderline serum testosterone levels, where there are no contraindications to androgen therapy, a short therapeutic trial of testosterone may also be justified with careful monitoring of any improvement in symptoms. There are many different methods of testosterone treatment and a decision can be reached between the patient and the physician [32].

6. Conclusions

Diagnosing testosterone deficiency and identifying suitable patients for testosterone replacement is a challenge for many practicing physicians. Measurement of serum testosterone remains the cornerstone for diagnosis, but physicians must be aware of the differences in accuracy and reference ranges between methods and laboratories. Patients with serum total testosterone levels of <250 ng/dl and signs and symptoms of androgen deficiency are candidates for testosterone replacement therapy, whereas a short trial of testosterone replacement may be justified in those with borderline testosterone levels and symptoms suggestive of androgen deficiency.

Conflicts of interest

Research support from Solvay, GSK, Ardana, BMS, Indevus. Temporary consultant for Indevus, Bayer-Schering AG.

References


