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

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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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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

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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

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.

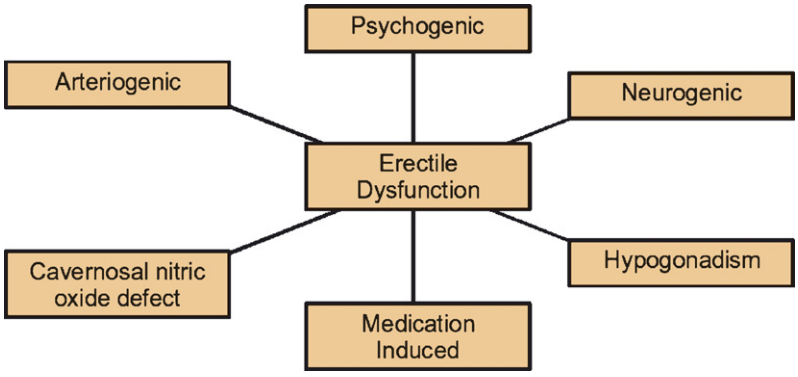

Fig. 1 – Pathogenesis of erectile dysfunction.