SEXUAL MEDICINE REVIEWS

Testosterone Replacement—Freedom From Symptoms or Hormonal Shackles?

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ABSTRACT

Introduction: The question of whether to initiate men on testosterone replacement therapy (TRT) and for how long remains a relevant question to be answered.

Aim: To determine when to start patients on TRT, determine the benefits of TRT, and whether starting patients on TRT condemns them to a lifetime of hormonal replacement.

Methods: A literature review of relevant publications in PubMed was used.

Main Outcome Measures: Main outcome measures were evidence for initiating TRT, benefits of TRT, pathophysiology of TRT, and evidence for duration of TRT.

Results: Although the exact threshold of serum testosterone levels that define hypogonadism is still strongly debated, the presence of symptoms associated with low levels of testosterone can be considered to help make the diagnosis. Although the proper duration of TRT has yet to be established, maintenance of symptom improvement after discontinuing TRT has been observed, which is a promising result. Studies also have shown a return to hormonal baseline after discontinuation of TRT.

Conclusion: It has been established that patients with testosterone deficiency benefit from TRT. Preliminary evidence seems to show that men who are initiated on TRT are not condemned to a lifetime of hormonal therapy, although many men might choose to continue treatment because of improvement in their symptoms.

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Key Words: Testosterone; Testosterone Replacement; Testosterone Replacement Therapy; Hypogonadism; Testosterone Deficiency

INTRODUCTION

Testosterone (T) is an important sex hormone that plays a major role in maintaining primary and secondary sexual male characteristics. T also exerts its effects on muscle, bone, fat metabolism, and behavior.[1] The diagnosis of hypogonadism (T deficiency) can be made in patients presenting with low levels of T and a cluster of clinical symptoms. These symptoms include decreased libido, erectile dysfunction, decreased sexual thoughts, decreased energy, and depressed mood. Low T also has been associated with decreased bone mineral density, anemia, reduced muscle mass, increased body fat, and metabolic syndrome.[2]

The exact threshold defining low serum T is yet to be established. Further studies involving healthy young men are required to determine a proper range for normal serum T levels and help create a universal threshold for low T. Currently, there is a lack of consensus for what constitutes low T; the threshold based on different recommendations ranges from 200 to 400 ng/dL. Although some organizations have recommended strict cutoffs, this could prevent treatment in men with T deficiency whose levels are above the cutoff levels and initiate unnecessary treatment in men with levels below these strict cutoffs. Thus, signs and symptoms of low T should considered, as should low serum T levels, to diagnose hypogonadism.[3,4] The Testosterone Trials recently published in the *New England Journal of Medicine* set 275 ng/dL as their cutoff level for participation in the trials.[5]

Because symptoms are mostly non-specific, clinical judgment should be used, in addition to symptoms and T levels, to make the diagnosis of hypogonadism. The physical examination also is non-specific and can include obesity, loss of body hair, gynecomastia, mild anemia, osteoporosis, and decreased testicular volume. During the initial workup, it also is important to address

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any other treatable medical issues that could be the cause of these symptoms.[6]

Hypogonadism can be classified as primary, when the dysfunction originates from the testes, or secondary, when there is dysregulation of the hypothalamic-pituitary-target organ axis.[1,6] It has been established that men's T levels decrease as they age. Specifically, there is a 0.4% to 2% annual decrease in T levels after 30 years of age.[7] Thus, late-onset hypogonadism (LOH), or androgen deficiency in the aging man, is becoming increasingly important for physicians to identify.[7] Because symptoms of hypogonadism are non-specific, LOH was introduced to differentiate symptoms of hypogonadism from other conditions such as aging. LOH has been defined as a total T level lower than 300 ng/dL in combination with decreased frequency of morning erections, erectile dysfunction, and decreased frequency of sexual thoughts.[6]

The prevalence of hypogonadism has been reported to be as high as 38.7%.[8] However, there might have been some limitations associated with this specific study, and it is important to note that most studies have instead shown the prevalence of symptomatic hypogonadism to be approximately 3% to 6%.[4,7,9] Regardless, it is clear that hypogonadism is a common condition, especially in the aging population and thus must not be overlooked.

INITIATION OF TESTOSTERONE REPLACEMENT THERAPY

Once the diagnosis of hypogonadism is made, T replacement therapy (TRT) should be considered, because TRT has been shown to improve sexual function, decrease body fat, increase lean muscle mass and function, and improve bone mass.[6,10] In fact, TRT is considered the gold standard for treating hypogonadism if the patient is not interested in fertility.[11] The American Urological Association recommends initiating TRT for patients with clinically significant hypogonadism, whether or not it is related to aging, after discussing possible side effects.[2] Thus, it is important to identify patients with low T who are symptomatic, because they would likely benefit from TRT.[6] Trials of treatment need to be initiated for at least 6 and ideally 12 months to achieve adequate levels of T in the mid to upper normal range.[12]

Although these recommendations are in place, there remain a significant number of men who are not being treated for LOH. In an observational study of a random sample from Boston, Massachusetts, 87.8% of 97 men with T deficiency were not receiving treatment, although they had access to health care.[13] Studies such as this stress the importance of screening for hypogonadism in men with symptoms suggestive of the condition and of acknowledging the likely benefit from treatment that these men would experience.[6,13] However, it is critical to note that TRT in the absence of hypogonadism is inappropriate, so proper diagnosis must be made before starting a patient on TRT.[2]

Before initiating TRT, it is important to consider contraindications to initiation of therapy. These include prostate cancer, New York Heart Association class III or IV congestive heart failure, and hematocrit level higher than 52%.[3,5]

ASSOCIATED COMORBIDITIES OF T DEFICIENCY AND BENEFITS OF TRT

In addition to T deficiency being associated with sexual symptoms, there have been many studies showing an association between low T and comorbid diseases such as type 2 diabetes mellitus, moderate to severe chronic obstructive pulmonary disease, and obesity. In fact, one study found a highly significant negative correlation ($P < .001$) between plasma free T levels and body mass index.[14] In a study of men with type 2 diabetes, mortality also was found to be higher in the low T group at 17.2% vs 9% in the normal T group ($P = .003$).[15]

The benefit of TRT in these comorbid conditions has been highlighted in several studies. For example, when evaluating the effect of long-term TRT (up to 8 years) in hypogonadal men with different obesity classes, TRT was shown to produce significant weight loss and a decrease in waist circumference and body mass index.[16] In a systematic review with meta-analysis of controlled and randomized studies, TRT was reported to increase muscle mass in elderly men.[17] Another review from 2013 reported that TRT increased lean body mass, decreased central obesity, and increased glycemic control in patients with metabolic syndrome.[18]

An article determining the benefits of TRT based on the Testosterone Trials was recently published in the *New England Journal of Medicine*. The Testosterone Trials were seven double-blinded, placebo-controlled trials assessing the effect of TRT on sexual function, physical function, and vitality of men older than 65 years with hypogonadism. TRT was found to have a moderate, yet statistically significant, impact on sexual function but no significant impact on vitality or physical function. However, participants who received TRT reported slightly better mood and vitality, as evidenced by a decrease in depressive symptoms, which could be of clinical significance. Although no significant difference was shown in the physical function trials, when all three trials were considered together, there was a significant difference, showing once again that this could be of clinical significance. This study is important for physicians as they consider when to initiate TRT (Figure 1).[5]

LIFETIME OF HORMONAL REPLACEMENT?

T production is regulated by the hypothalamic-pituitary-gonadal axis. Pulsatile secretion of gonadotropin-releasing hormone from the hypothalamus leads to the release of luteinizing hormone from the anterior pituitary, which then stimulates Leydig cells in the testicles to produce T. High T levels lead to negative feedback on the hypothalamus and anterior pituitary. Therefore, the use of TRT results in negative