COMMENTARY

Commentary: Who Is a Candidate for Testosterone Therapy? A Synthesis of International Expert Opinions

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ABSTRACT

Introduction. Despite increasing use of testosterone therapy (TTh) for men with testosterone deficiency (TD), there remains uncertainty determining who is a candidate for treatment.
Aim. The aim if this study was to report the opinions of international experts on TTh, as initially presented at the meeting of the World Meeting on Sexual Medicine in Chicago, United States in August 2012.
Methods. Expert responses to questions regarding the diagnosis of TD based on their own clinical and research experience.
Results. All experts emphasized the primacy of symptoms for the diagnosis of TD. Total testosterone (T) thresholds used to identify TD ranged from 350 ng/dL to 400 ng/dL (12–14 nmol/L); however, experts emphasized the diagnostic limitations of this test. Free T was obtained by all, with some valuing this test more than total T for clinical decision making. Only one expert routinely used a screening questionnaire. None used age-adjusted values. Bioavailable T and the free androgen index were not used. Luteinizing hormone (LH) and sex hormone-binding globulin levels were routinely obtained at evaluation. Additional supportive evidence for TD diagnosis included small testicular volume, high androgen receptor CAG repeats, elevated LH, and presence of diabetes or metabolic syndrome. Two T tests were generally obtained but not always required. Some experts did not require morning testing in men 50 years and older. All monitored prostate-specific antigen and hematocrit after initiation of TTh. All but one expert would consider a trial of TTh to a symptomatic man with total T within the normal range. Recent studies suggesting increased cardiovascular risk with T therapy were not found to be credible.
Conclusions. Determining who is a candidate for TTh requires clinical assessment based on symptoms and signs, with confirmatory laboratory evaluation. These expert opinions differed from some published guidelines by the emphasis on symptoms as paramount, recognition of the limitations of total T as a diagnostic test, and the potential utility of a therapeutic trial in symptomatic cases with normal total T concentrations. **Morgentaler A, Khera M, Maggi M, and Zitzmann M. Commentary: Who is a candidate for testosterone therapy? A synthesis of international expert opinions. J Sex Med 2014;11:1636–1645.**

Key Words. Testosterone; Hypogonadism; Treatment; Diagnosis; Evaluation; Monitoring

Introduction

Abraham Morgentaler, MD—In August 2012 at the World Meeting on Sexual Medicine in Chicago, I was honored to lead a postgraduate course entitled: Who is a candidate for testosterone therapy? The topic was chosen to address one of the most contentious and confusing aspects of testosterone therapy (TTh). An international panel of experts was selected as faculty, and each was asked to present his or her views and practices, based on their own extensive clinical experiences and androgen-related research interests. The expert panelists were Mario Maggi from

Italy, Michael Zitzmann from Germany, and Mohit Khera from the United States. The purpose of this report is to share the valuable perspectives of these expert clinician-researchers with the Journal readership.

Testosterone (T) has been available as a medical therapy since the 1930s; however, its use was limited until the last 10–15 years, at which point prescription rates began to increase at a rapid rate. This increase in TTh appears due to a combination of factors, including increased awareness of T deficiency (TD) (also known as hypogonadism or late-onset hypogonadism) as a treatable condition, the publication of numerous studies documenting benefits of TTh, decreased concern regarding safety risks, particularly prostate cancer, and the introduction of new commercial T formulations with associated marketing efforts. However, despite the long history of TTh, there has been little standardization regarding the evaluation and management of TD.

This lack of consensus causes confusion among clinicians and represents a significant hurdle impeding the appropriate use of TTh. The confusion stems from a number of factors: availability of multiple assays to determine androgen status, such as total, free, and bioavailable T, with proponents for each; widely differing laboratory reference ranges; limited clinical correlation between serum T concentrations and symptoms; and clinical experiences that differ from published guidelines.

Several expert groups and specialty societies have attempted to address these issues with published guidelines or recommendations. These include the Endocrine Society in the United States [1], joint guidelines on behalf of a number of international andrological societies [2], and recommendations from the International Consultation on Sexual Medicine [3].

With minor variations, those guidelines assert that the diagnosis of TD should only be made in men with characteristic symptoms or signs of TD in combination with a documented serum T that is low. In the 2006 version of the Endocrine Society guidelines [4], a serum T below 300 ng/dL (10.4 nmol/L) was set as the diagnostic threshold; however, in the 2010 updated version, clinicians were referred to their own laboratory's reference ranges [1]. Recommendations from the joint international societies indirectly support a threshold of 350 ng/dL (12 nmol/L) by asserting that men with serum T concentrations above this level generally do not benefit from treatment [2]. The International Consultation on Sexual Medicine repeats this threshold, but notes that treatment may be reasonably offered to symptomatic men with higher concentrations based on clinical judgment [3]. All groups recommend obtaining a second confirmatory total testosterone (TT) test prior to initiating treatment. The use of free or bioavailable T has been recommended by these groups only as a secondary test when serum T provides unclear results.

These guidelines provide a valuable guide for clinicians new to the field. However, guidelines have important limitations [5]. First, in the specific case of guidelines regarding T, each of the published documents acknowledges that the quality of supporting evidence for their major recommendations is poor. No studies have revealed any specific T concentration that reliably distinguishes men who will respond to treatment from men who will not.

Second, guidelines represent consensus documents created by groups of individuals, whose own practices may differ substantially from each other. As a result, final guidelines and recommendations may not reflect the actual clinical practice of any of the committee members. Third, guidelines have a tendency to produce recommendations that reflect "ideal" practices, which may differ from circumstances "on the ground" for the practicing clinician.

There is thus considerable value in learning how individual experts approach the problem of identifying candidates for TD. The practices of each of the experts contributing to this report have been honed by years of experience and informed by their own observations and research. Below are presented the questions and answers for each of the three panelists.

Questions and Answers

Q: How do you diagnose TD in your own practice? What symptoms, signs, and blood tests do you require in order to offer TTh?

Mohit Khera: I diagnose TD based on two criteria: low serum total or free T and signs or symptoms of TD. However, I must stress that in my practice, symptoms are the key driver for TTh rather than any specific value for blood test results.

In my experience, sexual symptoms such as low libido and erectile dysfunction (ED) are the most sensitive and specific symptoms. Many patients with TD also commonly present with fatigue, lack of energy, and reduced motivation. Because not all patients with TD present with sexual symptoms, I