Review Article

The Laboratory Diagnosis of Testosterone Deficiency

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The evaluation and treatment of hypogonadal men has become an important part of urologic practice. Fatigue, loss of libido, and erectile dysfunction are commonly reported, but nonspecific symptoms and laboratory verification of low testosterone (T) are an important part of evaluation in addition to a detailed history and physical examination. Significant intraindividual fluctuations in serum T levels, biologic variation of T action on end organs, the wide range of T levels in human serum samples, and technical limitations of currently available assays have led to poor reliability of T measurements in the clinical laboratory setting. There is no universally accepted threshold of T concentration that distinguishes eugonadal from hypogonadal men; thus, laboratory results have to be interpreted in the appropriate clinical setting. This review focuses on clinical, biological, and technological challenges that affect serum T measurements to educate clinicians regarding technological advances and limitations of the currently available laboratory methods to diagnose hypogonadism. A collaborative effort led by the American Urological Association between practicing clinicians, patient advocacy groups, government regulatory agencies, industry, and professional societies is underway to provide optimized assay platforms and evidence-based normal assay ranges to guide clinical decision making. Until such standardization is commonplace in clinical laboratories, the decision to treat should be based on the presence of signs and symptoms in addition to serum T measurements. Rigid interpretation of T ranges should not dictate clinical decision making or define coverage of treatment by third party payers. UROLOGY 83: 980–988, 2014.

The laboratory diagnosis of testosterone (T) deficiency is a challenge. Serum T levels are subject to temporal variation—diurnal, seasonal, and age-related. Illness and certain medications, such as opiates and glucocorticoids, can temporarily affect T concentrations through central and peripheral effects. Total testosterone (TT) concentrations are affected by alterations in sex-hormone binding globulin (SHBG), which in turn can vary for a variety of reasons, including age, medications, and medical comorbidities. There are several different assays for measurement of T levels, and performance characteristics, linearity, reproducibility, low-level limits of detection, and preanalytic requirements differ among the assay platforms. The populations on which the normal assay ranges are established differ between assays, leading to a wide variety of normal ranges reported by different laboratories. Lastly, T circulates in the blood primarily bound specifically to SHBG or nonspecifically to albumin, with only 2%-3% of TT being free. Whether TT or free testosterone (FT) measurements most closely correlate with symptomatic androgen deficiency is a matter of debate.

Androgen deficiency may become apparent at different ages within an individual or a population. T levels are affected by age, body mass index, and comorbidities, such as type 2 diabetes mellitus, depression, anxiety, thyroid disorders, malnutrition, alcohol consumption, and physical activity. There is no large population-based study of T values from healthy, fertile men with normal sexual activity and reproductive function assessed by commonly accepted validation methods. The lack of these types of studies confuses clinical decision making and impairs comparison of assays on the same subject obtained in different laboratories.

Because of the multitude of factors affecting the laboratory evaluation and interpretation of T levels, it is no surprise that a significant, universally accepted definition of T deficiency is lacking. The American Urological Association (AUA), together with the Endocrine Society and the Centers for Disease Control and Prevention (CDC), has been a leading force in addressing technical difficulties in T measurements, establishing clinically relevant normal assay ranges and harmonizing T assay performance across different platforms.[1] Improving assay accuracy, sensitivity, and reproducibility and advocating that laboratories disclose information about their methodologies with results and provide a standardized definition of normal populations used to establish normal assay ranges should help clinicians to deliver better care for their patients.

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In this study, we discuss the currently used assays for T measurement, their utility and limitations, and the implications for clinical practice relevant to practice of urology and andrology.

DEFINING TESTOSTERONE DEFICIENCY

There is no consensus among endocrinologists, urologists, and clinical pathologists as to what defines a "low" T level. Published normal assay ranges for serum T are mostly based on studies in older men (>65 years) and were not specifically designed to establish normal assay ranges in men with normal sexual and reproductive function.[2,3] It is clear that T level correlates with overall health status and normal sexual function. To best serve our patients, it is our belief that the normal ranges should be based on a predefined, healthy index population representing the demographic structure of the United States. The Endocrine Society recommends that total low T be defined using local, normal assay ranges in the presence of characteristic signs or symptoms diagnostic of hypogonadism.[4] The Food and Drug Administration uses a cutoff value of 300 ng/dL to define hypogonadism for clinical trial development and enrollment.[5] Meanwhile, a consensus statement from the International Society of Andrology, the International Society for Study of the Aging Male, the European Association of Urology, the European Association of Andrology, and the American Society of Andrology recommended that TT levels above 350 ng/dL do not require treatment, and levels below 230 ng/dL (with symptoms) may require T replacement therapy.[6] For levels between 230 and 350 ng/dL, the recommendation is to repeat the TT with SHBG for calculation of FT or direct measurement of FT by equilibrium dialysis.[6] Similarly, it has been previously recommended that men with TT < 200 ng/dL be treated as hypogonadal, those with TT > 400 ng/dL be considered normal, and those with TT 200-400 ng/dL be treated on the basis of their clinical presentation, if symptomatic.[7]

Considering that serum T level is used as a surrogate of target organ concentration of T and based on a review of the published literature and the best clinical judgment of the authors of this article, this panel emphasizes that signs and symptoms suggestive of hypogonadism and laboratory measured T level are equally important indicators of hypogonadism and indicators for treatment until more research is done. We believe that rigid use of T cutoff (300 ng/dL) may lead to unnecessary treatment of asymptomatic men and undertreatment of men with persistent signs and symptoms.

Use of FT or bioavailable T may aid in the biochemical diagnosis of hypogonadism, especially when results of the TT assay are equivocal or fail to reflect clinical presentation.[6] There are no generally accepted lower limits of normal FT for the diagnosis of hypogonadism. According to expert opinion, a FT level below 65 pg/mL may provide supportive evidence for treatment.[6] Corresponding values for bioavailable T depend on the method used and are not generally available for healthy young men.[8] Calculated FT using measured TT and SHBG values is a feasible approach to include the SHBG variability in the interpretation of TT.[9]

It is no surprise that attempts to establish a uniform laboratory threshold that accurately distinguishes hypogonadal and eugonadal men among the broad range of patients of different ages and ethnic background have been difficult, given lack of agreement on what constitutes the definition of a "normal" patient, tendency to select men older than 65 years for published studies on hypogonadism, different inclusion and exclusion criteria among studies, and technical differences in assays used. Mean age of patients enrolled in the largest population studies on male hypogonadism was 75.4 years for the osteoporotic fractures in men arm in Sweden, 73.7 years in the United States based arm of osteoporotic fractures in men, and 60 years for the European Male Ageing Study.[2,3,10] More studies focused on demographically matched healthy male populations are clearly needed to establish normal assay ranges for diverse age group of men.

PREVALENCE OF TESTOSTERONE DEFICIENCY

In a multiethnic, population-based observational study of 1475 men aged 30-79 years in the United States, Araujo et al[11] observed the prevalence of symptomatic androgen deficiency in hypogonadal men (TT <300 ng/dL) to be 5.6% (95% confidence interval 3.6%-8.6%). Symptomatic hypogonadism was defined as presence of low libido, erectile dysfunction, osteoporosis, or fracture or 2 or more of following symptoms: sleep disturbance, depressed mood, lethargy, or diminished physical performance. The prevalence of hypogonadism was lower in men younger than 70 years (3.1%-7.0%), but increased substantially with age to 18.4%. Men older than 50 years with a T level below 300 ng/dL were more likely to have hypogonadism-related symptoms (8.4%) as compared with younger hypogonadal men (4.2%). Longitudinal population-based studies of aging men have also demonstrated that both TT and FT decline with age, with a concomitant increase in SHBG levels.[12-14] Given this evidence, it is estimated that by 2025, there will be approximately 6.5 million American men aged 30-80 years diagnosed with androgen deficiency.[11] Mulligan et al[15] reported prevalence of hypogonadism (TT <300 ng/dL) to be 38.7% among men ≥45 years attending general clinical practice, but the mean age of patients in this study was 60 years, thus limiting the conclusions of study. The ability to relate the symptoms of androgen deficiency to accurate and reliable laboratory values has obvious clinical implications.