Performance of Total Testosterone Measurement to Predict Free Testosterone for the Biochemical Evaluation of Male Hypogonadism

Bradley D. Anawalt,* James M. Hotaling, Thomas J. Walsh and Alvin M. Matsumoto

From the Departments of Medicine (BDA, AMM) and Urology (JMH, TJW), University of Washington and Geriatric Research, Education and Clinical Center (AMM), Veterans Administration Puget Sound Health Care System (TJW, AMM), Seattle, Washington

Purpose: Guidelines recommend serum total testosterone measurement as the initial test to evaluate male hypogonadism, reserving free testosterone assessment for men with suspected sex hormone-binding globulin abnormalities or total testosterone near the lower limit of normal. We determined the performance of total testosterone measurement as a test to identify men with normal vs low free testosterone.

Materials and Methods: We examined the electronic medical records of all 3,672 men evaluated for hypogonadism by a serum testosterone panel, including total testosterone, sex hormone-binding globulin, albumin and calculated free testosterone, from January 1, 1997 through December 31, 2007 in a network that serves veterans in Washington.

Results: The sensitivity and specificity of low total testosterone (less than 280 ng/dl) to rule out and predict low calculated free testosterone was 91.0% and 73.7%, respectively. At thresholds of less than 350 and less than 400 ng/dl the sensitivity of total testosterone for low calculated free testosterone increased to 96.8% and 98.2%, and at thresholds of less than 150 and less than 200 ng/dl specificity increased to 98.9% and 92.6%, respectively.

Conclusions: Total testosterone between 280 and 350 ng/dl is not sensitive enough to reliably exclude hypogonadism. Total testosterone must exceed 350 to 400 ng/dl to reliably predict normal free testosterone. Except when levels are less than 150 ng/dl total testosterone measurement has low specificity for the biochemical diagnosis of hypogonadism.

Key Words: testis, hypogonadism, testosterone, sex hormone-binding globulin, diagnosis

Abbreviations and Acronyms

AUROC = area under receiver operating characteristic

cFT = calculated FT

FT = free testosterone

LR = likelihood ratio

SHBG = sex hormone-binding globulin

TT = total testosterone

Submitted for publication July 28, 2011.

Study received approval from the Veterans Administration Puget Sound Research and Development, and Human Subjects Review committees.

Supported by the National Institute of Child Health through Cooperative Agreements U54 HD-12629 and U54-HD-42454 (BDA), and the Department of Veterans Administration (TJW, AMM).

* Correspondence and requests for reprints: 1959 Northeast Pacific St., Seattle, Washington 98195 (telephone: 206-897-1409; FAX: 206-616-4663; e-mail: banawalt@medicine.washington.edu).

MALE hypogonadism is a common disorder that affects an estimated 5% to 10% of men older than 30 years in the United States and the prevalence increases to 20% to 40% in men older than 70 years.[1–3] Evaluation for hypogonadism may be indicated in men with weakness, low libido, infertility and osteoporosis.[4] Also, clinicians often measure serum testosterone to assess possible hypogonadism in various clinical settings, including diabetes mellitus, obesity, exogenous corticosteroid and opiate use, depression and sarcopenia.

To our knowledge the best laboratory test to use for initial screening for hypogonadism is unknown. TT assays are easy to perform, inexpensive, widely available and generally accurate.

0022-5347/12/1874-1369/0
THE JOURNAL OF UROLOGY®

Vol. 187, 1369-1373, April 2012
Printed in U.S.A.
DOI:10.1016/j.juro.2011.11.095

However, many common conditions, eg obesity, diabetes mellitus and aging, affect circulating SHBG and, therefore, affect circulating TT without necessarily affecting free (unbound) and weakly bound (bound to albumin) testosterone. Serum FT and weakly bound testosterone represent the bioavailable forms of circulating testosterone.[5]

FT measured by equilibrium dialysis is generally considered the clinical gold standard for the biochemical diagnosis of hypogonadism. This method of measuring FT is costly, time-consuming and not often used in clinical practice. FT can also be calculated by measuring serum TT, SHBG and albumin, and using one of the published, validated formulas.[6,7] cFT corresponds well with FT measured by equilibrium dialysis.[3,6,7]

The original and the recently updated Endocrine Society guidelines to evaluate hypogonadism recommend TT measurement as the initial screening test with FT or bioavailable testosterone measured only in men in whom testosterone is "near the lower limit of normal range and in whom alterations of SHBG are suspected."[3,8] To our knowledge it has not yet been determined in a large population of men how well TT measurement performs as a predictor of FT, which is the benchmark for biochemical confirmation of hypogonadism.

We determined how well TT performed as a predictor of low cFT using a cFT assay methodology that correlates well with FT measurements by equilibrium dialysis.[9,10] We examined data on a large cohort of male veterans evaluated for hypogonadism from 1997 through 2007. We hypothesized that 1) low TT less than 280 ng/dl (multiply by 0.0347 to convert to nmol/l) is sensitive to rule out but not specific to predict low FT and 2) TT less than 150 ng/dl, a level associated with severe hypogonadism,[3] is specific to predict low FT.

MATERIALS AND METHODS

To determine the performance of low TT to predict low serum FT we examined the electronic medical records of all men seen at the Veterans Administration Puget Sound Health Care System from January 1, 1997 through December 31, 2007. This institution includes a large network of outpatient clinics and a 504 bed teaching hospital that serves veterans from Washington, Idaho and Alaska.

We identified all men evaluated for hypogonadism during this period with a serum testosterone panel, including TT, SHBG, albumin, cFT and calculated bioavailable testosterone. If a patient had multiple panels done during the study, we used the first panel for analysis. Men prescribed androgen therapy (testosterone or gonadotropin treatment) at initial testing were excluded from study.

The 3,672 men included in analysis tended to be middle-aged or older (mean ± SEM age 59.7 ± 2.0, range 20 to 98), white and obese (table 1). We abstracted the electronic medical record for ICD-9-CM inpatient and outpatient diagnostic codes, pharmacy and laboratory data for conditions such as diabetes mellitus, glucocorticoids and prescription opiates (United States Food and Drug Administration schedule II only) that commonly perturb SHBG. About a third of the men had diabetes mellitus, defined as a recorded ICD-9 code, hemoglobin A1c greater than 6.5%, or use of insulin or another glucose lowering drug. Almost half of them were obese, defined as a body mass index of greater than 30 kg/m^2 (table 1). Within 90 days of the testosterone panel, about half of the men were prescribed potent opioids and about a tenth were prescribed a systemic glucocorticoid.

Table 1. *Patient characteristics*

	% Pts
Race:	
White	59.4
Black	17.1
Asian	10.1
Native American	3.2
Unknown	10.2
Diabetes mellitus	32.6
Obesity	45.0
Prescription medication:	
Opioids	48.4
Glucocorticoids	9.4

All data were abstracted and aggregated by a single research coordinator. All information was de-identified to expunge any potential relationship between data and specific individuals. The Veterans Administration Puget Sound Research and Development Committee, and the human subjects review committee approved the study. An informed consent waiver was authorized.

Hormone Assays

TT was determined using the Elecsys® monoclonal antibody test kit. The measuring range for the TT assay was 2.0 to 1,500.0 ng/dl (normal range 280 to 800). SHBG was determined using the Cobas® electrochemiluminescence immunoassay kit. The measuring range of the SHBG assay was 0.35 to 200 nmol/l (normal range 10 to 80). Albumin was determined using the VITROS® 5,1 analytic platform assay. The measuring range of the albumin assay was 1 to 6 gm/dl (normal range 3.5 to 2). FT was calculated using the Vermeulen formula and the normal range was 34 to 194 pg/ml.[6] All TT and cFT levels were determined at a central laboratory.

Statistical Analysis

We used standard descriptive statistics to characterize the patients. We generated ROC curves to determine the performance of TT measurements to predict low cFT (less than 34, 35, 36, 37, 38, 39 and 40 pg/ml, respectively). Using the ROC for TT as the continuous variable vs cFT less than 34 pg/ml, which was the lower limit of normal for this assay, we determined the sensitivity, specificity, and negative and positive LRs for the TT thresholds 100, 150, 200, 250, 280, 300, 350, 400, 450 and 500 ng/dl.

cFT served as the benchmark for the biochemical confirmation of hypogonadism. We determined the discrimination of low TT for low cFT using a nonparametric