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Letter to the Editor

Reevaluating the Threshold for Low Total Testosterone

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To the Editor:

Total testosterone (TT) results are a key criterion for diagnosing hypogonadism (1). The threshold for low testosterone at 300 ng/dL (10.4 nmol/L) was based on studies correlating immunoassay-measured TT levels with patient-reported symptom severity surveys (2). However, there are differences in TT measurements between LC-MS/MS and immunoassay methods, with variability observed at the lower end of the TT reference interval (3). Over the past 20 years, there have been efforts to standardize immunoassays against LC-MS/MS methods, leading to their widespread adoption for measuring TT. The accuracy of measurements by laboratories over time has been monitored by participation in the Center for Disease Control and Prevention's accuracy-based proficiency testing program (4). However, given the historical variation between methods and subsequent evolution of TT assays, it may be appropriate to reevaluate the 300 ng/dL cutoff based on the current state of LC-MS/MS methods.

We used the National Health and Nutritional Examination Surveys data from survey cycles that measured TT levels (2001–2002, 2003–2004, 2011–2012, 2013–2014, 2015–2016), self-reported health status, age, and sex. Responses of "very good" or "excellent" to the overall health status question were used to denote self-reported healthy individuals. We accounted for the complex survey design of the National Health and Nutritional Examination Surveys to estimate quantiles for TT levels in each survey year and the fraction of participants with TT less than 300 ng/dL. The Yale University Institutional Review Board waived this study from review because it used publicly available deidentified population-level data. Data analysis was performed with R version 4.1.2. The code to reproduce analyses is publicly available at https://doi.org/10.5281/zenodo.14908077.

The median TT levels measured in ng/dL among self-reported healthy males greater than 18 years were 495 (17.2 nmol/L), 500 (17.3 nmol/L), 418 (14.5 nmol/L), 409 (14.2 nmol/L), and 433 (15.0 nmol/L) in 2001–2002, 2003–2004, 2011–2012, 2013–2014, and 2015–2016, respectively. The 2 earliest cycles (2001–2002, 2003–2004) were measured using the Roche Elecsys immunoassay whereas the later cycles (2011 onwards) used an LC-MS/MS assay. Between the 2003–2004 and 2011–2012 cycles, median TT levels dropped 16.4%. The percent of healthy adult males with TT below 300 ng/dL was 11% and 12% in the earlier cycles and 22%, 21%, and 18% in the later cycles (Fig. 1). A nearly 100% increase in healthy adult males with low TT was observed over a decade.

The most recent American Urological Association guideline in 2018 for testosterone deficiency recommends a 300 ng/dL cutoff (1). The 2018 Endocrine Society Practice Guideline, for the first time, recommended a cutoff of 264 ng/dL (9.2 nmol/L) given the assay changes that took place during the prior decade (5). The marked increase in the fraction of healthy males with TT less than 300 ng/dL from 2004 (12%) to 2011 (22%) coincides with the migration from immunoassay to LC-MS/MS (Fig. 1). However, the percent of healthy adult males with TT below a 264 ng/dL cutoff in 2011–2012, 2013–2014 and 2015–2016 were 13%, 14% and 11%, respectively. These values are in line with the percent of healthy adult males with TT below 300 ng/dL in 2003–2004 (11%) and 2011–2012 (12%). This suggests that, due to these assay changes, the Endocrine Society's proposed low cutoff of 264 ng/dL may be a more accurate threshold going forward, than the historically used 300 ng/dL. Further, large professional bodies differ in recommendations; for example, the American Urological Association recommends 300 ng/dL, while the European Association of Andrology recommends 349 ng/dL (12.1 nmol/L). Only recently has the Endocrine Society shifted its threshold, which for low testosterone should be reevaluated. Newer immunoassays are generally aligned with LC-MS/MS, and a single cutoff such as 264 ng/dL can be used for LC-MS/MS and immunoassays.

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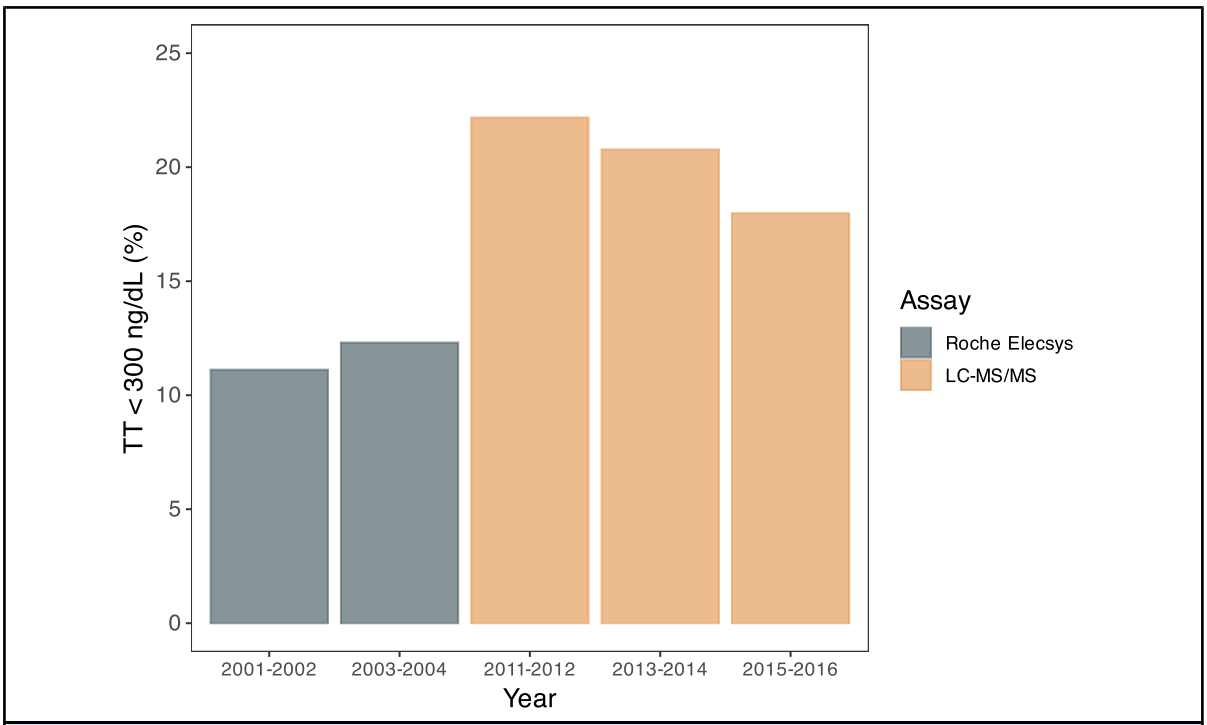

Fig. 1. Estimated percent of healthy US adult males with TT less than 300 ng/dL (10.4 nmol/L) based on National Health and Nutritional Examination Surveys data from 2001–2002, 2003–2004, 2011–2012, 2013–2014, and 2015–2016 cycles.

The consequence of inappropriate identification of pathologically decreased TT measurements is possible misdiagnoses of hypogonadism, resulting in unnecessary treatments and their side effects, excess costs, and delays in further workup. In postpubertal males, hypogonadism diagnoses are made using patient-reported symptoms along with measured low TT levels (1). Fatigue, decreased libido, and depressed mood are commonly reported symptoms, particularly among aging patients, and are not specific for hypogonadism. The percentage of self-reported healthy adult males with low TT increased by at least 50% (using the 300 ng/dL cutoff relative to 264 ng/dL), suggesting that there has been a significant overestimation of low TT since the introduction of LC-MS/MS assays into clinical practice. Given the history of variation between immunoassay and LC-MS/MS-based methods and attempts at their subsequent standardization, as well as differences in threshold recommendations from the American Urological Association and Endocrine Society, it may be important to reevaluate the 300 ng/dL TT threshold. This reassessment could improve the evaluation of hypogonadism.

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