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Does Calculated Free Testosterone Overcome Total Testosterone in Protecting From Sexual Symptom Impairment? Findings of a Cross-Sectional Study

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ABSTRACT

Background: Although erectile dysfunction (ED) has been associated with low circulating total testosterone (TT) levels, the utility of free testosterone (FT) over TT is debatable.

Aim: To assess the relative impact of low TT and low calculated FT (cFT) on androgen-related sexual symptoms in men with ED.

Methods: Data from 485 men were analyzed. Comorbidities were scored with the Charlson Comorbidity Index (CCI). Patients completed the International Index of Erectile Function (IIEF) and the Beck Inventory for Depression (BDI). Descriptive statistics tested differences between patients with normal TT levels (>3 ng/mL) and normal cFT levels (>65 pg/mL; group 1) and men with normal TT and low cFT (group 2), low TT and normal cFT (group 3), and low TT and low cFT (group 4). Linear regression models tested the association between clinical predictors and sexual function impairment.

Outcomes: We assessed the impact of different hormonal categories on androgen-related symptoms and the clinical utility of measuring cFT in men with ED.

Results: Groups 1, 2, 3, and 4 were composed of 338 (69.6%), 44 (9.1%), 34 (7.0%), and 69 (14.3%) patients, respectively. Compared with group 1, patients in group 2 were older ($P < .001$), had a higher body mass index ($P < .01$), and had a larger proportion with CCI scores of at least 1 ($P = .006$). Likewise, group 2 presented lower scores for the IIEF erectile function ($P = .07$), sexual desire ($P = .04$), and orgasmic function ($P = .007$) domains and lower BDI scores ($P = .02$) than group 1. Similar findings were found for group 4 vs 1. Conversely, patients in group 3 had similar scores on the questionnaires to those in group 1. Low cFT and normal or low TT achieved independent predictor status for pathologic IIEF domains and BDI scores after accounting for age, CCI, and body mass index. Conversely, low TT and normal cFT status was not associated with pathologic scores on the questionnaires.

Clinical Implications: The inclusion of cFT in the first-line assessment of hypogonadal symptoms in men with ED has major clinical utility.

Strengths and Limitations: This is the first study evaluating the concomitant impact of TT and cFT on men with ED using well-validated instruments to assess patients' sexuality and depressive symptoms. Limitations are the retrospective nature of the study and lack of physical function data and bone ultrasound measurements.

Conclusions: Although normal cFT was not associated with signs and symptoms suggestive of testosterone deficiency, even when concomitant with low TT or low cFT irrespective of TT values, it was indicative of poorer clinical profiles and impaired sexual and depressive parameters compared with normal TT and normal cFT in a cohort of patients with ED. **Boeri L, Capogrosso P, Ventimiglia E, et al. Does Calculated Free Testosterone Overcome Total Testosterone in Protecting From Sexual Symptom Impairment? Findings of a Cross-Sectional Study. J Sex Med 2017;14:1549–1557.**

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INTRODUCTION

Erectile dysfunction (ED) can occur from multifaceted mechanisms involving disruptions in neural, vascular, and hormonal signaling.[1] Epidemiologic studies have shown that up to 80% of ED cases originate from organic causes, with vascular disease representing the most common factor, whereas the endocrine system has typically been considered of marginal importance.[2,3]

It is widely accepted that testosterone (T) plays a role in male sexual anatomy and function,[3,4] but its physiologic contribution to human erectile function (EF) remains a matter of some controversy.[4–7]

Data from the European Male Ageing Study clearly outlined that total T (TT) is associated with overall sexual function and that free T (FT) is associated with ED and masturbation frequency.[8] In this context, several previous studies have demonstrated that ED incidence increases with the concomitant decrease of androgen levels,[7,9–11] whereas other studies have not.[12] Overall, T deficiency (TD) is the most common hormonal cause of ED.[6,7] Although observations are not completely homogeneous, the T threshold required to maintain an erection is low and ED is usually a symptom of more severe hypogonadism.[13,14]

The prevalence of TD in men with established ED has been found to range from 23% to 36%, depending on the sample population and cutoff values adopted for diagnosis.[6] Moreover, current guidelines and recommendations suggest testing TT and, if indicated, the bioavailable or calculated FT (cFT) as part of the diagnostic workup in men with ED.[6,13,15] Conversely, opponents of universal screening for TD in men with ED cite the controversy regarding diagnostic thresholds and the potential for overtreatment as arguments against broad screening in this population.[6]

Several large epidemiologic studies of aging men have described an association between low TT or low FT and symptoms of TD.[16,17] For instance, Cunningham et al[17] found that baseline FT and TT were independently associated with measures of sexual desire, EF, and sexual activity, but not with vitality or physical function, in older men with low T levels and symptoms of sexual dysfunction.

However, to date, the literature has focused primarily on the association between TT or FT and a specific clinical variable of TD. In this context, the aim of our study was to examine the concomitant impact of low cFT and low TT on androgen-related symptoms and the clinical utility of measuring cFT in a cohort of European Caucasian sexually active men seeking medical help for ED as a primary complaint in the real-life setting.

METHODS

Analyses of this cross-sectional study were based on a cohort of 500 consecutive heterosexual, sexually active, European Caucasian men assessed for ED as a primary complaint at a single academic center from January 2012 through September 2016. Patients were included if they had incomplete clinical data, including measured body mass index (BMI), and health-significant comorbidities, as scored with the Charlson Comorbidity Index (CCI),[18] according to the *International Classification of Diseases, 9th Revision*. For the specific purpose of this analysis, CCI score was categorized as 0 vs at least 1. Conversely, patients with a history of radical prostatectomy, radical cystectomy, pelvic radiation therapy, current or prior androgen deprivation, or a history of known TD or T therapy were excluded.

Patients completed the International Index of Erectile Function[19] (IIEF; EF, sexual desire [SD], orgasmic function [OF], intercourse satisfaction [IS], and overall satisfaction [OS] domains) and the 21-item Beck Inventory for Depression (BDI).[20] IIEF-EF score was categorized according to the classification by Cappelleri et al.[21] Depressive symptoms were defined as a BDI score of at least 11.

Venous blood samples were drawn from each patient from 7 to 11 AM, after an overnight fast. In all cases, fasting glucose levels were measured using a glucose oxidase method (Aeroset Abbott, Rome, Italy). Total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured with the automated enzymatic colorimetric method (Aeroset Abbott). Luteinizing hormone (LH), thyroid-stimulating hormone, and 17-β-estradiol (E_2) were measured using a heterogeneous competitive magnetic separation assay (Bayer Immuno 1 System; Bayer Corp, Tarrytown, NY, USA). TT levels were measured using a direct chemiluminescence immunoassay (ADVIA Centaur; Siemens Medical Solutions Diagnostics, Deerfield, IL, USA), and sex hormone binding globulin (SHBG) levels were measured using a solid-phase chemiluminescent immunometric assay (Immulite 2000; Medical Systems SpA, Genoa, Italy). Serum albumin and SHBG values were measured and used to determine cFT using the validated formula of Vermeulen et al.[22] Abnormal values were retested for confirmation.

From baseline TT and cFT levels, a 4-category variable was constructed based on a TT level lower vs higher than 3 ng/mL and a cFT level lower vs higher than 65 pg/mL.[23] The 4