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Longitudinal change instead of baseline testosterone predicts depressive symptoms

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ABSTRACT

Background: The association between total testosterone (T) and depression mostly relies on single sex hormone assessment and remains inconclusive. Thus, we investigated the comparative predictive performance of baseline T and change in T with development of depressive symptoms and incident depressive episodes.

Methods: We used data from 6493 primary care patients (2653 men and 3840 women) of the DETECT study (Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment), including four-year follow-up, repeated immunoassay-based measurement of serum T and depressive symptoms assessed by the Depression Screening Questionnaire (DSQ). Cross-sectional and longitudinal associations of baseline T and one-year change in T with prevalent and incident depression were investigated using age- and multivariable-adjusted regression models.

Results: Baseline T showed no association with prevalent or incident depressive symptoms and episodes in both sexes. In men, a positive change in T (higher T at one-year follow-up compared to baseline) was associated with a lower burden of depressive symptoms (β-coefficient per unit change in T: −0.17; 95% CI: −0.31 to −0.04) and lower risk of incident depressive symptoms (odds ratio per unit change in T: 0.84; 95% CI: 0.72–0.98) at four-year follow-up. In women, the association of T change with incident depressive episodes was rendered non-significant after multivariable adjustment.

Discussion: The present study observed a sex-specific inverse association of T change, but not baseline T, with increased depressive symptom burden in men. Future studies should assess longitudinal changes in sex hormone status as predictor of adverse health outcomes related to low T.

1. Introduction

Mental disorders are a preeminent public health issue with depressive disorders representing the third leading cause of lifetime disability (Vos et al., 2016). Consequently, depression has been consistently associated with adverse health outcomes, increased morbidity and all-cause mortality in both sexes (Walker and Druss, 2016). At this, the pervasive sex discrepancy in prevalence of mental disorders (Seedat et al., 2009), with doubled lifetime risk of major depression among women compared to men, remains to be fully understood. The strongest explanation for the observed sex disparity remains the potential role of sex hormones, particularly total testosterone (T) (McHenry et al.,

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2014). Among men with reduced T concentrations, observational evidence suggests a higher prevalence of depressive symptoms (Westley et al., 2015). On contrary, men with depressive disorders, such a major depressive disorder (MDD) or dysthymic disorder (DD), do not consistently show lower T concentrations (Seidman et al., 2009). Additionally, longitudinal association studies of T and depression report either absent or inconsistent findings (Berglund et al., 2011; Joshi et al., 2010; Kratzik et al., 2007; Shores et al., 2005; Westley et al., 2015). Similarly, clinical evidence from randomized trials of T supplementation does not support a causal effect in men with MDD (Seidman et al., 2001b). Thus, the potentially modulating role of T related to cognitive function remains inconclusive (Resnick et al., 2017).

An alternative explanation for the observed associations relates to the genetic background, particularly the androgen receptor CAG repeat. Results of the Massachusetts Male Aging Study (MMAS) suggest that the variability in receptor transactivation may contribute to variability in the expression of androgen-mediated psychiatric symptoms (Seidman et al., 2001a). At this, CAG repeat length was examined as a genetic marker associated with androgen receptor activity and low versus high testosterone was associated with a five-fold increased likelihood of depressive symptoms in men with shorter CAG repeat length.

Given the suggested hormonal interplay, it is intriguing that data on change in T as predictor of incident depression are very limited. Most observational studies, excluding the community-based cohort MAILES study (Shi et al., 2013), exclusively investigated baseline sex hormone status in the onset of depressive symptoms, although the longitudinal analysis of T change offers the possibility to decipher the substantial phenomenological overlap between aging, comorbidity, depressive symptom progression and hormonal changes (Shores et al., 2005).

We therefore examined both, baseline T and one-year change in T associated with incident depressive symptoms and depressive episodes during 4-year follow-up using data of 6493 men and women from a primary care patient-based sample. We hypothesized that decreasing T over time, rather than low baseline T, is associated with development of depressive symptoms and incident depressive episodes.

2. Methods

2.1. Study population

Diabetes Cardiovascular Risk-Evaluation: Targets and Essential Data for Commitment of Treatment (DETECT) is a large, multistage and nationally representative study in Germany (Wittchen et al., 2005). 3188 GPs completed a standardized assessment of the diagnostic and therapeutic profile of 55,518 unselected consecutive patients over 17 years on 16th and 18th September 2003. Physicians were successfully recruited, meeting the recruitment criteria, including enrolment from signature, willingness to adhere to the complex laboratory, completion of pre-study questionnaire, and follow-up procedures. The baseline response rate among physicians was 60.2%. Further adjustments for non-response, regional distribution, and attrition were performed.

Of 55,518 eligible patients, a random subsample of 7519 patients in 851 primary care settings additionally attended a standardized laboratory screening program and were part of the prospective component of DETECT. Between September and December 2004 or 2007, 6826 patients (2782 men and 4044 women) participated in a one-year and/or four-year follow-up, respectively. The follow-up response rate among patients was 90.8%. All patients gave written informed consent and the study was approved by the ethics committee of the Technical University of Dresden.

We excluded patients with missing T data (N = 896), baseline age above 86 years (N = 30), and patients receiving anti-androgens (N = 100). None of the women were pregnant. Regarding age, waist circumference, physical activity, current smoking and blood pressure; no significant differences were found between excluded and included patients in the present study. Valid data were available in 2653 men and 3840 women.

2.2. Measures

Age, sex, socio-demographic characteristics and medical histories were assessed by primary care physicians using standardized interviews and medical records. Physicians as well as study nurses were advised to measure blood pressure, height, weight, and waist circumference according to written, standardized instructions. Smoking was categorized into current smokers and non-smokers. Participants who participated in physical activity during summer or winter for at least two hour a week were classified as being physically active. Menopausal status was assessed by self-reported menopause. In post-menopausal women the duration of menopause was determined. Alcohol consumption was categorized in self-reported sobriety, infrequent, occasional or daily alcohol consumption.

Depressive symptoms were assessed using the Depression Screening Questionnaire (DSQ). Characteristics and background of the DSQ were previously published (Höfler and Wittchen, 2000). Briefly, the DSQ questionnaire includes 11 items on a three point scale (0: never, 1: some days, 2: on most days in the last two weeks). Additional questions assess age at the episodes and number of episodes following the criteria of major depression in DSM-IV and ICD-10. Following the criteria of DSM-IV and ICD-10, the DSQ shows high diagnostic sensitivity and specificity for diagnosis of depression (Winter et al., 2000), as well as high internal consistency (Höfler and Wittchen, 2000). We used a continuous DSQ score as an indicator for depressive symptom burden (Pieper et al., 2008), defined a binary depression variable by a DSQ score ≥ 8 (Pieper et al., 2011) and used ICD-10 criteria on unipolar depression requiring a minimum of three items coded with “on most days” and a minimum DSQ score ≥ 7 to define depressive episode as third outcome variable (Pieper et al., 2008).

2.3. Laboratory measures

Blood samples were taken between 8.00 and 10.00 a.m. either fasting or non-fasting with recording of the fasting state. Serum blood samples were shipped by courier at room temperature within 24 h to the central laboratory at the Medical University of Graz in Austria, where they were centrifuged immediately and stored at $-20\,^{\circ}C$ until further processing. Serum T was measured with an electrochemiluminescence immunoassay (Modular analytics, Roche Diagnostics, Mannheim, Germany). Intra- and interassay coefficients of variation were 2.7% and 5.6%, respectively. The measurement range of the assay was between 0.02 ng/ml and 15 ng/ml, including eight patients with a T concentration of 0.02 ng/ml. The producer has calibrated the assay against gas chromatography-mass spectrometry, with the result of a strong positive correlation (r = 0.997). The analytical sensitivity was 0.02 ng/ml. T was measured at baseline and one-year follow-up. Reagents and secondary standard were used as recommended by the manufacturer.

2.4. Statistical analyses

Categorical data are given as percentage and continuous data as mean with standard error or median (p25th, p75th), respectively. All analyses were performed sex-specific. First, cross-sectional and longitudinal associations of T with DSQ outcomes were analyzed using age- and multivariable-adjusted linear regression models, with effects reported as β-coefficients and their 95% confidence interval (CI), and logistic regression models, with effects presented as odds ratios (OR) and their 95% CIs. Second, T change was defined as absolute difference between baseline and one-year follow-up T, with associations between T change and depression investigated by linear regression models for continuous DSQ scores and logistic regression models for categorized