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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

Table 1
Sex-specific baseline characteristics of the study population.

Variable	Women (N = 3840)	Men (N = 2653)	p-value*
Age, years,	56.8 (14.6)	58.4 (13.4)	< 0.01
Total testosterone, ng/ml	0.41 (0.27; 0.61)	4.4 (3.3; 5.5)	< 0.01
One-year change in T, ng/ml	−0.13 (−0.23; −0.04)	−0.07 (−0.73; 0.65)	< 0.01
Waist circumference, cm	90.1 (14.5)	101.6 (12.5)	< 0.01
Current smoker, %	19.9	22.9	< 0.01
Physically inactive, %	34.4	27.3	< 0.01
Sobriety, %	23.3	11.8	< 0.01
Systolic blood pressure, mmHg	130 (120, 140)	130 (120, 145)	< 0.01
Diastolic blood pressure, mmHg	80 (70; 85)	80 (75; 85)	< 0.01
Menopause, %	89.2	–	–
DSQ score	3 (1; 6)	2 (1; 5)	< 0.01
Depressive episode, %	7.2	5.4	< 0.01
Depression by DSQ cut-off, %	14.2	11.4	< 0.01

Data are percentages, mean (SD) or median (Q1, Q3).
DSQ, depression screening questionnaire.
*Statistical comparisons were performed with χ^2 test (nominal data) or Mann-Whitney-U-test (continuous data).

depression. Multivariable models were adjusted for age, waist-circumference, smoking habits, physical activity, alcohol consumption, and blood pressure. To maximize sample size and statistical power, longitudinal analyses were adjusted for baseline DSQ, instead of excluding participants with baseline depression. All analyses were performed with robust standard errors and p-values < 0.05 considered as statistically significant.

Sensitivity analyses comprised additional adjustment for hormone therapy (women using hormone therapy N = 234), age at menopause, and stratification by menopausal status (premenopausal women, N = 139). To address potential attrition bias, we included inverse probability weights into longitudinal multivariable analyses. All statistical analyses were performed with Stata 14.2 (Stata Corp., College Station, TX, USA).

3. Results

Sex-specific baseline characteristics of the study population are presented in Table 1. Significant sex-specific differences were observed for all considered variables. Exemplarily, women were younger, smoked less and showed a higher burden of depressive symptoms compared to men (Table 1). DSQ-score at one-year and four-year follow-up was 3 (1;5) and 3 (1;6) for women and 1 (1;4) and 2 (1;4) for men, respectively. Prevalence of depressive episodes at one-year follow-up was 5,4% for women and 4,1% for men and 6,2% for women and 4,8% for men at four-year follow-up, respectively. One-year incidence of depressive episodes was 3,4% (N = 97 cases of 3098 women) for women and 3,0% (N = 60 of 2104) for men and 4,0% (N = 80 of 2177) for women and 3,5% (N = 47 of 1425) for men at four-year follow-up, respectively.

Cross-sectional and longitudinal analyses showed no association of T with prevalent or incident depressive episodes at one-year and four-year follow-up, respectively (Table 2). Sex-specific analyses of change revealed a significant association of T change in men with depressive symptoms incident depressive symptoms at four-year follow-up (Table 3). At this, a positive change in T, with higher follow-up concentrations compared to baseline, was associated with a lower burden of depressive symptoms (DSQ-score: β-coefficient per unit change in T: −0.17; 95% CI: −0.31, −0.04) (DSQ-cut-off: OR per unit change in T: 0.84; 95% CI: 0.72, 0.98). To illustrate the revealed inverse association, we plotted values for T change against DSQ scores at four-year follow-up including a fitted regression line (Fig. 1). None of the reported associations were observed during one-year follow-up. In men, change in T only showed borderline significance in association with depressive episodes (OR per unit change in T: 0.76; 95% CI: 0.57, 1.00). Furthermore, the association of T change with incident depressive episodes in women was rendered non-significant after multivariable adjustment (Table 3). The performed sensitivity analyses did not change the revealed estimates substantially.

4. Discussion

The present patient-based study investigated the predictive value of baseline T vs. change in T related to depressive symptom burden and depressive episodes. At this, we observed a sex-specific inverse association of T change, but not for baseline T, with increased depressive symptom burden in men. In women, neither baseline T nor change in T was associated with development of depressive symptoms or incident depressive episodes. The observed sex-specific patterns will be discussed separately.

4.1. Men

In men, several lines of evidence suggest that conditions related to a reduced functional activity of the gonads, resulting in decreased T concentrations, are linked to a significantly higher prevalence of mental disorders including depression (Zarrouf et al., 2009). However, association studies between low T and incident depression provide inconclusive evidence. While older studies reported positive findings (Barrett-Connor et al., 1999), more recent studies and meta-analysis failed to detect a consistent association (Zarrouf et al., 2009).

Exemplarily, the nine-year follow-up of the Health in Men study revealed a borderline significant association of low baseline T with incident depression after adjustment for relevant confounders (Ford et al., 2016), whereas we previously published prospective findings from the Study of Health in Pomerania showing an inverse association between baseline T and development of depressive symptoms that was rendered non-significant after multivariable adjustment for relevant confounders including body mass index, smoking, and physical inactivity (Kische et al., 2017). In line with these results, our analyses of baseline T with prevalent and incident depressive symptoms in men yielded no statistically significant associations.

On contrary, the present association between T change and depressive symptoms reflects the considerable phenomenological overlap between aging, hormonal changes, and clinical comorbidity. This protective effect of a positive change in T related to lower depressive symptom burden might reflect reductions in overall risk factor burden and/or healthy lifestyle changes. This reasoning is backed up by findings from a Mendelian Randomization study suggesting non-causal associations of low T with comorbidity and overall mortality (Haring et al., 2013). Consequently, a negative change in T and low T in general could be interpreted as an epiphenomenon of increased comorbidity, instead of a causal risk factor. Thus, the commonly reduced T concentrations among men with depression (vs. non-depressed men) can be largely explained by this interplay − wherefore low T is commonly not significantly associated with depression, independent of comorbidity (Almeida et al., 2008).

Results from clinical trials similarly question an independent causal role of T in the onset and progression of depressive symptoms and depression. T and other sex hormones have been used in the treatment of depression for more than a hundred years (Altschule and Tillotson, 1948; Reiling, 2000). However, synthesized evidence from current meta-analysis indicates that T treatment may improve mood, but its efficacy for treatment of depression has not been established yet. The results from randomized controlled trials of T treatment are inconsistent, producing positive, negative, and inconclusive results (Joffe, 2011). Lately, results from the T-trial showed no effect of T treatment

Table 2
Sex-specific associations of baseline total testosterone with depressive symptoms and depression.

	Women Cross-sectional	Men	Women 1-year follow-up	Men	Women 4-year follow-up	Men
DSQ score	β-coefficient					
age-adjusted	−0.08 (−0.22; 0.05)	0.002 (−0.07; 0.07)	0.02 (−0.09; 0.14)	−0.02 (−0.08; 0.04)	−0.04 (−0.19; 0.09)	0.05 (−0.03; 0.14)
mv-adjusted	−0.08 (−0.23; 0.06)	0.01 (−0.06; 0.09)	0.03 (−0.09; 0.15)	−0.02 (−0.08; 0.04)	−0.05 (−0.21; 0.10)	0.07 (−0.02; 0.17)
Depression (DSQ score ≥ 8)						
age-adjusted	0.88 (0.75; 1.02)	0.98 (0.92; 1.05)	1.08 (0.91; 1.27)	1.00 (0.91; 1.11)	0.82 (0.62; 1.09)	1.07 (0.97; 1.17)
mv-adjusted	0.88 (0.73; 1.06)	1.01 (0.94; 1.09)	1.09 (0.91; 1.30)	0.96 (0.86; 1.07)	0.80 (0.57; 1.13)	1.08 (0.97; 1.21)
Depressive episode	Odds Ratio					
age-adjusted	0.93 (0.75; 1.15)	1.04 (0.94; 1.14)	1.10 (0.90; 1.35)	1.03 (0.90; 1.17)	0.69 (0.34; 1.39)	1.03 (0.90; 1.18)
mv-adjusted	0.95 (0.75; 1.21)	1.06 (0.95; 1.18)	1.12 (0.91; 1.39)	1.00 (0.87; 1.17)	0.68 (0.28; 1.63)	1.02 (0.86; 1.21)

Data are β-coefficients or odds ratio and their 95% confidence interval, respectively, with $p < 0.05$ marked as *.
Multivariable models were adjusted for age, waist circumference, smoking status, physical inactivity, alcohol consumption, and blood pressure.
Longitudinal analyses were additionally adjusted for baseline DSQ.
DSQ, depression screening questionnaire; mv, multivariable.

Table 3
Sex-specific associations of change in total testosterone with depressive symptoms and incident depression at four-year follow-up.

	Women	Men
DSQ score	β-coefficient	
age-adjusted	0.01 (−0.18; 0.15)	−0.17 (−0.30; −0.04)*
multivariable-adjusted	0.005 (−0.18; 0.17)	−0.17 (−0.31; −0.04)*
Depression (DSQ score ≥ 8)	Odds Ratio	
age-adjusted	1.12 (0.90; 1.39)	0.81 (0.71; 0.95)*
multivariable-adjusted	1.14 (0.89; 1.47)	0.84 (0.72; 0.98)*
Depressive episode		
age-adjusted	1.29 (1.08; 1.54)*	0.76 (0.57; 1.00)
multivariable-adjusted	1.34 (0.98; 1.66)	0.79 (0.59; 1.05)

Data are odds ratio and their 95% confidence interval, with $p < 0.05$ marked as *.
The multivariable model was adjusted for age, waist circumference, smoking status (three categories), physical inactivity, alcohol consumption, blood pressure, baseline DSQ, and weighted for drop out.
DSQ, depression screening questionnaire; mv, multivariable.

on cognitive function and age-related memory impairment (Resnick et al., 2017). Potential explanation for these discrepancies include sample size, differences in age, comorbidity and severity of hypogonadism, as well as timing, dose, duration, and application of T treatment. Finally, the inconclusive clinical evidence needs to be weighed against the potential side effects of T treatment (Fernandez-Balsells et al., 2010; Xu et al., 2013). Given these mixed results from T treatment trials, even a strong theoretical rationale does not necessarily yield robust clinical findings and further research is needed before definitely concluding the clinical utility of T in the treatment of depression. Additionally, further basic research is needed to elucidate the neurobiological mechanisms underlying potentially protective effects of T and to establish causal relationships with mental disorders (McHenry et al., 2014).

4.2. Women

In women, fluctuations in sex hormone concentrations occurring with the menstrual cycle, as well as the postpartum and peri/postmenopausal period, are associated with greater vulnerability for depressive symptoms and depression (Solomon and Herman, 2009). However, the absent associations of baseline T and change in T with depressive symptom burden in the present study still add to the limited evidence about the potential antidepressant role of T in women. While some studies suggest that reduced, as well as increased T may negatively impact mental health in women and contribute to the onset of depressive symptom (Rohr, 2002), most studies reported no significant associations (Giltay et al., 2017; Kische et al., 2017; Morsink et al., 2007). Consequently, an according Cochrane review concludes that

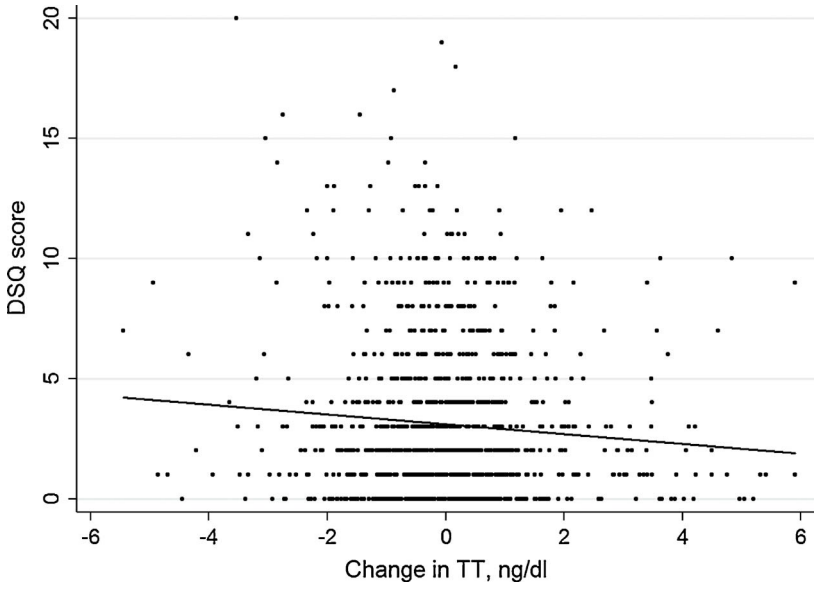

Fig. 1. DSQ score at four-year follow-up by one-year change in T among men.
DSQ, depression screening questionnaire; T, total testosterone. The black line represents the continuous regression line with a slope of −0.17 (95% CI: −0.30; −0.04) and a p-value of 0.006.

hormone therapy in women is not indicated for primary or secondary prevention of dementia, nor for prevention of deterioration of cognitive function in postmenopausal women (Marjoribanks et al., 2017).

Strengths of the present study include the large sample size, repeated T measurements and the comparative assessment of baseline vs. change in T status among men and women. Our study is limited by the lack of data regarding PCOS, menstrual cycle timing and assessment of additional sex hormones. But although we were not able to investigate free T, dihydrotestosterone, estradiol or other sex hormones related to depression, previous studies lacked consistent associations of these sex hormones with depression (Almeida et al., 2008; Ford et al., 2016). Similarly, women with PCOS have an increased risk of depression (Cooney et al., 2017), but this evidence itself is limited to findings from cross-sectional studies Given our DSQ-based assessment of depressive episodes, we estimated two-week-point prevalence estimates, which are lower than generally reported prevalence estimates of depressive episodes among primary care patients (Ansseau et al., 2004). Furthermore, we were not able to analyze the mediating role of the genetics, since CAG repeat data were not available in our study. Compared to a population-based study design, the higher level of co-morbidity in our sample of primary care patients limit the generalizability of our findings and might have mitigated the strength of association between sex hormones and depressive symptoms.

In summary, the present study provides important insights into the role of T in the onset and progression of depressive symptom burden. This is the first study to comparatively investigate the predictive value of baseline T vs. change in T related to incident depressive symptoms and episodes. Our results indicate the importance of assessing repeated measures of sex hormone status. Given the dynamic interplay between sex hormones, comorbidity, and mental health, future investigations should assess longitudinal change in sex hormone status to augment evidence on the predictive importance of physiological T changes related to adverse health outcomes.

Ethical approval, consent or animal equivalent

All patients gave written informed consent and the study was approved by the ethics committee of the Technical University of Dresden.

Conflict of interest

There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

Disclosure statement

The authors have nothing to disclose.

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