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Calculated bioavailable testosterone levels and depression in middle-aged men

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Summary
Background: The association between circulating total testosterone (TT) levels and depressive symptoms remains unclear. We sought to determine the relationship between physiologically active bioavailable testosterone (BT) and depressive symptoms in middle-aged men with and without major depressive disorder (MDD).
Methods: We assessed and compared calculated BT levels in two groups of middle-aged men (40–65 years): untreated subjects meeting DSM-IV-TR-defined criteria for a major depressive episode as part of major depressive disorder ($N = 44$) and a matched non-depressed control group ($N = 50$).
Results: Depressed men had lower mean BT levels (3.51 ± 1.69 vs. 4.69 ± 2.04 nmol/L; $p = 0.008$) and TT levels (11.94 ± 4.63 vs. 17.64 ± 1.02 nmol/L; $p < 0.001$) when compared to the control group. Biochemical hypogonadism (i.e., BT level $\leqslant 2.4$ nmol/L or TT level $\leqslant 12.14$ nmol/L) was also more prevalent in depressed men vs. non-depressed controls (34% vs. 6%, $p < 0.001$; 61% vs. 14%, $p < 0.001$, respectively).
Conclusions: Changes in physiologically active BT concentration may be a vulnerability factor for depressive symptoms in middle-aged depressed men.

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1. Introduction

Results from cross-sectional and longitudinal studies suggest that subpopulations of depressed men may be hypogonadal (Seidman, 2003). Therapeutic studies have also reported that supplemental testosterone (T) may improve depressive symptoms, neurocognition and sexual function (Gray et al., 2005; Haren et al., 2005). Moreover, supraphysiological doses of androgens can be associated with manic symptom induction and depressive symptoms upon withdrawal (Pope et al., 2000).

It is well established that total testosterone (TT) levels decline linearly with age and it has been estimated that a substantial proportion of men between the ages of 30 and 80 may be classified as hypogonadal (Moffat et al., 2002; Seidman, 2003; Lamberts et al., 1997). The age-related decline in TT concentration is associated with a symptom complex phenotypically similar to a major depressive episode (e.g., fatigue, irritability, dysphoria, loss of libido). The plausibility that T may be salient to the pathophysiology of depression is suggested by its organizational and activational effects on brain morphology and neuronal cytoarchitecture (Hammond et al., 2001).

Extant investigations reporting on the association between circulating TT levels and depressive symptoms have provided inconsistent evidence that relative or absolute T deficiency may be a relevant vulnerability factor in some depressed persons (Seidman, 2003). These variable results are likely due to study heterogeneity including enrollment criteria, definition of hypogonadism, and laboratory assays utilized to evaluate circulating TT levels, and importantly an absence of studies that have separately examined the physiologically active bioavailable "B" moiety.

Most of the circulating plasma TT is protein bound with approximately 2–3% available as a free form. In men, circulating TT is 44–65% bound to sex hormone binding globulin (SHBG) and 33–54% is bound to albumin. Albumin has a high capacity for binding to sex steroids but binds to T with low affinity, and as a result, the T is loosely bound and physiologically active (Emadi-Konjin et al., 2003). Bioavailable testosterone (BT) is the bioactive fraction of circulating TT that is not tightly bound to SHBG and is thought to more accurately reflect the clinical androgen state of the patient (vs. serum TT levels) (Emadi-Konjin et al., 2003).

To our knowledge, there are no published studies that have reported on putative associations between depressive symptoms and physiologically active BT levels in a clinically depressed sample. In keeping with the view, and evident plausibility, that T may be associated with depressive symptoms, we hypothesized that calculated BT levels would be significantly lower among middle-aged (age 40–65 years), untreated depressed men when compared to a matched non-depressed control sample.

2. Methods and materials

Depressed ($N = 44$) and non-depressed men ($N = 50$) (40–65 years) were evaluated at the Mood Disorders Psychopharmacology Unit, University Health Network, Toronto, Canada. Most men were recruited by advertisement throughout the hospital and nine men were recruited from four primary-care sites. Eligible depressed subjects met Diagnostic Statistical Manual IV Text-Revision (DSM-IV-TR) criteria for major depressive disorder (MDD), current major depressive episode, with a 17-item Hamilton Depression Rating Scale (HAMD-17) total score of >16 (Hamilton, 1960). The diagnostic criteria were confirmed using the Mini International Neuropsychiatric Interview, Version 5 (M.I.N.I) (Sheehan et al., 1998).

All depressed subjects were currently untreated at the time of enrollment; however, they could have received an antidepressant during the index episode or for a previous episode of illness. A washout period commensurate with each antidepressant's pharmacokinetic profile (i.e., $5 \times t_{1/2}$) was required for any depressed subject who was receiving an antidepressant at the time of enrollment (Kennedy et al., 2001). All subjects were judged to be in generally good health, although overweight was not exclusionary i.e. body mass index between 20 and 29 kg/m^2.

Subjects were excluded from the study if they were suffering from a clinically unstable comorbid medical (e.g., neurological, respiratory etc.) or psychiatric disorder. Other exclusionary criteria included a history of DSM-IV-TR-defined drug or alcohol abuse/dependence (within the past 6 months), uncorrected thyroid disease, use of other psychotropic medications, herbal preparations with putative antidepressant properties (e.g., St. John's Wort), and electroconvulsive therapy (ECT) within the past 3 months.

This study was approved by the University Health Network Research Ethics Board and the Institutional Review Board Services, Aurora, Canada. All eligible subjects were required to provide written informed consent before participating in this study.