ORIGINAL ARTICLE

Low Free Testosterone Concentration as a Potentially Treatable Cause of Depressive Symptoms in Older Men

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Context: Serum concentrations of gonadal hormones have been associated with various measures of well-being, but it is unclear whether their association with mood is confounded by concurrent physical morbidity.

Objective: To determine whether the association between serum testosterone concentration and mood in older men is independent of physical comorbidity.

Design: Cross-sectional study.

Setting: Community of Perth, Western Australia.

Participants: A community sample of men aged 71 to 89 years.

Main Outcome Measures: We used the 15-item Geriatric Depression Scale (GDS-15) to assess depressed mood. Clinically significant depression was defined a priori as a GDS-15 score of 7 or greater. Physical health was assessed using the weighted Charlson index and the Physical Component Summary score of the 36-Item Short Form Health Survey.

Results: Of 3987 men included in the study, 203 (5.1%; 95% confidence interval [CI], 4.4%-5.8%) had depression. Participants with depression had significantly lower total and free testosterone concentrations than nondepressed men ($P<.001$ for both). However, they were also more likely to smoke and to have low educational attainment, a body mass index categorized as obese, a Mini-Mental State Examination score less than 24, a history of antidepressant drug treatment, and greater concurrent physical morbidity. After adjusting for these factors and for age, men with depression were 1.55 (95% CI, 0.91-2.63) and 2.71 (95% CI, 1.49-4.93) times more likely to have total and free testosterone concentrations, respectively, in the lowest quintile.

Conclusions: A free testosterone concentration in the lowest quintile is associated with a higher prevalence of depression, and this association cannot be adequately explained by physical comorbidity. A randomized controlled trial is required to determine whether the link between low free testosterone level and depression is causal because older men with depression may benefit from systematic screening of free testosterone concentration and testosterone supplementation.

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DEPRESSION IS A LEADING cause of disability worldwide,[1] affecting 2% to 5% of the population at any point in time.[2] The prevalence of depression is higher in women than in men throughout the lifespan, but sex differences all but disappear after age 65 years.[3] The results of several experimental and observational studies and randomized trials suggest that gonadal corticosteroids might be partly responsible for such a sex-related phenomenon.[4-6] Currently available evidence suggests that estradiol has clinically relevant antidepressant properties,[6-10] but data in support of a potential role for testosterone in the modulation of mood remain scant.

Testosterone binds to an intranuclear androgen receptor that is ubiquitously distributed throughout the body, including the central nervous system.[11] This receptor, in turn, binds to DNA and affects the production of messenger RNA, which modifies protein synthesis by the cell.[11] The androgen receptor has a polymorphic CAG microsatellite coding for a variable length of glutamine residues, and men with shorter sequences of CAG repeats who have higher total testosterone levels seem to be less prone to experiencing clinically significant depressive symptoms.[12] In target cells, testosterone can also be converted to 2 active metabolites: dihydrotestosterone, a highly potent activator of androgen receptors, and estradiol.[13] It seems plausible, therefore, that low concentrations of testosterone will result in reduced androgen receptor activation and a decline in the concentration of estradiol

in the brain. In addition, preliminary evidence[14] suggests that testosterone has short- and long-term γ-aminobutyric acid (GABA)-ergic properties, and these actions may further contribute to the modulation of mood in men.

Pope et al[15] found that 8 of 50 men aged 20 to 50 years treated with high doses of testosterone developed symptoms of hypomania. Moreover, testosterone levels have been inversely correlated with depression scores,[16,17] and preliminary evidence suggests that men with depression have deficient testosterone secretion.[18] Depression scores seem to increase with chemical castration[19] and typically decrease with testosterone supplementation,[20-22] which is consistent with a possible causal link between the two. However, the association between testosterone and health outcomes is not specific to depression. Total testosterone and free testosterone levels decline with increasing age, but the concentration of free testosterone declines more markedly.[23-26] The resulting relative androgen deficiency in later life has been linked to decreased lean mass and increased fat mass, osteopenia, decreased muscle strength, fatigue, decreased hematocrit values, systemic illness and increased risk of coronary heart disease, and poor concentration, among other problems.[27,28] This raises the possibility that the association between low testosterone concentration and depression in later life might be due to the presence of concurrent poor physical health.

We designed this study to examine the association between depressive symptoms and testosterone concentrations in older men. We hypothesized that men with clinically significant depression would have lower concentrations of free testosterone than nondepressed men and that this association would be independent of poor physical health.

METHODS

RECRUITMENT OF THE STUDY COHORT

These analyses are based on a cross-sectional study of a community-derived sample of older male residents of Perth, Western Australia, who collectively constitute the cohort for the prospective Health in Men Study. Details regarding the enrollment of participants have been described elsewhere.[29] Briefly, 12 203 men aged 65 years or older were recruited via random sampling from the Australian electoral roll between May 1, 1996, and December 24, 1998, enrollment to vote being compulsory for all adult Australian citizens. The participants represented 70.5% of all invitations issued to eligible men. Between June 1, 2001, and October 31, 2004, men who were still alive were contacted and invited for a follow-up assessment. This article refers to those who were still alive and consented to follow-up. The Human Research Ethics Committee of the University of Western Australia approved the study.

PROCEDURES AND ASSESSMENT

Consenting men were asked to complete a self-report questionnaire that included items assessing demographic and clinical information. Age was calculated as the difference in years between the date of the assessment and the participant's date of birth. Participants were considered to come from a non–English-speaking background if they reported that the first language they learned as a child was not English. Education was rated as the highest level of education attained: no schooling, primary school, some high school, completed high school, completed college, or other tertiary degree. We obtained the Socio-Economic Indicator for Areas Index for each participant's postcode of residence from data published by the Australian Bureau of Statistics; ratings lower than 1000 indicate relative socioeconomic disadvantage.[30]

Participants were also asked to indicate whether they had ever smoked ("Have you ever smoked cigarettes, cigars, or a pipe regularly?" [yes/no]) and whether they were still smoking at the time of the assessment ("How often do you smoke now?" [every day/not every day/not at all]). Men were considered to be current smokers if they answered "every day" or "not every day." Participants were then asked whether they had been previously treated for an emotional or nervous illness, such as depression (yes/no), and whether they were currently being treated (medication or psychotherapy) for an emotional or nervous illness such as depression (yes/no).

All the men were asked to complete the 15-item Geriatric Depression Scale (GDS-15), and a priori, those with a total score of 7 or more were considered to display clinically significant depressive symptoms (point prevalence). This relatively high cutoff point was chosen to ensure high specificity for the diagnosis of depression in this sample.[31] A trained research assistant then administered the Standardized Mini-Mental State Examination,[32] with scores lower than 24 indicating the presence of cognitive impairment.[33] The research assistant also measured participants' height (to 0.5 cm) and weight (to 0.2 kg). Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was then used to group men into 4 categories: underweight (BMI <18), normal weight ($18 \leq$BMI <25), overweight ($25 \leq$BMI <30), and obese (BMI ≥ 30).

MEASUREMENT OF PHYSICAL COMORBIDITY

Assessment of physical comorbidity involved 2 components. First, we used the weighted Charlson index to determine the presence of significant medical comorbidity in the sample.[34] The index takes into account 17 common medical conditions that predict 1-year mortality: myocardial infarction, congestive heart failure, peripheral arterial disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, liver disease, diabetes mellitus (including diabetes with end-stage organ damage), hemiplegia, renal disease, leukemia, lymphoma, other tumors, metastatic tumors, and AIDS. Charlson et al[34] used adjusted relative risks to assign integer weights to these conditions within a composite index score that ranges from 0 to 37. To calculate the index, we obtained administrative medical information from the Western Australian Linked Database.[35] Briefly, the database links together records of all hospital admissions (private and public) since 1980 with the Mental Health Information System, Western Australian cancer register, and Western Australian death register. We retrieved linked data for all participants until the end of 2004, which was the time of the last assessment for the Health in Men Study. Coding algorithms to define comorbidities followed the procedures described by Quan et al,[36] and scores were calculated using the Stagg Charlson index Stata routine (StataCorp, College Station, Texas). Second, participating men used the 36-Item Short Form Health Survey to rate their health.[37] For the purposes of this study, the analyses were limited to the Physical Component Summary (PCS) measure. The mean (SD) PCS score for the Australian population is 50 (10).[38] Participants with PCS

scores less than 30 (ie, ≥2 SDs below the population mean) were considered to have poor perceived physical health at the time of assessment.

BIOCHEMICAL ANALYSES

Blood samples were collected between 8 and 10:30 AM. Serum was prepared immediately after phlebotomy and stored at –80°C until assayed. Biochemical and hormone assays were performed in the Department of Biochemistry, PathWest, Royal Perth Hospital. Serum concentrations of total testosterone and sex hormone–binding globulin (SHBG) were determined using chemiluminescent immunoassays and an Immulite 2000 analyzer (Diagnostic Products Corp–Biomediq, Doncaster, Australia). The coefficient of variation for testosterone was 11.2% at 207 ng/dL (to convert to nanomoles per liter, multiply by 0.0347) and 8.9% at 519 ng/dL and for SHBG was 6.7% at 0.6 µg/mL (to convert to nanomoles per liter, multiply by 8.896) and 6.2% at 9.1 µg/mL. The working range of the testosterone assay was 20 to 1585 ng/dL, whereas the sensitivity of the SHBG assay was 0.2 µg/mL. Free testosterone, which is the amount of testosterone not bound to either SHBG or albumin, was calculated using the Vermeulen method.[39]

ANALYSIS OF DATA

The data were analyzed using a statistical software package (Stata release 9.2; StataCorp). Participants were divided into 2 groups according to whether they met the study criterion for clinically significant depressive symptoms. We used unpaired *t* tests to compare the differences between the groups for age and the Mann-Whitney test for the serum concentrations of total and free testosterone. The 95% confidence intervals (95% CIs) of the median were estimated using the binomial-based distribution option of Stata. We measured the association between ranked ordinal variables using the Spearman correlation coefficient (Spearman ρ). We calculated odds ratios (ORs) and corresponding 95% CIs from 2×2 tables to measure the strength of the association among demographic, lifestyle, and clinical characteristics of participants with and without depression. We then used multiple logistic regression to clarify whether the evident associations between depression and total and free testosterone, as measured using the OR, could be explained by other measured factors, particularly physical comorbidity.

RESULTS

Of the 5438 men who completed the self-rating questionnaire at the follow-up assessment for the Health in Men Study in 2001-2004, 340 (6.3%; 95% CI, 5.6%-6.9%) reported clinically significant depressive symptoms (GDS-15 score ≥7), and 4165 had a venous blood sample collected. Participants who scored within the depression range were 2.17 (95% CI, 1.71-2.74) times less likely to consent to blood tests, and men who did not have a blood test had a higher weighted Charlson index than those who did ($z=6.01$; $P<.001$). Another 149 participants were later excluded from the analyses because of concurrent use of androgen supplementation (n=26), androgen blockage therapy (n=73), or documented history of orchidectomy (n=50). Of the remaining 4016 men, 29 did not complete the GDS-15. Participants who were excluded or had incomplete GDS-15 data were older than their participating counterparts (mean [SD] age: 78.0 [3.8] vs 77.0 [3.6] years; $t=3.40$; $P=.001$). The groups did not differ in the distribution of educational attainment ($P=.63$) or socioeconomic background ($P=.79$), as measured by the Socio-Economic Indicator for Areas Index.

The ages of the 3987 available participants ranged from 71 to 89 years, and 203 (5.1%) had a total GDS-15 score within the depression range. Depressed men were older than their nondepressed counterparts (mean [SD] age: 77.6 [3.8] vs 77.0 [3.6] years; $t=2.30$; $P=.02$). **Table 1** summarizes other demographic and clinical characteristics of men according to whether depression was present. Men with depression reported lower educational attainment and were more likely than nondepressed men to be former or current smokers, to have a BMI of 30 or greater or a Mini-Mental State Examination score less than 24, to report treatment for depression, and to have greater physical comorbidity.

Total testosterone concentration ranged from 20 to 1602 ng/dL and had a positively skewed distribution. The shape of the distribution did not change substantially after logarithmic transformation (Shapiro-Wilks test for normality, $z=14.33$; $P<.001$). There was a weak inverse correlation between total testosterone level and GDS-15 score (Spearman $\rho=-0.07$; $P<.001$) as well as the weighted Charlson index of comorbidity (Spearman $\rho=-0.10$; $P<.001$). Likewise, there was a direct weak correlation between total testosterone level and PCS score (Spearman $\rho=0.16$; $P<.001$). Median total testosterone levels were 389 ng/dL (95% CI, 360-403 ng/dL) and 424 ng/dL (95% CI, 418-429 ng/dL) for men with and without clinically significant depression, respectively (Mann-Whitney rank sum test, $z=4.05$; $P<.001$).

Participants were subsequently grouped into quintiles according to total testosterone concentration (**Table 2**), as previously described.[26] Relative to men in the highest quintile of total testosterone, the odds of depression in men in the lowest quintile was 1.94 (95% CI, 1.27-2.97). The association between depression and total testosterone quintile became nonsignificant after the analysis was adjusted for age, educational level, smoking, BMI, presence of cognitive impairment, current or previous treatment for depression, Charlson index, and PCS score (OR, 1.55; 95% CI, 0.91-2.63).

We used a similar approach to investigate the association between depression and free testosterone concentration (Table 2). The distribution of free testosterone concentration was positively skewed, and its shape did not change significantly after logarithmic transformation (Shapiro-Wilks test for normality, $z=16.59$; $P<.001$). There was a weak inverse correlation between free testosterone concentration and GDS-15 score (Spearman $\rho=-0.10$; $P<.001$) and the weighted Charlson index of comorbidity (Spearman $\rho=-0.11$; $P<.001$). Free testosterone concentration was directly correlated with PCS scores (Spearman $\rho=0.16$; $P<.001$). Median free testosterone concentrations were 7.1 ng/dL (95% CI, 6.6-7.4 ng/dL) and 7.8 ng/dL (95% CI, 7.6-7.8 ng/dL) for men with and without depression, respectively (Mann-Whitney rank sum test, $z=4.88$; $P<.001$). Men in the lowest quintile of free testosterone had increased odds of depression in rela-

Table 1. Sociodemographic and Clinical Characteristics of 3987 Men With and Without Depression

	Men, %		
	No Depression (n=3784)	Depression (n=203)	OR (95% CI)
Educational attainment			
None or primary school	13.9	20.7	1 [Reference]
Some high school	37.3	36.9	0.67 (0.45-0.98)
Completed high school	26.8	23.6	0.59 (0.39-0.91)
Completed college or tertiary degree	22.0	18.7	0.57 (0.36-0.90)
Non–English-speaking background	13.7	18.2	1.40 (0.97-2.03)
Disadvantaged area of residence	29.7	34.0	1.22 (0.90-1.65)
Smoking status			
Never smoked	35.7	23.2	1 [Reference]
Former smoker	59.5	67.1	1.70 (1.22-2.38)
Current smoker	4.8	9.7	3.05 (1.77-5.26)
BMI			
Normal	23.4	18.9	1 [Reference]
Underweight	0.3	0.5	2.39 (0.30-19.2)
Overweight	61.8	56.1	1.13 (0.77-1.65)
Obese	14.5	24.5	2.09 (1.35-3.26)
Cognitive impairment (MMSE score <24)	13.4	27.6	2.47 (1.74-3.51)
Previously treated for depression	8.8	30.7	4.60 (3.34-6.33)
Current treatment for depression	3.5	15.3	5.00 (3.28-7.62)
Charlson index (weighted)			
0	49.6	29.2	1 [Reference]
1-2	33.0	30.7	1.58 (1.10-2.27)
3-4	11.5	24.3	3.60 (2.42-5.33)
≥ 5	6.0	15.8	4.51 (2.87-7.09)
SF-36 PCS score <30	14.0	40.2	4.12 (3.06-5.56)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; MMSE, Mini-Mental State Examination; OR, odds ratio; PCS, Physical Component Summary; SF-36, 36-Item Short-Form Health Survey.

Table 2. Risk Ratio of Depression According to Total and Free Testosterone Quintiles

	Men, %			
	No Depression (n=3784)	Depression (n=203)	OR (95% CI)	Adjusted OR (95% CI)[a]
Total testosterone concentration, ng/dL				
≥ 556	20.3	17.2	1 [Reference]	1 [Reference]
455 to <556	20.7	15.3	0.87 (0.53-1.42)	0.96 (0.54-1.71)
386 to <455	20.2	17.7	1.03 (0.64-1.66)	1.10 (0.63-1.94)
308 to <386	20.0	18.7	1.10 (0.69-1.76)	0.86 (0.48-1.53)
<308	18.8	31.0	1.94 (1.27-2.97)	1.55 (0.91-2.63)
Free testosterone concentration, ng/dL				
≥ 10	20.5	11.8	1 [Reference]	1 [Reference]
8 to <10	20.3	17.7	1.52 (0.90-2.56)	1.99 (1.05-3.77)
7 to <8	20.1	18.2	1.57 (0.93-2.66)	1.84 (0.97-3.50)
6 to <7	20.0	17.7	1.54 (0.91-2.60)	1.59 (0.83-3.03)
<6	19.1	34.5	3.12 (1.94-5.02)	2.71 (1.49-4.93)

Abbreviations: CI, confidence interval; OR, odds ratio.
SI conversion factor: To convert total and free testosterone to nanomoles per liter, multiply by 0.0347.
[a] Adjusted for age, educational level, smoking, body mass index, cognitive impairment, current or previous treatment of depression, Charlson index, and Physical Component Summary score.

tion to men in the highest quintile (OR, 3.12; 95% CI, 1.94-5.02). This association remained significant after the analysis was adjusted for confounding for age, educational level, smoking, BMI, presence of cognitive impairment, current or previous treatment for depression, Charlson index, and PCS score (OR, 2.71; 95% CI, 1.49-4.93). Finally, we excluded 548 men with Mini-Mental State Examination scores less than 24 to minimize possible confounding due to the overlap between cognitive impairment and depression. Logistic regression confirmed that the lowest quintile of total testosterone was associated with depression (OR, 2.10; 95% CI,

1.22-3.59), as was the lowest quintile of free testosterone (OR, 3.77; 95% CI, 1.97-7.23).

COMMENT

The results of this study show that total and free testosterone concentrations are only weakly associated with depressive symptoms. However, when the concentration of free testosterone is lower than 6 ng/dL, the risk of depression increases 3-fold compared with men with concentrations greater than 10 ng/dL.The observed increased risk of depression in older men associated with low free testosterone levels is independent of age, educational level, smoking history, BMI, cognitive impairment, current or previous treatment for depression, and poor physical health. These data suggest that there may be a causal relationship between low free testosterone concentrations and depression in elderly men and that restoring physiologic concentrations of testosterone may improve mood and reduce depression.

These findings should be interpreted in light of the strengths and limitations of the study. This survey has the merit of having used a large and well-established community-representative sample of older men for whom a wealth of relevant clinical information was available. In addition, we used a comprehensive measure of physical health that included information obtained from administrative health data (weighted Charlson index) and a subjective rating of physical health (PCS score). This enabled us to adjust carefully for physical health when investigating the association between testosterone concentration and depression. We also adjusted the results for relevant sociodemographic and lifestyle factors that could potentially explain the association between testosterone and depression, and we took into account the potential role of antidepressant drug treatment. We acknowledge, however, that we cannot infer causality between the factors being investigated because of the cross-sectional nature of the study. Evidence also indicates that the older men with depression were less likely to agree to a blood test and that those who did not have a blood test had greater comorbidity (a higher weighted Charlson index). This would have biased the results toward a healthier sample and diminished the ability to adjust the analyses for any effect of poor physical health when investigating the association between depression and testosterone concentration.

We used a validated scale and a demanding cutoff point to establish the presence of depression in this sample. We recognize, however, that the classification of depression was not based on a formal assessment of mental state leading to the diagnosis of a depressive episode. As a result, we cannot be certain that the findings would be directly transferable to patients meeting *DSM-IV* criteria for major depression or *International Statistical Classification of Diseases, 10th Revision (ICD-10)*[40] criteria for depressive episodes. We also acknowledge that the study included men only and that the findings may not necessarily apply to women, although the results of previous studies suggest that testosterone and free testosterone are also associated with depressed mood in premenopausal and perimenopausal women.[41]

Data from the Massachusetts Male Aging Study[42] (1265 men aged 40-70 years) suggested that every additional unit in the concentration of total serum testosterone was associated with a 10% decrease in the risk of depression (95% CI, −9% to 25%), as measured by a score of 16 or more on the Center for Epidemiological Studies Depression Scale. In the Rancho Bernardo Study, Barrett-Connor et al[17] found an inverse relationship between scores on the Beck Depression Inventory and quartile of free testosterone in 856 men aged 50 to 89 years, but confounding was not taken into account in the analysis of the data. Although these studies included men spanning middle to older age, the present findings establish the relationship between lower free testosterone levels and depression in men older than 70 years.

There is some evidence that low testosterone concentration might increase the incidence of depression, although the psychophysiologic mechanism of age-related hypogonadism has not yet been sufficiently characterized.[22] Shores et al[43] reviewed the medical records of 278 men aged 45 years or older (mean [SD] age, 62.6 [9.8] years) who had no history of depression. Twenty-three men met the study criteria for hypogonadism (total testosterone concentration ≤200 ng/dL or free testosterone concentration ≤1 ng/dL). During 2-year follow-up, a significantly larger proportion of hypogonadal (21.7%) than eugonadal (7.1%) men had a recorded diagnosis of depression (hazard ratio, 4.2; 95% CI, 1.5-12.0; after adjustment for age, ethnicity, number of clinic visits, presence of alcohol-related disorders, prostate cancer, and chronic disease score). Other studies have shown that men with a depressive disorder have lower concentrations of total and free testosterone than controls[44,45] and that remission of symptoms is not followed by an increase in the serum concentration of the hormone[46,47] (ie, reverse causality seems to be an unlikely explanation for the present findings). The present data indicate that the relationship between lower free testosterone level and depression in older men is independent of physical comorbidity.

Seven small randomized trials have examined the effect of testosterone on the mood of eugonadal[48,49] and hypogonadal[50,51] men with depression as well as hypogonadal men without major depression.[20,52,53] Their results indicate that the administration of testosterone improves mood, but its efficacy when used in isolation for the treatment of depression has not been established. For example, Seidman et al[51] randomized 30 men with major depression and a total testosterone concentration of 349 ng/dL or less to receive testosterone (n=13) or placebo (n=17). They found that 5 of 13 participants (38%) treated with testosterone and 7 of 17 (41%) who received placebo experienced a reduction of 50% or more in their score on the Hamilton Depression Rating Scale. Preliminary evidence from small studies also suggests that testosterone supplementation may improve response to antidepressant agents in hypogonadal men with treatment resistance[54] but not in eugonadal men.[55] Larger clinical trials are necessary to clarify the potential role of tes-

tosterone therapy to prevent or treat depression in older hypogonadal men.

In conclusion, we found that men with a free testosterone concentration lower than 6 ng/dL have a substantially higher prevalence of depression and that this association cannot be adequately explained by sociodemographic factors or concurrent physical comorbidity. Alternatively, these results could be interpreted as indicating that free testosterone concentrations greater than 10 ng/dL reduce the risk of depression. These findings suggest a causal relationship. A randomized controlled trial is required to determine whether reducing prolonged exposure to low free testosterone is associated with a reduction in the prevalence of depression in elderly men. If so, older men with depression may benefit from systematic screening of free testosterone concentration, and testosterone supplementation may contribute to the successful treatment of hypogonadal older men with depression.

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