ORIGINAL ARTICLE

Increased Incidence of Diagnosed Depressive Illness in Hypogonadal Older Men

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Context: Age-associated hypogonadism (testosterone deficit) occurs in 30% of men after the age of 55; it is associated with decreased muscle mass, bone mineral density, and libido, and with anorexia, fatigue, and irritability. Although some of these symptoms overlap with those of depression, the association between the 2 disorders is unclear.

Objective: To determine if hypogonadal men have an increased incidence of depressive illness compared with eugonadal men.

Design: Historical cohort study using computerized medical records, followed by a manual medical record review.

Setting: Veterans Affairs Puget Sound Health Care System.

Participants: Two hundred seventy-eight men 45 years and older, without prior diagnosed depressive illness and with consistently normal or low testosterone levels (total testosterone level ≤200 ng/dL [≤6.94 nmol/L]; or free testosterone level ≤0.9 ng/dL [≤0.03 nmol/L]) at baseline and during a 2-year follow-up period.

Main Outcome Measures: Incidence of, and time to, a depression diagnosis.

Results: The 2-year incidence of diagnosed depressive illness was 21.7% in hypogonadal men vs 7.1% in others (χ^2_1=6.0, *P*=.01). A Kaplan-Meier survival analysis showed a significant difference between hypogonadal and eugonadal men in time to diagnosed depression (log-rank test χ^2_1=6.9, *P*=.008). We used Cox proportional hazards regression models to examine the association of hypogonadism and time to depression diagnosis, adjusting for age, race, number of clinic visits, alcohol use disorders, prostate cancer, and overall medical comorbidity. The unadjusted hazard ratio for depression with hypogonadism was 3.5 (95% confidence interval, 1.3-9.4) (*P*=.01). Controlling for all covariates, hypogonadism remained significantly associated with depression (adjusted hazard ratio, 4.2; 95% confidence interval, 1.5-12.0) (*P*=.008).

Conclusions: Hypogonadal men showed an increased incidence of depressive illness and a shorter time to diagnosis of depression. Further prospective studies are needed to confirm these preliminary findings and to clarify the role of testosterone in the treatment of depressive illness in older men.

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AGE-ASSOCIATED TESTOSTERone deficiency is a common condition in older men, occurring in 30% after the age of 55.[1] Total testosterone levels peak in early adulthood, and then decrease by approximately 1% per year after the age of 40.[2] Age-associated hypogonadism reflects a decline in hypothalamic and testicular function. In addition, severe illness, malnutrition, and drugs (such as corticosteroids and alcohol) may also decrease testosterone levels.[3-5] Although there is no uniformly accepted threshold level for testosterone in older men, experts in geriatric andrology suggest that most men with age-associated hypogonadism have total testosterone levels between 150 and 350 ng/dL (5.20-12.14 nmol/L).[4,6]

Symptoms of hypogonadism include diminished muscle mass and strength, decreased bone mineral density, anorexia, decreased libido, fatigue, dysphoria, and irritability.[3-6] Some of these symptoms overlap with those of depressive illness. However, the association between hypogonadism and depression is unclear. Prior studies have revealed mixed findings on the relation of testosterone and mood in older men. Endocrinologic studies[7-10] of testosterone replacement have shown an improvement in general well-being in older hypogonadal men. However, these studies focused primarily on the effects on muscle, bone, and sexual function. Moreover, they used samples from specialty clinics and used nonstandardized mood measures.[11,12] Psychiatric studies that have specifically examined the as-

sociation of testosterone and mood have yielded conflicting results. One large cross-sectional study[13] of older men found that testosterone levels were inversely associated with scores on the Beck Depression Inventory. Another study[14] found that low testosterone levels were associated with dysthymic disorder, but other reports[15-17] drew no correlation between testosterone level and depression in young or middle-aged men. Testosterone treatment trials in depressed subjects have shown similarly conflicting results. Several studies[18,19] found that depressed hypogonadal human immunodeficiency virus–positive men were effectively treated with testosterone. Two small studies[20,21] found that testosterone effectively augmented antidepressant treatment in hypogonadal men with refractory depression. In contrast, a randomized, double-blind, placebo-controlled trial[22] found no difference in treatment response between testosterone and placebo in older, depressed, hypogonadal men.

We, therefore, sought to examine the longitudinal relation of hypogonadism and incident depression in older men. We hypothesized that, compared with men with normal testosterone levels, those with low testosterone levels would have an increased incidence of depressive illness and a correspondingly shortened time to the development of depression.

METHODS

SAMPLE

We examined computerized clinical records of older male patients from the Veterans Affairs Puget Sound Health Care System to assess the relation of testosterone level and 2-year incidence of diagnosed depression. The records contained demographic information, laboratory and pharmacy data, and inpatient and outpatient *International Classification of Diseases, 9th Revision, Clinical Modification* (*ICD-9-CM*), diagnostic codes.[23] We first identified all male patients meeting the following inclusion criteria: (*a*) 45 years or older as of January 1, 1998, (*b*) seen at the medical center at least twice a year, (*c*) available baseline (January 1, 1995–December 31, 1997) and follow-up (January 1, 1998–December 31, 1999) testosterone levels, and (*d*) testosterone levels stable at values either above or below specified threshold levels of total or free testosterone. We excluded men treated with antiandrogens and those with diagnoses of depressive illness before 1998 (*ICD-9-CM* codes 296.2-296.9 [major depressive disorder], 300.4 [dysthymic disorder], and 311.0 [depressive disorder not otherwise specified]). These *ICD-9-CM* codes were recorded by clinicians following routine clinical care in outpatient and inpatient settings.

CLASSIFICATION OF GONADAL STATUS

To ensure that men with low testosterone levels would have meaningful hypogonadism, likely to benefit from testosterone replacement,[24] we used a stringent cutoff value for repeated testosterone levels (≤200 ng/dL [≤6.94 nmol/L] for total testosterone or ≤0.9 ng/dL [≤0.03 nmol/L] for free testosterone) to define hypogonadism. In instances of disagreement in classification by total vs free testosterone, we accepted the more reliable total testosterone categorization as definitive. Because testosterone levels have a circadian fluctuation, we compared the time of day for plasma acquisition from hypogonadal and eugonadal men.

OUTCOMES

We then ascertained the occurrence of clinically diagnosed depressive illness during an analytic period from January 1, 1998, through December 31, 1999. Using the same *ICD-9-CM* diagnostic codes previously described, we noted the dates when clinical diagnoses of depressive illness were first entered. From the same medical records, we abstracted potentially relevant covariates, including age, race, total number of clinic visits, alcohol use disorders, prostate cancer, and the Chronic Disease Score (CDS).[25] The CDS, which is obtained algorithmically from the Veterans Affairs Computerized Patient Record System, represents a simple count of 29 different chronic medical conditions, yielding a score of 0 to 29. It has been validated as an index of general medical comorbidity.[25,26]

A research assistant who was blinded to testosterone level category next performed a manual medical record review, confirming diagnoses of depressive illness and noting the indication for testosterone assays and the specialty of the practitioners who ordered these assays. The research assistant had been instructed to consult a research psychiatrist (M.M.S.) (also blinded to testosterone level category) regarding any ambiguities in depression diagnoses and indications for a testosterone assay. Then, the psychiatrist performed a more comprehensive medical record review of men with depression diagnoses, further evaluating and corroborating these diagnoses and their first recorded dates. In 17 (6.1%) of the instances of disagreement between the psychiatrist's review and original computerized data acquisition, we used the psychiatrist's review for our analysis.

STATISTICAL ANALYSIS

We examined differences between groups with independent sample *t* tests for continuous measures and χ^2 tests for categorical observations. We used a Kaplan-Meier survival analysis to compare time to diagnosed depressive illness.[27] Survival curves and median time to diagnosed depression were compared using the log-rank χ^2 test.[28] Cox proportional hazards regression models were used to examine the association of testosterone category and time to diagnosed depression while adjusting for the influence of covariates.[29] These analyses included all named covariates (age, race, number of clinic visits, alcohol use disorders, prostate cancer, and CDS), although CDS was the only significant factor in these models.

RESULTS

SAMPLE

From the computerized clinical data, we identified 398 men 45 years or older who had testosterone level results before and after January 1, 1998, but who showed no diagnosis of a depressive disorder before this date. Of these men, 294 (73.9%) had repeated low or repeated normal testosterone levels, as previously described. Because acute illness, medications, and intermittent testosterone treatment could cause testosterone fluctuations that would be difficult to identify using historical methods, our primary analyses excluded the 104 men (26.1%) with inconsistent testosterone level categories. We also excluded 16 subjects following the manual medical record review, 15 because of a preexisting diagnosis of depression and 1 because of antiandrogen treatment.

Of the remaining 278 men, 23 had repeated low testosterone levels while 255 had repeated normal levels.

Characteristics of the Eugonadal and Hypogonadal Men Included in the Study*

Characteristic	Entire Group (N = 278)	Eugonadal Men (n = 255)	Hypogonadal Men (n = 23)	*P* Value
Age, y	62.6 ± 9.8	62.4 ± 9.6	64.5 ± 12.1	.33
Ethnicity†				
White	221 (79.5)	205 (80.4)	16 (69.6)	
African American	40 (14.4)	34 (13.3)	6 (26.1)	.59
Other	17 (6.1)	16 (6.3)	1 (4.3)	
Chronic Disease Score	3.5 ± 2.5	3.5 ± 2.4	3.9 ± 2.9	.41
Prostate cancer†	11 (4.0)	10 (3.9)	1 (4.3)	.92
Alcohol disorder†	24 (8.6)	23 (9.0)	1 (4.3)	.44
Testosterone level, ng/dL				
Total	490 ± 310	520 ± 310	150 ± 50	<.001
Free	1.40 ± 0.86	1.53 ± 0.84	0.51 ± 0.30	<.001
Total No. of clinic visits	55.3 ± 51.9	56.2 ± 53.0	45.4 ± 36.4	.33

SI conversion factor: To convert testosterone to nanomoles per liter, multiply by 0.0347.
*Data are given as mean ± SD unless otherwise indicated.
†Data are given as number (percentage) of each group.

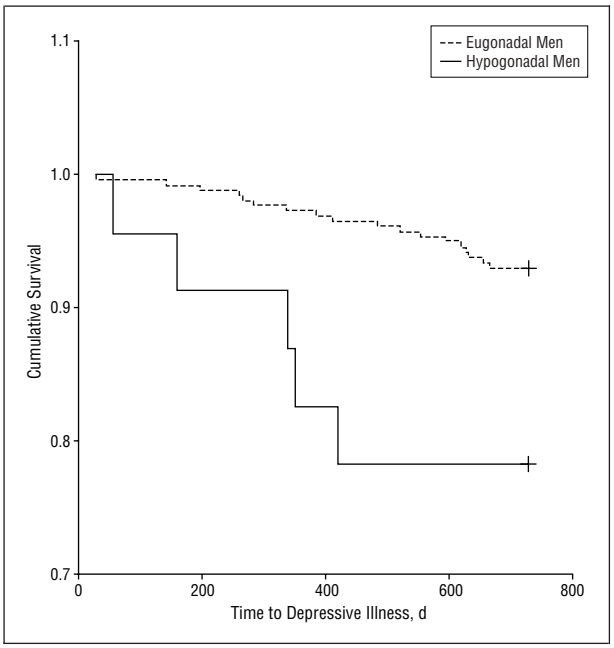

Figure 1. Kaplan-Meier survival analysis showing time to diagnosed depression in hypogonadal vs eugonadal men. The hypogonadal men had a significantly shorter time to diagnosed depressive illness (log-rank $\chi^2_1=6.9$, $P=.008$).

The **Table** demonstrates a lack of significant difference between the hypogonadal and eugonadal men for age, ethnicity, alcohol use disorders, prostate cancer, CDS, or clinic visits. Surprisingly, the eugonadal men had more clinic visits, although this was not statistically significant.

INDICATION FOR TESTOSTERONE LEVELS

Testosterone assays were obtained by clinicians for the following indications: evaluation of sexual dysfunction (31.6%), osteoporosis (21.6%), current testosterone treatment or follow-up of a prior low testosterone level (15.4%), geriatric rehabilitation (10.4%), other genitourinary conditions (9.0%), cancer (3.2%), endocrine conditions (3.0%), and other or unknown reasons (5.8%). Most clinicians ordering testosterone levels were in primary care (60.2%), followed by urology (10.3%), endocrinology (8.6%), geriatrics (7.3%), oncology, rheumatology, or neurology (6.5%), and psychiatry (0.3%). (Data were missing in 6.8% of the cases.) There were no significant ($P=.98$) differences in the phlebotomy times for the men with low vs normal testosterone levels (data not shown).

OUTCOMES

During the 2-year follow-up period, the hypogonadal men had a significantly increased occurrence of diagnosed depressive illness (crude rates, 21.7% vs 7.1%; $\chi^2_1=6.0$, $P=.01$). The 104 men with inconsistent testosterone level results showed an intermediate crude occurrence of depression (15.1%). Small differences were observed in depressed vs nondepressed men for total number of clinic visits ($P=.98$) and total number of mental health visits ($P=.69$), but these differences did not reach statistical significance.

A Kaplan-Meier survival analysis (**Figure 1**) showed that hypogonadal men had a significantly shorter time to diagnosed depression (log-rank $\chi^2_1=6.9$, $P=.008$). In Cox proportional hazards regression models, the unadjusted hazard ratio for diagnosed depression with a low testosterone level was 3.5 (95% confidence interval, 1.3-9.4) ($P=.01$). Overall medical comorbidity proved to be the only covariate significantly associated with time to diagnosed depression. After adjustment for all covariates, the adjusted hazard ratio was 4.2 (95% confidence interval, 1.5-12.0) ($P=.008$).

Finally, we performed a sensitivity analysis to assess whether our results would vary using different testosterone threshold levels to define hypogonadal and eugonadal status. **Figure 2** shows that lower testosterone thresholds were associated with an increase in incident depression. The 2-year incidence of depression in men with a total testosterone level below 150 ng/dL (5.20 nmol/L) was 29%. By contrast, use of the least stringent threshold of 350 ng/dL (12.14 nmol/L) reduced the incidence of depression to 13%. At all total testosterone

thresholds below 280 ng/dL (9.72 nmol/L), hypogonadal men showed a significant increase in incident depression compared with eugonadal men.

COMMENT

We observed an increased incidence of depressive illness in hypogonadal older men. Others have examined correlations between testosterone levels and mood[13,16,17] or the utility of testosterone treatment or testosterone augmentation for depression.[19-22] To our knowledge, this is the first study to examine the longitudinal relation of hypogonadism and incident depression in older men. Compared with eugonadal patients, hypogonadal men with total testosterone levels of 200 ng/dL or less (≤6.94 nmol/L) showed an approximate 4-fold increase in the risk of incident depression. Post hoc dose-response analyses showed that depression risk was inversely related to testosterone level, with statistically significant findings observed at testosterone levels lower than 280 ng/dL (9.72 nmol/L). Negative or mixed results from prior testosterone treatment trials[22,30] of depression in elderly men may have been due to the inclusion of eugonadal men or men with less marked hypogonadism with testosterone levels above 280 ng/dL.

Several plausible biological mechanisms may explain the association between hypogonadism and depressive illness. Hypogonadism may directly cause symptoms such as muscle wasting, anorexia, fatigue, and decreased libido, which may have an effect on mood. Hypogonadism might also cause depressive illness directly through alterations in central neurotransmitter function, because testosterone is known to have multiple central effects.[31] For example, in animal models, testosterone increases cortical serotonin$_{2A}$ receptor binding densities[32,33]; and in humans, cortical serotonin$_{2A}$ receptors decrease with depression[34] and aging.[35] Thus, a low testosterone level may cause depression via decreased serotonin$_{2A}$ receptor density. If so, older men would be particularly vulnerable to these effects, because serotonin$_{2A}$ receptors are already decreased from normal aging.[35] Another potential biological mechanism may be that testosterone influences affective illness similar to the manner in which thyroid hormone modulates affective illness (ie, marked thyroid deficiency can precipitate or exacerbate a depressive illness, and thyroid augmentation may enhance antidepressant response in patients with treatment-refractory depression).[36]

Given our reliance on medical records, these results should be viewed as preliminary. Our methods may be subject to several forms of bias. These include selection bias, detection bias, exposure (testosterone level) misclassification, incomplete control on phlebotomy times, and susceptibility to other unsuspected or unmeasured confounding factors. We discuss these briefly, in turn noting some arguments on why they do not explain our results in full.

Selection bias might have occurred if testosterone levels had been ordered preferentially in subjects who seemed depressed. Testosterone levels were rarely ordered for the evaluation of a mood disorder, however. Most testosterone levels were ordered because of sexual

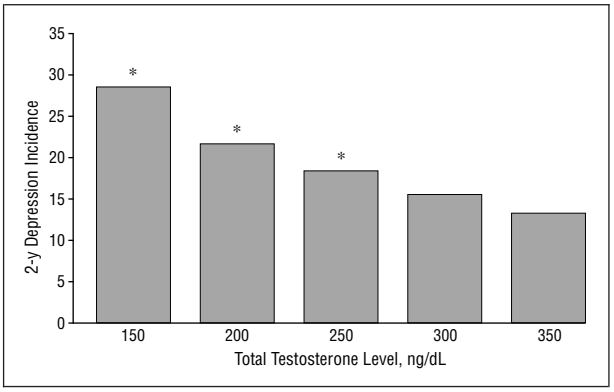

Figure 2. Two-year incidence of depression in hypogonadal men, using different total testosterone threshold levels to define hypogonadism. There is an increase in incident depression as the severity of hypogonadism increases. Asterisk signifies that at all total testosterone thresholds below 280 ng/dL, hypogonadal men showed a significant increase in incident depression compared with eugonadal men ($P<.05$). To convert testosterone to nanomoles per liter, multiply by 0.0347.

dysfunction, osteoporosis, rehabilitation assessment, and endocrine illness. Detection bias might have occurred because depression is frequently unrecognized in primary care settings. Thus, it is likely that depression was not detected in many cases. During the period covered by the study, depression screening (2 questions about dysphoria and anhedonia) was mandated in Veterans Affairs primary care settings. Such depression screening would likely increase the detection of depressive illness and minimize the underdiagnosis of depression. In contrast, another type of detection bias could occur if hypogonadal men had more frequent clinic visits than eugonadal men. In this case, hypogonadal men could have spurious increases in depression rates that might simply reflect increased surveillance. In fact, although the number of clinic visits was comparable between the 2 groups, the eugonadal men had more clinic visits than the hypogonadal men. Thus, oversurveillance of the hypogonadal group does not seem to be a factor in the higher rate of depression diagnoses in that group. Even so, the similar symptoms of hypogonadism and depression may have led to greater recognition of depressive illness in hypogonadal subjects. In future studies, this concern might be addressed by examining all participants for depression using standardized techniques.

In this historical study, depression diagnoses do not have the rigorous validity of a prospective study. We attempted to address this problem in part through a manual medical record review that yielded greater clinical detail than the computerized database. Nevertheless, a systematic prospective study would yield more robust diagnoses.

Testosterone levels are known to show circadian variation, particularly in younger men. We, therefore, examined the phlebotomy times for systematic differences between the hypogonadal and the eugonadal men, but found none. Furthermore, in older men, the circadian variation of testosterone secretion is markedly diminished or absent.[37] Thus, we believe that the effect of variable phlebotomy times is minimal, because there were no significant differences in phlebotomy times between

the 2 groups and the circadian secretion of testosterone is markedly attenuated in older men.

It is possible that low testosterone and depression are associated only because both are related to some other common factor. For example, prostate cancer, sexual dysfunction, and overall medical comorbidity are associated with hypogonadism and depression.[38-40] We, therefore, repeated our analyses, excluding men with prostate cancer, but found no changes in our results. Furthermore, there were no appreciable differences in prostate cancer, overall medical morbidity, ethnicity, or sexual dysfunction; and the prevalence of sexual dysfunction was actually lower in the hypogonadal vs the eugonadal group (30.4% vs 35.7%; $P = .61$). Thus, it does not seem that our results can be explained by an association with these covariates, because there were no significant differences in them between groups. Our results could also be confounded by ethnicity, because African American men have a lower incidence of depression[41] and, at least at younger ages, a higher testosterone level.[42] However, there were no differences in ethnicity between groups, and we repeated our analyses excluding African American men, but found no changes in our results (data not shown).

Despite its limitations, our study suggests a relationship between testosterone level and depression that could have significant public health implications. Even without concomitant depression, hypogonadism has several probable deleterious effects and is a common disorder in older men.[4] If hypogonadism also provokes an increased risk of depression, it would then have significant resulting implications for morbidity, mortality, and quality of life.[43] Because depression is a major risk factor for suicide, and older men have the highest suicide rate of any age group in the United States,[44] identifying conditions (such as low testosterone) that increase the risk of depressive illness could generate important opportunities for early intervention and treatment. If these findings are substantiated, the detection of low testosterone could aid in the early identification and treatment of depressive illness in older men—a group noted to experience underdetection and undertreatment of depressive illness.[45]

Our results do not speak to the possible effectiveness of testosterone treatment or augmentation in patients with depressive disorders, but it would be of interest to know whether such treatment might be beneficial in particular diagnostic subgroups (eg, those with dysthymic disorder) or other categories (eg, the oldest-old). In addition, although testosterone replacement in hypogonadal men has not been shown to increase the risk of prostate cancer,[4-6] this remains a concern. Thus, future large prospective studies of testosterone replacement are needed to clarify if potential benefits outweigh the risks, and to systematically study the effects of testosterone replacement on the health and welfare of older men.

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