Low Testosterone Levels Predict Incident Depressive Illness in Older Men: Effects of Age and Medical Morbidity

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Objective: Prior studies found that chronic low testosterone levels are associated with an increased risk of depression. We investigated whether low testosterone levels in older men predict depressive illness over 2 years, while controlling for age and medical morbidity.

Method: Participants were 748 men, aged 50 years or older, without prior ICD-9–diagnosed depressive illness, with a testosterone level obtained between 1995 and 1997. Measures were age, mean total testosterone levels (low: ≤ 2.5 ng/mL), medical morbidity, and incidence and time to depressive illness.

Results: Men with low testosterone levels had a greater 2-year incidence of depressive illness (18.5% vs. 10.4%, df = 1, p = .006) and a shorter time to onset of depressive illness (log-rank χ^2 = 8.1, df = 1, p = .004). The unadjusted hazard ratio (HR) for depressive illness in men with low testosterone levels was 1.9 (95% confidence interval [CI] = 1.2 to 3.0, p = .005). After adjustment for age and medical morbidity, men with low testosterone levels continued to have a shorter time to depressive illness (adjusted HR = 2.1; 95% CI = 1.3 to 3.2, p = .002). Due to a significant interaction between age and medical morbidity, we conducted stratified Cox regression analyses and found that low testosterone levels and high medical morbidity or an age of 50 to 65 years were associated with increased depressive illness (p = .002).

Conclusion: Low testosterone levels are associated with an earlier onset and greater incidence of depressive illness. Men with low testosterone levels who had high medical morbidity or were aged 50 to 65 years had an increased risk for depressive illness. Further prospective studies are needed to examine the role of testosterone in depressive illness in older men.

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Testosterone levels decline gradually with aging, with approximately 20% of men in their 60s and 50% of men over the age of 80 years demonstrating low total testosterone levels.[1] In addition to aging, low testosterone levels are also associated with acute and chronic medical illnesses and medications. However, the symptoms of low testosterone are similar regardless of whether the etiology of low testosterone is primarily due to aging, medical illness, medications, or a combination of these factors.[2] The term *andropause* has been used to describe the clinical syndrome of low testosterone levels and symptoms of androgen deficiency in older men. However, *andropause* is not an accurate term. In contrast to menopause, in which estrogen secretion ceases entirely, resulting in negligible estrogen levels, in andropause, androgen secretion does not totally cease and androgen levels are highly variable.[3] In fact, total testosterone levels remain within a normal range in approximately 80% of men at age 60 years and 50% of men at age 80 years.[1] Thus, although a significant number of men have low testosterone levels, the majority of older men have total testosterone levels that would be considered normal, even for younger men.

An association between testosterone and mood has been of interest for years, in part because some symptoms of low testosterone, such as irritability, decreased libido,

and fatigue, overlap with symptoms of depressive illness. However, despite studies[4,5] since the 1940s, the association between testosterone and depressive illness in older men remains unclear. Although testosterone generally improves mood in hypogonadal men,[6,7] studies[8–10] of testosterone replacement in depressed men with low testosterone levels have been conflicting. Several methodological issues may explain the inconsistent results. Such issues include controversy regarding appropriate testosterone threshold levels in older men, the potential for a high placebo response to testosterone treatment, and heterogeneous effects of low testosterone levels on mood, possibly related to androgen receptor status.[4,11]

In a recent study,[12] we found that men who had repeatedly low testosterone levels over several years had significantly increased incident depressive illness compared with men who had repeatedly normal testosterone levels. We wondered, on the basis of that study, if a single testosterone measurement could predict incident depressive illness. If so, then low testosterone levels could potentially serve as a marker to identify men at increased risk for depressive illness.

In contrast to our earlier study[12] of men with repeatedly low testosterone levels, in this study, we examined men with baseline testosterone levels who had a less severe testosterone deficiency (testosterone cutoff level of 2.5 ng/mL in contrast to 2.0 ng/mL). We used this cutoff level so that we could assess men with less severely low testosterone levels and yet remain consistent with testosterone threshold levels recognized as low, even for older men.[13,14] In the current study, we also were able to examine the influence of the covariates of age and medical morbidity on incident depressive illness because of a much larger sample size of men with low testosterone levels. We examined the effect of age and medical morbidity, because these covariates are independently associated with decreased testosterone levels and depressive illness.[1,2,15,16] We hypothesized that low testosterone levels would predict depressive illness and that the greatest risk for depressive illness would be in older men with high medical morbidity.

METHOD

We utilized data from computerized clinical records of men aged 50 years and older from the Veterans Affairs (VA) Puget Sound Health Care System (Seattle, Wash.). The computerized medical records contained demographic information, laboratory and pharmacy data, and inpatient and outpatient *International Classification of Diseases* (ICD-9) diagnostic codes.[17] For men meeting the inclusion criteria, we abstracted testosterone levels from the baseline period (1995–1997) and then the occurrence and date of documented depressive illness during the follow-up period (1998–1999).

Sample Selection

We identified male patients meeting the following inclusion criteria: (1) age ≥ 50 years as of 1998, (2) seen at the medical center at least twice a year during the baseline period, and (3) at least 1 available testosterone level obtained during the baseline period (1995–1997). We excluded men who had a diagnosis of depressive illness prior to or during the baseline period. The following ICD-9 codes were used for depressive illness diagnoses: 296.2–296.9 (major depressive disorder and bipolar disorder), 300.4 (dysthymic disorder), or 311.0 (depressive disorder not otherwise specified). These ICD-9 codes were recorded by clinicians following routine evaluation in any outpatient or inpatient setting. Thus, the depressive illness diagnoses were not necessarily made by mental health practitioners. Besides excluding men with prior depressive disorders, we excluded men (N = 25) with high testosterone levels more than 2 standard deviations above the mean (≥ 8.7 ng/mL) due to reports that high testosterone levels may be associated with mood dysregulation.[18] We also excluded men with chronic low testosterone levels who were in our prior study[12] and men treated with antiandrogens. This study of existing data was approved by the University of Washington Human Subjects Division as exempt from written informed consent by patients.

Testosterone Measures

Because we required only 1 testosterone level for entry into the study, we did not characterize the subjects as hypogonadal since that diagnosis is established by repeatedly low testosterone levels and a clinical evaluation.[2] Some men, however, had more than 1 testosterone level obtained (N = 135, 18.0%), and in these cases, the mean testosterone level was used. Our original study[12] of low testosterone levels and depressive illness used a very low threshold level of total testosterone of 2.0 ng/mL, which is a lower threshold level than that used in most studies. In this study, we used a higher testosterone threshold level of 2.5 ng/mL. This level was selected because our earlier study found that increased depressive illness occurred at testosterone levels up to 2.8 ng/mL. We did not select 2.8 ng/mL as the cutoff level, however, because it has not been identified as a potential testosterone threshold level in older men. However, a total testosterone threshold level of 2.5 ng/mL has been identified as a testosterone level that is "frankly low, even for older men,"[13(p41)] and is associated with symptoms of clinical hypogonadism in older men.[14] Thus, we used a threshold level of total testosterone of ≤ 2.5 ng/mL to designate low testosterone. For conciseness, we called the remaining testosterone levels (> 2.5 ng/mL) "normal" testosterone, even though levels between 2.5 and 3.5 ng/mL are frequently considered borderline low testosterone levels.[13,14]

Of note, we used total testosterone levels and did not include free testosterone levels in our study. Although as-

says for free testosterone levels done with equilibrium dialysis, or bioavailable testosterone done with ammonium sulfate precipitation, are the most accurate ways to assess testosterone status, these assays are very expensive and are usually only available at commercial reference labs. Most clinical laboratories, including our own laboratory, use analog immunoassay kits or automated platform assays to measure free testosterone. These assays are influenced by changes in sex-hormone–binding globulin (SHBG) and may underdiagnose or overdiagnose low testosterone levels in older men, who often demonstrate alterations in SHBG.[19] Since the analog-free testosterone immunoassay did not offer advantages over the total testosterone measurement and created variability in the study measures, we did not use free testosterone levels.

Indication for Testosterone Levels

The computerized database did not contain information on the indications for obtaining testosterone levels. However, in a prior study,[12] we manually reviewed the charts of nearly 300 patients who had testosterone levels drawn during the same time period. From that chart review, we found that testosterone assays were obtained for the following indications: 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%), genitourinary conditions (9.0%), cancer (3.2%), endocrine conditions (3.0%), and other or unknown reasons (5.6%). Most clinicians ordering testosterone levels were primary care practitioners (60.2%), urologists (10.3%), endocrinologists (8.6%), and geriatricians (7.3%). Mental health practitioners ordered only 0.3% of testosterone level tests. Since the current study involved a much larger sample, we were unable to manually review all of the charts. However, it is highly likely that the findings from the prior chart review are somewhat representative of the current sample, given the large sample size of the original chart review and that the levels were ordered from the same medical facility during a similar time period.

Outcomes

We ascertained the occurrence and initial date of clinically diagnosed depressive illness during a 2-year follow-up period from January 1, 1998, through December 31, 1999, using the ICD-9 diagnostic codes for depressive illness (296.2–296.9, 300.4, 311.0). Information was not available on testosterone levels in the follow-up period, since most of the men did not have repeated blood draws for testosterone levels. We did not include testosterone treatment in the follow-up period as a variable in our analysis, because we discovered from the manual chart review that the computerized records for testosterone treatment were inaccurate during that time period because intramuscular testosterone injections were frequently recorded in a paper chart rather than in the computerized medical record.

Covariates

Our major covariates of interest were medical morbidity and age, since these are both known to be associated with low testosterone levels. We used the Chronic Disease Score (CDS)[20] as an estimate of overall medical morbidity. The CDS is obtained algorithmically from the VA computerized patient record system and gives a score of 0 to 29 that represents a count of 29 chronic medical conditions. It has been validated as an index of general medical morbidity among VA patients.[21] The CDS was based on medical conditions that were present prior to or during the baseline period.

Statistics

All statistical analyses were done with SPSS software, version 11 (Chicago, Ill.). Differences between groups were examined with independent sample t tests for continuous measures and χ^2 tests for categorical measures. Survival curves and median time to diagnosed depression were compared using the log-rank χ^2 test.[22] Cox proportional hazards regression models[23] were used to adjust for the influence of categorical covariates of age and medical morbidity and to examine potential interactions between the covariates. After finding a significant interaction between age and medical morbidity, we used a stratified Cox regression analysis to examine the risk for incident depressive illness within subgroups defined by age and medical morbidity. Finally, since there is no clear threshold level for low testosterone in older men,[2,13,14] we performed an analysis to assess whether our results would vary using different testosterone threshold levels to define low and normal testosterone levels.

RESULTS

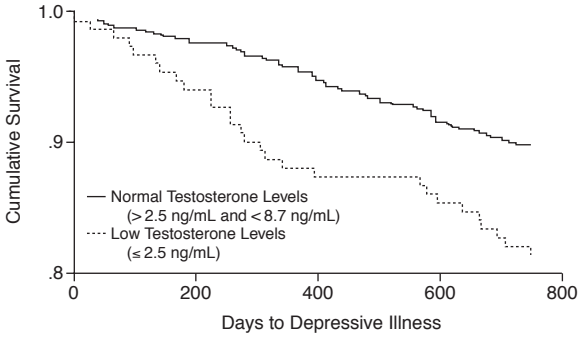
From the computerized clinical data, we identified 748 men who met study inclusion criteria. The mean ± SD age of the entire sample was 67.1 ± 9.1 years and the mean CDS score was 3.6 ± 2.4. There were 151 men (20.2%) with low testosterone levels and 597 men (79.8%) with normal testosterone levels. There were no significant differences between men with low and normal testosterone levels in the mean ± SD number of baseline testosterone levels (1.3 ± 0.7 vs. 1.3 ± 0.6; $t = .39$, $df = 746$, $p = .70$) or in the proportion with multiple testosterone levels (19.2% vs. 17.8.%; $\chi^2 = 1.7$, $df = 1$, $p = .68$). The men with low total testosterone levels had a mean ± SD testosterone level of 1.8 ± 0.7 ng/mL compared with 4.4 ± 1.3 ng/mL in men with normal levels ($t = 23.0$, $df = 746$, $p < .001$). The men with low testosterone levels were older (69.1 ± 9.4 vs. 66.5 ± 8.9 years; $t = 3.1$, $df = 746$, $p = .002$) and had higher medical mor-

Table 1. Comparison of Men With Low Versus Normal Testosterone Levels[a]

Variable	Low Testosterone Level[b] (N = 151)	Normal Testosterone Level[c] (N = 597)	Test Statistic
Age, mean (SD), y	69.1 (9.4)	66.5 (8.9)	t = 3.1; p = .002
50–65	45 (29.8)	248 (41.5)	χ^2 = 7.0; p = .008
> 65	106 (70.2)	349 (58.5)	
Chronic Disease Score, mean (SD)	3.9 (2.5)	3.5 (2.3)	t = 1.8; p = .07
Low score (0–3)	73 (48.3)	310 (51.9)	χ^2 = 0.6; p = .43
High score (≥ 4)	78 (51.7)	287 (48.1)	
Ethnicity, N (%)			
White	127 (84.1)	480 (80.4)	χ^2 = 3.4; p = .18
Black	18 (11.9)	67 (11.2)	
Other	6 (4.0)	50 (8.4)	
Total testosterone level, mean (SD), ng/mL	1.8 (0.7)	4.4 (1.3)	t = 23.0; p < .001
> 1 testosterone value, N (%)	30 (19.2)	106 (17.8)	χ^2 = 1.7; p = .68

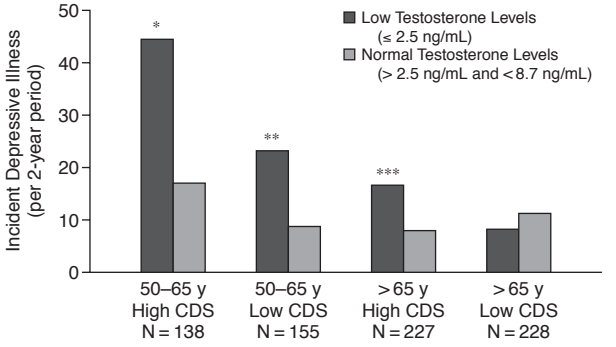
[a]Significant differences were noted in testosterone levels and age. There were no significant differences in ethnicity or Chronic Disease Score.
[b]Low total testosterone level: ≤ 2.5 ng/mL.
[c]Normal total testosterone level: > 2.5 ng/mL and < 8.7 ng/mL.

Figure 1. Survival Time to Depressive Illness in Men With Low Versus Normal Testosterone Levels[a]



[a]Men with low testosterone levels had a significantly shorter time to onset of depressive illness than men with normal testosterone levels (log-rank χ^2 = 8.1, df = 1, p = .004).

Figure 2. Incident Depressive Illness in Men With Low Versus Normal Testosterone Levels by Age and Chronic Disease Score (CDS)[a,b]



[a]Men aged 50–65 years with low testosterone levels had significantly more depressive illness at both high and low CDS than men of the same age and medical morbidity, but with normal testosterone levels. Men with low testosterone levels who were older than age 65 years with high medical morbidity had an increase in incident depression compared with men of the same age and medical morbidity, but with normal testosterone levels, although this did not reach statistical significance.
[b]Low CDS: 0–3; high CDS: ≥ 4.
*p < .01.
**p ≤ .05.
***p = .06.

bidity (CDS), although this did not reach statistical significance (3.9 ± 2.5 vs. 3.5 ± 2.3; t = 1.8, df = 746, p = .07). There were no significant differences in ethnicity (Table 1).

Over the 2-year follow-up period, men with low testosterone levels had significantly more depressive illness than men with normal testosterone levels (18.5% vs. 10.4%; χ^2 = 7.6, df = 1, p = .006) and had a significantly shorter time to onset of depressive illness (log-rank χ^2 = 8.1, df = 1, p = .004) (Figure 1). The unadjusted hazard ratio (HR) for depressive illness in men with low testosterone levels was 1.9 (95% confidence interval [CI] = 1.2 to 3.0; χ^2 = 7.1, df = 1, p = .005). After adjusting for categorical covariates of age and medical morbidity in Cox proportional hazards regression models, low testosterone levels continued to be associated with a shorter time to onset of depressive illness (adjusted HR = 2.1, 95% CI = 1.3 to 3.2; χ^2 = 11.3, df = 1, p = .002).

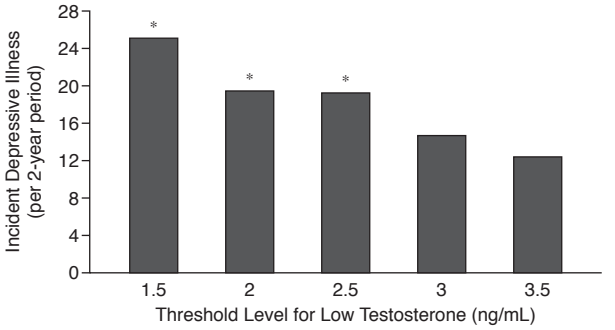
The Cox regression analysis was repeated to examine for significant interactions between the covariates. We found that there was a significant interaction between age and medical morbidity (χ^2 = 3.7, df = 1, p = .054). Due to the interaction between age and medical morbidity, we conducted stratified Cox regression analyses of subgroups on the basis of age and medical morbidity, with the referent group being men in the same subgroup but with normal testosterone levels. Figure 2 and Table 2 show the results of the stratified analyses. Among men aged 50 to 65 years, those with low testosterone levels had a significantly increased risk for incident depressive illness compared with those with normal testosterone levels (HR = 3.2, 95% CI = 1.7 to 5.9; χ^2 = 14.9, df = 1,

Table 2. Cox Regression Stratified Subgroup Analyses of Risk of Incident Depressive Illness in Men With Low Testosterone Levels Versus Men With Normal Testosterone Levels[a]

Low Testosterone Levels	N	Hazards Ratio (95% CI) (vs normal testosterone levels)	Test Statistic
Total	151	1.9 (1.2 to 3.0)	$\chi^2 = 7.1$; p = .005
Age 50–65 y	45	3.2 (1.7 to 5.9)	$\chi^2 = 14.9$; p < .001
Age > 65 y	106	1.4 (0.7 to 2.6)	$\chi^2 = 0.9$; p = .34
Chronic Disease Score			
Total			
Low score	73	1.3 (0.6 to 2.7)	$\chi^2 = 0.4$; p = .51
High score	78	2.4 (1.4 to 4.3)	$\chi^2 = 9.9$; p = .002
Age 50–65 y			
Low score	22	2.8 (0.99 to 8.2)	$\chi^2 = 4.1$; p = .053
High score	23	3.5 (1.6 to 7.4)	$\chi^2 = 11.3$; p = .002
Age > 65 y			
Low score	51	0.7 (0.3 to 2.1)	$\chi^2 = 0.4$; p = .55
High score	55	2.3 (0.97 to 5.3)	$\chi^2 = 3.8$; p = .059

[a]The table shows subgroup analyses with calculated hazard ratios for each subgroup of men with low testosterone levels, with men with normal testosterone levels as the referent group. There is significantly increased risk of depressive illness in men aged 50–65 years (hazard ratio = 3.2, p < .001) and in men with high Chronic Disease Scores (hazard ratio = 2.4, p = .002). The greatest risk for incident depressive illness occurred in men aged 50–65 years with a high Chronic Disease Score (hazard ratio = 3.5, p = .002).

Figure 3. Depression Incidence in Men With Low Testosterone Levels Using Different Threshold Levels for Low Total Testosterone



*p < .05; significant difference in incident depression between men with low vs. normal testosterone levels.

p < .001). Among men with high medical morbidity, those with low testosterone levels had an increased risk for depressive illness compared with those with normal testosterone levels (HR = 2.4, 95% CI = 1.4 to 4.3; $\chi^2 = 9.9$, df = 1, p = .002). Men with low testosterone levels who had both high medical morbidity and were aged 50 to 65 years had the greatest risk for depressive illness (HR = 3.5, 95% CI = 1.6 to 7.4; $\chi^2 = 11.3$, df = 1, p = .002) and had incident depressive illness at a rate of 43.5% over the 2-year follow-up period. Men older than age 65 years with high medical morbidity also had an increased risk for depressive illness (HR = 2.3, 95% CI = 0.97 to 5.3; $\chi^2 = 3.8$, df = 1, p = .059), although this did not reach statistical significance.

Finally, we performed an analysis to assess whether our results would vary using different testosterone threshold levels to define low and normal testosterone levels. Figure 3 shows that lower testosterone threshold levels were associated with greater incident depression. When the threshold level for low testosterone was 1.5 ng/mL, the 2-year incidence of depression was 24.6%. By contrast, at a total testosterone threshold level of 3.5 ng/mL, incident depressive illness was 12.5%, which was comparable with the overall rate of depressive illness of 12.0% in the entire sample.

DISCUSSION

In a cohort analysis of 748 older men, we found that low total testosterone levels (≤ 2.5 ng/mL) predicted significantly greater incident depressive illness. Our primary covariates of interest were medical morbidity and age due to the known decrease in testosterone levels that occurs with medical illnesses and aging.[1,2] However, we found that even after controlling for age and medical morbidity, low testosterone levels continued to be associated with increased depressive illness, with risk for incident depressive illness nearly doubling in men with low testosterone levels.

From stratified analyses, we found that men with low testosterone levels who had the greatest risk for depressive illness were men with high medical morbidity who were aged 50 to 65 years. Medical morbidity has been found to be associated with increased depressive illness in several studies.[24,25] However, we do not believe that the increase in depressive illness in the men with high medical morbidity was due primarily to medical morbidity because the comparison group had similarly high medical morbidity, but normal testosterone levels.

We had not anticipated that the younger men in the cohort, aged 50 to 65 years, with low testosterone levels would have significantly higher incident depressive illness than older men (> 65 years) with low testosterone levels. The increase in depressive illness in men with low testosterone levels, aged 50 to 65 years, may be because low testosterone levels are less common in this age group. Population-based studies[1] indicate that less than 20% of men younger than age 65 years have total testosterone levels below 2.5 ng/mL and that the mean total testosterone level for men aged 50 to 65 years is approximately 5.0 ng/mL.[1,15] Thus, low total testosterone levels at this age represent an early onset of gonadal decline, which may result in greater depressive illness than in older men. For active men in their 50s to early 60s, an early onset of symptoms of testosterone deficiency, such as fatigue, poor concentration, and decreased libido, may be more distressing to them than to older men who may have a more limited lifestyle.

Given the complex relationship between gonadal status and mood,[26] there probably are several biological mechanisms involved in the association between low testosterone levels and depressive illness. Some of these potential mechanisms include changes in central neurotransmitters.[27] For example, in animal models, testosterone increases cortical 5-HT_{2A} receptor–binding densities,[28,29] and in humans, cortical 5-HT_{2A} receptors decrease with depression[30] and aging.[31] Thus, low testosterone levels may cause depression via alterations in central serotonin function and decreases in 5-HT_{2A} receptor density. If so, older men may be at greater risk for this type of depressive illness, since 5-HT_{2A} receptors may already be decreased from aging.[31] Low testosterone levels also may create a biological vulnerability for depressive illness, analogous to other hormone changes associated with affective disorders, such as postpartum and premenstrual conditions or hyperthyroidism or hypothyroidism.[32–34]

Of note, we found higher rates of incident depressive illness than rates reported for major depression in community elders (1.4%–1.9%/year).[35,36] Factors that may explain this include the following: (1) The study included subjects receiving outpatient medical care for chronic medical illnesses. Studies have found that depressive illness increases as medical morbidity and intensity of medical care increases.[24,25] All subjects in our study were followed in VA outpatient clinical settings and had moderately high medical morbidity with a mean of more than 3 chronic medical conditions. In prior studies, elderly patients followed in outpatient clinics or by home health services had incident depressive illness of 5.2% to 11.9%/year[37,38] and prevalent depressive illness ranging from 13.5% to 25.0%. Thus, the rates of incident depressive illness we found in men with normal testosterone levels (5.2%/year) and low testosterone levels (9.3%/year) are consistent with findings of other studies of depressive illness in the elderly in outpatient medical settings. (2) The incidence rate included diagnoses for any depressive illness. Although major depression in community elderly has been estimated to be less than 5%,[35,36] the prevalence of subsyndromal depressive illness is common in the elderly and is associated with morbidity and mortality.[37,38] Studies that have estimated the incidence of clinically significant depressive illness in community dwelling elders have found rates from 5.2% to 11.7%/year.[39,40] Thus, the incident rate of depressive illness in our study is likely to be higher in part because the study included diagnoses for any depressive illness rather than diagnoses solely for major depression.

The results from this study could be limited by several factors such as selection bias, detection bias, survival bias, differing phlebotomy times, or other unmeasured or confounding factors. We discuss each of these factors briefly, noting some reasons why these potential biases probably do not fully explain our results.

Selection Bias

The VA patient population has greater medical morbidity and socioeconomic stressors than a community-based sample,[41] so it is unclear if these results would generalize to other populations of middle-aged and older men. In addition, if testosterone levels were ordered preferentially in men who reported depressive symptoms or who appeared depressed, one would expect increased depressive illness in this sample. However, based on a prior chart review, testosterone levels were rarely ordered by mental health practitioners or for evaluation of a mood disorder. Nevertheless, it is possible that men with prodromal depressive illness had testosterone levels drawn for symptoms such as fatigue or low libido or even that symptoms of low testosterone are indistinguishable from mild, chronic depressive illness such as dysthymia. A potential association between low testosterone levels and dysthymia is supported by a study that found an increase in low testosterone levels in men with dysthymia, but not in men with major depression.[42]

Detection Bias

Since depression is frequently underdiagnosed in primary care settings, it is likely that depression was not detected in some cases. However, at the time period covered by this study, depression screening was mandated in VA primary care, which would tend to minimize the problem of underdetection of depressive illness.

Survival Bias

Our findings could also be influenced by survival bias due to early mortality in men with low testosterone levels. This possibility is supported by studies that noted increased mortality in men with low testosterone levels[43–45] and by studies that have linked depressive illness to increased mortality.[46] However, to conduct a prospective study free of survival bias would require great time and expense.

Variable Phlebotomy Times

The phlebotomy times for the testosterone samples were not standardized. In younger men, testosterone has a diurnal variation with peak testosterone levels occurring in the morning. However, in older men, the diurnal variation of testosterone is markedly diminished or absent.[47] Thus, we believe that the effect of variable phlebotomy times is minimal, since the circadian secretion of testosterone is markedly attenuated in older men.

Other Known or Suspected Confounders

We did not have information regarding testosterone levels or treatment during the follow-up period. However, these effects would seem to bias the results conservatively. For example, if a man with low testosterone levels in the baseline period was subsequently treated with tes-

tosterone in the follow-up period, his testosterone levels would increase, and this would tend to minimize the differences between groups and bias the results toward the null hypothesis.

These results should be viewed as preliminary given these potential limitations and our reliance on medical records. However, despite these limitations, our study suggests that low testosterone levels are associated with increased depressive illness, particularly in men who are aged 50 to 65 years and have high medical morbidity. If these results are confirmed in other studies, low testosterone levels could be a marker for preventive treatment or increased surveillance for depressive illness. If so, such a marker could help to enhance the care of older men, particularly since they suffer from poor detection of depressive illness,[48] yet have the highest suicide rate[49] in the United States.

Further prospective studies are needed to clarify these findings and the role of testosterone replacement in depressive illness in older men. In men with current depressive illness, the therapeutic potential of testosterone is unclear. A recent study of testosterone replacement for major depression in older, hypogonadal men found that testosterone was no more effective than placebo.[10] However, several factors may have limited the ability of that study to find a significant difference between testosterone treatment and placebo. These factors include a high placebo response rate (41%), small sample size, and a lower testosterone dose than that used in prior positive studies.[8,9,50] In addition, the study included men with mild testosterone deficiency (threshold level for low total testosterone of ≤ 3.5 ng/mL) who may be less responsive to testosterone replacement. This hypothesis is supported by a study[51] of hypogonadal men with osteoporosis, which found that increased treatment response occurred in men with lower baseline testosterone levels. In contrast to this negative study, a different study[9] found that testosterone replacement was significantly more effective than placebo in treating major depression in hypogonadal, human-immunodeficiency-virus–positive men with major depression, and 2 small studies found that testosterone augmentation significantly decreased depressive symptoms[8,50] in hypogonadal men with refractory depression. Thus, testosterone replacement in depressive illness may be beneficial in men with refractory depressive illness or potentially beneficial in men with more severe testosterone deficiency. Further prospective trials are needed to examine which subgroups of men with depressive illness are most likely to benefit from testosterone replacement. In addition, although prior testosterone studies have not found an increased risk of prostate cancer, this remains a concern, because these studies have been too small to adequately evaluate that risk.[52] Thus, despite our findings that low testosterone levels are associated with increased depressive illness and some prior studies that found testosterone was beneficial for hypogonadal men with depressive illness, large prospective trials are needed to clarify the overall risks and benefits of testosterone before it can be routinely used in the treatment of older, hypogonadal men with depressive illness.

Drug names: estrogen (Cenestin, Premarin, and others), testosterone (Androderm, Testim, and others).

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