ORIGINAL ARTICLE

Depression Is Associated With Decreased 25-Hydroxyvitamin D and Increased Parathyroid Hormone Levels in Older Adults

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Context: Depression has incidentally been related to altered levels of 25-hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH), but this relation has never been studied systematically.

Objective: To determine in a large population-based cohort whether there is an association between depression and altered 25(OH)D and PTH levels.

Design: Population-based cohort study (Longitudinal Aging Study Amsterdam).

Participants: One thousand two hundred eighty-two community residents aged 65 to 95 years.

Setting: The Netherlands.

Main Outcome Measure: Depression was measured using self-reports (Center for Epidemiologic Studies–Depression scale) and diagnostic interviews (Diagnostic Interview Schedule). Levels of 25(OH)D and PTH were assessed. Potentially confounding factors (ie, age, sex, smoking status, body mass index, number of chronic conditions, and serum creatinine concentration) and explanatory factors (ie, season of data acquisition, level of urbanization, and physical activity) were also measured.

Results: Levels of 25(OH)D were 14% lower in 169 persons with minor depression and 14% lower in 26 persons with major depressive disorder compared with levels in 1087 control individuals ($P < .001$). Levels of PTH were 5% and 33% higher, respectively ($P = .003$). Depression severity (Center for Epidemiologic Studies Depression Scale) was significantly associated with decreased serum 25(OH)D levels ($P = .03$) and increased serum PTH levels ($P = .008$).

Conclusion: The results of this large population-based study show an association of depression status and severity with decreased serum 25(OH)D levels and increased serum PTH levels in older individuals.

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SIGNIFICANT DEPRESSIVE SYMPtoms are highly prevalent in older persons (13%)[1] and result in high morbidity and mortality.[2] Schneider et al[3] suggested that psychiatric disorders, in particular depression, may be associated with low serum concentrations of 25-hydroxyvitamin D [25(OH)D]. Underlying causes of vitamin D deficiency such as less sun exposure as a result of decreased outdoor activity, different housing or clothing habits, and decreased vitamin intake[4] may be secondary to depression, but depression may also be the consequence of poor vitamin D status. Moreover, poor vitamin D status causes an increase in serum parathyroid hormone (PTH) levels. Primary hyperparathyroidism, in turn, is frequently accompanied by depressive disorders, and mood usually normalizes after treatment of hyperparathyroidism.[5,6]

Serum 25(OH)D and PTH abnormalities, while common, are highly treatable, which may enable prevention of depression. Therefore, it is surprising that there have been few studies of these abnormalities in relation to depression. Only a few small studies have been performed, with conflicting data in persons with major depressive disorder (MDD).[3-5,7,8] To our knowledge, the association of 25(OH)D and PTH abnormalities with minor depression or with the severity of depression have not been assessed. Therefore, the present study assesses the association between both major and minor depression and depression severity and serum 25(OH)D and PTH levels in a large population-based study of older adults.

METHODS

The Longitudinal Aging Study Amsterdam is an ongoing cohort study of the predictors and

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consequences of changes in mood, autonomy, and well-being in an aging population in the Netherlands. A random sample of older men and women (age, 55-85 years), stratified by age, sex, urbanization, and expected 5-year mortality, was drawn from the population registers of 11 municipalities in areas in the west, south, and northeast of the Netherlands. A total of 3107 subjects, 99% white, participated in the baseline examination (1992-1993). The sampling and data collection procedures have been previously described in detail.[9,10]

The present study was limited to those participants aged 65 or older (ie, born during or before 1930) (n=2525) who participated in the first follow-up in 1995-1996 (n=1720) and from whom blood could be obtained (n=1285) and 25(OH)D and PTH levels were available (n=1282). Between the first and second cycles, attrition (n=805 [51.7%]) was primarily because of death. Respondents in 1995-1996 who did not participate in the blood-drawing procedure were older ($P<.000$), more often women ($P=.003$), and more often depressed ($P=.008$). Informed consent was obtained from all respondents, and the study was approved by the medical ethics committee of Vrije Universiteit Amsterdam, Amsterdam, the Netherlands.

At the first follow-up in 1995-1996, depression status and depression severity were assessed using the Center for Epidemiologic Studies–Depression (CES-D) scale.[11] Persons scoring above the generally accepted cut-off point for clinically relevant symptoms (CES-D score ≥16) were approached to undergo a diagnostic psychiatric evaluation using the Diagnostic Interview Schedule.[12]

Blood samples were obtained and centrifuged in the morning. Subjects were allowed to have tea and toast but no dairy products. The serum samples were stored at –25°C until assays were performed in 1997-1998. Repeating some of the measurements in 2005 yielded similar results. The serum 25(OH)D concentration was determined using a competitive binding protein assay (Nichols Institute Diagnostics Inc, San Juan Capistrano, California), with an interassay coefficient of variation of 10% and a normal range of 10 to 40 ng/mL (to convert to nanomoles per liter, multiply by 2.496). The serum PTH level was measured using an immune-radiometric assay (Incstar Corp, Stillwater, Minnesota) as described by Pluijm et al,[13] with an interassay coefficient of variation of 7% and a normal range of 0.7 to 7 pg/mL (to convert to nanograms per liter, multiply by 1).

Potentially confounding factors were also measured. Smoking status was classified as current smoker or nonsmoker. We controlled for body mass index (BMI) because Wortsman et al[14] showed that the increase in serum vitamin D_3 after sun exposure was 57% less in obese compared with nonobese subjects. The most common chronic physical illnesses, including stroke, cancer, lung disease, cardiac disease, diabetes mellitus, osteoarthritis, and peripheral artery disease, were measured using self-reports and data from general practitioners.[15] Because mild renal impairment could affect vitamin D and PTH homeostasis, we adjusted for serum creatinine concentration.

Several possible explanatory factors that may explain a link between depression and vitamin D and PTH levels were determined. Because vitamin D status is dependent in part on sunlight exposure, it was recorded whether data were collected in winter, spring, summer, or fall. In addition, the levels of physical activity (total activity or outdoor activities only in minutes per day) and urbanization (number of inhabitants per square kilometer) were assessed as described by Snijder et al.[10] The use of antidepressants was determined because Zhou et al[16] described enhancement of vitamin D catabolism with medication.

All analyses were performed using commercially available software (SPSS for Windows version 14.0; SPSS Inc, Chicago, Illinois). χ^2 Tests were performed to determine differences in age, sex, BMI, smoking status, physical activity, number of chronic conditions, serum creatinine concentration, season when data were collected, and level of urbanization between persons with no depression, minor depression, or MDD. Multiple linear regression analyses were performed to study the associations between depression variables (independent variables) and serum 25(OH)D or PTH levels (dependent variables). Because the distribution of serum PTH was skewed, we used logarithmically transformed values. In addition, we adjusted the regression models for potential confounding variables and, in a separate step, for those potential explanatory variables that were univariately associated with depression status. Potential effect modification by sex was examined by additionally including product terms of hormone levels × sex in the adjusted regression analyses.

RESULTS

Twenty-six persons had a current (1-month recency) diagnosis of MDD according to the Diagnostic Interview Schedule, 169 had minor depression (defined as CES-D score ≥16 but Diagnostic Interview Schedule negative for MDD), and 1087 persons were not depressed (**Table 1**). Compared with nonpressed persons, depressed persons were significantly ($P<.05$) older, were more often women, were more often smokers (MDD only), had higher BMI (MDD only), had more chronic conditions, and more often lived in highly urbanized areas, which underscores the need to consider these factors in the analyses. Creatinine concentration, season of assessment, and physical activity levels did not differ significantly between depressed and nondepressed persons. Only 1% of the participants used low-dose vitamin D or calcium supplements. According to the serum 25(OH)D and PTH levels, this did not influence our results. Less than 1% of the participants (ie, 7 persons with minor depression and 4 with MDD) used antidepressants, which did not influence our results when added to the model (data not shown).

The mean (SD) serum 25(OH)D level was 21 (10) ng/mL (**Figure**, A), and the mean serum PTH level was 3.6 (1.7) pg/mL (Figure, B). The Pearson correlation coefficient between serum 25(OH)D and PTH levels was –0.30 ($P<.001$). In 4.5% of the men and 7.7% of the women, the serum 25(OH)D level was less than 10 ng/mL, indicating a deficient status as defined by Lips.[17] In 38.8% of the men and 56.9% of the women, the serum 25(OH)D level was less than 20 ng/mL, indicating an insufficient status.

The 25(OH)D levels were 14% lower in the 169 persons with minor depression (mean, 19 ng/mL) and 14% lower in the 26 persons with MDD (mean, 19 ng/mL) compared with those in the 1087 nondepressed persons (mean, 22 ng/mL) ($P<.001$). The PTH levels were 5% higher in persons with minor depression (mean, 3.72 pg/mL) and 33% higher in persons with MDD (mean, 4.69 pg/mL) compared with those in nondepressed persons (mean, 3.53 pg/mL) ($P=.003$).

Depression severity (CES-D scale score) was associated with decreased serum 25(OH)D levels ($P<.001$) and increased serum PTH levels according to quartiles of 25(OH)D and PTH levels ($P<.001$; **Table 2**). After adjustment for age, sex, BMI, smoking status, and number

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Table 1. Study Variables Across Depression Status

Variable	No Depression (n = 1087)	Minor Depression (n = 169)	MDD (n = 26)	*P* Value
Age, mean (SD), y	75.1 (6.5)	76.6 (6.5)	77.7 (6.6)	.004
Sex, % female	47.7	71.0	80.8	<.001
Smoker, %	18.1	14.2	34.6	.04
Body mass index, mean (SD),[a]	26.9 (4.1)	26.5 (4.4)	28.6 (4.1)	.04
No. of chronic conditions, mean (SD)	1.2 (1.0)	1.6 (1.2)	1.9 (1.0)	<.001
Serum creatinine concentration, mean (SD), mg/mL	0.08 (0.04)	0.07 (0.04)	0.08 (0.05)	.19
Season when data acquired, %				.21
Winter	26.7	20.7	23.1	
Spring	27.7	23.7	38.5	
Summer	16.1	20.1	19.2	
Fall	29.5	35.5	19.2	
Level of urbanization, No. of inhabitants/km^2, %				.01
<500	20.3	13.0	3.8	
500-1000	22.4	16.6	23.1	
1000-1500	16.8	18.9	7.7	
1500-2500	16.7	22.5	26.9	
>2500	23.6	29.0	38.5	
Physical activity, mean (SD), min/wk	141 (104)	138 (96)	136 (82)	.91

SI conversion factor: To convert serum creatinine to micromoles per liter, multiply by 88.4.
[a] Calculated as weight in kilograms divided by height in meters squared.

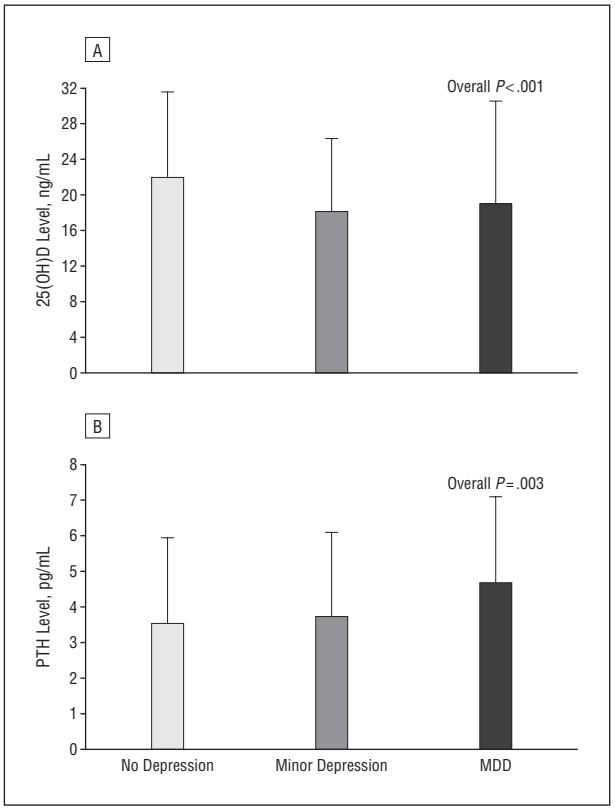

Figure. Serum levels of 25-hydroxyvitamin D [25(OH)D] (A) and parathyroid hormone (PTH) (B). MDD indicates major depressive disorder. Values are given as mean (SD). To convert PTH to nanograms per liter, multiply by 1; 25(OH)D to nanomoles per liter, multiply by 2.496.

of chronic conditions, CES-D scale scores were still associated with decreased 25(OH)D ($P=.01$) and increased PTH levels ($P=.002$). After additional adjustment for level of urbanization, which was the only explanatory variable that differed across depression status, these associations remained significant ($P=.03$ and .008, respectively). Insofar as the link with depressive symptoms, no significant interaction terms were found for sex × 25(OH)D ($P=.70$) or sex × PTH ($P=.82$), indicating that associations were consistent across sex. Additional adjustment for PTH levels did not weaken the association between the CES-D scale score and 25(OH)D level, whereas PTH remained significantly associated with the CES-D scale score after adjustment for the 25(OH)D level.

COMMENT

This large population-based study shows, for the first time, an association of depression status and depression severity with decreased serum 25(OH)D levels and increased serum PTH levels in older subjects. This association was adjusted for the potentially confounding factors of age, sex, BMI, smoking status, and number of chronic conditions and is not explained by differences in season of data acquisition, level of physical activity, or use of antidepressants. Only the level of urbanization had a small explanatory effect, which confirms that decreased light exposure contributes to a decreased serum 25(OH)D level and depression. That the PTH level was also associated with depression after adjustment for the 25(OH)D level suggests that PTH may also have a role in the pathogenesis of depression. This is in accord with the high prevalence of depression in primary hyperparathyroidism.

Low levels of 25(OH)D could be involved in the pathogenesis of depression in several ways. Autoradiography and immunohistochemistry in rodents showed that the target tissues of 25(OH)D are related to exocrine and endocrine secretory and somatotrophic processes rather than to calcium metabolism alone. Moreover, the distribution of target neurons of 25(OH)D suggests an influ-

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Table 2. Results of Regression Analyses for the Association Between Serum Levels of 25(OH)D and PTH With Depression Severity Before and After Adjustment

Variable	Depression Severity (CES-D Scale Score): Unadjusted Coefficient (95% CI)	*P* Value	Coefficient Adjusted for Potential Confounders[a] (95% CI)	*P* Value	Coefficient Additionally Adjusted for Explanatory Variable[b] (95% CI)	*P* Value
25(OH)D						
Continuous level, ng/mL	22.6 (29.5 to 15.8)	<.001	9.6 (16.9 to 2.4)	.01	8.0 (15.2 to 0.8)	.03
Categorical level						
First quartile, ≤14.7 ng/mL	1 [Reference]		1 [Reference]		1 [Reference]	
Second quartile, 14.7-20.4 ng/mL	−1.02 (−2.18 to 0.15)	.09	−0.12 (−1.25 to 1.00)	.83	−0.01 (−1.12 to 1.11)	.99
Third quartile, 20.4-27.4 ng/mL	−2.78 (−3.94 to −1.62)	<.001	−1.19 (−2.36 to −0.02)	.05	−1.09 (−2.25 to 0.07)	.07
Fourth quartile, >27.4 ng/mL	−3.35 (−4.51 to −2.19)	<.001	−1.33 (−2.55 to −0.11)	.03	−1.07 (−2.28 to 0.14)	.08
PTH						
Continuous level, pg/mL	0.49 (0.26 to 0.73)	<.001	0.36 (0.13 to 0.58)	.002	0.30 (0.08 to 0.53)	.008
Categorical level						
First quartile, <2.4 pg/L	1 [Reference]		1 [Reference]		1 [Reference]	
Second quartile, 2.4-3.2 pg/mL	1.20 (0.02 to 2.37)	.05	0.85 (−0.26 to 1.95)	.13	0.73 (−0.37 to 1.82)	.19
Third quartile, 3.2-4.3 pg/mL	1.70 (0.53 to 2.87)	.004	1.14 (0.03 to 2.25)	.05	0.93 (−0.17 to 2.04)	.10
Fourth quartile, >4.3 pg/mL	2.76 (1.59 to 3.93)	<.001	2.02 (0.89 to 3.16)	<.001	1.70 (0.57 to 2.84)	.003

Abbreviations: CES-D, Center for Epidemiologic Studies Depression scale; CI, confidence interval; 25(OH)D, 25-hydroxyvitamin D; PTH, parathyroid hormone.
SI conversion factors: To convert 25(OH)D to nanomoles per liter, multiply by 2.496; PTH to nanograms per liter, multiply by 1.
[a] Age, sex, smoking status, number of chronic conditions, body mass index.
[b] Level of urbanization.

ence of synthesis levels of nerve growth factor,[18] acetylcholine acetylase, serotonin, testosterone, thyroid hormone, and tyrosine hydroxylase messenger RNA,[19,20] which have all been implicated in the pathogenesis of depression in human beings. Recently, vitamin D deficiency restricted to late gestation was found to result in hyperlocomotion in the adult rat, suggesting a role in the pathogenesis of neuropsychiatric disorders.[21] In human beings, the distribution of the vitamin D receptor seems to be similar to that in rodents, with the strongest staining occurring in the hypothalamus,[22] suggesting a role in neuroendocrine functioning. In earlier work, we found that the human hypothalamus is likely implicated in the pathogenesis of depression because a number of neuron types show altered levels of neuropeptides and corresponding gene expression in postmortem brain tissue from depressed patients compared with control subjects.[11,23-26] However, more pathophysiologic research on the vitamin D receptor in the human hypothalamus and eventual alterations in depression is needed to confirm its relevance for the pathogenesis of the disorder.

From the patient's perspective, our findings may be of clinical relevance because the prevalence of minor depression in older persons is high (13%)[1] and both decreased serum 25(OH)D levels and increased serum PTH levels can, in theory, be treated with higher dietary intake of vitamin D_3 or calcium and increased exposure to daylight.[27] Moreover, vitamin D status was found to predict physical performance and its decline in older persons.[28] Vitamin D and PTH status may also be improved indirectly by adequate antidepressant treatment, resulting in increased food intake and activity patterns.[4] Moreover, the clinical relevance of the present study is underscored by our finding that 38.8% of men and 56.9% of women in our community-based cohort had an insufficient vitamin D status.

To date, no reliable data are available on the outcome of vitamin D or light intervention studies in persons with minor depression or MDD, and results in subjects with seasonal affective disorder or healthy subjects with seasonal mood changes are conflicting.[29,30] We did not find an effect of season on 25(OH)D level. Only one trial[31] has shown a significant positive effect of phototherapy on 25(OH)D. In this study, vitamin D medication had a positive effect on both 25(OH)D level and depression severity, but the number of subjects receiving vitamin D was small (n=8) and the data deserve follow-up. Therefore, we suggest that future large-scale intervention studies on, for example, osteoporosis[32] in older persons, use of vitamin D_3, and exposure to daylight, also use mood as an outcome measure.

In conclusion, we found that depression and depression severity, as measured with the CES-D scale, is strongly associated with lower serum 25(OH)D levels and higher PTH levels, even after adjustment for age, sex, BMI, smoking status, health status, level of physical activity, and level of urbanization. Long-term longitudinal studies with repeated assessments should be performed to explore the question of whether decreased 25(OH)D levels and increased PTH levels precede depression or follow it. In other words, are these biological changes a cause or a consequence of depression?

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