Vitamin D Status and Cardiometabolic Risk Factors in Long-Term Psychiatric Inpatients

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ABSTRACT

Objective: Low vitamin D levels are common in psychiatric patients, but a need for vitamin D supplementation in these individuals remains controversial. Low vitamin D levels are reportedly associated with high prevalence of cardiometabolic risk factors, and both are common in psychiatric patients, but the relationship between diagnosis and severity of illness and cardiometabolic risk status and the effect of vitamin D treatment on them is not known. We studied these relationships and effect of vitamin D_3 treatment on them in 290 long-term psychiatric inpatients.

Method: All patients admitted to the hospital during April 2009–March 2010 who agreed to 25-hydroxyvitamin-D testing were included. Serum 25-hydroxyvitamin D level, Brief Psychiatric Rating Scale (BPRS) score, body mass index, blood pressure, and fasting levels of blood glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) were measured at baseline, and changes after vitamin D_3 treatment for up to 12 months were observed. For the purposes of this study, 25-hydroxyvitamin-D levels < 32 ng/mL were considered as "low"; < 20 ng/mL, as "insufficient"; and < 12 ng/mL, as "deficient."

Results: A serum 25-hydroxyvitamin-D level < 32 ng/mL was found in 90.0% of patients, and a level < 20 ng/mL was found in 48.6% of patients. A BPRS score > 36 was present in 56.0% of patients; obesity, in 75.7%; hypertension, in 44.8%; low HDL-C, in 43.6%; high triglycerides, in 31.2%; high LDL-C, in 17.8%; and increased glucose, in 14.6%. Serum 25-hydroxyvitamin-D levels correlated poorly with BPRS score and the other variables listed above (*R*, −0.02 to −0.22). After vitamin D_3 treatment, 25-hydroxyvitamin-D level increased to ≥ 20 ng/mL in all patients and ≥ 32 ng/mL in 85% of patients, but despite > 124% increase in mean 25-hydroxyvitamin-D level, mean improvement in other variables was < 12%.

Conclusions: Nearly half of our patients had vitamin D levels < 20 ng/mL, putting them at risk for poor bone health and requiring vitamin D supplementation. Cardiometabolic risk factors were also highly prevalent, but correlated poorly with vitamin D levels in their severity. Increasing vitamin D levels to ≥ 32 ng/mL was not associated with improvement in BPRS score or any cardiometabolic risk factor, emphasizing that intensification of therapeutic measures other than vitamin D supplementation is required.

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Psychiatric patients have been reported to have lower vitamin D levels than the general population.[1–5] Cardiovascular risk factors including hypertension, diabetes, obesity, and metabolic syndrome have been reported to be associated with vitamin D levels below 32 ng/mL.[6–9] As cardiometabolic risk factors are more common in psychiatric patients than in the general population and are also aggravated by antipsychotic drugs,[10,11] low vitamin D levels may be of added significance in psychiatric patients. The relationship of vitamin D status of psychiatric patients with their diagnosis and severity of psychiatric illness and cardiometabolic risk status has never been reported. This study reports serum 25-hydroxyvitamin-D (25D) levels in long-term patients at a state psychiatric hospital, the relationship of 25D levels with diagnosis and severity of psychiatric illness and demographic and cardiometabolic variables, and the effects on these variables of increasing the levels to ≥ 32 ng/mL.

METHOD

All patients admitted to our hospital during April 2009–March 2010 who agreed to 25D testing were included. All patients treated with vitamin D were followed up approximately every 4 months for up to 1 year. The study was approved by the hospital's institutional review board.

Age, gender, race, blood collection date, and duration of hospital stay on that date were recorded. Patients were grouped as follows according to their primary Axis I diagnosis: (1) schizophrenic disorders (*ICD-9* codes 295), (2) affective disorders (*ICD-9* codes 296), and (3) other psychiatric disorders. Brief Psychiatric Rating Scale (BPRS)[12] scores were used as approximate measures of severity of psychiatric illness. A score of > 36, which would include individuals with at least 3 residual psychiatric symptoms scoring a 5 (moderately severe) or 4 symptoms scoring a 4 (moderate), was considered high. Blood pressure was measured, and body mass index (BMI) was calculated as weight (kg)/height $(m)^2$. Fasting blood samples were tested for glucose, triglycerides, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) at the hospital's clinical laboratories. Measurement of 25D was done by LabCorp, Burlington, North Carolina, using an immunochemiluminometric assay measuring D_2 and D_3 together and reporting total 25-hydroxyvitamin-D.[13]

For purposes of this study, 25D levels < 32 ng/mL were considered as "low"; < 20 ng/mL, as "insufficient"; and < 12 ng/mL, as "deficient." All patients with 25D < 32 ng/mL who agreed to vitamin D treatment were given 4,000 international units (IU) of vitamin D_3 (cholecalciferol) orally once daily. Other treatments were continued as prescribed by the patients' physicians. At the first follow-up, if 25D level was > 40 ng/mL, vitamin D_3 dose was reduced to 2,000 IU/d. At subsequent follow-ups, the dose was further reduced to 1,000 IU if 25D level was > 40 ng/mL, increased to 4,000 IU if 25D level was

Clinical Points

- Low vitamin D levels are reportedly associated with cardiometabolic risk factors such as obesity, hypertension, diabetes, and dyslipidemia, which are known to be common in psychiatric patients.
- Nearly half of long-term hospitalized psychiatric patients had vitamin D levels < 20 ng/mL, putting them at risk for poor bone health, indicating the need for vitamin D screening and supplementation in such populations.
- Cardiometabolic risk factors were also common, but correlated poorly with vitamin D levels. Increasing vitamin D levels to ≥ 32 ng/mL did not improve BPRS score or any cardiometabolic risk factor, suggesting that intensification of therapeutic measures other than vitamin D supplementation is required.

< 32 ng/mL, and continued at 2,000 IU/d if 25D level was 32–40 ng/mL.

Statistical analyses were done and graphs were generated using Microsoft Excel 2007. The Student *t* test was used to compare means, and percentages were compared by 2-tailed 2-proportion *z* test. Significance level was set at < .05. Pearson correlation was performed to explore associations between 25D and other variables.

RESULTS

Prevalence of Vitamin D Deficiency and Other Variables

In the 290 patients tested at baseline (Table 1), a 25D level of < 32 ng/mL was found in 261 (90.0%), < 20 ng/mL in 141 (48.6%), and < 12 ng/mL in 45 (15.5%). Of the cardiometabolic risk factors, obesity (BMI > 25 kg/m^2) was most frequent (75.7%), followed by elevated systolic and/or diastolic blood pressure (44.8%), low HDL-C (43.6%), elevated fasting triglycerides (31.2%), elevated LDL-C (17.8%), and elevated fasting blood glucose (14.6%).

Vitamin D Levels and Other Variables at Baseline

There were 185 patients with schizophrenic disorders, 49 with affective disorders, and 56 with all other psychiatric diagnoses. The mean 25D level (21.2 ng/mL) and prevalence of low 25D (88.6%) in the schizophrenic group were not significantly different from those in the other 2 groups (20.7 and 19.7 ng/mL, and 89.8% and 92.9%, respectively, in the affective disorders and all other psychiatric diagnoses groups).

The sample comprised 102 whites and 188 nonwhites including 177 African-Americans and 11 Hispanics and Asians. The mean ± SD 25D level of the sample was 20.9 ± 9.4 ng/mL, with a range of 4.0–71.6 ng/mL. Baseline 25D values of each patient by age, race, and gender are displayed in Figure 1, and other details are presented in Table 2.

Mean 25D level at baseline was significantly lower ($P < .05$) and prevalence of low 25D (< 32 ng/mL) was significantly higher ($P < .05$) in nonwhites and in patients with a shorter hospital stay (< 12 months) and increased LDL-C (≥ 130 mg/dL). In the group aged < 25 years and in the group with higher BMI (≥ 30 kg/m^2), mean 25D level was significantly lower ($P < .05$), but prevalence of low 25D was not significantly different from those in the 2 older age groups. Mean 25D level was low (< 21.8 ng/mL) and prevalence of low 25D was high (> 85.7%) in all patient groups, but the results were not significantly different in men and women or during summer and winter, or in patients with low and high BPRS scores; normal and increased blood pressure, fasting blood glucose, and fasting triglycerides; or normal and decreased HDL-C levels. There was a weak significant negative correlation of 25D with LDL-C levels ($R = -0.22$, $P < .001$) and a weak significant positive correlation with age ($R = -0.13$, $P = .003$), but no significant correlation with duration of hospital stay, BPRS score, BMI, blood pressure, fasting blood glucose, fasting triglycerides, or HDL-C (Table 2). In summary, patients with low 25D were more often nonwhite and younger, had higher BMI, had higher LDL-C, and had been in the hospital for a shorter period.

Changes in Vitamin D Levels and Other Variables After Vitamin D_3 Treatment

Of the 261 patients with 25D level < 32 ng/mL at baseline, 235 agreed to take vitamin D treatment. Since many patients were discharged from the hospital before their next follow-up and some refused to continue vitamin D treatment or allow follow-up testing, only 145, 90, and 67 patients were available for follow-up at ~ 4, 8, and 12 months after treatment, respectively (Table 3).

Mean baseline 25D level for all 290 patients was 20.9 ng/mL (range, 4.0–71.6 ng/mL). It was < 32 ng/mL in 261, < 20 ng/mL in 141, < 12 ng/mL in 45, and ≥ 32 ng/mL in 29 patients, including 2 patients with > 50 ng/mL (1 patient with 71.6 ng/mL and 1 with 56.1 ng/mL) (Table 4).

Mean 25D level for 261 patients with 25D levels < 32 was 18.8 ng/mL at baseline. Twenty-six of the patients refused vitamin D treatment. Mean baseline 25D level for 235 patients starting treatment was 18.9 ng/mL. In 145 patients completing treatment with vitamin D_3 4,000 IU/d for ~ 4 months, 25D increased to 45.2 ng/mL, an increase of 139% from baseline (Table 4). Of those patients, 119 achieved 25D levels ≥ 32 ng/mL, including 50 equal to or exceeding 50 ng/mL, and the highest level attained was 87.9 ng/mL. But 3 patients remained < 20 ng/mL, and 1 remained < 12 ng/mL (Table 4).

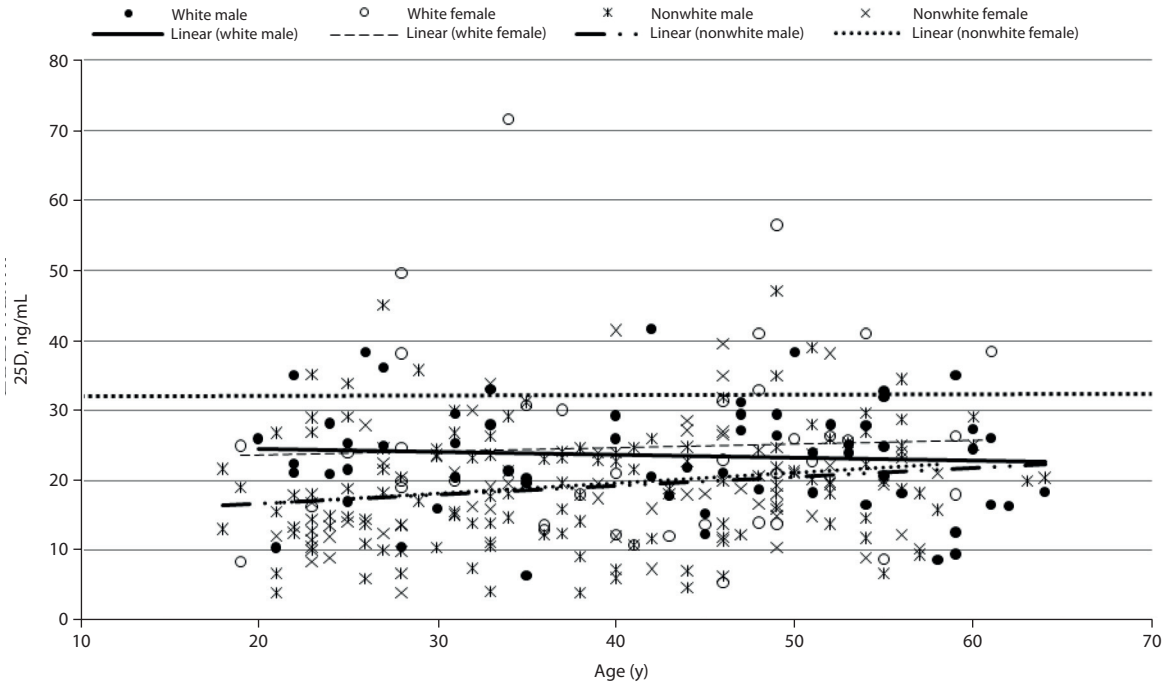
Of the 90 patients completing treatment for ~ 8 months, 55 who had attained 25D > 40 ng/mL at 4-month follow-up maintained their 25D level at ≥ 32 ng/mL even after reducing their vitamin D doses to 2,000 IU/d. However, of the 35 patients whose levels were < 40 ng/mL and who continued on 4,000 IU/d, 9 remained at a 25D level of < 32 ng/mL, and 1 had a level of < 20 ng/mL, but none had a level < 12 ng/mL (Table 4).

Table 1. Prevalence of Low 25-Hydroxyvitamin-D (25D) Level and Other Abnormal Variables at Baseline[a]

Variable	Cutoff for Abnormal Values	Total No. of Patients Tested[b]	No. of Patients With Abnormal Values	Prevalence (%)
25D	< 32 ng/mL	290	261	90.0
	> 20 to < 32 ng/mL[c]	290	120	41.4
	< 20 ng/mL[d]	290	141	48.6
	< 12 ng/mL[e]	290	45	15.5
BPRS score	> 36	241	135	56.0
BMI	> 25 kg/m^2	280	212	75.7
Blood pressure	Systolic > 130 mm Hg and/or diastolic > 85 mm Hg	286	128	44.8
Fasting blood glucose	> 110 mg/dL	287	42	14.6
Fasting triglycerides	> 150 mg/dL	282	88	31.2
HDL-C	Male < 40 mg/dL/female < 50 mg/dL	282	123	43.6
LDL-C	> 130 mg/dL	281	50	17.8

[a]Conversions to SI units are as follows. To convert to mmol/L: glucose × 0.0555, triglycerides × 0.0133, cholesterol × 0.0259. To convert to nmol/L: 25D × 2.496. [b]Numbers differ because some variables were not tested in some patients. [c]Classified as "low" 25D. [d]Classified as "insufficient" 25D. [e]Classified as "deficient" 25D.
Abbreviations: BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol.

Figure 1. Baseline 25-Hydroxyvitamin-D (25D) Levels Versus Age by Race and Gender Showing Poor Overall Correlation ($R = 0.13$) and Nearly Horizontal and Overlapping Trendlines for All Race and Gender Groups[a]



[a]The dotted horizontal line marks 25D level at 32 ng/mL; levels below this were considered low.

Of the 67 patients completing ~12 months' treatment, 35 maintained their 25D level ≥ 32 ng/mL at a dose of 1,000 IU/d of vitamin D_3, and 22 required 2,000 IU/d to maintain this level. Ten patients did not achieve 32 ng/mL even with 4,000 IU/d, but all of them did attain > 20 ng/mL (Table 4).

The mean BPRS score at baseline was 38.7, which did not change significantly after vitamin D treatment. Mean BPRS change from baseline was less than 5%, although in 16.1% of treated patients, BPRS score improved to < 36 at 12-month follow-up (Table 3).

The mean BMI was 30.0 kg/m^2 at baseline, which increased to 31.6, 32.1, and 31.3 kg/m^2, respectively, at ~4-, 8-, and 12-month follow-ups. Very few patients (1.6%) were able to reduce their BMI to normal even after 12 months of vitamin D_3 treatment (Table 3).

Mean systolic and diastolic blood pressure were not significantly different from baseline, and mean change from baseline was < 5% at follow-up points up to 12 months, although 19.1%–24.6% of patients improved their systolic and/or diastolic blood pressure to normal (Table 3).

Table 2. Vitamin D Status of Patients and Correlation With Other Variables at Baseline[a]

Variable	Total No. of Patients	Variable Mean ± SD	Variable Range	Correlation With 25D level R^b	Correlation With 25D level P	25D Level Mean, ng/mL	25D Level P	25D < 32 ng/mL No. of Patients	25D < 32 ng/mL Prevalence (%)	25D < 32 ng/mL z	25D < 32 ng/mL P
25D (ng/mL)											
All	290	20.9 ± 9.4	4.0–71.6	…	…	20.9	…	261	90.0	…	…
Schizophrenic disorder[c]	185					21.2	Ref	164	88.6	Ref	
Affective disorder[d]	49					20.7	.256	44	89.8	0.22	NS
Others[e]	56					19.7	.615	52	92.9	0.90	NS
Race											
White	102					24.0	Ref	86	84.3	Ref	
Nonwhite	188					**19.2**	< .001	175	**93.1**	2.32	< .05
Gender											
Male	199					20.4	Ref	183	92.0	Ref	
Female	91					21.8	.307	78	85.7	1.61	NS
Season											
Summer[f]	265					20.9	Ref	238	89.8	Ref	
Winter[g]	25					21.0	.944	23	92.0	0.35	NS
Age (y)											
All	290	40.0 ± 12.1	18–64	0.13	.03	20.9	…	261	90.0	…	…
< 25 y	36					17.2	Ref	34	94.4	Ref	
25–50 y	184					**21.1**	.011	164	89.1	0.93	NS
> 50 y	70					**22.1**	.003	63	90.0	0.75	NS
Hospital stay (mo)											
All	290	21.0 ± 46.2	0.1–354	0.05	.42	20.9	…	261	90.0	…	…
< 3 mo	121					19.5	Ref	112	92.6	Ref	
≥ 3 to < 12 mo	75					19.8	.838	70	93.3	0.20	NS
≥ 12 mo	94					**23.4**	.002	79	**84.0**	1.89	< .05
BPRS score											
All	241	39.5 ± 12.1	22–80	0.10	.12	20.5	…	219	90.9	…	…
< 36	106					20.2	Ref	94	88.7	Ref	
≥ 36	135					20.8	.612	125	92.6	1.02	NS
BMI (kg/m^2)											
All	280	29.6 ± 6.5	15.6–60.2	−0.12	.61	20.8	…	254	90.7	…	…
< 25	68					22.2	Ref	60	88.2	Ref	
≥ 25 to < 30	126					21.5	.650	116	92.1	0.85	NS
≥ 30	86					**18.7**	.023	78	90.7	0.48	NS
Blood pressure (mm Hg)											
Systolic, all patients	286	125 ± 52.6	86–172	−0.02	.70	20.9	…	257	89.9	…	…
Diastolic, all patients	286	78 ± 9.7	53–110	…	…	20.9	…	257	89.9	…	…
Systolic ≤ 130 mm Hg and/or diastolic ≤ 85 mm Hg	158					20.9	Ref	142	89.9	Ref	
Systolic > 130 mm Hg and/or diastolic > 85 mm Hg	128					20.9	.959	115	89.8	0.01	NS
Fasting blood glucose (mg/dL)											
All	287	90 ± 22.6	50–186	−0.09	.13	20.9	…	258	89.9	…	…
< 110 mg/dL	245					21.4	Ref	219	89.4	Ref	
≥ 110 mg/dL	42					18.2	.051	39	92.9	0.69	NS
Fasting triglycerides (mg/dL)											
All	282	130 ± 75.4	29–478	−0.10	.10	21.0	…	254	90.1	…	…
< 150 mg/dL	194					21.1	Ref	171	88.1	Ref	
≥ 150 mg/dL	88					20.7	.710	83	94.3	1.59	NS
HDL-C (mg/dL)											
All	282	46 ± 12.5	23–84	−0.06	.28	20.9	…	253	89.7	…	…
Male ≥ 40 mg/dL/female ≥ 50 mg/dL	170					20.6	Ref	146	85.9	Ref	
Male < 40 mg/dL/female < 50 mg/dL	123					21.2	.569	107	87.0	0.26	NS
LDL-C (mg/dL)											
All	281	98 ± 28.6	34–219	−0.22	< .001	20.9	…	252	89.7	…	…
< 130 mg/dL	243					21.6	Ref	215	88.5	Ref	
≥ 130 mg/dL	50					**16.3**	< .001	37	**74.0**	2.62	< .01

[a]Boldface indicates values significantly different from reference values. [b]Pearson correlation coefficient. [c]*ICD-9* code 295. [d]*ICD-9* code 296. [e]All other psychiatric diagnoses. [f]April–October. [g]November–March.

Abbreviations: 25D = 25-hydroxyvitamin-D, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, ref = reference group.

Mean fasting blood glucose increased significantly from 90.2 mg/dL at baseline to 96.4 mg/dL, 97.4 mg/dL, and 96.6 mg/dL at ~4, 8, and 12 months, respectively ($P < .04$). Mean increase was 6.8%, 8.0%, and 7.1%, and 5.2%, 6.8%, and 10.6% of patients had normalized levels at ~4-, 8-, and 12-month follow-up, respectively (Table 3).

Fasting triglycerides, HDL-C, and LDL-C showed no significant improvement from baseline except that mean HDL-C increased significantly from 47.8 mg/dL at baseline to 50.8 mg/dL at 8 months ($P < .03$), but at 12-month follow-up it was 45.9 mg/dL, which was not significantly different from baseline (Table 3).

Table 3. Variables at Baseline and Changes After Treatment With Vitamin D_3[a]

Variable	No. of Patients[b]	Mean Value of Variable	*P*[c]	Mean % Change in Variable Compared to Baseline	Patients With Variable Normalized, %[d]
25D (ng/mL)					
Baseline	235	18.9	Ref	Ref	…
4 mo	145	**45.2**	<.001	139.2	82.1
8 mo	90	**44.5**	<.001	135.7	90.0
12 mo	67	**42.3**	<.001	124.2	85.1
BPRS score					
Baseline	198	38.7	Ref	Ref	…
4 mo	127	38.4	.84	−0.7	20.5
8 mo	82	42.2	.03	9.1	17.1
12 mo	62	40.1	.38	3.6	16.1
BMI (kg/m^2)					
Baseline	230	30.0	Ref	Ref	…
4 mo	131	**31.6**	.02	5.4	0.8
8 mo	87	**32.1**	.01	7.0	0.0
12 mo	62	31.3	.12	4.4	1.6
Blood pressure, systolic (mm Hg)					
Baseline	232	125.0	Ref	Ref	…
4 mo	131	123.7	.40	−1.0	19.1
8 mo	86	125.2	.86	−0.2	20.9
12 mo	65	126.5	.39	1.2	20.0
Blood pressure, diastolic (mm Hg)					
Baseline	232	77.9	Ref	Ref	…
4 mo	131	76.0	.07	−2.5	20.6
8 mo	86	77.7	.81	−0.4	23.3
12 mo	65	77.3	.67	−0.8	24.6
Fasting blood glucose (mg/dL)					
Baseline	233	90.2	Ref	Ref	…
4 mo	135	**96.4**	.01	6.8	5.2
8 mo	88	**97.4**	.03	8.0	6.8
12 mo	66	**96.6**	.02	7.1	10.6
Fasting triglycerides (mg/dL)					
Baseline	229	137.1	Ref	Ref	…
4 mo	134	146.6	.31	6.9	8.2
8 mo	88	149.1	.26	8.8	10.2
12 mo	67	144.7	.49	5.5	10.4
HDL-C (mg/dL)					
Baseline	229	45.3	Ref	Ref	…
4 mo	135	47.8	.10	5.5	0.0
8 mo	87	**50.8**	.02	11.9	14.9
12 mo	66	45.9	.77	1.3	7.6
LDL-C (mg/dL)					
Baseline	228	100.1	Ref	Ref	…
4 mo	134	100.9	0.80	0.8	3.7
8 mo	87	97.8	0.51	−2.2	5.7
12 mo	66	98.5	0.68	−1.5	1.5

[a]Boldface indicates values significantly different from reference values. [b]Includes only patients who were treated with vitamin D_3 and had the variable measured. [c]*P* compared to mean value of variable at baseline. [d]Normal 25D is ≥ 32 ng/mL. Cutoffs for abnormal values for other variables are as in Table 1.

Abbreviations: 25D = 25-hydroxyvitamin-D, BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, ref = reference group.

DISCUSSION

Prevalence and Severity of Vitamin D Deficiency

To our knowledge, this is the first report of vitamin D status of long-term hospitalized psychiatric patients in the United States. The 2010 report of the Food and Nutrition Board of the Institute of Medicine (IOM)[14] concluded that persons are "at risk of deficiency of vitamin D at serum 25D of < 12 ng/mL, and that ≥ 20 ng/mL is sufficient for > 97.5% of the American population for skeletal health." As shown in Table 1, nearly half of our patients had 25D levels < 20 ng/mL, which may not be sufficient in vitamin D for skeletal health. Some authorities have suggested that a minimum 25D level of 32 ng/mL may be required to meet nonskeletal needs for vitamin D,[15,16] but according to IOM,[14] evidence for this is inconclusive. Therefore, the significance of a 25D level of ≥ 20 but < 32 ng/mL in 120 (or 41.4%) of our patients at baseline (Table 1) is uncertain.

The mean baseline 25D level in this study was 20.9 ± 9.4 ng/mL (Table 2), which was lower than the levels found in other studies: 24 ng/mL, found in a nationally representative sample of American adults (National Health and Nutrition

Table 4. Vitamin D_3 Doses and Changes in 25-Hydroxyvitamin-D (25D) Level

Vitamin D_3 Dose, IU/d	No. of Patients	Time of 25D Testing	25D Level, Mean ± SD, ng/mL	25D Level, Range, ng/mL	25D Level, No. of Patients				
					< 12 ng/mL	< 20 ng/mL	< 32 ng/mL	≥ 32 ng/mL	≥ 50 ng/mL
290 Patients had 25D measured									
…	290	Baseline	20.9 ± 9.4	4.0–71.6	45	141	261	29	2
261 Patients had 25D < 32 ng/mL									
…	261	Baseline	18.8 ± 6.8	4.0–31.9	45	141	261	0	0
235 Patients started vitamin D_3 treatment at baseline									
4,000	235	Baseline	18.9 ± 6.8	4.0–31.9	40	126	235	0	0
145 Patients completed treatment up to first follow-up (~4 mo after baseline)									
4,000	145	Baseline	19.3 ± 6.9	4.0–31.9	22	75	145	0	0
	145	First follow-up	45.2 ± 13.7	10.0–87.9	1	3	26	119	50
90 Patients completed treatment up to second follow-up (~8 mo after baseline)									
2,000	55	Baseline	21.1 ± 6.9	4.0–31.9	4	23	55	0	0
	55	Second follow-up	51.0 ± 8.2	40.2–71.6	0	0	0	55	26
4,000	35	Baseline	19.4 ± 5.7	9.5–31.4	4	16	35	0	0
	35	Second follow-up	34.3 ± 4.7	18.1–40.0	0	1	9	26	0
67 Patients completed treatment up to third follow-up (~12 mo after baseline)									
1,000	35	Baseline	22.0 ± 5.4	10.8–31.9	1	12	35	0	0
	35	Third follow-up	49.6 ± 8.5	40.1–76.7	0	0	0	35	14
2,000	22	Baseline	20.7 ± 7.2	4.0–29.5	2	8	22	0	0
	22	Third follow-up	37.3 ± 2.4	32.0–39.9	0	0	0	22	0
4,000	10	Baseline	21.5 ± 7.5	9.5–31.4	2	3	10	0	0
	10	Third follow-up	28.1 ± 2.8	21.9–31.5	0	0	10	0	0

Examination Survey [NHANES]-2004)[17]; 26.1 ng/mL, found in residents of southern Arizona[18]; and 67.7 nmol/L (27.1 ng/mL), found in a survey of the Canadian population.[19] The level was higher in our psychiatric patients than in general medical inpatients of an acute care hospital in Boston, Massachusetts[20] (15.9 ng/mL), a general medical hospital in Italy[21] (13.1 ng/mL), and in psychiatric inpatients and outpatients in Norway[8] (43.1 nmol/L, or 17.2 ng/mL) and Australia[7] (46.4 nmol/L, or 18.5 ng/mL). All 17 psychiatric inpatients in one London hospital[22] (< 25 nmol/L, or < 10 ng/mL) and 11 of 12 psychiatric inpatients in another London hospital[9] (< 20 ng/mL) were found deficient in vitamin D. In our patients, the prevalence of low 25D was not as high, since only 48.6% of them had 25D levels < 20 ng/mL (Table 1). Some of these differences may be due to differences in methods for 25D assay used at different laboratories.[23]

Vitamin D Deficiency and Demographic Characteristics

Our findings of lower mean 25D and higher prevalence of low 25D in nonwhites compared to whites were similar to those reported in 2 US national surveys (NHANES 1988–2001 and NHANES 2001–2004),[17] but, unlike these surveys, our study found no significant difference between males and females and lower mean 25D level in younger (< 25 years) than in older age groups (Tables 2 and 3). The latter finding may be due to the small number of patients younger than 25 years at our hospital or related to their shorter length of hospital stay. We found that patients who had been in the hospital for > 12 months had a significantly higher mean 25D level and lower prevalence of low 25D than those who were in the hospital for < 3 months (Table 2). This may be due to their healthier lifestyle with regard to diet and physical activity in the controlled environment of the long-term psychiatric hospital compared to the lifestyle of those outside, but it was not enough to increase their mean 25D level to ≥ 32 ng/mL. In the NHANES surveys, mean 25D concentrations were significantly higher in summer than in winter,[24] but we found no significant difference in mean 25D level or prevalence of low 25D between the 2 seasons (Tables 2 and 3). This may be due to the small number (25 of 290) of patients who had their baseline 25D level tested in the winter in this study, and perhaps also because their levels of physical activity and exposure to sun were not very different in the 2 seasons in the moderate climate of the area.

Vitamin D Deficiency and Cardiometabolic Risk Factors

As shown in Table 2, prevalence of cardiometabolic risk factors was high among our patients, especially obesity, hypertension, low HDL-C, and high fasting triglycerides. Elevated LDL-C and fasting blood glucose were also common but relatively less frequent. Several investigators have reported association of low vitamin D levels with obesity,[4] hypertension,[25] diabetes,[26] and dyslipidemias.[27] We also found decreased mean 25D levels in cases with obesity, diabetes, and increased LDL-C, but not hypertension, and there was no significant correlation between the severity of the associated risk factors and degree of 25D deficiency. This makes it unlikely that low vitamin D levels played a significant role in the causation of these risk factors.

Vitamin D_3 Doses and Correction of Vitamin D Deficiency

Optimal vitamin D_3 doses needed to correct low 25D are not established. Doses reported in the literature vary from 600,000 IU intramuscular once per year[28] to 1,000 IU orally once daily.[17] The tolerable upper limit for safe vitamin D_3 administration proposed by the IOM Food and Nutrition Board in 1997 is 2,000 IU/d, but a review[29] based on data

published later, in 2007, concluded that doses up to 10,000 IU/d cause no toxic effect. We chose to start at a dose of 4,000 IU/d and decrease it to 2,000 and then 1,000 IU/d depending on response. We found that patients with lower 25D levels at baseline generally required higher doses of vitamin D_3 for longer periods to normalize their 25D level, but the dose response was quite variable and unpredictable in many cases.

All of our patients attained 25D levels of ≥ 20 ng/mL, and 57 of the 67 patients who completed treatment for ~ 12 months achieved ≥ 32 ng/mL, but 10 patients remained at levels < 32 ng/mL (Table 4). The reasons for poor response may be insufficient vitamin D doses or noncompliance with medication, increased catabolism of vitamin D in liver by drugs (eg, barbiturates, phenytoin, glucocorticoids), decreased hepatic synthesis of 25D in advanced liver disease, intestinal malabsorption of vitamin D by disease or drugs such as orlistat or cholestyramine, or excessive loss of 25D in urine in nephrotic syndrome.[6] Of the 10 patients who showed poor response, 1 had nephrotic syndrome, 2 were taking orlistat, and 5 had their vitamin D_3 dose reduced at the previous follow-up (from 2,000 IU to 1,000 IU/d in 2 patients and from 4,000 IU to 2,000 IU/d in 2 patients), and in 2 patients the reason could not be determined.

No patient developed hypercalcemia, and the maximum 25D level attained by any patient at any time during treatment was 87.9 ng/mL, well below the level of 150 ng/mL that is generally considered safe.[30] However, there are reports of 25D > 89 ng/mL in 59.4% of cases of ischemic heart disease versus 22.1% of controls[31] and a 2-fold increased risk of pancreatic cancer associated with 25D > 100 nmol/L (or > 40 ng/mL),[32] and, because of such reports, IOM[14] has expressed concern about undesirable long-term effects at serum 25D levels above 50 ng/mL. Nearly half of our prompt responders to vitamin D_3 at every follow-up had 25D ≥ 50 (Table 4), requiring reduction of their vitamin D_3 doses. Among the 29 patients with 25D ≥ 32 at baseline who were not treated with vitamin D, 2 had 25D > 50 ng/mL. Whether any intervention to reduce 25D to < 50 ng/mL is required in such patients is not known.

Correction of Vitamin D Deficiency and Improvement in Cardiometabolic Risk Factors

One systematic review concluded that vitamin D supplementation may reduce cardiovascular disease mortality,[33] another found no significant effect on cardiometabolic outcomes,[34] and a third review was inconclusive.[35] We found that although low vitamin D levels occurred frequently together with many cardiometabolic risk factors and 25D increased by > 124% by vitamin D_3 supplementation, there was no significant improvement in any of the cardiometabolic risk factors studied, and some (eg, BMI and fasting blood glucose) worsened even as 25D improved (Table 3). Jorde et al[36] also found no improvement in cardiovascular risk factors after correction of low 25D by vitamin D_3 for 1 year. It is noteworthy that Tzotzas et al[37] found that lipid levels and insulin resistance improved significantly after 10% reduction in BMI due to a 20-week low-calorie diet, and mean 25D level also improved from 15.4 ng/mL at baseline to 18.3 ng/mL at the end of study even without vitamin D supplementation. Prospective cohort studies from the United States[38] and Europe[39] have found independent associations of low 25D with cardiovascular mortality. Our findings and those of other studies cited above[34,36,37] suggest that if vitamin D deficiency affects cardiovascular disease and mortality, it is probably by mechanisms other than by improving these risk factors. Large randomized controlled trials such as those currently underway[40] may resolve these issues.

This study documents for the first time the lack of correlation between degree of decrease in 25D and diagnosis or severity of psychiatric illness or cardiometabolic risk factors. The long-term hospital setting provided us the opportunity to treat patients with vitamin D and follow them for up to 12 months. However, the number of patients completing treatment for 12 months was small, and this study was not a randomized controlled trial planned primarily to study treatment effect. Most of the patients achieved 25D levels > 20 ng/mL after ~ 4 months of receiving vitamin D_3 4,000 IU/d, and it is possible that for many of them doses of 600–800 IU/d, as recommended by IOM,[14] may have been sufficient. However, many patients needed doses of 2,000 or 4,000 IU/d for longer periods, and a few did not reach 32 ng/mL even at a dose of 4,000 IU/d, while others reached > 50 ng/mL on smaller doses, indicating that response to oral vitamin D_3 is not uniform (Table 4). Additional research is needed to determine any benefit of increasing 25D levels to ≥ 32 ng/mL and the optimum dose and duration of vitamin D treatment to achieve and maintain a 25D level appropriate for both skeletal and extraskeletal health without causing long-term untoward effects.

In conclusion, in this study of vitamin D status of long-term psychiatric inpatients, low 25D was common, and the patients' mean 25D level was lower than those reported in the general population in the United States, Canada, and Europe, but higher than in acute general medical patients in the United States and in psychiatric patients in Norway, Australia, and the United Kingdom. There was no correlation between 25D levels and either diagnosis or severity of psychiatric illness. Cardiometabolic risk factors including obesity, hypertension, diabetes, and dyslipidemias were also highly prevalent, but their severity did not correlate with severity of low 25D. Correction of low 25D was easy, inexpensive, and without side effects over the course of 1 year of follow-up, but the doses of vitamin D_3 required were variable, and correction of low 25D was not associated with significant improvement in BPRS score or any cardiometabolic risk factor. These findings suggest that while vitamin D supplementation may be of questionable value in improving patients' psychiatric illness or cardiometabolic risk factors, nearly half of these patients had 25D levels < 20 ng/mL, putting them at risk of vitamin D insufficiency for bone health and requiring vitamin D supplementation.

Drug names: cholestyramine (Locholest and others), orlistat (Xenical), phenytoin (Dilantin, Phenytek, and others).

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