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Original Article

Children and Adolescents with Severe Mental Illness Need Vitamin D Supplementation Regardless of Disease or Treatment

Olivier Bonnot, M.D., Ph.D.,[1] Rachida Inaoui, M.D., Ph.D.,[2] Marie Raffin-Viard, M.D.,[1] Nicolas Bodeau, M.Sc.,[1] Christiane Coussieu, M.D., Ph.D.,[3] and David Cohen, M.D., Ph.D.[1]

Abstract

Background: To protect against osteoporosis, keeping the vitamin D blood level (25[OH]D; VDBL) above 30 ng/mL is recommended.. It is established that regular intake of vitamin D, calcium intake, and physical exercise contribute to maximizing bone mineral mass during childhood and adolescence. Recent articles suggest that patients with schizophrenia treated with antipsychotics have low VDBL and may have a higher risk of hip fractures in their later years than the general population.
Objectives: To evaluate whether adolescent psychiatric inpatient VDBL is lower than the 30-ng/mL optimal threshold and to document low-VDBL risk factors.
Method: We determined the VDBL of all consecutive inpatients from three adolescents units in 2009 ($N = 136$). Univariate analyses explored the influence on VDBL of (1) well-documented risk factors (e.g., age, gender, ethnic origin, body mass index, or season) and (2) suspected risk factors (e.g., disease type or antipsychotic treatment).
Results: All but six patients had a VDBL <30 ng/mL (mean [± SD]: 15.9 [± 8.4] ng/mL). VDBL was significantly lower for all patients during the first quarter of the year compared to the other three (all $p < 0.01$). VDBL was also lower for blacks/North Africans 12.8 (±7.0) than for Caucasians/Europeans 17.2 (±8.5): $t = 2.62$, $p = 0.009$. We found no differences between patients regarding disease category ($K = 3.75$, $p = 0.154$) or antipsychotic treatment ($t = 0.127$, df = 124, $p = 0.89$).
Conclusion: VDBL in an adolescent population with severe mental illness is lower than current recommendations of optimal level for bone health regardless of treatment or disease type. Because adolescence is a period of bone construction and could represent a critical window of opportunity for maximizing bone mass, especially among patients with severe mental illness, we recommend vitamin D supplementation.

Introduction

Prolactin-increasing antipsychotics (APs) have been suggested as a risk factor for osteoporosis (Hummer et al. 2005; O'Keane and Meaney 2005; Halbreich 2007). Moreover, patients treated with APs may also be exposed to other osteoporosis risk factors such as lack of sun exposure, poor nutrition, excessive weight, or alcohol or tobacco abuse. Given that osteoporosis is a pediatric-determined disease with a geriatric onset, adolescent patients with psychiatric diseases are of special interest.

Vitamin D and calcium supplementation in childhood is recommended for bone construction and osteoporosis prevention (Bonjour et al. 1997). Vitamin D supplementation throughout childhood and adolescence optimizes bone-mass peak (which usually occurs between 20 and 30 years of age). Disturbances in bone constitution, which may occur during adolescence, are known risk factors for osteoporosis, may lead to hip fracture, and are a major public health issue. Keeping one's vitamin D blood level (25[OH]D; VDBL) >30 ng/mL (Dawson-Hughes et al. 2005) may protect against osteoporosis in elderly men and women. Indeed, results from several studies have suggested that vitamin D has positive effects on bone growth during adolescence (Valimaki et al. 2004; Hogstrom et al. 2006).

Risk factors for osteoporosis include age and bone mineral density (BMD) (Klotzbuecher et al. 2000; Kanis et al. 2001). Documented risk factors for low BMD and osteoporosis include the following: low physical activity, low calcium intake, smoking addiction, dark skin, and low sunlight exposure. Sunlight plays a key role in vitamin D metabolism. Upon contact with skin, the ultraviolet spectrum of sunlight facilitates the conversion of

[1]Child and Adolescent Department and Reference Center for Rare Disease with Psychiatric Expression, Groupe Hospitalier Pitié Salpétriere, Assistance Publique Hopitaux de Paris, Paris, France.
[2]Department of Rheumatology, Groupe Hospitalier Pitié Salpétriere, Assistance Publique Hopitaux de Paris, Paris, France.
[3]Department of Biochemistry, Endocrinology and Metabolism, Groupe Hospitalier Pitié Salpétriere, Assistance Publique Hopitaux de Paris, Paris, France.

7-dehydrocholesterol present in the skin cells to pro-vitamin D, which undergoes thermal isomerization to become vitamin D3. Successive hydroxylations of vitamin D3 in the liver and kidney lead to active 1,25(OH)2D3. Exogenous vitamin D2, available through nutritional supplements, is hydroxylated in a similar manner. Vitamin D is necessary for calcium absorption in the intestine. Measuring the storage of 25(OH)D, which is related to vitamin D activity, is relevant. The current consensus regarding 25(OH)D blood level threshold recommends over 30 ng/mL (or 75 mmol/L), although some studies suggest a threshold of 20 ng/mL may be sufficient. Moreover, recent data suggest that positive effects of vitamin D go beyond bone demineralization prevention: Vitamin D may prevent some forms of cancer, autoimmune disease, or diabetes.

Adolescent patients with severe mental illness such as schizophrenia, pervasive developmental disorders, borderline personality disorder, and severe mood disorders may be at risk for low vitamin D (Bonnot et al. 2009). For example, BMD decreases are frequent in patient with schizophrenia (Halbreich 2007), who frequently have alcohol or tobacco dependence (Abraham et al. 1995), low levels of physical activity, and insufficient sun exposure (Halbreich and Palter 1996).

In addition to weight gain, chronic antipsychotic treatment may disturb bone phosphocalcic regulation. Hummer et al. showed that treated adult patients with schizophrenia have low VDBLs (Hummer et al. 2005). In a hospital database of 16,341 patients with hip fractures, Howard et al. (2007) showed that relative risk for hip fracture in the elderly was twice as high in patients with history of antipsychotic treatment compared with patients matched in age, sex, and medical history who had not been treated for mental illness. Exposure to prolactin-raising APs was associated with hip fracture ($p = 0.042$), independent of schizophrenia diagnoses and with a relative risk of 2.6 (95% CI: 2.43–2.78).

The aim of the current study was to (1) measure the 25(OH)D blood level in adolescent patients with severe psychiatric conditions and (2) assess whether antipsychotic prescriptions are associated with low VDBLs.

Method

Participants

All inpatients from the Child and Adolescent Psychiatric Department of La Salpêtrière University Hospital admitted from January 1 to December 31, 2009, participated. The department is the largest facility for child and adolescent psychiatry in the Paris area (35 beds for adolescents; 15 for children); 150 adolescent inpatients are admitted each year. We excluded patients with eating disorders that can induce vitamin D deficiency. Our university ethics committee approved this study.

Variables

We prospectively recorded patients' sociodemographic data, skin color [Caucasian or North African or black (Cavalli-Sforza et al. 1994)], treatment, body mass index (BMI), blood results, and date of sample collection. Type of disease was assessed according to International Classification of Disease, 10th Revision. We divided participants' disorders into three categories: (1) psychotic spectrum disorders, including schizophrenia, schizoaffective disorder, psychotic disorder unspecified, organic psychotic disorder, and mood disorders with psychotic features; (2) developmental conditions, including pervasive developmental disorders, intellectual disabilities, and other developmental neuropsychiatric conditions; and (3) other illnesses, including borderline personality disorder, conduct disorder, adaptation disorder, and mood disorder with no psychotic features.

All 25(OH)D measurements were performed in the same laboratory in our hospital, using electrochemiluminescent immunoassay of total 25(OH)vitamin D (Liaison DiaSorin, Stillwater, MN). This assay measures serum 25(OH)D2 and 25(OH)D3 equally well. Intra- and interassay coefficients of variation were $<8\%$ and $<13\%$, respectively.

Data analysis

All statistical analyses were performed using R 2.7 (The R Foundation for statistical computing). Spearman's rank correlation coefficient calculated relationships between vitamin D levels and continuous variables such as age, duration of treatment, and BMI. After taking into account age and BMI, univariate analyses compared 25(OH) D levels in the adolescent inpatient sample within sex (female vs. male), ethnic origin (Caucasian vs. North African), disease type (Group 1 vs. Group 2 vs. Group 3), and APs (treated vs. untreated). In a complementary analysis, we compared patients treated with risperidone to patients treated with other APs. Student's *t*-test made two-group comparisons when the data were normally distributed (with a Welch correction in cases of heteroscedasticity); otherwise, we used the Mann–Whitney test. The Kruskal–Wallis test made three-group comparisons. We used the quarter of the year as a proxy measure for the effect of sun exposure. Following a linear regression on a logarithm-transformed dependant variable to normalize residuals, a contrast analysis determined whether season influenced vitamin D level. All tests were two-tailed; we considered $p \leq 0.05$ significant.

Results

In 2009, 136 out of 146 admitted patients were enrolled in the study. Of the 10 patients not included, seven stayed <48 hours, one participant's data were lost, and two patients had anorexia nervosa. The final sample included 105 males and 31 females aged 13.8 ($\pm$2.8) years on average. Fifty-one patients were treated with APs. Other medications included antidepressants (primarily serotonin reuptake inhibitor, 15%), benzodiazepine (7%), or mood stabilizers (4%); given the low rates, other medications than AP were not taken into account. None of our patients had undergone vitamin D substitutive treatment.

Table 1 summarizes vitamin D levels according to sex, ethnicity, disease category, and AP treatment. Overall, 25(OH)D levels were remarkably low (mean $\pm$ SD = 15.9 $\pm$ 8.4 ng/mL), for both males and females. Moreover, only six patients (4.5%) had a vitamin D level > 30 ng/mL, whereas 97 patients (72.4%) had levels <20 ng/mL.

Regarding documented vitamin D deficiency risk factors, we found no differences between males ($n = 105$) and females ($n = 29$) regarding 25(OH) D blood levels ($w = 1552.5$, $p = 0.65$). We also did not find significant correlations between age (range 6–25, although 114 out of 136 participants [85%] were between 10–17) and 25(OH) D levels ($r_s = 0.12$, $p = 0.886$), nor did we find significant correlations between BMI and 25(OH) D blood levels ($r_s = -0.13$; $p = 0.179$). As expected, we found a significant difference between ethnicity [blacks/North Africans (Cavalli-Sforza et al. 1994) vs. Caucasians*] and 25(OH) D blood levels ($t = 2.62$; $df = 130$;

*We only had 7 black-skinned patients and they were included in the Caucasoid group ($n = 31$).

Table 1. Serum 25-OH-Vitamin D Level (Mean ± SD) in Adolescent Psychiatric Inpatients ($N = 136$) According to Sex, Ethnicity, Disease Category, and Antipsychotic Treatment

	Age (years)	*Body mass index (kg/m^2)*	*Serum 25(OH)D level (ng/mL)*
Sex			
Female ($n = 31$)	15.2 + 1.4	23.9 + 5.0	16.9 + 10.2
Male ($n = 105$)	13.4 + 3.0	20.7 + 5.1	15.9 + 7.9
	$t = 4.61$, $p = 0$[a]	**$t = 2.68$, $p = 0.009$**[b]	$t = 0.56$, $p = 0.574$[b]
Ethnicity			
Caucasian ($n = 101$)	14.0 + 2.3	21.2 + 5.6	17.2 + 8.5
Black/North African ($n = 35$)	13.3 + 4.1	22.1 + 3.7	12.8 + 7.0
	$t = 0.85$, $p = 0.4$[a]	$t = -0.91$, $p = 0.365$[a]	**$t = 2.62$, 0.009**[b]
Disease category			
Psychosis ($n = 31$)	15.5 + 3.5	22.6 ± 5.9	17.9 + 6.6
Developmental ($n = 29$)	13.0 + 2.9	21.0 + 5.0	16.6 + 9.2
Other ($n = 76$)	13.5 + 2.4	21.3 + 5.3	13.8 + 7.8
	$F = 9.56$, $p = 0.002$[c]	$K = 2.21$, $p = 0.331$[d]	$K = 3.75$, $p = 0.154$[d]
Treatment			
Antipsychotics ($n = 51$)	13.9 + 3.1	22.7 + 5.8	14.5 + 8.6
No antipsychotics ($n = 85$)	13.7 + 2.4	19.8 + 3.8	17.7 + 9.2
	$F = 1.32$, $p = 0.19$[b]	**$t = 2.11$, $p = 0.038$**[b]	$t = -0.13$, $p = 0.889$[b]

[a]*t*-test (Welch correction).
[b]*t*-test.
[c]Analysis of variance (ANOVA).
[d]Kruskal–Wallis test.
Boldface numbers denote statistically significant values.

$p = 0.0099$). After linear regression on a logarithm-transformed dependent variable to normalize residuals, a contrast analysis revealed a significant difference between the first quarter (January to March mean = 12.87 + 8.9) and the following three quarters (Table 2).

Regarding treatment, we found no differences between patients treated with APs and patients who were not treated with APs ($t = 0.127$, df = 124, $p = 0.89$). Similarly, we found no differences for 25(OH)D levels between patients taking risperidone and patients taking other APs (aripiprazole, olanzapine, or clozapine; Kruskal–Wallis chi-squared = 2.74, df = 2; $p = 0.253$). We found no significant correlation between treatment duration and 25(OH) D levels ($r_s = -0.04$, $p = 0.757$). Finally, we found a significant difference between patients taking APs and those who were not with regard to BMI (22.6 + 6.0 vs. 20.5 + 4.4 respectively; $t = 2.11$, $p = 0.038$).

Table 2. Vitamin D Level (Mean ± SD) in Adolescent Psychiatric Inpatients ($N = 136$) Based on Blood Sample Time Period

	Mean	*Standard deviation*	*Number of subjects*
Vitamin D level			
T1 (1/1 to 31/3)	12.87	8.9	37
T2 (1/4 to 30/6)	16.06	8.2	59
T3 (1/7 to 30/9)	18.32	7.4	18
T4 (1/10 to 31/12)	19.13	7.8	22
Statistical analysis[a] *between quarters*			
Quarter contrasts	*t*-value	*p*-Value	
T1	T2	2.660	**0.008779**
T1	T3	2.918	**0.004149**
T1	T4	3.499	**0.000638**
T2	T3	1.079	0.28254
T2	T4	1.538	0.12643
T3	T4	0.270	0.78757

[a]Contrast analysis after linear regression of the logarithm-transformed dependant variable.
Boldface numbers denote statistically significant values.

Discussion

The main finding of this study is that adolescents with severe mental illness (i.e., who need full time hospitalization) showed a VDBL (25(0H)D) deficiency; 95.5% of patients had a VDBL <30 ng/mL, the consensus level for good bone health. This deficiency was significant regardless of antipsychotic treatment, duration of treatment, or disease type.

To our knowledge, no previous study has examined VDBL in an adolescent psychiatric population; however, this result is in line with previous studies finding that 50% of adult psychiatric patients had low 25(OH)D levels (Hummer et al. 2005). In this previous study, the authors used a lower laboratory reference level (i.e., 20 ng/mL rather than 30 ng/mL). However, even had we chosen 20 ng/mL as the reference level, 72.4% of the adolescent patients would have still been below the threshold. When compared to healthy subjects, large epidemiological studies in the United States and Europe show higher vitamin D levels in general population, including adolescents. For example, the third U.S. National Health and Nutrition Examination Survey (NHANES 1988–1994) showed that only 29% of Caucasian adolescents (12–19 years old) had a 25(OH)D blood level under the 30 ng/mL threshold (25(OH)D mean level in adolescents = 38 ng/mL) (Ginde et al. 2009). A decade later, 67% of adolescents participating in NHANES 2001–2004 had a serum 25(OH)D level under 30 ng/mL (mean level in adolescents = 28 ng/mL) (Ginde et al. 2009). European data are older but agree with the American data (Krabbe et al. 1986). In summary, epidemiological data reveal vitamin D deficiencies in

the adolescent population in general; however, this deficiency is higher in adolescents with severe psychiatric diseases. However, this results need to be confirmed within a case–control design (e.g., psychiatric inpatients versus patients hospitalized for a traumatic issue), since the lack of control group is the main limitation of this study.

Age, sex, and BMI were not associated with Vitamin D risk factors in our sample; however, this may be explained by the limited age range of this study. As expected, ethnicity and sun exposure were associated with VDBL. However, we failed to show an association between disease types and 25(OH) D blood level or between antipsychotic medication and vitamin D deficiency. Regarding our secondary analysis on risperidone, our sample size allowed for statistical comparison because 38 patients were treated with risperidone; however, we found no correlation with treatment duration.

Comparison is only possible with adult samples. Hummer et al. showed low VDBLs in 50% of 75 patients with schizophrenia (Hummer et al. 2005). This deficiency was significantly associated with a low BMD but not with antipsychotic treatment (Hummer et al. 2005). Given that patients were adults, they had a much longer duration of illness (on average 10 years). BMD measurement could be of great interest in further studies.

Severe psychiatric conditions in adolescents appear to aggravate the environmental factors associated with osteoporosis, such as poor physical activity, smoking, poor diet, and alcohol use. Despite the lack of specific data, we know that our patients usually did not practice much exercise. These results raise concerns of whether preventive and curative treatments such as calcium intake and vitamin D supplementation can play positive roles in bone construction during childhood and adolescence (Bonjour et al. 1997). Vitamin D supplementation may prevent bone loss in the elderly (Holick 2006) and may strengthen bones due to its positive role in bone construction, especially in youth (Rizzoli et al. 2010). In the absence of clearly established threshold, some authors recommend as a consensus position to keep a 25(OH)D blood level >30 ng/mL (Dawson-Hughes et al. 2005).

The American Academy of Paediatrics recently doubled the recommended amount of vitamin D intake for children and adolescents (from 200 to 400 IU/day) (Wagner and Greer 2008), but the risks of vitamin D supplementation and side effects are not well reported from clinical trials. An acceptable upper limit for vitamin D intake has been set at 2,000 IU per day since the ''no observed adverse event level'' is 10,000 IU per day (Wagner and Greer 2008). There are no warnings or precautions for use of vitamin D unless cardiac or renal dysfunction is present. Supplementation with vitamin D and calcium should be undertaken with caution in individuals with renal insufficiency. High dose supplementation carries a risk of hypercalcaemia with subsequent impairment of kidney function. Special caution is also required in the treatment of patients with cardiovascular disease, as the effect of cardiac glycosides may be accentuated by supplementation with vitamin D and calcium (Rizzoli et al. 2009).

Conclusion

Vitamin D deficiency is becoming a major public healthcare issue. Our results show that adolescent patients with severe mental illnesses are at risk for this deficiency. Adolescence is also a key period for bone construction. For these reasons, systemic supplementation of vitamin D in adolescent psychiatric patients is reasonable. In addition, offering nutritional education to prevent later loss of BMD and early osteoporosis should be considered.

Disclosures

All authors report no biomedical financial interests or potential conflicts of interest.

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Address correspondence to:
Olivier Bonnot, M.D., Ph.D.
Child and Adolescent Department and Reference Center for Rare Disease with Psychiatric Expression
Groupe Hospitalier Pitié Salpétriere
Assistance Publique Hopitaux de Paris
47-83 Boulevard de l'hopital, Paris 75013
France

E-mail: olivier.bonnot@psl.aphp.fr