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ORIGINAL PAPER

Hypovitaminosis D is associated with negative symptoms, suicide risk, agoraphobia, impaired functional remission, and antidepressant consumption in schizophrenia

G. Fond[1,2,3] · M. Faugere[1,2,3] · C. Faget-Agius[1,2,3] · M. Cermolacce[1,2,3] · R. Richieri[1,2,3] · L. Boyer[1,2,3] · C. Lançon[1,2,3]

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Abstract

Hypovitaminosis D has been associated with, respectively, major depressive disorder, schizophrenia (SZ), and cognitive disorders in the general population, and with positive and negative symptoms and metabolic syndrome in schizophrenia. The objective was to determine the prevalence of hypovitaminosis D and associated factors in a non-selected multicentric sample of SZ subjects in day hospital. Hypovitaminosis D was defined by blood vitamin D level < 25 nM. Depressive symptoms were assessed by the Calgary Depression Rating Scale Score and Positive and Negative Syndrome Scale Score. Anxiety disorders and suicide risk were evaluated by the Structured Clinical Interview for Mental Disorders. Functioning was evaluated with the Functional Remission of General Schizophrenia Scale. Hypovitaminosis D has been found in 27.5% of the subjects. In multivariate analysis, hypovitaminosis D has been significantly associated with, respectively, higher suicide risk (aOR = 2.67 [1.31–5.46], $p = 0.01$), agoraphobia (aOR = 3.37 [1.66–6.85], $p < 0.0001$), antidepressant consumption (aOR = 2.52 [1.37–4.64], $p < 0.001$), negative symptoms (aOR = 1.04 [1.01–1.07], $p = 0.04$), decreased functioning (aOR = 0.97[0.95–0.99], $p = 0.01$), and increased leucocytosis (aOR = 1.17 [1.04–1.32], $p = 0.01$) independently of age and gender. No association with alcohol use disorder, metabolic syndrome, peripheral inflammation, insulin resistance, or thyroid disturbances has been found (all $p > 0.05$). Despite some slight abnormalities, no major cognitive impairment has been associated with hypovitaminosis D in the present sample (all $p > 0.05$ except for WAIS similarities score). Hypovitaminosis D is frequent and associated with suicide risk, agoraphobia and antidepressant consumption in schizophrenia, and more slightly with negative symptoms. Patients with agoraphobia, suicide risk and antidepressant consumption may, therefore, benefit in priority from vitamin D supplementation, given the benefit/risk profile of vitamin D. Further studies should evaluate the impact of vitamin D supplementation on clinical outcomes of SZ subjects.

Keywords Vitamin D · Schizophrenia · Depression · Anxiety · Metabolic syndrome · Antidepressant · Agoraphobia · Suicide risk

Introduction

Patients with SZ are at higher risk of hypovitaminosis D [8] and this association has been replicated in first episode psychosis in another recent meta-analysis [17] (for review see [1]). Hypovitaminosis D is frequent in schizophrenia (SZ) [10] and has been extensively associated with MDD in general population (for meta-analysis see [23] and for review see [27]) and with cognitive abnormalities during major depressive episode [9]. Vitamin D deficiency may play a role in mediating hippocampal volume deficits, possibly through neurotrophic, neuroimmunomodulatory, and glutamatergic effects [32]. Studies exploring the association of vitamin D deficiency with psychotic symptomatology have yielded

✉ G. Fond
guillaume.fond@ap-hm.fr

1 Department of Psychiatry, La Conception University Hospital, 13005 Marseille, France

2 Faculté de Médecine, Secteur Timone, EA 3279, EA 3279: CEReSS-Centre d'Etude et de Recherche sur les Services de Santé et la Qualité de vie, Aix-Marseille Univ, 27 Boulevard Jean Moulin, 13005 Marseille, France

3 SHU Adult Psychiatry, Sainte Marguerite University Hospital, 13274 Marseille, France

inconsistent findings [3, 15, 29, 39]. The association of vitamin D deficiency and depression in schizophrenia has been explored in only one study with positive results [29], and no study has explored the association between hypovitaminosis D and anxiety disorders or suicide risk in SZ subjects to date. Preliminary findings have suggested that vitamin D supplementation may improve cognition in schizophrenia [26]; however, the association of hypovitaminosis D with cognitive impairment has not been explored to date. Vitamin D insufficiency has been associated with metabolic syndrome in psychotic disorders [38], with insulin resistance [20], with thyroid dysfunction [25, 36], and high vitamin D blood levels have been suggested to reduce peripheral low-grade inflammation [40]. There is a current debate on the association between alcohol use disorder and vitamin D deficiency [34].

The objective of the present study was to determine the prevalence of hypovitaminosis D in a non-selected sample of stabilized community-dwelling SZ outpatients and its associated factors.

Methods

Study participants

The study evaluated all prospective patients attending daytime hospital hours in the academic adult psychiatry hospital over a period of 5 years from October 2010 to May 2015. The inclusion criteria were: (1) age 18–85 years old, (2) diagnosis of schizophrenia according to the DSM-IV-TR criteria, (3) antidepressant medication stable for a minimum of 3 months, and (4) French as native language. The exclusion criteria were as follows: (1) major non-psychiatric disease and (2) mental retardation. The data collection was approved by the Commission Nationale de l'Informatique et des Libertés (CNIL number 1223715). The study was designed in accordance with the Declaration of Helsinki and French good clinical practice. All of the patients were informed of the study and gave written informed consent.

Data collection

The following data were collected:

1. Socio-demographic information: gender, age, education level.
2. Clinical characteristics: illness duration; body mass index (BMI); tobacco consumption; alcohol consumption assessed by the Alcohol Use Disorders Identification Test (AUDIT) [31]; depressive symptoms based on the Calgary Depression Rating Scale [2]. Schizophrenic symptomatology assessed using the Positive And Negative Syndrome Scale (PANSS) [24].
3. Functioning was assessed by a psychiatrist with the Functional Remission of General Schizophrenia (FROGS) [14, 28] [8,9]. The FROGS is a French instrument comprising 19 items and evaluating 3 domains: daily life (4 items), treatment (4 items), and social functioning (11 items). Construct validity and internal consistency/reliability have been reported as satisfactory (in particular Cronbach' s alpha > 0.8). A higher score represents a higher level of functioning.
4. Drug information: first-generation antipsychotic, antidepressant, anxiolytic, and mood stabilizer medication. The antipsychotic treatments were classified according to their Anatomical-Therapeutic-Clinical ATC class. First-generation antipsychotics (FGA) were defined by ATC class N05AA to AC (phenothiazines), NO5AD (butyrophenones), and NO5AF (thioxanthenes). Second-generation antipsychotics (SGA) were defined by ATC class N05AH (diazepines, oxazepines, thiazepines, and oxepines) and NO5AL (benzamides).
5. Metabolic Syndrome [22]. Sitting blood pressure (BP) and anthropometrical measurements were recorded. Two BP measurements were made 30 s apart in the right arm after the participant had sat and rested for at least 5 min. A third BP measurement was made only when the first two BP readings differed by more than 10 mm Hg. The average of the two closest readings was used in the analysis. Waist circumference was measured midway between the lowest rib and the iliac crest with the subjects standing. This was performed with a tape equipped with a spring-loaded mechanism to standardize tape tension during measurement. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters. Overnight fasting blood was collected for metabolic profiles analysis. Fasting levels of serum triglyceride (TG) and fasting plasma glucose were measured by an automated system, and serum high-density lipoprotein cholesterol (HDL-C) level was measured by electrophoresis. Metabolic syndrome was defined according to the modified criteria of the International Diabetes Federation (IDF) [4], which requires the presence of three or more of the following five criteria: high waist circumference (> 94 cm for men and > 80 cm for women), hypertriglyceridemia (≥ 1.7 mM or on lipid lowering medication), low HDL cholesterol level (< 1.03 mM in men and < 1.29 mM in women), high blood pressure (≥ 130/85 mmHg or on antihypertensive medication), and high fasting glucose concentration (≥ 5.6 mM or on glucose-lowering medication).
6. Seric 25-hydroxy-vitaminD3 (25(OH)VD3) was quantified in the hospital Laboratories using a commercial

radioimmuno-assay (Diasorin,Stillwater,MN, USA). Hypovitaminosis D severity was defined in two classes according to the French National Nutrition Health Study 2006–2007: severe to moderate (< 25 nM) vs mild or no hypovitaminosis D (≥ 25 nM) [35]. Chronic inflammation marker: serum CRP levels were determined using sensitive regular immunoassays (ELISA). The results were expressed as milligram per liter. The detection limit was 0.08 µg/ml. Patients were classified into two groups: normal CRP level (≤ 3.0 mg/l) and high CRP (> 3.0 mg/l) [37].

7. The record of the data was blinded of vitamin D status and vitamin D blood dosage was blinded of clinical evaluation.

Statistical analysis

Socio-demographics, clinical characteristics, cognitive scores, addictive behavior, treatments, and biological variables are presented using measures of means and dispersion (standard deviation) for continuous data and frequency distribution for categorical variables. The data were examined for normal distribution with the Shapiro–Wilk test and for homogeneity of variance with the Levene test. Comparisons between individuals with or without hypovitaminosis D, regarding all above-mentioned characteristics were performed using the Chi-square test for categorical variables. Continuous variables were analyzed with Student's *t* tests for normally distributed data and in case of normality violation; additional Mann–Whitney tests were performed to confirm the result.

Multiple logistic regressions were then performed to confirm the association between hypovitaminosis D, and respectively, PANSS negative score, PANSS depressive score, CDRS score, major depressive disorder, suicide risk, agoraphobia, panic disorder, current daily tobacco smoking, antidepressant consumption, and biological and cognitive variables, after adjusting for age and gender. Adjustment variables were selected based on their clinical interest (age) and on threshold *p* value ≤ 0.05 as calculated from the univariate analyses (gender). The final models included odds ratios and 95% confidence intervals. This study was a confirmatory analysis. No correction for multiple testing has, therefore, been carried out, which is consistent with recommendations [11]. Analyses were conducted using the SPSS version 20.0 software package (SPSS Inc., Chicago, IL, USA). All statistical tests were two-tailed, with α level set at 0.05.

Results

Overall, 251 SZ outpatients were included in the study (72.1% males and mean aged 35.4 (11.2) years) (Table 1). The mean PANSS score was 72.1(24.2) and the mean illness duration of 16.0 (9.1) years.

Hypovitaminosis D has been found in 27.5% of the subjects. In multivariate analysis, hypovitaminosis D has been significantly associated with, respectively, higher suicide risk (aOR = 2.67 [1.31–5.46], $p = 0.01$), agoraphobia (aOR = 3.37 [1.66–6.85], $p < 0.0001$), antidepressant consumption (aOR = 2.52 [1.37–4.64], $p < 0.001$), negative symptoms (aOR = 1.04 [1.01–1.07], $p = 0.04$), decreased functioning (aOR = 0.97[0.95–0.99], $p = 0.01$), and increased leucocytosis (aOR = 1.17 [1.04–1.32], $p = 0.01$) independently of age and gender. No association with a specific class of antidepressant or antipsychotics, mood stabilizer, alcohol use disorder, metabolic syndrome, peripheral inflammation, insulin resistance, or thyroid disturbances has been found (all $p > 0.05$). Despite some slight abnormalities, no major cognitive impairment has been associated with hypovitaminosis D in the present sample (all $p > 0.05$ except for WAIS similarities score).

Discussion

The main findings of the present study may be summarized as follows: in a non-selected sample of SZ outpatients, 27% were identified with hypovitaminosis D. This hypovitaminosis D has been associated with agoraphobia, suicide risk, and antidepressant consumption, more slightly with negative symptoms and with increased leukocytosis. No significant association with other biological disturbances or cognitive impairment (except for one WAIS subscore) has been found.

A prevalence of hypovitaminosis D of 27.5% has been found, which is slightly lower than the rate of 34% found in 202 SZ Dutch outpatients [12] and comparable with the data in the French general population of healthy adults (34% of vitamin D levels < 20 ng/mL) [33].

A strong association between hypovitaminosis D and agoraphobia has been found for the first time in the present study (29.4 vs. 11.5%, adjusted $p < 0.0001$) and has never been explored before. This association may be a bilateral association. The two main sources of Vitamin D are through diet and sun exposure. SZ subjects may have both decreased sun exposure and poor diet (with lower fresh food). Daily sun exposure and diet have not been reported in the present study, which is a limit that should be taken into account in future studies.

Table 1 Factors associated with severe hypovitaminosis D (defined by 25-OH-vitD blood level < 25 nM) in a non-selected sample of stabilized outpatients with schizophrenia (SZ)

	Hypovitaminosis D (< 25 nM)				p^*	B or exp(B)*	IC95	IC95	Adjusted p value*
	No (n = 182)		Yes (N = 69)						
	72.5%		27.5%						
Demographic characteristics									
Gender (male)	44	24.2%	26	37.7%	0.03				
Age (years), mean (SD)	35.17	11.44	36.11	10.80	0.41				
Education level (universitary), n (%)	99	55.3%	37	53.6%	0.81				
Clinical variables									
Illness duration (years), mean (sd)	16.49	9.39	14.79	8.34	0.40				
Winterbirth, n (%)	42	23.1%	17	24.6%	0.79				
Panss total score. mean (sd)	70.60	23.52	74.49	27.20	0.25				
PANSS positive score	12.46	5.78	12.89	5.73	0.50				
PANSS negative score	**24.50**	**8.40**	**26.74**	**8.34**	**0.06**	**2.42**	**0.02**	**4.83**	**0.04**
PANSS disorganized score	20.16	6.61	20.50	7.07	0.84				
PANSS excited score	6.55	2.83	7.24	4.03	0.77				
PANSS depressed score	7.33	3.34	8.11	3.45	0.12	0.64	− 0.32	1.60	0.19
CDRS score	3.59	4.07	4.85	5.04	0.07	1.05	− 0.20	2.29	0.11
Suicide risk, n (%)	**21**	**11.6%**	**18**	**26.5%**	**0.004**	**2.67**	**1.31**	**5.46**	**0.01**
Agoraphobia, n (%)	**21**	**11.5%**	**20**	**29.4%**	**0.001**	**3.37**	**1.66**	**6.85**	**< 0.0001**
Social phobia, n (%)	24	13.2%	10	14.7%	0.76				
General anxiety disorder, n (%)	27	14.8%	11	16.2%	0.79				
Panic disorder, n (%)	31	17.0%	7	10.3%	0.19	0.57	0.24	1.40	0.22
Functioning (FROGS score)	**59.94**	**14.46**	**54.06**	**15.81**	**0.47**	**0.97**	**0.95**	**0.99**	**0.01**
Comorbidities									
Current daily tobacco smoking, n (%)	97	53.3%	44	63.8%	0.14	1.66	0.93	2.97	0.09
Current alcohol use disorder, n (%)	24	13.3%	12	17.4%	0.41				
Current cannabis use disorder, n (%)	24	13.3%	12	17.4%	0.42				
Treatment									
First-generation antipsychotic	34	18.7%	12	17.4%	0.81				
Antidepressant	**37**	**20.3%**	**27**	**39.1%**	**0.002**	**2.52**	**1.37**	**4.64**	**< 0.0001**
Mood stabilizer	13	7.1%	2	2.9%	0.21				
Biological variables									
Metabolic syndrome	38.00	20.9%	13.00	18.8%	0.72				
Chronic peripheral inflammation (hsCRP > 3 mg/L)	66.00	37.9%	34.00	51.5%	0.06	1.66	0.93	2.98	0.09
Fasting glucose (nM)	4.60	1.09	4.71	1.26	0.47				
Abdominal perimeter (cm)	68.09	38.18	75.04	37.88	0.29				

Table 1 (continued)

	Hypovitaminosis D (< 25 nM)				p^*		B or exp(B)*	IC95	IC95	Adjusted p value*
	No ($n = 182$)		Yes ($N = 69$)							
	72.5%		27.5%							
Leucocytes (nM)	**7.36**	**2.39**	**8.45**	**2.91**	**0.01**	**1.10**		**0.32**	**1.88**	**0.01**
Vitamin B9	15.20	5.82	14.22	5.97	0.45					
Vitamin B12	361.21	128.15	407.09	176.71	0.37					
Homocysteinemia (µM)	15.28	5.51	18.80	4.71	0.11	2.71		− 2.49	7.91	0.27
Body mass index	26.38	5.01	26.86	6.37	0.99					
Triglyceridemia (mM)	1.48	0.90	1.68	1.29	0.45					
TSHus blood level	3.53	15.57	2.45	1.28	0.15	− 0.83		− 4.79	3.12	0.69
Current and premorbid intellectual ability										
fNART-based premorbid IQ. mean (SD)										
Full-scale IQ, mean (SD)	79.42	16.19	74.14	15.31	0.04		− 4.58	− 9.59	0.44	0.07
Performance IQ, mean (SD)	75.01	16.12	70.98	16.39	0.05		− 3.61	− 8.73	1.52	0.16
Verbal IQ, mean (SD)	85.35	17.52	80.48	14.92	0.05		− 4.10	− 9.40	1.20	0.13
Working memory										
Digit span (standard score), mean (SD)	5.76	1.41	5.26	0.93	0.23					
Arithmetic (standard score), mean (SD)	10.77	4.97	8.33	5.65	0.02		− 1.30	− 3.50	0.89	0.23
Learning abilities. episodic and semantic memory										
CVLT short delay free recall, mean (SD)	14.30	2.30	13.93	1.95		0.21				
CVLT short delay cued recall, mean (SD)	10.76	2.92	10.19	2.79		0.41				
CVLT long delay free recall, mean (SD)	10.85	3.10	10.47	2.95		0.84				
CVLT long delay cued recall, mean (SD)	9.88	3.32	11.40	8.78		0.24				
CVLT recognition, mean (SD)	10.63	3.15	10.03	3.06		0.35				
Executive functions and problem solving										
Trail making test B (time), mean (SD)	1.19	1.87	0.83	2.81	0.07		− 9.02	− 26.50	8.47	0.31
Trail making test B (errors), mean (SD)	70.64	53.34	62.54	53.96	0.18		− 0.68	− 1.91	0.55	0.31
Matrix reasoning (standard score), mean (SD)	15.41	5.34	13.79	5.95	0.12		− 1.35	− 3.31	0.61	0.17
Similarities (standard score), mean (SD)	**17.12**	**5.97**	**14.96**	**4.74**	**0.02**		− 2.16	− 4.14	− 0.18	0.03
Visual attention and speed of processing										
Trail making test A (time), mean (SD)	0.61	2.28	0.10	0.30	0.36					
Trail making test A (errors), mean (SD)	42.89	21.00	47.88	22.88	0.14		− 0.44	− 1.47	0.59	0.50
Digit symbol coding (standard score), mean (SD)	6.67	3.50	5.48	2.58	0.19		0.99	0.97	1.01	0.16
Picture completion (standard score), mean (SD)	7.32	3.45	6.25	3.76	0.10		0.95	0.88	1.04	0.27

*Adjusted for age and gender

Hypovitaminosis D has been associated with antidepressant consumption (39.1 vs. 20.3%, adjusted $p < 0.0001$), but not with depressive symptoms in the present study. This discrepancy with previous results [29] is probably due to discrepancies in antidepressant treatments across studies. It is probable that antidepressant consumption has erased the association between hypovitaminosis D and depression. No data have suggested to date that antidepressant may lead to lower vitamin D blood levels to date. Treating depression in schizophrenia remains a challenge in the current state of the art [5, 18], and vitamin D may be suggested as a low-cost and high benefit/risk ratio add-on therapy in SZ patients with depressive and anxiety symptoms. Hypovitaminosis D has been associated with negative symptoms in the present study, which is consistent with previous findings [16, 21]. However, the odd ratio was rather low in the present sample. Negative symptoms and depressive symptoms have been independently associated with impaired quality of life in SZ subjects [5], future studies should determine if vitamin D supplementation may help in improving quality of life in SZ subjects. This association may probably further contribute to the association of hypovitaminosis D with slightly impaired functional remission that has been described for the first time in the present study.

Hypovitaminosis D has been associated for the first time with suicide risk in schizophrenia in the present sample. A study carried out in a non-SZ Korean sample has found no association between low vitamin D levels and suicidal ideation [30]. While vitamin D has been extensively associated with depression, the association with suicide remains poorly explored to date and should be included in future studies.

Contrary to what could have been expected, vitamin D has not been associated with metabolic syndrome, insulin resistance (proxy by fasting blood glucose), and chronic low-grade inflammation (hs-CRP blood level). The association of hypovitaminosis D with metabolic syndrome has been mostly validated in non-SZ populations [6, 7, 41], which may suggest that metabolic syndrome may have some specificities in SZ subjects due to antipsychotic-induced metabolic disturbances. No association between vitamin D blood level and hs-CRP blood level has been found, while extensive works have shown the impact of vitamin D on peripheral inflammation [20, 29]. In the present study, only hs-CRP has been explored as an inflammatory marker, future studies should explore other inflammatory markers such as cytokines IL1ß, IL6, and TNF-α.

A previous study has suggested that sun exposure was not sufficient to increase vitamin D blood levels in SZ subjects [13], which suggests that vitamin D supplementation should be recommended in case of SZ subjects with hypovitaminosis D.

Limits

No information on vitamin D supplementation in the previous year has been reported in the present study, as well as information on diet and lifestyle habits, skin phototype, and season of dosage. Despite its large sample size, this study was a monocentric study. These results should be replicated in larger samples and confirmed in longitudinal studies. In addition to the limits mentioned in the discussion, omega-3 fatty acid deficiency may potentiate hypovitaminosis D impact on brain disturbances and should be explored in future studies. It may be suggested that the lifetime duration of hypovitaminosis D may determine its association with clinical features in schizophrenia, which may explain discrepant results between studies. There is no way to date to determine lifetime hypovitaminosis D duration to date.

Strengths

The present sample is one of the largest studies exploring the association between hypovitaminosis D and clinical variables in schizophrenia. The use of standardized questionnaires and a comprehensive neuropsychological battery may be mentioned in the strengths of the present study.

Perspectives

As hypovitaminosis D has been found to be highly prevalent in healthy adults in France, a cost-effectiveness study should be further carried out to determine if supplementing systematically all patients (and potentially the whole population) during winter months may be recommended to improve the general health outcomes of the population. Another issue is the professionals' point of view on complementary agent's prescription in psychiatry. Some health professionals may be favorable to non-psychotropic prescriptions for their benefit/risk ratio, while some others may not be convinced of their effectiveness or estimate that the role of psychiatrist should be limited to psychotropic drug prescription.

Conclusion

Hypovitaminosis D has been associated with anxiety and negative symptoms, antidepressant consumption and impaired recovery in stabilized outpatients with schizophrenia. Future studies should determine in supplementing these patients with vitamin D which may improve these outcomes.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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