Published in final edited form as:
Schizophr Res. 2014 November ; 159(0): 543–545. doi:10.1016/j.schres.2014.08.031.

Low Vitamin D levels predict clinical features of schizophrenia

Kristina Cieslak, BS[a], **Jordyn Feingold, BS**[a], **Daniel Antonius, PhD**[a,b], **Julie Walsh-Messinger, PhD**[b,c], **Roberta Dracxler, MD**[a], **Mary Rosedale, PhD**[a], **Nicole Aujero, BS**[a], **David Keefe, MD**[d], **Deborah Goetz, MA**[a], **Raymond Goetz, PhD**[a], and **Dolores Malaspina, MD**[a,e,*]

[a] Department of Psychiatry, New York University School of Medicine, InSPIRES Institute for Social and Psychiatric Initiatives, New York, NY, USA

[b] University at Buffalo, State University of New York, Buffalo, NY, USA

[c] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[d] Department of Obstetrics and Gynecology, New York University School of Medicine, New York, NY, USA

[e] Creedmoor Psychiatric Center, NY State Office of Mental Health, Queens, N.Y, USA

Abstract

Vitamin D plays crucial roles in neuroprotection and neurodevelopment, and low levels are commonly associated with schizophrenia. We considered if the association was spurious or causal by examining the association of Vitamin D with Leukocyte Telomere Length (LTL), a marker of cellular aging. Vitamin D levels in 22 well-characterized schizophrenia cases were examined with respect to symptoms, cognition, and functioning. LTL was assessed using quantitative polymerase chain reaction (qPCR). The results showed that 91% (20) had deficient or insufficient Vitamin D levels, which were associated with excitement and grandiosity, social anhedonia, and poverty of speech. Sex-specific analyses showed strong associations of hypovitamintosis D to negative symptoms and decreased premorbid adjustment in males, and to lesser hallucinations and emotional withdrawal, but increased anti-social aggression in females. In females LTL was furthermore associated with Vitamin D levels. This study demonstrates a relationship of low vitamin D levels with increased cellular aging in females. It is also the first study to demonstrate potential sex-specific profiles among schizophrenia cases with hypovitaminosis.

[*]**Correspondence to:** Dolores Malaspina, InSPIRES, Department of Psychiatry, New York University School of Medicine, 1 Park Avenue, 8th Floor, Rm 222, New York, NY 10016. Tel: (646) 584-2044; Dolores.malaspina@nyumc.org.

CONTRIBUTORS

Authors Kristina Cieslak and Dolores Malaspina were responsible for study conception and design. Daniel Antonius, Julie Walsh-Messinger, Roberta Dracxler, Mary Rosedale, Nicole Aujero, David Keefe, Deborah Goetz, and Dolores Malaspina performed data collection and management. Kristina Cieslak, Jordyn Feingold, Raymond Goetz, and Dolores Malaspina were responsible for analysis and interpretation of data. Drafting of the manuscript was completed by Kristina Cieslak, Jordyn Feingold, and Dolores Malaspina. All authors were responsible for revising the manuscript critically for important intellectual content and final approval.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Keywords

Schizophrenia; Vitamin D; hypovitaminosis D; telomere length; aggression; negative symptoms

1. INTRODUCTION

An estimated one billion individuals worldwide have classifiable Vitamin D deficiency (serum levels less than 25-50nmol/L) or insufficiency (<75nmol/L) (Holick, 2007). Within the central nervous system, Vitamin D is involved in neurotransmitter synthesis, neuroprotection from injury and inflammation, regulation of circadian rhythms and sleep, and key roles in neurodevelopment (Eyles et al., 2013). Psychiatric and neurological diseases with potential connections to Vitamin D deficiency (hypovitaminosis D) include schizophrenia, autism, Parkinson's disease, amyotrophic lateral sclerosis, Alzheimer's disease, and multiple sclerosis (Deluca et al., 2013).

Ties between Vitamin D and schizophrenia include a “season-of-birth effect” in which a greater proportion of individuals with schizophrenia are born in late winter and early spring and thus exposed to lower levels of Vitamin D in their prenatal and perinatal periods. There is also an increased incidence and prevalence of schizophrenia at latitudes farther from the equator (Deluca et al., 2013). Individuals with darker skin are particularly more vulnerable to schizophrenia when they live at higher latitudes (Kinney et al., 2009).

The disease process of schizophrenia is associated with activation of cell-mediated and inflammatory pathways. Strong associations between schizophrenia and smoking, obesity, sleep disorders, and poor oral health may further augment this inflammation (Berk et al., 2013). Leukocyte Telomere length (LTL) is a marker of oxidative stresses that shorten telomere length to eventually trigger earlier cell senescence and apoptosis (Epel et al., 2004; von Zglinicki, 2002). As Vitamin D has documented modulatory effects on reduction of oxidative stress and inflammation (Jain et al., 2013), the relationship of Vitamin D to telomere length, particularly in schizophrenia, is an important avenue to pursue as a biomarker for neuroprotection that may have therapeutic implications. A significant relationship between vitamin D and LTL would suggest that the association is not simply spurious, resulting from decreased outside activity, but that it could play a role in pathogenesis.

This pilot study explored the association between Vitamin D levels and illness features in schizophrenia cases, including sex-stratified analyses. We hypothesized that in individuals with schizophrenia, Vitamin D levels would be in the deficient range, inversely correlate to the severity of symptoms, and be associated with telomere length.

2. METHODS

2.1 Participants

Patients (N=22, males=59.1%) with schizophrenia or schizoaffective disorder were recruited from inpatient and outpatient research centers of Bellevue Hospital Psychiatric services, with informed consent obtained. All cases were clinically stable for at least one month with

no changes in medication. Mental health professionals performed all procedures, diagnostic interviews, and assessments of symptoms and functioning. The Diagnostic Interview for Genetic studies (DIGS) (Nurnberger et al., 1994) was used to assess psychiatric diagnoses, as well as to obtain demographic information about sex, age, education, duration of illness, and current and past Global Assessment of Symptoms (GAS).

2.2 Measures

Vitamin D measurements were determined at the NYU Clinical and Translational Science Institute (CTSI) blind to subject classification. The Premorbid Adjustment Scale (PAS) assessed social accessibility, peer relationships, ability to function outside the family, education, and capacity to form socio-sexual ties across four periods of patient lives (Cannon-Spoor et al., 1982). Verbal, physical, and anti-social aggression were measured with The Life History of Aggression (LHA) (Brown et al., 1979) rating instrument, modified by Coccaro et al. (Coccaro et al., 1997). Current (state) symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987), and trait symptoms were measured using the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick et al., 1989). Telomere length was assayed using qPCR, as recently reported (Malaspina et al., 2014).

2.3 Statistics

Descriptive statistics and distributions of all measures, whether continuous or categorical, were examined along with measures of non-normal distribution, outliers, and skewness. Cross-tabulations with chi-square statistics were used to examine the categorical variables. All measures and scales were examined for sex differences among the patients using the t-test statistic. Correlation coefficients were calculated among Vitamin D levels, the aforementioned measurements, and continuous LTL lengths for the entire sample and then in sex stratified analyses.

3. RESULTS

3.1 The Sample

The mean Vitamin D level for individuals with schizophrenia was 17.3+8.87 (females vs. males: 18.4+7.5 vs. 16.5+9.9, ANCOVA [age as covariate] F=0.09, p=.770), classified as deficient, and levels and status did not differ significantly by sex (Table 1). PANSS and SDS also did not differ by sex, other than an excess of certain PANSS negative symptoms in males, including emotional withdrawal (t=2.76, p=.013) active social avoidance (t=2.32, p=.040), and diminished sense of purpose (t=2.64, p=.032).

3.2 Vitamin D Levels and illness features

Vitamin D levels were unrelated to age, ethnicity, parental ages, or mood symptoms. Vitamin D levels were significantly inversely associated with PANSS positive symptoms of excitement (r=-.447, n=20, p=.048) and grandiosity (r=-.466, n=20, p=.038), as well as an increased SDS poverty of speech (r=.614, n=12, p=.037). Among males with schizophrenia, low Vitamin D levels predicted a greater PANSS negative symptom total (r=-.680, n=11, p=.021), and worse premorbid adjustment (r=.928, n=6, p=.008). Among females with

schizophrenia, those with decreased levels of Vitamin D had less hallucinations (r=.878, n=9, p=.002) and less emotional withdrawal (r=.704, n=9, p=.034), but showed increased anti-social aggression (-.772, n=9, p=.015). Additionally, among females, increased Vitamin D was associated with an increased telomere length (r=.729, n=9, p=.029).

4. DISCUSSION

It was of note that 20 of the 22 patients with schizophrenia had Vitamin D levels in the deficient or insufficient range. This deficit is consistent with a recent mini meta-analysis showing lower Vitamin D levels in individuals with psychotic disorders, particularly schizophrenia, as compared to healthy controls (Belvederi Murri et al., 2013). The association between low Vitamin D and neuropsychiatric illness is also observed in multiple sclerosis and major depression (Eyles et al., 2013). Preliminary studies have demonstrated significant improvement in depressive symptomatology following Vitamin D administration (Mozaffari-Khosravi et al., 2013; Zanetidou et al., 2011), and Vitamin D levels in the early course of multiple sclerosis have been found to be strongly predictive of disease progression, with increased Vitamin D levels protective of new lesions and disability (Ascherio et al., 2014).

Low Vitamin D in males with schizophrenia was associated with increased overall negative symptoms and decreased premorbid adjustment. A recent study also found an association between increased negative symptom severity and low Vitamin D levels among 20 individuals with schizophrenia (Graham et al., 2014); together, our findings suggest that, especially in males, low Vitamin D may be one of the factors responsible for the burden of increased negative symptoms.

Among females, decreased Vitamin D was associated with lesser hallucinatory behavior and emotional withdrawal, but did predict higher anti-social aggression. Increased aggression is seen among women with schizophrenia, though is not a ubiquitous finding. In a study of admitted patients with schizophrenia, 53% of women were noted to exhibit aggressive behavior, compared to 75% of men (Steinert et al., 1999). Should further analyses corroborate this correlation, Vitamin D may be considered as a potential therapy in women who present with aggressive manifestations of schizophrenia.

Importantly, the associations of Vitamin D with illness features of the disease, particularly in females, do not appear to be spurious, as Vitamin D levels were significantly correlated with LTL in female cases. A recent analysis demonstrated increased LTL in schizophrenia (Nieratschker et al., 2013), and our own study showed that the increase was explained by a family history of schizophrenia and, in male cases, later paternal age (Malaspina et al., 2014). Despite the evidence for lengthened LTL in some cases with the disease, it is compelling to note that shortening of LTL might occur in response to decreased vitamin D. This is consistent with literature showing shorter LTL in other cases with severe, treatment-refractory schizophrenia (Fernandez-Egea et al., 2009; Kao et al., 2008; Yu et al., 2008). A robust link between increased Vitamin D concentration and longer LTL was also shown in a large population-based cohort of female twins (Richards et al., 2007). Vitamin D

supplementation, particularly in women with schizophrenia, may provide valuable neuroprotective effects as a buffer of oxidative stress.

This is the first study to demonstrate potential sex-specific symptom and feature profiles among individuals with schizophrenia and hypovitaminosis D, in addition to a relationship of low Vitamin D with more rapid cellular aging. A major limitation of this study was the lack of comparison of our findings to a matched control population. Additionally, the sample size for this study remained rather small, at 22 individuals. However, taken on its own, this data from a cohort of individuals rigorously diagnosed with schizophrenia has demonstrated mean decreased Vitamin D levels from what is considered optimal for the general population, as well as significant differences between sex and symptomatology with respect to hypovitaminosis D. Additional lifestyle factors including diet and outdoor activity level were not assessed in this exploratory analysis, and likely interact with both mental illness and levels of vitamin D. Further studies should be conducted with larger samples to investigate these preliminary findings and to advance towards an ultimate goal of intervention recommendation.

Acknowledgments

None

ROLE OF THE FUNDING SOURCE

This research was supported by RC1MH088843-02 and the NYU CTSA grant UL1TR000038 from the National Center for Advancing Translational Sciences (NCATS), NIH.

REFERENCES

Ascherio A, Munger KL, White R, Köchert K, Simon KC, Polman CH, Freedman MS, Hartung H-P, Miller DH, Montalbán X. Vitamin D as an Early Predictor of Multiple Sclerosis Activity and Progression. JAMA neurology. 2014

Belvederi Murri M, Respino M, Masotti M, Innamorati M, Mondelli V, Pariante C, Amore M. Vitamin D and psychosis: Mini meta-analysis. Schizophrenia research. 2013; 150(1):235–239. [PubMed: 23906618]

Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML. So depression is an inflammatory disease, but where does the inflammation come from? BMC medicine. 2013; 11(1):200. [PubMed: 24228900]

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. Aggression in humans correlates with cerebrospinal fluid amine metabolites. Psychiatry research. 1979; 1(2):131–139. [PubMed: 95232]

Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. Schizophrenia Bulletin. 1982; 8(3):470. [PubMed: 7134891]

Coccaro EF, Berman ME, Kavoussi RJ. Assessment of life history of aggression: development and psychometric characteristics. Psychiatry research. 1997; 73(3):147–157. [PubMed: 9481806]

Deluca G, Kimball S, Kolasinski J, Ramagopalan S, Ebers G. Review: the role of vitamin D in nervous system health and disease. Neuropathology and applied neurobiology. 2013; 39(5):458–484. [PubMed: 23336971]

Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, Cawthon RM. Accelerated telomere shortening in response to life stress. Proceedings of the National Academy of Sciences of the United States of America. 2004; 101(49):17312–17315. [PubMed: 15574496]

Eyles DW, Burne TH, McGrath JJ. Vitamin D, effects on brain development, adult brain function and the links between low levels of vitamin D and neuropsychiatric disease. Frontiers in neuroendocrinology. 2013; 34(1):47–64. [PubMed: 22796576]

Fernandez-Egea E, Bernardo M, Heaphy CM, Griffith JK, Parellada E, Esmatjes E, Conget I, Nguyen L, George V, Stöppler H. Telomere length and pulse pressure in newly diagnosed, antipsychotic-naive patients with nonaffective psychosis. Schizophrenia bulletin. 2009:sbn169.

Graham KA, Keefe RS, Lieberman JA, Calikoglu AS, Lansing KM, Perkins DO. Relationship of low vitamin D status with positive, negative and cognitive symptom domains in people with first-episode schizophrenia. Early Intervention in Psychiatry. 2014 n/a-n/a.

Holick MF. Vitamin D deficiency. New England Journal of Medicine. 2007; 357(3):266–281. [PubMed: 17634462]

Jain SK, Manna P, Micinski D, Lieblong BJ, Kahlon G, Morehead L, Hoeldtke R, Bass PF III, Levine SN. In African American type 2 diabetic patients, is vitamin D deficiency associated with lower blood levels of hydrogen sulfide and cyclic adenosine monophosphate, and elevated oxidative stress? Antioxidants & Redox Signaling. 2013; 18(10):1154–1158. [PubMed: 22852873]

Kao H, Cawthon R, Delisi L, Bertisch H, Ji F, Gordon D, Li P, Benedict M, Greenberg W, Porton B. Rapid telomere erosion in schizophrenia. Molecular psychiatry. 2008; 13(2):118–119. [PubMed: 18202693]

Kay SR, Flszbein A, Opfer LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophrenia bulletin. 1987; 13(2):261. [PubMed: 3616518]

Kinney DK, Teixeira P, Hsu D, Napoleon SC, Crowley DJ, Miller A, Hyman W, Huang E. Relation of schizophrenia prevalence to latitude, climate, fish consumption, infant mortality, and skin color: a role for prenatal vitamin d deficiency and infections? Schizophrenia bulletin. 2009; 35(3):582–595. [PubMed: 19357239]

Kirkpatrick B, Buchanan RW, McKenny PD, Alphs LD, Carpenter WT Jr. The schedule for the deficit syndrome: an instrument for research in schizophrenia. Psychiatry research. 1989; 30(2):119–123. [PubMed: 2616682]

Malaspina D, Dracxler R, Walsh-Messinger J, Harlap S, Goetz RR, Keefe D, Perrin MC. Telomere length, family history, and paternal age in schizophrenia. Mol Genet Genomic Med. 2014; 2(4): 326–331. [PubMed: 25077175]

Mozaffari-Khosravi H, Nabizade L, Yassini-Ardakani SM, Hadinedoushan H, Barzegar K. The effect of 2 different single injections of high dose of vitamin D on improving the depression in depressed patients with vitamin D deficiency: a randomized clinical trial. Journal of clinical psychopharmacology. 2013; 33(3):378–385. [PubMed: 23609390]

Nieratschker V, Lahtinen J, Meier S, Strohmaier J, Frank J, Heinrich A, Breuer R, Witt SH, Nöthen MM, Rietschel M. Longer telomere length in patients with schizophrenia. Schizophrenia research. 2013; 149(1):116–120. [PubMed: 23870621]

Nurnberger JI, Blehar MC, Kaufmann CA, York-Cooler C, Simpson SG, Harkavy-Friedman J, Severe JB, Malaspina D, Reich T. Diagnostic Interview for Genetic Studies: rationale, unique features, and training. Archives of general psychiatry. 1994; 51(11):849–859. [PubMed: 7944874]

Richards JB, Valdes AM, Gardner JP, Paximadas D, Kimura M, Nessa A, Lu X, Surdulescu GL, Swaminathan R, Spector TD. Higher serum vitamin D concentrations are associated with longer leukocyte telomere length in women. The American journal of clinical nutrition. 2007; 86(5): 1420–1425. [PubMed: 17991655]

Steinert T, Wiebe C, Gebhardt RP. Aggressive behavior against self and others among first-admission patients with schizophrenia. Psychiatric Services. 1999; 50(1):85–90. [PubMed: 9890585]

von Zglinicki T. Oxidative stress shortens telomeres. Trends in Biochemical Sciences. 2002; 27(7): 339–344. [PubMed: 12114022]

Yu W-Y, Chang H-W, Lin C-H, Cho C-L. Short telomeres in patients with chronic schizophrenia who show a poor response to treatment. Journal of psychiatry & neuroscience: JPN. 2008; 33(3):244. [PubMed: 18592039]

Zanetidou S, Murri MB, Buffa A, Malavolta N, Anzivino F, Bertakis K. Vitamin D supplements in geriatric major depression. International journal of geriatric psychiatry. 2011; 26(11):1209–1210. [PubMed: 23658119]

Table 1

Demographic measures, Vitamin D level, Leukocyte Telomere Length (LTL), PANSS Five Symptom Factors, and Premorbid Adjustment compared between Male and Female Schizophrenia Patients. Test Statistics: t-test and ANCOVA.

	Males		**Females**			
	N = 13		**N = 9**			
	Mean	**sd**	**Mean**	**sd**	**t-test**	**p**
Current Age	44.3	(7.2)	41.9	(9.6)	0.68	.501
Onset Age	20.6	(8.3)	19.0	(3.7)	0.54	.593
Education (years)	11.2	(3.8)	12.8	(2.9)	1.08	.294
Vitamin D	16.5	(19.9)	18.4	(7.5)	F[1/19]=0.09, p=.770 Age is co-varied	
LTL	N=9		N=9		1.52	.149
	1.94	(.427)	1.60	(.527)		
Positive	10.9	(5.8)	10.1	(4.0)	0.35	.729
Negative	15.7	(3.1)	14.8	(4.9)	0.53	.604
Dysthymia	13.8	6.1)	11.0	(3.6)	1.22	.238
Activation	8.8	(1.8)	8.2	(3.5)	0.50	.627
Autistic Preoccupation	10.8	(3.3)	9.0	(2.9)	1.29	.214
Premorbid Adjustment	N=6		N=3		0.12	.909
	.35	(.28)	.37	(.123)		