Psychiatry Research 243 (2016) 390–394

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Association between serum levels of bioavailable vitamin D and negative symptoms in first-episode psychosis

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ARTICLE INFO

Article history:
Received 15 February 2016
Received in revised form
20 June 2016
Accepted 3 July 2016
Available online 5 July 2016

Keywords:
First-episode psychosis
Schizophrenia
Vitamin D
Tropical

ABSTRACT

Total vitamin D levels had been commonly reported to be lowered in patients with chronic psychotic illnesses in countries from the higher latitudes. However, studies on patients with first episode psychosis (FEP) are limited. In this study we investigated serum concentrations of total and bioavailable vitamin D levels in FEP patients compared to healthy controls and the association between symptom severity and vitamin D components. A total of 31 FEP patients and 31 healthy controls were recruited from Institute of Mental Health, Singapore. FEP patients were identified using Structured Clinical Interview for DSM-IV Axis I disorders (SCID-1) and severity symptoms were assessed using the positive and negative syndrome scale (PANSS). Sera from participants were analyzed for total vitamin D, vitamin D-binding protein (DBP) and bioavailable vitamin D. Linear regressions were performed to examine the associations between serum total and bioavailable vitamin D and the PANSS subscales. Current study noted a significantly lower bioavailable vitamin D was in the FEP group and an association between bioavailable vitamin D and negative symptoms in FEP patients in a population with a consistent supply of sun exposure throughout the year.

1. Introduction

There is an increasing focus on the importance of vitamin D levels in mental health (Graham et al., 2015). A growing body of evidence suggests that vitamin D plays neuroprotective roles in a number of brain processes including neurodevelopment, neurotransmitter expression, neurotropic and growth factor regulation (Eyles et al., 2013). Its receptor and enzyme are required for hydroxylation to active form and 1-α-hydroxylase is reportedly expressed in many brain regions (hippocampus, thalamus, hypothalamus, amygdala, prefrontal cortex, cingulate gyrus and temporal lobe) which are associated to psychosis (Eyles et al., 2005).

Total vitamin D is hydroxylated in the liver and kidneys to produce 25-hydroxyvitamin D and 1, 25-dihydroxyvitamin (Johnsen et al., 2014). 85–90% of these metabolites are then circulated via binding to DBP and approximately 1% of the metabolites bind weakly to albumin to circulate in the bloodstream (Johnsen et al., 2014). Based on the free-hormone hypothesis, the free fraction of a hormone is the biologically active component (Johnsen et al., 2014). Therefore, bioavailable vitamin D is believed to correlate more strongly with biological actions of vitamin D (Johnsen et al., 2014).

Recent meta-analyses reported significantly lower serum total vitamin D levels in patients with psychiatric disorders, especially in schizophrenia when compared to healthy controls (Belvederi Murri et al., 2013; Valipour et al., 2014). These studies focused on both chronic patients in European and non-European populations (Abdullah et al., 2012; Graham et al., 2015; Higuchi et al., 1987; Itzhaky et al., 2012; Jamilian et al., 2013; Menkes et al., 2012; Norelli et al., 2010; Yüksel et al., 2014). Thus far, only three studies have been conducted in patients with first episode psychosis (FEP) and their findings are equivocal. Crews et al. found significantly lower total vitamin D level in both white and black patients but not in Asian patients, compared to healthy controls (Crews et al., 2013). Graham et al., on the other hand did not find any patient/control differences (Graham et al., 2015). The latest study in 2015 by Nerhus et al. found no difference between first and multiple episode patients with psychosis and healthy controls (Nerhus et al., 2015).

Several observational studies suggested vitamin D levels to be related to the development of psychosis. Many studies had also reported on the correlation between early life vitamin D statuses and the development of schizophrenia from as early as 1977. One related observation was an increase in schizophrenia births during winter when vitamin D deficiency was expected be to more prevalent (Torrey et al., 1977). Another study reported on the

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http://dx.doi.org/10.1016/j.psychres.2016.07.003

association between dark-skinned immigrants and schizophrenia risk after relocation to higher latitudes with reduced sun exposure (Dealberto, 2007). A Swedish cohort study reported a lowered risk of psychotic symptoms in woman with high intake of fish, omega-3 or omega-6 PUFA and vitamin D intake (Hedelin et al., 2010). Similarly, the risk of developing schizophrenia was reduced in Finnish male infants who were given 2000 IU of daily vitamin D supplement during their first year of life (McGrath et al., 2004). Several studies too reported a relationship between low vitamin D levels during prenatal and early life and schizophrenia in United States, Finland and Australia and suicide rates in active military members (McGrath et al., 2004; McGrath et al., 2010; Torrey et al., 1977; Umhau et al., 2013).

Much of the focus in vitamin D status had been on populations living at higher latitudes with seasonal periods, with limited work done in populations living closer to the equator as one may assume variation in vitamin D between sub-populations is unlikely in regions with regular sunlight. There are also numerous studies reporting differential vitamin D levels among HIV patients (Phabphal et al., 2009; Wiboonchutikul et al., 2012), epileptic patients (Phabphal et al., 2009), patients with hip fractures (Ramason et al., 2014), obese children (Khor et al., 2011; Moy and Bulgiba, 2011) and healthy populations (Hawkins, 2013; Hawkins, 2009; Nurbazlin et al., 2013; Wakayo et al., 2015) in countries with regular sun exposure.

To the best of our knowledge, there is no published study examining total and bioavailable vitamin D levels in FEP patients from a specific geographic location of tropical setting with regular sun exposure. Thus, current study aims to evaluate and compare serum levels of total and bioavailable vitamin D in patients with FEP and healthy controls based in Singapore, as well as to compare the relationships between serum levels of total and bioavailable vitamin D with symptom severity (Jiang et al., 2013).

2. Materials and methods

2.1. Study participants

The current study was conducted at the institute of Mental Health, Singapore. Cases were individuals diagnosed with FEP and have not exceeded 4 weeks of anti-psychotic treatment. Controls were healthy individuals with no past history of mental illness. Controls were matched for age, ethnicity and gender. Ethics approval for the study was provided by the Domain Specific Review Board of the National Healthcare Group, Singapore.

2.2. Data collection

Socio-demographic data such as age, gender, ethnicity, current smoking status, height, weight, and duration of untreated psychosis (DUP) were obtained from all study participants.

2.3. Assessments

All FEP participants were assessed using the SCID-1. Clinical symptoms were assessed on the PANSS by trained raters with established inter-rater reliability at >0.8. Controls were assessed on the SCID-I to determine history of mental illness at recruitment.

2.4. Measurement and calculation of serum DBP and vitamin D components

Venous blood was collected from all study participants into serum separating tubes. After blood collection, blood samples were allowed to coagulate at room temperature for 30 min, centrifuged at 4 °C and serum collected. Serum total vitamin D, albumin and calcium levels were determined by chemiluminescence immunoassay. DBP concentrations were measured by commercial enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, USA).

Calculations for bioavailable vitamin D were done using a general formula formulated by Vermeulen et al. (1999) and adjusted for vitamin D specifically by Powe et al. (2013) (see Supplementary material).

2.5. Statistical analysis

Data was analyzed on SPSS Statistics version 23 (IBM Co., Armonk, NY, USA). Descriptive statistics were tabulated for case and control groups. Statistical significance was set at $p<0.05$ and was examined using chi-squared test for categorical variables and either independent Student's *t*-test or Mann-Whitney *U* test for continuous variables. Univariate linear regression was used to identify predictors of total and bioavailable vitamin D. Multivariate linear regression models were employed to examine associations of total and bioavailable vitamin D with symptom severity using a PANSS 5-factor model that was previously published by our group (Jiang et al., 2013). Positive factor items include delusion, hallucination, suspiciousness, and unusual thought. Negative factor items include emotional withdrawal, poor rapport, passive social withdrawal, lack of spontaneity in conversation, and motor retardation. Excitement factor items include hyperactivity, hostility, and poor impulse control. Depression factor items include anxiety, guilt-feeling and depression. Cognitive factor items include disorientation and lack of judgment. In the regression models, we adjusted for gender and ethnicity as these variables were found to influence levels of vitamin D in the local population (Hawkins, 2013; 2009).

3. Results

3.1. Comparison of FEP and control groups demographics

Overall, 31 patients with FEP and 31 controls were enrolled. There was no significant difference in age, gender, ethnicity and smoking status distribution noted between the FEP group and the control group. The FEP group was noted to have significantly lower Body Mass Index (BMI, $t=-2.492$, $df=60$, $p=0.015$) when compared to controls (22.07 vs. 25.24) (Table 1).

3.2. Comparison of serum vitamin D levels

Although there was no significant difference in baseline serum albumin, calcium and total vitamin D levels between FEP and control groups, the FEP group had higher levels of DBP ($t=2.479$, $df=55$, $p=0.016$) and lower levels of bioavailable vitamin D (Mann-Whitney $U=280$, $p=0.046$) when compared to the control group (Table 1).

Upon further analysis, there was a statistically significant difference in total vitamin D levels between ethnic groups ($F=7.913$, $df=2, 54$, $p=0.001$). A Bonferroni post-hoc revealed that the serum total vitamin D level was statistically significantly lower in Malays (45.83 ± 22.83 nmol/L, $p=0.001$) when compared to Chinese (70.20 ± 21.83 nmol/L) and no statistical significance was noted between Chinese and Indian (50.00 ± 10.00 nmol/L, $p=0.280$). A Krustal-Wallis H test showed that there was a statistically difference in serum bioavailable vitamin D between the ethnic groups ($X^2=6.351$, $df=2$, $p=0.042$), with a mean rank serum bioavailable vitamin D levels of 33.06 for Chinese, 23.11 for Malays and 15.67 for Indians.