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Vitamin D status is associated with anxiety levels in postmenopausal women evaluated for osteoporosis

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Abstract

Vitamin D status has been previously associated with a wide range of acute and chronic diseases. The nervous system express vitamin D receptors and thus vitamin D may be involved in mental health. Poor data exist about the correlation between vitamin D and anxiety levels.

Our aim was to investigate the association of vitamin D status with anxiety severity. A group of 177 postmenopausal women (mean age 65.5±8.22 yr.)

referring to an outpatients clinic for the prevention of osteoporosis were evaluated. Severity of perceived anxiety symptoms was measured by the Hamilton Anxiety rating scale (HAMA). Depression levels were also evaluated using the Beck Depression Inventory-second edition scale (BDI-II). 25(OH)D serum levels, indicative of vitamin D status, were detected by high-performance liquid chromatography. 25(OH)D levels were significantly related HAMA-score (r=-0.15, p=0.04); particularly a deep association was observed between 25(OH)D levels and somatic symptoms (r=-0.195, p=0.009). HAMA score was associated with BDI-II score (r=0.487, p=<0.001); HAMA psychic symptom score was also related with age and time since menopause (r=0.149, p=0.039 and r=0.222, p=0.003, respectively). At a multiple regression analysis, after correcting for age and depression levels, 25(OH)D was predictive of HAMA score (β =-0,05961, p= 0.02, SE=-2.206), but the strength of association was lost further correcting for time since menopause.

In conclusion, in a setting of postmenopausal women, we observed a significant association between anxiety levels and serum 25(OH)D concentrations irrespective of age and depression levels.

Key words: vitamin D, anxiety, depression, postmenopausal women, osteoporosis

Introduction

Vitamin D is considered a key regulator of calcium homeostasis and bone health (Catalano et al., 2015a). Since vitamin D receptor (VDR) has been discovered in many tissues and cells that are not involved in mineral and bone metabolism, a growing interest about possible extraskeletrical effects of vitamin D has been seen (Holick, 2007).

Recently, a mounting evidence in previously unrecognized roles of vitamin D both in the human physiology of and pathophysiology is emerging, involving a wide range of clinical disorders and including cancer, cardiovascular, infective, immune, metabolic and neurological diseases (Holick, 2007; Timpini et al., 2011;

Wu et al., 2016; Smolders et al., 2011; Goodwill & Szoeke, 2017; Atteritano et al., 2016; Chu et al., 2017; Fedotova et al., 2017; Catalano et al., 2015b).

Mental disorders are considered major public health concern. The global lifetime prevalence of psychological disorders in adults is estimated to be between 12,2%-48,6% (Charara et al., 2017). Such diseases are also an enormous contributor to the global disease burden: in 2013, 5.4% of global DALYs (Disability-Adjusted Life Years) and 17.4% of global YLDs (Years Lived with Disability) were caused by mental disorders (Vos et al., 2016).

Anxiety disorders cover a large amount of mental illnesses and their world-wide prevalence is estimated of 7.3 %, ranging from 5.3 % in African cultures to 10.4 % in Euro/Anglo cultures, and suggesting that one in 14 people around the world at any given time has an anxiety disorder (Charara et al., 2017). As known, anxiety has been often related to several chronic physical diseases, as well as hypertension, heart disease, chronic respiratory disorders, gastrointestinal conditions and osteoporosis (Baxter et al., 2013; Hong-Jhe et al., 2016; Pino et al., 2018; Montserrat-Capdevila et al., 2018; Rhoten et al., 2018; de Beurs et al., 1999; Bierman et al., 2008). Older adults frequently show anxiety symptoms that contribute to reduced well-being and lower quality of life (de Beurs et al., 1999); moreover, although measurement of anxiety symptoms has not been considered predictive of cognitive decline in later life, a curvilinear effect of anxiety on cognitive performance was found (Bierman et al., 2008).

Anxiety symptoms and depression are related conditions, and it was previously observed that 43% of older persons with depression and 15% without depression reported anxiety symptoms [20](Mehta et al., 2003).

Depressive symptoms have been previously associated with reduced serum 25-hydroxyvitamin D [25(OH)D] concentrations 25(OH)D (Nguyen, Tsujiguchi, Kambayashi, 2017; Atteritano et al., 2013; Ju, Lee, Jeong, 2013). However, poor and conflicting data currently exist regarding the relationship between the vitamin D status and anxiety symptoms (De Koning et al., 2017; Armstrong et al., 2007; Callegari et al., 2017).

The aim of our research was to investigate the possible association between serum 25(OH) D concentrations and anxiety levels.

Methods

We selected a group of postmenopausal women, consecutively referred at the Outpatients Clinic for the Prevention and Treatment of Osteoporosis in the Department of Clinical and Experimental Medicine of the University Hospital of Messina, Italy, who fulfilled the WHO criteria for osteopenia/osteoporosis (Catalano et al., 2013).

Women were excluded if affected by a known psychiatric or neurological condition or under psychopharmacological treatment (Merendino et al., 2004; De Domenico et al., 1999; Martino et al., 2017; D'Aguanno, Langher, Velotti, 2017) , moderate to severe kidney or liver failure, hearth failure with NYHA (New York Heart Association) class ≥2, moderate and severe respiratory failure, cancer, malabsorption, chronic infective diseases or endocrine disorders (Catalano et al., 2015; Caputo, Giacchetta, Langher, 2016). Oral vitamin D medications, were not an exclusion criteria whether the amount of supplementation was in accordance to what established by the Institute of Medicine (Ros et al., 2011).

Recruited women were divided in tertiles according to their 25(OH) D levels.

Severity of perceived anxiety symptoms was measured by the Hamilton Anxiety rating scale (HAMA) which investigates 14 symptom-defined elements - scoring of 0 (not present) to 4 (severe) - and caters for both psychological and somatic symptoms, comprising anxious mood; tension (including startle response, fatigability, restlessness); fears (including of the dark/strangers/crowds); insomnia; ‘intellectual’ (poor memory/difficulty concentrating); depressed mood (including anhedonia); somatic symptoms (including aches and pains, stiffness, bruxism); sensory (including tinnitus, blurred vision); cardiovascular (including tachycardia and palpitations); respiratory (chest tightness, choking); gastrointestinal (including irritable bowel syndrome-type symptoms); genitourinary (including urinary frequency, loss of libido); autonomic (including

dry mouth, tension headache) and observed behaviour at interview (restless, fidgety, etc.) (Hamilton, 1959).

Depression levels were also evaluated using the Beck Depression Inventory-second edition (BDI-II) scale, consisting of 21 items (Beck, Steer, Brown, 1996), together with a clinical psychological investigation (Langher, Caputo, Martino, 2017).

25(OH)D plasmatic levels were detected by high-performance liquid chromatography.

Our investigation was carried out according with the 1964 Declaration of Helsinki and its later amendments, and written informed consent was obtained from all the participants.

Statistical analyses were performed using MedCalc software (version 10.2.0.0; Mariakerke, 173 Belgium). Student's t-test for unpaired observations or Mann-Whitney test as appropriate were applied. The $\chi 2$ test was performed to calculate differences in the proportion of categorical variables. Correlations between two variables were evaluated by Pearson correlation coefficient. Multiple regression analysis was performed to analyse the relationship between a dependent variable and one or more explanatory variables. Values of $P < 0.05$ were considered to indicate statistical significance.

Results

The main clinical characteristics of recruited postmenopausal women were reported in table 1.

Women of the three groups presented not significantly different age and time since menopause. BMI was significantly lower in subjects of group 3 in comparison with group 1, and the same was observed as for 25(OH)D levels ($p<0.05$).

	Total ***(n=177)***	Group-1 ***(n=57)***	Group-2 ***(n=60)***	Group-3 ***(n=60)***

Age (yr.)	65.5±8.22	64.42±8.73	65.43±9.42	65.6±7.8
Age at menopause (yr.)	47.69±4.81	49.05±3.67	46.94±5.17	45.95±7.84
Time since menopause (yr.)	19.92±9.12	18.52±8.10	19.73±9.22	19.65±8.46
BMI (Kg/m²)	24.92±5.08	25.73±5.3	24.91±3.96	23.13±3.24*
Current smoking [n (%)]	19 (10)	6 (10)	4 (6)	9 (15)
Alcohol ≥3units/day [n (%)]	0 (0)	0 (0)	0 (0)	0 (0)
25(OH)D (ng/ml)	26.52±6.64	26.32±6.64	26.75±7.71	28.9±5.62*

Table 1 – Main clinical characteristics of recruited postemenopausal women.*= $p<0.05$ vs. group 1.

Depression symptoms, as measured by BDI-II score, were not significantly different among the groups; otherwise, anxiety levels, as detected by HAMA score, were significantly lower in group 3 in comparison with group 1 ($p<0.05$) (table 2). Although a statistical significance was not reached between the three groups, a trend to reduction of both somatic and psychic symptoms was noted group 3 vs. group 1.

	Total ***(n=177)***	Group-1 ***(n=57)***	Group-2 ***(n=60)***	Group-3 ***(n=60)***
Anxiety levels				
- HAMA score	27.72±6.84	28.9±5.6	26.75±7.71	26.52±6.64*
- HAMA somatic symptom score	11.79±3.81	12.4±3.30	11.2±3.69	11.15±4.09
- HAMA psychic symptom score	15.86±3.94	16.5±3.11	15.55±4.88	15.47±3.3
Depression levels				
- BDI-II score	7.26±3.34	6.94±2.8	7.45±2.98	6.75±3.32

Table 2 – Psychological features of recruited postmenopausal women. HAMA= Hamilton Anxiety Scale; BDI-II= Beck Depression Inventory-second edition. *= p<0.05 vs. Group-1.

By considering all the recruited subjects, 25(OH) D levels were significantly related with age (r=-0.207, p=0.006), BMI (r=-0.174, p=0.020) and HAMA-score (r=-0.15, p=0.04); particularly a deep association was observed between 25(OH)D levels and somatic symptoms (r=-0.195, p=0.009). HAMA score was associated with BDI-II score (r=0.487, p=<0.001); HAMA psychic symptom score was also related with age and time since menopause (r=0.149, p=0.039 and r=0.222, p=0.003, respectively) while, BDI-II was related to age (r=0.177, p=0.014).

At a multiple regression analysis, after correcting for age and depression levels, 25(OH)D was predictive of HAMA score (β=-0,05961, p= 0.02, SE=-2.206), but the strength of association was lost further correcting for time since menopause.

Discussion

Compelling evidence supports a role for vitamin D in the developing brain as well as in adult brain function. The VDR and the biosynthetic machinery for the hydroxylation of vitamin D have been found, in neurons, glial cells, and the pituitary gland (Buell, Dawson-Hughes, 2008) . Thus, neurological and psychological action of vitamin D have been claimed.

Our results suggest a cross-sectional association between anxiety levels and vitamin D status as detected from the 25(OH)D concentrations. These data are consistent with precedent findings derived from the Longitudinal Aging Study Amsterdam even if, after adjustment for demographic and lifestyle variables and depressive symptoms, de Koning et al. no longer observed any significant association (De Koning et al., 2017).

Anxiety and depression levels were significantly related in our population in accordance to other authors (De Koning et al., 2017; Armstrong et al., 2007; Callegari et al., 2017) . Armstrong et colleagues reported that vitamin D deficiency is common in fibromyalgia, and occurs more frequently in patients

with anxiety and depression; however they found no relationship between vitamin D levels and the anxiety or depression subscales of the Hospital Anxiety and Depression Score (Armstrong et al., 2007).

We observed that the association between severity of anxiety and 25(OH) D remained significant also after adjusting for age, time since menopause and depression levels.

Consequently, subjects with low 25(OH)D levels were more likely to exhibit higher anxiety symptoms and, particularly, we noticed a significant association between somatic symptoms and 25(OH)D levels.

The neuroprotective effect of vitamin D is believed to be linked to its influence on neurotrophin production and release, neuromediator synthesis, intracellular calcium homeostasis, and prevention of oxidative damage to nervous tissue (Jamali, Sorenson, Sheibani, 2018; Wrzosek et al., 2013). Furthermore, experimental evidences corroborate the psychological action of vitamin D. In a mouse model, the genetic deletion of VDR induced an increased anxiety-like behaviour (Kalueff et al., 2004) and, in a model of oestrogen deficiency, it was observed that high doses of cholecalciferol, the native vitamin D, produced a significant anxiolytic-like effect due to an increase in the monoamines levels (Fedotova, Pivina, Sushko, 2017).

These studies suggested that vitamin D and its receptors are involved in the brain activities, whose imbalance may significantly affect emotional behaviour (Wrzosek et al., 2013; Kalueff et al., 2004; Fedotova, Pivina, Sushko, 2017; Valipour, Saneei, Esmaillzadeh, 2014).

We considered for this research a setting of only women, so excluding men we avoided the introduction of gender differences. In addition, all the women were in postmenopausal age, thus the contribution of different hormonal status was possibly ruled out. We acknowledge however some limitations of this study. First, the cross-sectional design; second, the poor sample size; third, the selection of postmenopausal women which took place at a single university reference centre

for the prevention and treatment of metabolic bone disease, thus the studied sample may not reflect general population.

Nevertheless, the prevalence of vitamin D deficiency is very common in patients with psychotic disorders compared with general population (Valipour, Saneei, Esmaillzadeh, 2014), and low vitamin D levels were associated to poor health status and pain (Holick, 2007; Catalano et al., 2017; Windelinckx et al., 2007; Catalano et al., 2012; Pu et al., 2018).

Aging of the world's population is increasing the number of people living with sequelae of diseases and injuries, also contributing to the continued increase in the rate of years lived with disability (Fedotova, Pivina, Sushko, 2017).

Because psychological disease including anxiety may have a role in social burden and reduced quality of life, further controlled research with longitudinal design are needed to confirm the role of vitamin D on mental health and to investigate its therapeutic application in vitamin D deficient subjects.

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