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Vitamin D deficiency, depression course and mortality: Longitudinal results from the Netherlands Study on Depression in Older persons (NESDO)

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ABSTRACT

Objective: To study the effect of vitamin D levels on depression course and remission status after two years, as well as attrition and mortality, in an older cohort.
Methods: This study was part of the Netherlands Study on Depression in Older persons (NESDO), a prospective cohort study. 367 depressed older persons (≥60 years) were included. Baseline vitamin D status, reasons for loss to follow up, clinical depression diagnosis at two-year follow up, and six-monthly symptom scores were obtained. Data were analyzed by logistic regression and random coefficient models and adjusted for confounders of vitamin D status.
Results: Vitamin D had no effect on the course of depression or remission, except for a trend towards lower remission rates in the severely deficient subgroup (25-(OH) vitamin D < 25 nmol/l). Patients who died during follow up had significantly lower 25-(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels than patients with continued participation.
Conclusions: For the total sample we found no effect of vitamin D levels on the course of depression or remission rates. However, we did find an effect of lower vitamin D levels on mortality. This strengthens the interpretation of vitamin D deficiency being a marker for poor somatic health status. The trend towards lower remission rates in the severely deficient subgroup raises the question whether this group could benefit from supplementation. Randomized controlled trials are necessary to study this.

Introduction

Vitamin D deficiency is a major public health problem worldwide [1], particularly in older people [2]. Increased prevalence of vitamin D deficiency with age is explained by dietary deficiencies, decreased production of vitamin D in the skin, decreased conversion of calcidiol (25-(OH) vitamin D) to calcitriol (1,25-$(OH)_2$ vitamin D) in the kidney and lack of sunlight exposure in older people [3]. Besides its effect on calcium metabolism and bone health, vitamin D deficiency has been linked to various diseases [4,5] and proposed to be a universal risk factor for multiple multifactorial diseases [6]. Vitamin D directly affects gene regulation, thereby influencing cell proliferation, vascular calcifications and inflammatory responses, as well as indirectly affects the renin–angiotensin–aldosterone system [6]. In older populations vitamin D deficiency has also been associated with frailty and mortality [7–9]. Increased mortality rates may be explained by the association of vitamin D deficiency with several somatic diseases, particularly cardiovascular disease [10].

A meta-analysis of cross-sectional, population-based studies yielded a pooled odds ratio of 1.31 (95%-confidence interval (95%-CI) 1.00–1.71; p = .05) for association between low vitamin D levels and depression [11]. Furthermore, both younger and older patients suffering from depressive disorder had lower vitamin D levels compared to controls [12,13].

Current hypotheses about the pathophysiological mechanisms in the association between vitamin D and depression include a role for vitamin D in the regulation of neurotransmitters dopamine, noradrenaline and acetylcholine, as well as an effect on neurotrophic factors [14]. Moreover, vitamin D receptors are found in the prefrontal cortex and parts of the limbic system [15]. These brain areas have been implicated in the pathophysiology of depression [16]. Vitamin D might also reduce concentrations of inflammatory markers associated with depression

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[17]. A reverse causative mechanism might be that depression leads to decreased sun exposure, poorer dietary intake and more smoking, thereby causing vitamin D deficiency [18].

Longitudinal studies, however, are less consistent and mainly focused on vitamin D as a risk factor for the incidence of depression. Meta-analysis of three cohort studies in middle-aged to older populations [19–21] yielded a significant hazard ratio of depressive symptoms for the lowest vs. the highest vitamin D levels (2.21 (95%-CI 1.40–3.49; $p < .001$) [11]. Thereafter, in an older cohort no effect of vitamin D levels on the incidence of depressive symptoms was found [22]. To our knowledge, only one study has examined the effect of vitamin D status on course of depression [12]. In this sample of depressed younger adults higher vitamin D levels were associated with better depression outcomes [12]. In a meta-analysis of randomized controlled trials, vitamin D supplementation did not lead to a reduction of depressive symptoms. However, few participants were (clinically) depressed or vitamin D deficient [23].

Furthermore, nearly all studies have measured 25-(OH) vitamin D levels, while 25-(OH) vitamin D has to be converted in the kidney to the biologically active form, 1,25-$(OH)_2$ vitamin D. In previous cross-sectional analyses, our group found that 1,25-$(OH)_2$ vitamin D was lowered in depression as well [13].

The primary objective of the present study is to examine whether 25-(OH) vitamin D and 1,25-$(OH)_2$ vitamin D levels also predict remission of late-life depression at two-year follow-up, as well as its course. The second objective, essential in an older age sample, is to study the effect of vitamin D on attrition and mortality.

Methods

Sample

The present study was part of the Netherlands Study of Depression in Older persons (NESDO), an on-going cohort study designed to examine the determinants, course and consequences of late-life depression (for details, see [24]).

The cohort consisted of 378 depressed patients and 132 non-depressed comparison subjects aged 60 to 93, recruited between 2007 and 2010 from mental health institutions and general practitioners. Data was gathered about mental health outcomes, demographic characteristics and psychosocial, biological, cognitive and genetic determinants. At two-year follow up all measures open to change were evaluated again. Attrition and its reasons were recorded [25]. Interviews were performed by trained research assistants and were audio taped regularly to control for quality.

Exclusion criteria were a (suspected) diagnosis of dementia, a Mini Mental State Examination (MMSE) [26] score < 18/30 and insufficient command of the Dutch language. The ethical review boards of the five participating centers approved the study. All participants received oral and written information and provided their informed consent.

For the present study, we selected the patient group. Eleven patients were excluded due to missing vitamin D levels, leaving a study sample of 367 depressed persons at baseline.

Depression

At baseline and two-year follow-up, past-six months diagnoses of depression and dysthymia according to the Diagnostic and Statistic Manual of Mental Disorders (DSM-IV-TR)-criteria [27] were assessed with the Composite International Diagnostic Interview (CIDI; WHO version 2.1; life-time version), a structured clinical interview [28,29]. Additional questions were added to diagnose current minor depression according to the research criteria of the DSM-IV-TR [24].

The severity of depressive symptoms was assessed every six months with the Inventory of Depressive Symptoms — Self Report (IDS-SR) [30]. For 28 symptoms, severity and frequency were rated on a scale from 0 to 3, adding up to total scores ranging from 0 to 84, higher scores indicating more severe depression. Three subscale scores were derived, reflecting a mood (9 items), motivational (5 items) and somatic (8 items) dimension [31].

Laboratory testing

Vitamin D levels were assessed at baseline. Serum 25-(OH) vitamin D levels were measured using isotope dilution-online solid-phase extraction liquid chromatography–tandem mass spectrometry, as described previously [32]. Serum 1,25-$(OH)_2$ vitamin D levels were determined by radioimmunoassay.

The optimal 25-(OH) vitamin D level has been estimated to be between 50 and 100 nmol/l, since serum levels below 75 nmol/l induce parathyroid hormone (PTH) secretion [33]. Serum 25-(OH) vitamin D levels are often categorized as severely deficient (<10 nmol/l), deficient (10–25 nmol/l), insufficient (25–50 nmol/l), hypovitaminosis D (50–75 nmol/l), and sufficient (≥75 nmol/l) [34,35]. A recent study reported a reference interval for 1,25-$(OH)_2$ vitamin D between 59 and 159 pmol/l [36].

Covariates

Based on the literature [37,38], we a priori selected three sets of covariates.

The first set consisted of demographic characteristics (age, gender and years of education) and astronomical season of blood withdrawal (winter: 21 November–20 February; spring: 21 February–20 May; summer: 21 May–20 August; autumn: 21 August–20 November).

The second set included the lifestyle factors smoking (yes/no), use of alcohol and physical activity. We included the Alcohol Use Disorders Identification Test (AUDIT) [39] sum score as a proxy for (subclinical) alcohol dependence severity. To measure physical activity, the number of Metabolic Equivalent of Task (MET)-minutes per week was obtained using the eight-item International Physical Activities Questionnaire (IPAQ) [40].

Parameters of somatic functioning formed the third set of confounders: waist circumference (centimeters), serum levels of PTH (obtained as described earlier [13]) and glomerular filtration rates (GFR), estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.[41] The number of chronic diseases was assessed by means of self-report questions. This has been proven to be an accurate method when compared to data from general practitioners [42]. The MMSE was used to assess global cognitive functioning (range 0–30), higher scores indicating better cognitive functioning [26].

All covariates were assessed at baseline. Vitamin D supplementation, assessed at baseline and two-year follow-up, was not taken into account, as dosages were low and we were interested in the actual vitamin D levels. Nonetheless, a sensitivity analysis, excluding all patients with vitamin D supplementation will be performed.

Statistical analysis

All analyses were performed separately for 25-(OH) and 1,25-$(OH)_2$ vitamin D. Vitamin D levels were standardized using Z-scores. All statistical tests were two-sided, p-values below .05 were considered significant. To meet the test assumptions, 5 positive outliers for 1,25-$(OH)_2$ vitamin D levels, 6 positive outliers for PTH levels and 5 positive outliers for MET-minutes/week were trimmed at the level of the mean plus 3 standard deviations. AUDIT sum scores were log transformed.

Vitamin D levels and covariates at baseline were compared by participation status at two-year follow-up, i.e. 'participation', 'death' or