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SERUM CONCENTRATIONS OF 25-HYDROXYVITAMIN D AND DEPRESSION IN A GENERAL MIDDLE-AGED TO ELDERLY POPULATION IN FINLAND

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Abstract: *Objectives:* Low concentrations of serum 25-hydroxyvitamin D [25(OH)D] have been postulated to associate with an increased prevalence of depression. As there are a limited number of publications on this issue, we examined the association between serum 25(OH)D and depression in a general middle-aged or older population. *Design:* A population-based cross-sectional study. *Setting and participants:* A total of 1602 men and women from the population-based Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) in Eastern Finland, aged 53-73 y in 1998-2001, were analysed. *Measurements:* Depressive symptoms were assessed with the DSM-III depression scale, and those individuals who had scores over 4 (range 0-12) or had reported undergoing current antidepressant therapy, were considered as suffering from depression. Associations were estimated in serum 25(OH)D tertiles using logistic regression. *Results:* Among the participants, 183 subjects (11.4%) were considered to have depression. The mean age of the subjects was 62.6 years (SD 6.4, range 53.4-73.8 years). The mean serum 25(OH)D concentration was 43.8 nmol/L (SD 17.7, range 8.5-112.8 nmol/L), concentrations <50 nmol/L were observed in 65.0% of the subjects, and only 5.0% displayed concentrations ≥75 nmol/L. After multivariable adjustments, the odds ratios for having depression in the tertiles (from highest to the lowest) of serum 25(OH)D were 1, 1.35 (95 % CI: 0.87, 2.09) and 1.64 (95 % CI: 1.03, 2.59), P for trend=0.036. *Conclusion:* These findings indicate that a lower concentration of serum 25(OH)D is associated with a higher prevalence of depression in an elderly general population.

Key words: Vitamin D, 25-hydroxyvitamin D, depression, depressive symptoms.

Introduction

Vitamin D deficiency is considered as a worldwide problem with various health consequences. In addition to its classic effects on bone health, vitamin D deficiency has been related to many chronic illnesses, such as common cancers and diabetes, autoimmune diseases like multiple sclerosis and inflammatory bowel diseases, dementia, infectious diseases, as well as hypertension and cardiovascular disease (CVD), although the evidence is not conclusive (1-4). In a few studies, vitamin D deficiency has also been associated with mental disorders, including depression (5, 6).

The main sources of vitamin D include foods that are naturally rich in vitamin D, like fatty fish, and foods that are fortified with vitamin D (7, 8). Dietary supplements are also a commonly recommended source of vitamin D. Adequate amounts of vitamin D can be produced endogenously when there is sufficient exposure to UVB-radiation on a regular basis, so that one might not need to obtain any of it from the diet (9). In that case, vitamin D can rather be considered as a prohormone than a vitamin. Otherwise, one has to meet vitamin D needs through the diet (9).

Depression is a global health challenge and has an impact on disability, morbidity, mortality, quality of life and healthcare costs (5). Higher concentrations of serum 25-hydroxyvitamin D [25(OH)D] have recently been linked to decreased risk of depression (10). Similarly, in previous studies, lower concentrations of 25(OH)D have been reported to associate with higher prevalence of depressive symptoms in different age groups (11, 12). However, some studies have failed to show such an association (13, 14) and it is still unclear whether the association is causal. Especially, only few studies have examined the association between vitamin D and depression in older populations living at northern latitudes, where vitamin D production in the skin is limited only to few months per year. A previous study from Iceland reported that elderly men with deficient vitamin D status were more likely to have a current major depressive disorder (15). As there are age-related changes that affect vitamin D metabolism and increase the requirement for vitamin D in the elderly (16), it is important to also consider the association between vitamin D status and depression in different age groups.

The aim of the present study was to evaluate the association between serum 25(OH)D and depression in a general middle-aged to elderly population in Finland, where low vitamin D status has been common especially during the long wintertime.

Subjects and methods

Study population

The Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD) is an ongoing population-based study designed to

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investigate risk factors for CVD and other chronic diseases in middle-aged or older men and women in Eastern Finland. The study protocol was approved by the Research Ethics Committee of the University of Kuopio. All subjects gave their written informed consent.

The baseline examinations of the KIHD were conducted between 1984 and 1989 on a random sample of men living in the city of Kuopio and neighboring rural communities. A total of 2682 men who were 42, 48, 54 or 60 years old at baseline (82.9% of those eligible) were recruited in two cohorts. The first cohort consisted of 1166 men (83.3% of those eligible) who were 54 years old, enrolled between 1984 and 1986, and the second cohort included 1516 men (82.6%) who were 42, 48, 54 or 60 years old, enrolled between 1986 and 1989. During the years 1998-2001 all men from the second cohort were invited to the 11-year re-examinations of the study, and 854 men (85.6%) participated. The 11-year examinations were also the baseline for 920 postmenopausal women (78.4% of those eligible) from the same area, aged 53-73 years. The analyses of the current study were conducted based on the measurements of the 11-year examinations and the above described 854 men and 920 women were used as the study population. We excluded subjects without data on serum 25(OH)D (n = 18) or without information on depression status (n = 154) in the 11-year examinations, leaving 787 men and 815 women, a total of 1602 subjects for the analyses.

Measurements

The subjects gave fasting blood samples between 8.00 and 10.00 in the morning. They were instructed to abstain from ingesting alcohol for three days and from smoking and eating for 12 hours prior to giving the sample. Detailed descriptions of the determination of serum fatty acids, assessment of medical history and medications, family history of diseases, smoking, alcohol consumption, and socioeconomic status have been published elsewhere (17-19). Education was assessed in years by using a self-administered questionnaire. Annual income was obtained from a self-administered questionnaire. Physical activity was assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire (20). Body mass index (BMI) was computed as the ratio of weight in kilograms to the square of height in meters, both measured during the study visit. BMI is associated with both depression and vitamin D status and it has been documented that fat mass even has a greater influence on serum 25(OH)D concentrations than dietary vitamin D intake (21). Dietary intakes of foods, nutrients and energy were assessed at the time of blood sampling using 4-day food recording (22). History of mental diseases was assessed using self-administered questionnaire.

Determination of serum 25-hydroxyvitamin D

Each subject gave a blood sample once for this study. Blood samples for 25(OH)D analysis were taken into serum gel tubes at common laboratory conditions. After 30 minutes for clotting, serum was separated and stored at -70 °C for 9-11 years prior to 25(OH)D measurement. Serum 25(OH)D concentration was determined with an HPLC (Shimadzu, Kyoto, Japan) using diode array detector (Beckman, CA) as previously described (23). The limit of detection for both 25(OH)D3 and D2 was 1.5 nmol/L, and the limit of quantification 5 nmol/L. Few samples had detectable 25(OH)D2 concentrations, but they were mainly below the quantification limit. Therefore, only the results for 25(OH)D3 are reported. Intra- and inter-assay variation was monitored by analyzing in each assay duplicates of 2 control samples, a self-made serum pool 1 or 2, and a vitamin D control serum (Chromsystems GmbH, Germany). Inter-assay variation for serum pool 1 (53 nmol/L) was 15% and for vitamin D control serum (68 nmol/L) 16%. Variation for serum pool 2 (99 nmol/L) was 8.7%.

Assessment of depression

Depressive symptoms were assessed with the Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III), Depression Scale, which is a self-rated questionnaire consisting of 12 symptoms of depression based on the DSM-III diagnostic criteria (range 0-12) (24). We used the decile of the sample with the highest scores of DSM-III Depression Scale to form a group with elevated depressive symptoms in order to enable reliable statistical power for analyses (n = 68, 9.0% of the sample) (25). Those in the highest decile had DSM-III Depression Scale scores 4 or more.

Statistical analysis

The univariate relationships between serum 25(OH)D and the characteristics of the study population were assessed by linear regression (for continuous variables) and $\chi 2$-tests (for categorical variables). The association between serum 25(OH)D concentrations and depression was estimated as odds ratios (OR) by logistic regression. The model 1 included age, gender and examination year. The multivariable-adjusted model 2 included model 1 and examination month, socioeconomic status, marital status, leisure time physical activity, energy intake, alcohol intake, intake of fruits, berries and vegetables, and serum long-chain omega-3 polyunsaturated fatty acids (eicosapentaenoic acid (EPA) + docosahexaenoic acid (DHA) + docosapentaenoic acid (DPA)) and the history of mental diseases. These self-reported mental diseases included all psychiatric conditions diagnosed by a physician. We also conducted further statistical analyses with adjustment for BMI, smoking and the number of chronic diseases. Cohort mean was used to replace missing values (<1.2%) in covariates. The statistical significance of the interactions on a multiplicative scale was assessed by likelihood ratio tests using a cross-product term. Tests of linear trend were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. All P-values were 2-tailed ($\alpha = 0.05$). The data were analyzed using SPSS 19.0 for Windows (SPSS Inc., Chicago, IL, USA).

Table 1
Characteristics of the 1602 subjects in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD), according to serum 25 hydroxyvitamin D concentrations

	Serum 25 hydroxyvitamin D tertiles (nmol/L)						
	1 (8.5-34.3)		2 (34.4-50.7)		3 (50.8-112.8)		
	Mean or %	SD	Mean or %	SD	Mean or %	SD	P for trend†
Number of subjects	534		534		534		
Age (years)	62.1	6.6	63.0	6.3	62.6	6.3	0.264
Male gender (%)	55.4		47.8		44.2		<0.001
Marital status (married %)	73.8		75.3		77.5		0.120
Education (years)	9.5	3.6	9.6	3.5	9.9	3.4	0.093
Annual income (euro)	16 706	11 985	15 942	11 645	16 845	10 926	0.799
Socioeconomic status (scores)	8.5	4.3	8.1	4.2	7.8	4.2	0.007
Current smoker (%)	18.2		12.4		9.9		<0.001
Body mass index (kg/m2)	28.3	4.6	28.0	4.4	27.1	4.2	<0.001
Leisure-time physical activity (kcal/day)	169	188	176	181	213	236	<0.001
Energy intake (kcal/day)	1874	586	1827	584	1857	562	0.668
Alcohol intake (g/week)	60.4	130.6	45.8	82.6	44.8	82.1	0.014
Intake of fruits, berries & vegetables (g/day)	298	189	296	180	329	193	0.005
Vitamin D intake (μg/day)	6.0	6.1	6.5	6.4	7.4	6.0	<0.001
Serum long-chain omega-3 fatty acids (EPA, DHA, DPA) (%)	4.7	1.5	5.1	1.8	5.5	1.9	<0.001
Average number of chronic diseases	0.35	0.98	0.37	0.97	0.29	0.92	0.318
Mental diseases (%)	7.5		6.6		9.7		0.174
DSM-III score	1.63	2.00	1.43	1.89	1.46	1.82	0.153

Abbreviations: EPA, Eicosapentaenoic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; †The linear regression or χ2-test was used.

Ethical information

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects/patients were approved by the Research Ethics Committee of the University of Kuopio.

Results

Subject characteristic

The mean age of the subjects was 62.6 years (SD 6.4, range 53.4-73.8 years). The mean serum 25(OH)D concentration was 43.8 nmol/L (SD 17.7, range 8.5-112.8 nmol/L) in the whole population, with a strong seasonal variation (Figure 1). The mean serum 25(OH)D concentration was 42.3 nmol/L (SD 17.6) in men and 45.1 nmol/L (SD 17.6) in women (P for difference 0.001). Insufficient serum 25(OH)D concentrations (<50 nmol/L) were observed in 65.0% of the subjects (68.7% among men, 61.5% among women; P for difference 0.002), and 14.5% had deficient serum concentrations (<25 nmol/L) (16.1% among men, 13.0% among women; P for difference 0.044). Only 5.0% (3.8% in men, 6.1% among women; P for difference 0.033) had concentrations ≥75 nmol/L, which has been suggested as the desirable level. The mean serum 25(OH) D concentration was 41.6 nmol/L (SD 17.3) among those who had depression and 44.0 nmol/L (SD 17.7) among other subjects (P for difference 0.078).

Those with a higher serum 25(OH)D concentration were more likely to be female, have lower BMI and have higher leisure-time physical activity (Table 1). They were also more likely to have higher intake of fruits, berries and vegetables and vitamin D and also higher concentrations of serum long-chain omega-3 polyunsaturated fatty acids. They were less likely to smoke tobacco and had a lower alcohol intake.

Association of serum 25-hydroxyvitamin D with depression

Among the study participants, 183 (11.4%) were considered to have depression. The prevalence of depression was lower in the highest tertile of serum 25(OH)D (≥50.8 nmol/L) when compared to the lowest tertile (<34.4 nmol/L) (10.1% vs. 13.1%). After adjustments for age, gender and examination year (Model 1), the OR for depression was non-significantly increased by 43% in the lowest vs. highest serum 25(OH)D tertile (95% CI -3–112%, P for difference 0.074) (Table 2). After further multivariable adjustments for examination month, socioeconomic status, marital status, leisure-time physical activity, energy intake, alcohol intake, intake of fruits, berries

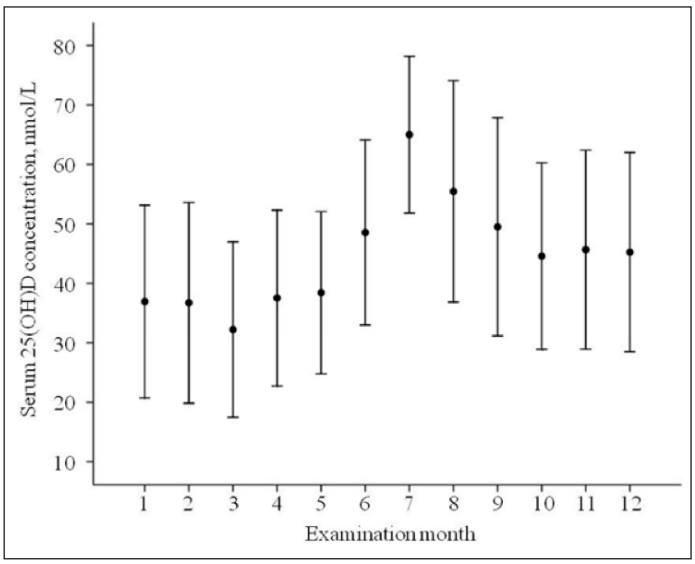
Table 2
Odds ratios for depression in tertiles of serum 25-hydroxyvitamin D in 1602 subjects in the Kuopio Ischaemic Heart Disease Risk Factor Study (KIHD)

	Serum 25(OH)D tertile (nmol/L)			
	1 (8.5–34.3)	**2 (34.4–50.7)**	**3 (50.8–112.8)**	**P for trend**
Number of depressed subjects/others				
(% of depressed subjects)	70/534 (13.1)	59/534 (11.0)	54/534 (10.1)	
Model 1†	1.43 (0.97–2.12)	1.13 (0.76–1.69)	1 (Ref.)	0.074
Model 2‡	1.64 (1.03–2.59)	1.35 (0.87–2.09)	1 (Ref.)	0.036

All values are odds ratios and 95% confidence intervals if not otherwise specified; †Model 1 is adjusted for age, gender and examination year; ‡Model 2 is adjusted for Model 1 and examination month, socioeconomic status, marital status, leisure-time physical activity, energy intake, alcohol intake, intake of fruits, berries and vegetables, serum omega-3 fatty acids (eicosapentaenoic acid + docosahexaenoic acid + docosapentaenoic acid) and mental diseases.

and vegetables, serum long-chain omega-3 polyunsaturated fatty acids, and history of mental disease (Model 2), the OR of having depression was increased by 64% in the lowest vs. highest serum 25(OH)D tertile (95% CI 3-159%, P for difference 0.036). Additional adjustments for BMI, smoking and the number of chronic diseases did not markedly change the associations (OR change <5%).

Figure 1
Monthly mean (±SD) serum 25(OH)D concentrations among men and women in the KIHD study population.



Reproduced with permission from Virtanen et al. (2011) Eur J Nutr 50, 305-312. Abbreviations: 25(OH)D, 25-hydroxyvitamin D; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study

Although serum 25(OH)D concentration had a strong seasonal variation (Figure 1), there was no higher odds for depression in the months with the lowest serum 25(OH)D concentrations (between January and May) when compared to the other months (OR 1.12, 95% CI: 0.79-1.60).

The prevalence of depression was higher among women than among men (Table 3). When the analyses were stratified by gender, the association between serum 25(OH)D and depression appeared to be stronger in men compared to women, although the interaction was not statistically significant (P for interaction 0.106, Model 2).

Discussion

The results of this study indicated that lower serum 25(OH)D concentrations were associated with higher odds for depression in a general middle-aged to elderly population in Finland. Our findings are consistent with previous epidemiological studies that suggest a relationship between vitamin D and depression (10, 11, 15), although some studies have failed to show such an association (13, 14). Differences in study populations (for example in terms of the ethnic group, geographical location, serum levels of 25(OH)D and age), and methods (such as unequal use of confounding variables) might explain the inconsistent results. However, our results are highly similar to the recent studies in the Finnish (10) and in the Icelandic populations (15). The mean age of the participants was 76-77 years in the Icelandic population and 62-63 years in our study. However, the study population was relatively younger in the previous Finnish study (age range 30-79 years) (10). The mean serum 25(OH)D was higher in the Icelandic study population; 59% of men and 50% of women had serum 25(OH) D concentrations above 50 nmol/l, whereas in our population only 31.3% of men and 38.5% of women had serum 25(OH)D concentrations above this level. In Iceland, it is common to use vitamin D containing cod liver oil, which may partly explain the differences. In a previous meta-analysis of cross-sectional studies (5), vitamin D status below 50 nmol/l was associated with increased likelihood of depressive symptoms (OR 1.31, 95 % CI 1.00-1.71), also in the elderly (≥65 years). Further meta-analyses are needed.

Our findings suggested that the association between low serum 25(OH)D and increased odds for depression may be stronger in men than in women, which is a similar finding

Table 3
Odds ratios for depression in tertiles of serum 25-hydroxyvitamin D by gender

	Tertiles of serum 25(OH)D (nmol/L)				
The whole study population	1 (8.5–34.3)	2 (34.4–50.7)	3 (50.8–112.8)	P for trend	P for interaction
Number of depressive cases/subjects (% of depressive cases)	Women 50/271 (18.5 %)	Women 42/273 (15.4 %)	Women 41/271 (15.1 %)		
	Men 21/262 (8.0 %)	Men 18/262 (6.9 %)	Men 11/263 (4.2 %)		
	Tertiles of serum 25(OH)D (nmol/L)				
Women	1 (8.5-36.1)	2 (36.2-52.2)	3 (52.3-112.8)		
Model 1†	1.19 (0.75–1.89)	0.99 (0.62–1.59)	1 (Ref.)	0.474	0.092
Model 2‡	1.39 (0.81–2.39)	1.25 (0.74–2.09)	1 (Ref.)	0.237	0.106
	Tertiles of serum 25(OH)D (nmol/L)				
Men	1 (8.9-32.3)	2 (32.4-48.3)	3 (48.4-110.7)		
Model 1†	1.89 (0.88–4.04)	1.65 (0.76–3.58)	1 (Ref.)	0.103	0.092
Model 2‡	2.10 (0.86–5.12)	1.94 (0.80–4.67)	1 (Ref.)	0.107	0.106

All values are odds ratios and 95% confidence intervals if not otherwise specified; †Model 1 is adjusted for age and examination year; ‡Model 2 is adjusted for Model 1 and examination month, socioeconomic status, marital status, leisure-time physical activity, energy intake, alcohol intake, intake of fruits, berries and vegetables, serum omega-3 polyunsaturated fatty acids, and mental diseases.

as reported in two previous studies (10, 15). In our study population, the mean serum 25(OH)D concentration was lower in men compared to women, as it was also in another previous study (14), which may partly explain the findings. In other studies on the topic, there were no reported differences in serum values of 25(OH)D between men and women (11-13). It is also possible that this finding is only a coincidence, especially, when the prevalence of depression is higher among women.

The exact mechanisms behind the association between vitamin D and depression are still to be elucidated, although several theories have been suggested. First, it has been discussed whether the vitamin D receptors in areas of the brain that are implicated in depression could be the link between vitamin D and depression (5, 26). According to the monoamine deficiency hypothesis of depression, impairments in monoamine (such as serotonin and norepinephrine) synthesis, release, reuptake and/or receptor binding are related to depression (27). In the promoter regions of serotonin genes, also vitamin D response elements have been identified (5, 28), which could also explain the association. Secondly, according to the hypothalamic-pituitary-cortisol hypothesis, abnormalities in the cortisol response to the stress might be involved in depression (29). It has been demonstrated that there is a linkage between vitamin D receptors and glucocorticoid receptors in the hippocampus (30). Vitamin D, in turn, has an antagonist effect on some of the glucocorticoid mediated functions (31). Finally, it has been suggested that depression is associated with chronic low-grade inflammation, which vitamin D might be able to moderate through its modulatory effects on immunity (31).

The strengths of this study are the population-based recruitment, high participation rate and extensive examination of potential confounders. Inclusion of both genders is also a strength. However, the study also has some limitations to be noted. The measured serum 25(OH)D concentrations were relatively low, so it was not possible to explore a larger scale of serum 25(OH)D concentrations and to investigate whether additional benefits could be observed with higher serum 25(OH)D concentrations. In addition, interview-based, clinical diagnosis made by a physician could have offered a more reliable measurement of depression compared to the self-rated DSM-III Depression questionnaires. Due to the cross-sectional study design, no conclusions of causal relation can be drawn. It is possible that lower serum 25(OH)D concentrations only reflect unhealthier lifestyle habits, such as lower fish consumption or less outdoor activities, and some other factors related to poor health and lifestyle might explain the results. Moreover, both depression and aging may affect serum 25(OH)D concentrations by reducing outdoor activities and thus decreasing the exposure to UVB-radiation of sunlight. In addition, depression can also lead to a poor diet and subsequently to a reduced intake of vitamin D. In these cases, lower serum 25(OH)D concentrations are the result of depression, not the cause of it. To determine and ensure the causal relationship between vitamin D and depression, more studies are required.

In conclusion, our findings support the earlier findings that vitamin D deficiency is associated with increased odds of depression. Overall, the role of vitamin D in the prevention and treatment of depression in elderly individuals still requires further exploration in large-scale randomized controlled trials.

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