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Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial

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Abstract. Jorde R, Sneve M, Figenschau Y, Svartberg J, Waterloo K (University of Tromsø and University Hospital of North Norway, Tromsø, Norway). Effects of vitamin D supplementation on symptoms of depression in overweight and obese subjects: randomized double blind trial. *J Intern Med 2008*; **264**: 599–609.

Objectives. The objective of the present study was to examine the cross-sectional relation between serum 25-hydoxyvitamin D [25-(OH) D] levels and depression in overweight and obese subjects and to assess the effect of vitamin D supplementation on depressive symptoms.

Design. Cross-sectional study and randomized double blind controlled trial of 20.000 or 40.000 IU vitamin D per week versus placebo for 1 year.

Setting. A total of 441 subjects (body mass index 28–47 kg m^{-2}, 159 men and 282 women, aged 21–70 years) recruited by advertisements or from the out-patient clinic at the University Hospital of North Norway.

Main outcome measures. Beck Depression Inventory (BDI) score with subscales 1–13 and 14–21.

Results. Subjects with serum 25(OH)D levels <40 nmol L^{-1} scored significantly higher (more depressive traits) than those with serum 25(OH)D levels ≥40 nmol L^{-1} on the BDI total [6.0 (0–23) versus 4.5 (0–28) (median and range)] and the BDI subscale 1–13 [2.0 (0–15) versus 1.0 (0–29.5)] ($P < 0.05$). In the two groups given vitamin D, but not in the placebo group, there was a significant improvement in BDI scores after 1 year. There was a significant decrease in serum parathyroid hormone in the two vitamin D groups without a concomitant increase in serum calcium.

Conclusions. It appears to be a relation between serum levels of 25(OH)D and symptoms of depression. Supplementation with high doses of vitamin D seems to ameliorate these symptoms indicating a possible causal relationship.

Keywords: depression, obesity, vitamins.

Introduction

Vitamin D is produced locally in the skin by sun exposure. To a minor extent, humans also acquire vitamin D from the diet, in particular, fatty fish and from supplements. To become biologically active, vitamin D has to be hydoxylated first in the liver and thereafter in the kidneys to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] [1]. Vitamin D is essential for the maintenance of the calcium homeostasis and for bone health [1], but appears also to be crucial for brain development and function [2–4]. In the brain there are specific nuclear receptors for $1,25(OH)_2D$ [5] and the enzymes necessary for the hydroxylation of vitamin D to $1,25(OH)_2D$ are also present in the central nervous system (CNS) [6]. Accordingly, the brain may locally

activate vitamin D which makes a role for vitamin D in brain function even more probable.

In clinical studies, low serum levels of 25-hydoxyvitamin D [25(OH)D], which is the storage form of vitamin D in the body [1], have been associated with reduced cognitive function [7, 8], anxiety [9] and depression [8, 9]. In particular, vitamin D has been implicated in seasonal affective disorder, a condition characterized by depression-like symptoms in the winter [10]. During the winter months, the serum 25(OH)D levels are low because of reduced sun light, and supplementation with vitamin D has improved symptoms of seasonal affective disorder in some [11, 12] but not in all studies [13, 14].

Low serum 25(OH)D levels are also seen in overweight subjects [15], and obesity is associated with depression [16]. However, to our knowledge there are no studies where the relation between serum levels of 25(OH)D and symptoms of depression has been evaluated in overweight and obese subjects. We have recently performed a 1 year study comparing high doses of 25(OH)D with placebo in 441 overweight and obese subjects with weight loss as the primary end-point. In addition, symptoms of depression were also recorded, which enabled us to evaluate the relation between vitamin D and depression both in a cross-sectional and a longitudinal study.

Methods

Subjects

Males and females 21 to 70 years old with body mass index (BMI) between 28.0 and 47.0 kg m^{-2} were recruited by advertisements in local newspapers and from our out-patient clinic at the University Hospital. Subjects with a history of coronary infarction, angina pectoris, stroke or renal stone disease were excluded. Subjects using antidepressant or weight reducing drugs, pregnant or lactating women and women below the age of 50 years without adequate contraception were not included. At attendance, blood samples were drawn for analysis of serum calcium, creatinine and parathyroid hormone (PTH). An oral glucose tolerance test was performed to exclude subjects with diabetes. Subjects with serum calcium >2.55 mmol L^{-1}, males with serum creatinine >129 μmol L^{-1} and females with serum creatinine >104 μmol L^{-1} were not included. If the serum calcium was in the range 2.50–2.55 mmol L^{-1}, inclusion required a serum PTH below 5.0 pmol L^{-1}.

Study design

At inclusion, any current supplements with calcium and vitamin D (including cod liver oil) were discontinued and all subjects were given supplementation with calcium 500 mg daily (Nycoplus Calcium®; Nycomed, Oslo, Norway) throughout the 1-year intervention period. The subjects were randomized into three groups, stratified by gender and smoking status: group DD, two capsules of vitamin D (20.000 IU cholecalciferol per capsule (Decristol®; Jenapharm, Jena, Germany) per week; group DP, one capsule of vitamin D and one placebo capsule per week; and group PP, two placebo capsules per week. The placebo capsules purchased from Hasco-lek (Wroclaw, Poland) had identical appearance as the vitamin D capsules. The subjects were supplied with new medication every third month. The unused calcium tablets and capsules were returned and counted. The subjects were classified as current smokers or current nonsmokers.

Measurements

Height and weight were measured wearing light clothing and no shoes. Blood samples for serum calcium were drawn every third month to detect any development of hypercalcaemia. If serum calcium increased >2.59 mmol L^{-1}, the subjects were asked to re-test, and if still >2.59 mmol L^{-1}, they were excluded from the study. Serum samples for analysis of 25(OH)D were drawn at all visits.

Depressed mood was judged with the Beck Depression Inventory (BDI) at inclusion and at the end of the study. BDI is a self-compiled questionnaire of 21 items in multiple choice format [17]. On each item, there are four statements and the subjects were instructed to choose the one that best described their

situation during the last 2 weeks. The statements are given the scores 0, 1, 2 and 3, with '0' for the 'normal' or least depressive statement and '3' for the most depressive statement. If more than one statement within each item were equally applicable, two or more statements could be chosen and the mean score was used in the calculations. The items constituting the BDI have been divided into two subscales. The first, the cognitive-affective, assesses the mental aspect of depression (items 1–13). The second, the somatic-vegetative, measures vegetative and somatic symptoms (items 14–21). The total BDI score and the subscale scores were obtained by adding together the scores for each item.

A questionnaire on physical activity (International Physical Activity Questionnaire, short last 7 days self-administered format) [18] were filled in at baseline and at the end of the study. The amount of physical activity was calculated based on reported vigorous, moderate and walking activities and given in units of metabolic equivalents (MET)-minutes per week, where METs are multiples of the resting metabolic rate.

Serum calcium, creatinine and PTH were measured as previously described [19]. Reference ranges in our laboratory at the time of the study were for serum calcium 2.20–2.60 mmol L^{-1}; for serum PTH, 1.1–6.8 pmol L^{-1} for those ≤50 years and 1.1–7.5 pmol L^{-1} for those >50 years; for serum creatinine, 70–120 μmol L^{-1} for men and 55–100 μmol L^{-1} for women. Urine for measurement of calcium excretion was collected for 24 h at baseline and at the end of the study. Urinary calcium was measured on a Modular P800 (Roche Diagnostics®, Mannheim, Germany), with reagents from the same company.

Serum 25(OH)D_3 was determined by immunometry (electrochemiluminiscence) using an automated clinical chemistry analyser (Modular E170; Roche Diagnostics®). According to the producer, the assay has, for total analytical precision, a coefficient of variation ≤7.8% as judged in any of three different concentrations (48.6, 73.8 and 177.0 nmol L^{-1}). The cross-reactivity with 25(OH)D_2 was <10% and the analytical sensitivity was 10 nmol L^{-1}. At present, the laboratory has no reference values for 25(OH)D_3, but the manufacturer provides a population-based reference range of 27.7–107.0 nmol L^{-1} for adults as a guideline. In our laboratory, this assay gives approximately 10% lower serum 25(OH)D values than the assay by Diasorin (Diasorin Inc., Stillwater, MN, USA). The trial was registered at ClinicalTrial.gov (NCT00243256).

Statistical analyses

The main dependent variables, the total BDI and the BDI subscales scores, were not normally distributed, nor did they attain normal distribution after logarithmic transformation. Therefore, nonparametric statistics were used throughout the study. Comparisons between unpaired groups were performed with the Mann–Whitney or chi-squared tests and between paired groups with the Wilcoxon-signed ranks test. Correlations were evaluated with the Spearman's rho coefficient. In the intervention study, the data were analysed both with an intention to treat (ITT) approach and with a per protocol approach. In the ITT analysis, we used the last observation carried forward method when comparing change in depression scores between the groups, and those that dropped out therefore were given a zero value for change. When comparing baseline values with those at the end of the study, the baseline values from the 441 subjects who were included were compared with the 334 who completed the study. Unless otherwise stated, data are expressed as median and range (minimum–maximum value). All tests were two-sided, and *P*-value <0.05 was considered statistically significant. The Statistical Package for Social Sciences, version 14.0, was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

Ethics

The study was approved by the Regional Ethics Committee. All participants gave written informed consent prior to the study.

Results

Cross-sectional study

The inclusion period started in November 2005 and the last subject was included in October 2006. A total of 496 subjects attended, 445 met the inclusion criteria and 441 subjects completed the BDI questionnaire. Their baseline characteristics are shown in Table 1. There was no apparent relation between time of year (month) and the serum 25(OH)D levels or the BDI scores (data not shown).

The serum 25(OH)D levels did not correlate significantly with the BDI, BDI subscale 1–13 or BDI subscale 14–21 scores (rho = −0.06, −0.06 and −0.04, respectively). However, when comparing those with serum 25(OH)D levels <40 nmol L^{-1} with the remaining cohort, they scored significantly higher on the total BDI (Table 1) and the BDI 1–13 subscale (Table 1 and Fig. 1).

There were nonsignificantly more males amongst those with serum 25(OH)D levels <40 nmol L^{-1}, they were significantly younger, there were significantly fewer smokers, they had a significantly higher BMI, a significantly higher serum PTH and a significantly lower physical activity score than the rest of the cohort (Table 1). To evaluate whether the differences in BDI scores between those with the lowest and those with higher serum 25(OH)D levels were the results of these differences, the cohort was further subdivided and analysed for BDI scores. As shown in Table 2, the females scored significantly higher than the males on the total BDI and subscales; those below the age of 47 years scored significantly higher on the BDI 1–13 subscale compared with the older subjects; smokers scored nonsignificantly higher on the total BDI and both subscales than the nonsmokers; those in the upper half of the BMI range scored nonsignificantly higher on the BDI 1–13 subscale compared with the leaner subjects; those in the lower and upper halves of the serum PTH range had identical median BDI scores; and those in the lower half of the physical activity score range had significantly higher score on the total BDI and BDI 14–21 subscale than those in the upper half of the physical activity score (Table 2).

Table 1 Characteristics of all subjects at baseline in the relation to serum 25(OH)D levels and treatment group

		Serum 25(OH)D	Serum 25(OH)D	Treatment group		
	All subjects	< 40 nmol L^{-1}	≥ 40 nmol L^{-1}	DD group	DP group	PP group
Gender (male/female)	159/282	41/58	118/224	57/93	51/91	51/98
Age (years)	47.0 (21–70)	42.0 (23–70)*	49.5 (21–70)	46.0 (21–70)	48.5 (23–70)	48.0 (24–69)
Smokers (%)	22.2	13.1**	24.9	23.3	21.8	21.5
BMI (kg m^{-2})	34.3 (28.4–47.1)	35.2 (28.6–47.1)***	33.7 (28.4–46.2)	34.1 (28.8–45.0)	33.4 (28.4–46.1)	34.7 (28.6–47.1)
Serum calcium (mmol L^{-1})	2.31 (2.00–2.55)	2.30 (2.11–2.51)	2.32 (2.00–2.55)	2.30 (2.02–2.54)	2.32 (2.10–2.55)	2.31 (2.00–2.55)
Serum PTH (pmol L^{-1})	5.0 (1.9–16.1)	5.8 (2.9–13.1)*	4.8 (1.9–16.1)	4.9 (2.3–10.2)	5.0 (2.8–13.8)	5.3 (1.9–16.1)
Serum 25(OH)D (nmol L^{-1})	52.5 (11.1–111.5)	32.7 (11.1–39.9)	56.8 (40.1–111.5)	54.5 (16.8–100.8)	49.1 (11.1–111.5)	52.3 (18.5–99.4)
Physical activity score (MET-min $week^{-1}$)	2013 (0–27837)	1520 (0–27837)**	2208 (0–25008)	1980 (0–25008)	1836 (0–27837)	2241 (0–16182)
BDI total score	5.0 (0.0–28.0)	6.0 (0–23)**	4.5 (0–28)	5.0 (0.0–19.0)	5.0 (0.0–28.0)	4.0 (0.0–24.5)
BDI (1–13) score	1.5 (0.0–19.5)	2.0 (0–15)**	1 (0–19.5)	1.5 (0.0–12.0)	1.8 (0.0–19.0)	1.5 (0.0–19.5)
BDI (14–21) score	3.0 (0.0–11.0)	3.5 (0–11)	3.0 (0–11)	3.0 (0.0–10.0)	3.0 (0.0–11.0)	3.0 (0.0–11.0)

BMI, body mass index; BDI, Beck Depression Inventory; PTH, parathyroid hormone; MET, metabolic equivalent.
*$P < 0.001$; **$P < 0.05$ and ***$P < 0.01$ versus serum 25(OH)D ≥40 nmol L^{-1} (Mann–Whitney or chi-squared test).

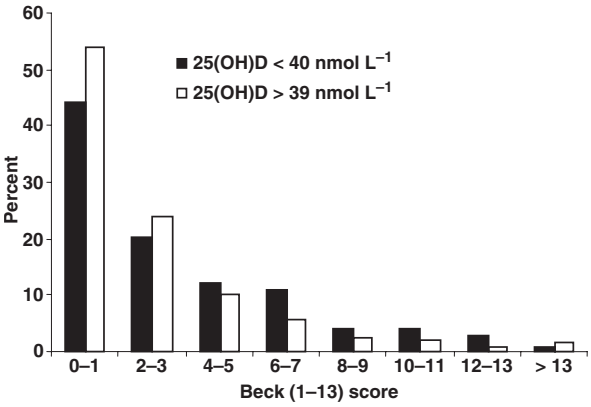

Fig. 1 Percentage of subjects with Beck (1–13) subscale scores from 0–1 to >13 in those with baseline serum 25(OH)D levels below 40 nmol L^{-1} (n = 99, solid columns) and in subjects with baseline serum 25(OH)D levels above 39 nmol L^{-1} (n = 342, open columns).

Regarding age, there was in the total cohort, a significant negative correlation between BDI 1–13 and age (rho = −0.10. P = 0.038). This negative relation was only observed in the younger subjects, whereas in those ≥47 years there was no correlation between BDI 1–13 and age (rho = 0.00, P = 0.99). In this latter group, those with serum 25(OH)D levels <40 nmol L^{-1} scored significantly higher than those with serum 25(OH)D levels ≥40 nmol L^{-1} both on the total BDI and the BDI 1–13 subscale (Table 2).

Similarly, there was in the total cohort, a positive nonsignificant correlation (Spearman's rho = 0.09, P = 0.054) between BMI and BDI 1–13. However, this relation was only seen in those with BMI >34.2 kg m^{-2} (rho = 0.15, P = 0.029), whereas no significant relation was seen in those with BMI <34.2 kg m^{-2} (rho = −0.02, P = 0.81). In this latter BMI group, those with serum 25(OH)D levels <40 nmol L^{-1} scored significantly higher on the total BDI and both BDI subscales than those with values ≥40 nmol L^{-1} (Table 2).

On the other hand, the relation between physical activity and BDI scores were seen equally in the upper and lower halves of the physical activity score

Table 2 BDI scores in relation to gender, age, smoking, BMI, serum PTH, physical activity score and serum 25(OH)D levels

	Male/female	BDI total score	BDI (1–13) score	BDI (14–21) score
Males	159/0	3.5 (0.0–24.5) *	1.0 (0.0–15.5) **	2.0 (0.0–9.5)*
Females	0/282	5.0 (0.0–28.0)	2.0 (0.0–19.5)	3.8 (0.0–11.0)
Age < 47 years	76/137	5.0 (0.0–24.5)	2.0 (0.0–15.0) ***	3.0 (0.0–11.0)
Age ≥ 47 years	83/145	5.0 (0–28.0)	1.0 (0–19.5)	3.0 (0.0–11.0)
Age ≥ 47 years				
Serum 25(OH)D < 40 nmol L^{-1}	15/21	6.0 (0.0.–19.5)***	2.0 (0.0–11.0)***	4.0 (0.0–11.0)
Serum 25(OH)D ≥ 40 nmol L^{-1}	68/124	4.5 (0.0–28.0)	1.0 (0.0–19.5)	3.0 (0.0–10.0)
Smokers	33/65	5.8 (0.0–24.5)	2.0 (0.0–15.0)	3.8 (0.0–11.0)
Non-smokers	126/217	4.5 (0.0–28.0)	1.5 (0.0–19.5)	3.0 (0.0–11.0)
BMI < 34.2 kg m^{-2}	84/136	5.0 (0.0–26.5)	1.0 (0.0–18.0)	3.0 (0.0–11.0)
BMI ≥ 34.2 kg m^{-2}	75/146	5.0 (0.0–28.0)	2.0 (0.0–19.5)	3.0 (0.0–10.0)
BMI < 34.2 kg m^{-2}				
Serum 25(OH)D < 40 nmol L^{-1}	17/22	6.0 (0.0–19.0)**	2.0 (0.0–11.0)***	4.0 (0.0–11.0)***
Serum 25(OH)D ≥ 40 nmol L^{-1}	67/114	4.0 (0.0–26.5)	1.0 (0.0–18.0)	3.0 (0.0–11.0)
Serum PTH < 5.0 pmol L^{-1}	69/142	5.0 (0.0–26.5)	1.5 (0.0–19.5)	3.0 (0.0–11.0)
Serum PTH ≥ 5.0 pmol L^{-1}	90/140	5.0 (0.0–28.0)	1.5 (0.0–19.0)	3.0 (0.0–11.0)
Physical activity score (MET-min per week) ≤ 2000	87/133	5.0 (0.0–24.5)***	2.0 (0.0–15.0)	3.0 (0.0–11.0)***
Physical activity score (MET-min per week) > 2000	72/149	4.0 (0.0–28.0)	1.5 (0.0–19.5)	2.5 (0.0–11.0)

BMI, body mass index; BDI, Beck Depression Inventory; PTH, parathyroid hormone; MET, metabolic equivalent.
*P < 0.001; **P < 0.01; ***P < 0.05 versus the group below (Mann–Whitney test).

range. Comparison between the lowest and the higher serum 25(OH)D groups within these physical activity subgroups could therefore not rule out a confounding effect of physical activity.

Intervention study

At baseline, there were no significant differences between the three treatment groups (Table 1). Of the 441 subjects randomized, 22.7% dropped out in the DD group, 25.3% in the DP group and 24.8% in the PP group. Thus, 334 subjects completed the study (Table 3). The compliance rate for the vitamin D/placebo capsules were 95% in all three groups, and 81%, 85% and 83% in the DD, DP and PP groups, respectively, for the calcium tablets.

After 3 months and throughout the study, the serum 25(OH)D levels were doubled in the DD group, whilst stable in the PP group, and in the DP group they were in between the DD and the PP groups (Table 3). Serum PTH decreased significantly in the DD and DP groups whereas serum calcium was unaltered in all three groups (Table 3). There was no significant change in weight or physical activity score in any of the three groups or between the groups (Table 3).

In the ITT analysis, at the end of the study, there was a significant reduction (improvement) in the total BDI and the BDI subscale scores in the DD group, a significant reduction in the BDI 14–21 subscale score in the DP group, but no significant change in the PP group. In the per protocol analysis, there was in both the DD and DP groups a significant reduction (improvement) in the total BDI and the BDI subscales scores at the end of the study, and also a significant reduction in the BDI 14–21 subscale score in the PP group (Table 3).

When evaluating delta values (value at baseline minus value at 12 months), there was for the BDI 1–13 subscale score a significantly higher value (improvement) at the end of the study in the combined vitamin D group (DD group and DP group together) compared with the PP group in the per protocol analysis

Table 3 Baseline and 12 months values in relation to treatment group in the 334 subjects who completed the study

	DD group		DP group		PP group	
	Baseline	12 Months	Baseline	12 Months	Baseline	12 Months
Gender (male/female)	47/69		40/66		41/71	
Age (years)	47.0 (26.0–70.0)		50.0 (23.0–70.0)		53.0 (24.0–69.0)	
BMI (kg m^{-2})	33.5 (28.8–45.0)	34.1 (27.0–45.6)	33.3 (28.7–46.1)	33.9 (27.6–45.6)	34.8 (28.6–47.1)	34.6 (27.4–46.9)
Smokers (%)	19.8	15.5	20.8	17.9	16.1	13.4
Serum calcium (mmol L^{-1})	2.30 (2.02–2.54)	2.30 (2.04–2.51)	2.31 (2.10–2.55)	2.31 (2.15–2.50)	2.32 (2.10–2.53)	2.28 (2.01–2.57)
Serum PTH (pmol L^{-1})	4.8 (2.3–9.9)	4.0 (1.5–10.5)*	5.0 (2.9–13.8)	4.4 (2.0–12.8)*	5.3 (2.3–11.0)	5.2 (1.7–10.8)
Serum 25(OH)D (nmol L^{-1})	55.2 (16.8–97.0)	112.1 (46.7–193.4)*	52.2 (15.4–111.5)	87.8 (51.5–162.3)*	52.4 (18.5–99.4)	50.0 (20.3–99.8)
Physical activity score (MET-min per week)	2215 (0–25008)	1627 (0–20796)	1674 (0–14238)	2022 (0–21408)	2240 (0–16182)	2090 (0–13812)
BDI total score	4.5 (0.0–24.0)	3.0 (0.0–23.0)**	5.0 (0.0.–28.0)	4.0 (0.0–26.0)**	4.0 (0.0–24.5)	3.8 (0.0.–18.0)
BDI (1–13) score	1.3 (0.0–14.0)	0.0 (0.0–13.0)**	2.0 (0.0–19.0)	1.0 (0.0–20.0)***	1.3 (0.0–19.5)	1.0 (0.0–10.5)
BDI (14–21) score	3.0 (0.0–10.0)	2.0 (0.0–11.0)***	3.0 (0.0–10.0)	3.0 (0.0–12.0)***	3.0 (0.0–10.0)	2.3 (0.0–9.0)***

BMI, body mass index; BDI, Beck Depression Inventory; PTH, parathyroid hormone; MET, metabolic equivalent.
*$P < 0.001$; **$P < 0.01$; ***$P < 0.05$ versus baseline (Wilcoxon-signed ranks test).

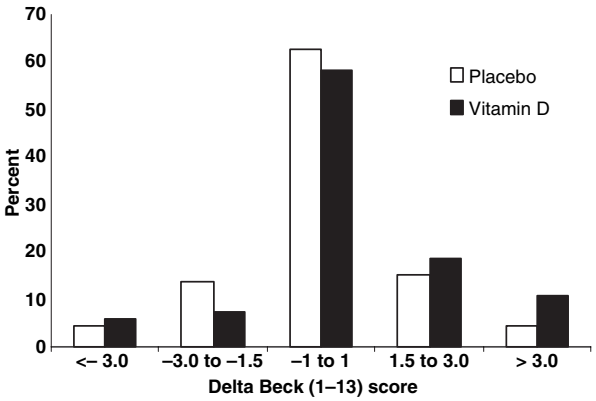

Fig. 2 Percentage of subjects with delta Beck (1–13) subscale scores (values at baseline minus values at end of the study) from <−3.0 to >3.0 in those given vitamin D (the DD group + the DP group, $n = 222$, solid columns) and in those given placebo (PP group, $n = 112$, open columns) and who completed the study.

($P < 0.05$) (Fig. 2), but not in the ITT analysis ($P = 0.051$).

To evaluate whether the improvement in the BDI 1–13 subscale score was related to gender, age and baseline BMI, serum 25(OH)D levels and BDI subscale 1–13 score or physical activity score, the cohort that completed the study was further subdivided according to these variables. As expected, the improvement in BDI 1–13 in the DD and DP groups was most clearly seen in the females (who scored significantly more depressive than the males) and in those with high baseline BDI 1–13 scores. Also, there were significant improvements in the age, BMI, serum 25(OH)D and physical activity subgroups, but without a distinct pattern compared with baseline values (Table 4).

Adverse events

In the DP group, one subject with a baseline serum calcium level of 2.30 mmol L^{-1} and serum PTH of 3.2 pmol L^{-1} had an increase in serum calcium to 2.62 mmol L^{-1} after 6 months. The retest values were 2.60 mmol L^{-1} for serum calcium and 1.6 pmol L^{-1} for serum PTH, and the subject was excluded from the study. Four subjects (three in the DD group and one in the PP group) had transient increases in serum calcium >2.59 mmol L^{-1} and were allowed to complete the study. Two subjects (one in the DP group and one in the PP group) were diagnosed as having primary hyperparathyroidism during the study. Both had a baseline serum calcium level of 2.48 mmol L^{-1} and their serum PTH levels were 8.5 and 7.8 pmol L^{-1}, respectively. In addition, 126 other adverse events were recorded, most of them recognized as gastrointestinal discomfort. There were no significant differences between the treatment groups regarding adverse events. There was an increase in urinary calcium excretion from baseline till the end of the study in all three group (median increases of 1.14, 0.77 and 0.78 mmol per day in the DD, DP and PP groups, respectively), but with no significant differences between the groups.

Discussion

In the present study, we have found that overweight and obese subjects with serum 25(OH)D levels <40 nmol L^{-1} have higher (more depressive) scores on the BDI total and BDI 1–13 subscale compared with those with serum 25(OH)D levels ≥40 nmol L^{-1}, and that supplementation with high doses of vitamin D for 1 year may improve these scores.

Regarding the cross-sectional results, we have in a previous study on neuropsychological function in 84 subjects found a significant and negative association between serum 25(OH)D levels and the total BDI and 1–13 subscale scores [19]. In that study, the subjects were divided in serum 25(OH)D quartiles, and those in the lowest quartile had BDI scores twice as high as those in each of the three higher quartiles where the BDI scores were almost identical. Similarly, in a study by Armstrong *et al.* [9] on the relation between 25(OH)D and depression in 75 subjects with fibromyalgia, those with vitamin D deficiency [defined as serum 25(OH)D levels <25 nmol L^{-1}] scored significantly more depressive on the Hospital Anxiety and Depression Score (HADS) than those with higher serum 25(OH)D levels.

There could be several explanations for the more depressive symptoms in the subjects with low

Table 4 Baseline and 12 months BDI 1–13 subscale score in the three treatment groups in relation to gender and baseline age, BMI, serum 25(OH)D levels and BDI 1–13 subscale score and physical activity score in the 334 subjects who completed the study

	DD group			DP group			PP group		
		Baseline	12 Months		Baseline	12 Months		Baseline	12 Months
	n	BDI 1–13 score	BDI 1–13 score	*n*	BDI 1–13 score	BDI 1–13 score	*n*	BDI 1–13 score	BDI 1–13 score
Males	47	1.0 (0.0–11.0)	0.0 (0.0–8.0)	40	1.0 (0.0–10.0)	1.0 (0.0–10.0)	41	1.0 (0.0–9.0)	1.0 (0.0–10.5)
Females	69	2.0 (0.0–14.0)	0.0 (0.0–13.0)*	66	2.8 (0.0–19.0)	1.0 (0.0–20.0)**	71	1.5 (0.0–19.5)	1.0 (0.0–9.0)
Age < 47 years	57	1.0 (0.0–11.0)	0.0 (0.0–8.0)	48	2.5 (0.0–14.0)	1.0 (0.0–14.0)**	38	2.0 (0.0–12.0)	1.3 (0.0–10.5)
Age ≥ 47 years	59	2.0 (0.0–14.0)	0.5 (0.0–13.0)**	58	1.0 (0.0–19.0)	1.0 (0.0–20.0)	74	1.0 (0.0–19.5)	1.0 (0.0–7.0)
BMI < 34.2 kg m^{-2}	63	1.0 (0.0–14.0)	0.0 (0.0–12.0)	60	2.0 (0.0–18.0)	1.0 (0.0–14.0)**	51	1.0 (0.0–11.0)	1.0 (0.0–10.5)
BMI ≥ 34.2 kg m^{-2}	53	2.0 (0.0–11.0)	1.0 (0.0–13.0)*	46	1.0 (0.0–19.0)	1.0 (0.0–20.0)	61	2.0 (0.0–19.5)	1.0 (0.0–10.0)
Serum 25(OH)D < 40 nmol L^{-1}	18	1.3 (0.0–11.0)	0.5 (0.0–7.0)**	26	2.0 (0.0–11.0)	1.0 (0.0–13.0)	23	2.0 (0.0–12.0)	2.0 (0.0–10.0)
Serum 25(OH)D ≥ 40 nmol L^{-1}	97	1.0 (0.0–10.0)	0.0 (0.0–13.0)**	80	1.5 (0.0–19.0)	1.0 (0.0–20.0)	89	1.0 (0.0–19.5)	1.0 (0.0–10.5)
BDI 1–13 subscale score ≤ 1.5	63	0.0 (0.0–1.5)	0.0 (0.0–6.0)	52	0.0 (0.0–1.5)	0.0 (0.0–10.0)	60	0.0 (0.0–1.5)	0.0 (0.0–9.0)
BDI 1–13 subscale score > 1.5	53	3.0 (2.0–14.0)	2.0 (0.0–13.0)***	54	4.8 (2.0–19.0)	3.0 (0.0–20.0)***	52	3.0 (2.0–19.5)	3.0 (0.0–10.5)
Physical activity score									
≤2000 MET-min per week	55	1.0 (0.0–11.0)	0.0 (0.0–13.0)*	60	2.5 (0.0–13.0)	1.8 (0.0–13.0)	54	2.0 (0.0–12.0)	1.0 (0.0–10.5)
>2000 MET-min per week	60	1.5 (0.0–8.0)	0.8 (0.0–9.0)	46	1.0 (0.0–19.0)	1.0 (0.0–20.0)	58	1.0 (0.0–19.5)	0.8 (0.0–9.0)

BMI, body mass index; BDI, Beck Depression Inventory; MET, metabolic equivalent.
*P < 0.01; **P < 0.05; ***P < 0.001 versus baseline (Wilcoxon-signed ranks test).

25(OH)D levels in our study. There were more males in the low 25(OH)D group, they were younger, fewer smoked and they had higher BMI and lower physical activity. As the BDI scores were not normally distributed, it was not possible to perform ordinary regression analyses to adjust for these confounders. However, males scored less depressive than the females, as did nonsmokers compared with smokers. Therefore, adjustment for these two factors would probably have increased the difference in BDI scores between the low and higher serum 25(OH)D groups. On the other hand, adjustments for age, BMI and physical activity could have the opposite effect. However, when looking at specific age and BMI groups, where there appeared to be no association between age and BMI with depression, those with low serum 25(OH)D levels still scored significantly higher than the others. However, we were not able to exclude a confounding effect by differences in physical activity, and in this respect, physical activity is an important factor. It is plausible that subjects with depression stay more indoors and therefore are less exposed to sunlight. Hence, their lower 25(OH)D levels could be the result and not the cause of their depressed mood.

There is a general agreement that the intake of vitamin D is suboptimal in most western societies [20], and in the intervention study we gave considerably higher vitamin D doses than the usually recommended 400–800 IU per day. Previous trials in healthy humans suggest that doses up to 10.000 IU per day are safe [21], and we therefore decided to give two doses of vitamin D, 20.000 IU per week and 40.000 IU per week, to ensure that a lack of effect could not be ascribed to suboptimal serum 25(OH)D levels. These vitamin D doses gave the expected increase in serum 25(OH)D levels, caused significant reductions in serum PTH levels and maintained normal serum calcium levels.

After 1 year, the subjects given 40.000 (DD group) or 20.000 (DP group) IU vitamin D per week had a significant improvement in BDI scores. As expected, the improvement was most pronounced in those with high BDI scores at baseline, but appeared unrelated to age and BMI. It is noteworthy that there was an improvement in BDI scores after vitamin D supplementation both in those with lower and higher baseline 25(OH)D levels.

So far, there are but a few other studies on the effect of vitamin D supplementation on mood and depression, and the results are divergent [11–14, 22], which may depend on the doses of vitamin D given. Thus, in the study by Harris *et al.* [14] 250 females were given 400 IU vitamin D for 1 year with no effect on the mood scores, and in a study by Dumville *et al.* [13] on 2117 women randomized to 800 IU per day versus placebo for 6 months, no improvement in mental health scores was seen. On the other hand, in a study by Vieth *et al.* [22] on 82 subjects randomized to 600 and 4000 IU vitamin D per day for 6 months, those given the high dose improved significantly more on a well-being scale than those given the lower dose.

There are several mechanisms whereby vitamin D might affect brain function. First, there could be a direct effect on the brain by vitamin D as receptors for its active form $1,25(OH)_2D$ have been found in the CNS [5] and the baseline serum 25(OH)D levels in our subjects were considerably lower than the estimated optimum of 90–100 nmol L^{-1} [23]. Furthermore, the effect of vitamin D on depression could be indirect, as vitamin D is important for muscle function [24] and supplementation could lead to increased physical activity and well-being. The observed reduction in serum PTH levels could also be of importance as there are receptors for PTH in the CNS [25] and high levels of PTH has been associated with central nervous dysfunction [26]. However, we did not observe increased physical activity after vitamin D supplementation in our study and those in the upper and lower halves of the serum PTH range did not differ in BDI scores.

The association between low serum 25(OH)D levels and depression and the apparent positive effect by vitamin D supplementation may indicate a causative relation. Even if that is true, lack of vitamin D is probably only one of many factors contributing to a depressed mood. However, in one clinical setting,

seasonal affective disorder, it is at least in theory possible that lack of vitamin D during the winter months may have a major pathogenetic role.

There are several limitations of the present study. First, we included only subjects with overweight and obesity and the results may therefore not apply to the general population. Second, we used only a single measure of depression, the BDI questionnaire, and more subtle measures like Montgomery Åsberg Depression Rating Scale and HADS could have yielded additional information. In the cross-sectional study, there was no apparent decrease in BDI scores with increasing serum 25(OH)D levels >40 nmol L^{-1}. This could indicate a threshold for 25(OH)D regarding effects on depression, but this was not substantiated in the intervention study where vitamin D supplementation also appeared to have an effect on those with serum 25(OH)D levels above that level. In the statistical analyses, we were not fully able to correct for confounding factors, in particular, for the differences in physical activity. We mainly compared baseline values with those at the end of the study and a slight improvement was also seen in those given placebo (PP group). Therefore, when comparing delta values (value at baseline minus value at end of the study), the DD and DP group had to be combined to see a significant difference in BDI score versus the PP group. Furthermore, this statistical significance was only seen in the per protocol analysis, and if doing an ITT analysis, the difference in delta values between those given vitamin D and those given placebo did not reach statistical significance ($P = 0.051$). Accordingly, the main outcome of the study must be considered as negative. If an effect of vitamin D on depression is not a direct one on the brain, but indirectly through its effects on the calcium metabolism, the calcium supplementation could have influenced the results considerably. In the intervention study, the results therefore have to be interpreted as effect of vitamin D plus calcium versus calcium alone, and not as vitamin D versus placebo. Most of the subjects included had low baseline BDI scores, and such were not clinically depressed. More pronounced effects might have been seen if we had selected subjects with clinical depression and/or very low serum 25(OH)D levels. The drop-out rate was high and closed to 25%, and for most of the subjects we have no information on reason for their withdrawal. However, similar or even higher drop-out rates are seen in most intervention studies for overweight and obesity [27]. And finally, although the effect of vitamin D supplementation was statistically significant in the per protocol analysis, it was rather modest.

In conclusion, there appears to be a relation between serum 25(OH)D levels and depression in overweight and obese subjects, and supplementation with vitamin D in high doses for 1 year may have a beneficial effect on depressive symptoms. However, further studies are needed before supplementation with high doses of vitamin D can be recommended in subjects with depression. In this respect, it would be of particular interest to include subjects with seasonal affective disorder and also subjects with clinical depression combined with hypovitaminosis D.

Conflict of interest statement

None

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References

1 Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357: 266–81.
2 Eyles D, Brown J, Mackay-Sim A, McGrath J, Feron F. Vitamin D3 and brain development. *Neuroscience* 2003; 118: 641–53.
3 Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. New clues about vitamin D functions in the nervous system. *Trends Endocrinol Metab* 2002; 13: 100–5.

4 McCann JC, Ames BN. Is there convincing biological or behavioral evidence linking vitamin D deficiency to brain dysfunction? *FASEB J* 2008; 22: 982–1001.
5 Stumpf WE, Sar M, Clark SA, DeLuca HF. Brain target sites for 1,25-dihydroxyvitamin D3. *Science* 1982; 215: 1403–5.
6 Zehnder D, Bland R, Williams MC *et al.* Extrarenal expression of 25-hydroxyvitamin d(3)-1 alpha-hydroxylase. *J Clin Endocrinol Metab* 2001; 86: 888–94.
7 Przybelski RJ, Binkley NC. Is vitamin D important for preserving cognition? A positive correlation of serum 25-hydroxyvitamin D concentration with cognitive function. *Arch Biochem Biophys* 2007; 460: 202–5.
8 Wilkins CH, Sheline YI, Roe CM, Birge SJ, Morris JC. Vitamin D deficiency is associated with low mood and worse cognitive performance in older adults. *Am J Geriatr Psychiatry* 2006; 14: 1032–40.
9 Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromyalgia. *Clin Rheumatol* 2007; 26: 551–4.
10 Schlager D, Schwartz JE, Bromet EJ. Seasonal variations of current symptoms in a healthy population. *Br J Psychiatry* 1993; 163: 322–6.
11 Gloth FM III, Alam W, Hollis B. Vitamin D vs broad spectrum phototherapy in the treatment of seasonal affective disorder. *J Nutr Health Aging* 1999; 3: 5–7.
12 Lansdowne AT, Provost SC. Vitamin D3 enhances mood in healthy subjects during winter. *Psychopharmacology* 1998; 135: 319–23.
13 Dumville JC, Miles JN, Porthouse J, Cockayne S, Saxon L, King C. Can vitamin D supplementation prevent winter-time blues? A randomised trial among older women. *J Nutr Health Aging* 2006; 10: 151–3.
14 Harris S, Dawson-Hughes B. Seasonal mood changes in 250 normal women. *Psychiatry Res* 1993; 49: 77–87.
15 Snijder MB, van Dam RM, Visser M *et al.* Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. *J Clin Endocrinol Metab* 2005; 90: 4119–23.
16 Dixon JB, Dixon ME, O'Brien PE. Depression in association with severe obesity: changes with weight loss. *Arch Intern Med* 2003; 163: 2058–65.
17 Beck AT, Ward CH, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* 1961; 4: 225–36.
18 Ainsworth BE, Macera CA, Jones DA *et al.* Comparison of the 2001 BRFSS and the IPAQ Physical Activity Questionnaires. *Med Sci Sports Exerc* 2006; 38: 1584–92.
19 Jorde R, Waterloo K, Saleh F, Haug E, Svartberg J. Neuropsychological function in relation to serum parathyroid hormone and serum 25-hydroxyvitamin D levels. The Tromsø Study. *J Neurol* 2005; 253: 464–70.
20 Vieth R, Bischoff-Ferrari H, Boucher BJ *et al.* The urgent need to recommend an intake of vitamin D that is effective. *Am J Clin Nutr* 2007; 85: 649–50.
21 Hathcock JN, Shao A, Vieth R, Heaney R. Risk assessment for vitamin D. *Am J Clin Nutr* 2007; 85: 6–18.
22 Vieth R, Kimball S, Hu A, Walfish PG. Randomized comparison of the effects of the vitamin D3 adequate intake versus 100 mcg (4000 IU) per day on biochemical responses and the wellbeing of patients. *Nutr J* 2004; 3: 8.
23 Bischoff-Ferrari HA, Giovannucci E, Willett WC, Dietrich T, Dawson-Hughes B. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. *Am J Clin Nutr* 2006; 84: 18–28.
24 Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial. *Arch Intern Med* 2006; 166: 424–30.
25 Weaver DR, Deeds JD, Lee K, Segre GV. Localization of parathyroid hormone-related peptide (PTHrP) and PTH/PTHrP receptor mRNAs in rat brain. *Brain Res Mol Brain Res* 1995; 28: 296–310.
26 Smogorzewski MJ. Central nervous dysfunction in uremia. *Am J Kidney Dis* 2001; 38(Suppl. 1): S122–8.
27 Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. *Int J Obesity* 2003; 27: 1437–46.

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