Eur J Nutr (2010) 49:401–407
DOI 10.1007/s00394-010-0098-7

ORIGINAL CONTRIBUTION

Cross-sectional and longitudinal relation between serum 25-hydroxyvitamin D and body mass index: the Tromsø study

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Received: 20 November 2009 / Accepted: 4 February 2010 / Published online: 4 March 2010
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Abstract
Purpose The serum 25-hydroxyvitamin D (25(OH)D) levels are lower in obese than lean subjects. The present study examines the cross-sectional and longitudinal relations between body mass index (BMI) and serum 25(OH)D, and the serum 25(OH)D response to vitamin D supplementation in relation to BMI.
Methods The Tromsø study is a longitudinal population-based multipurpose study. The fourth survey was conducted in 1994 and the sixth in 2008. The intervention study was a 1-year placebo-controlled randomized intervention trial, where the results from the 93 subjects given 40,000 IU per week are presented.
Results A total of 10,229 subjects were included in the 2008 cross-sectional study. There was a significant negative association between serum 25(OH)D levels and BMI which was also present during the winter months. Serum 25(OH)D levels varied through seasons, but not BMI. In the longitudinal study from 1994 to 2008 which included 2,656 subjects, change in BMI was a significant negative predictor of change in 25(OH)D. In the intervention study, there was a significant and negative correlation between BMI and serum 25(OH)D both at baseline and at the end of the study. The increase in serum 25(OH)D after 1 year was significantly and inversely related to baseline BMI.
Conclusions We have confirmed the strong association between serum 25(OH)D and BMI. The very obese need higher vitamin D doses than lean subjects to achieve the same serum 25(OH)D levels.

Keywords Body mass index · Vitamin D · Obesity · Longitudinal study · Intervention study

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Introduction

There appears to be a relation between vitamin D status and body fat [1–3], and vitamin D deficiency has even been suggested to be the cause of common obesity [4]. Thus, the serum 25-hydroxyvitamin D (25(OH)D) level, which is the major circulating form of the vitamin and the one used to evaluate a subject's vitamin D status [5], appears to be inversely associated not only with total body fat [2] but also separately with visceral adipose tissue as well as subcutaneous body fat [3]. The lower vitamin D status in obese subjects is accompanied by a compensatory increase

in serum parathyroid hormone, which in turn may promote weight gain through an effect on lipogenesis caused by increased calcium influx into adipocytes [2, 6, 7]. If that is the case, one would expect that an increase in serum 25(OH)D, like seen during the summer months, would cause a decrease in body weight. On the other hand, it has been suggested that the low serum 25(OH)D levels are the result and not the cause of obesity, as adipose tissue appears to store considerable amounts of vitamin D [8].

If there is a causal relation one would, regardless of the direction of the cause, expect corresponding changes in weight and serum 25(OH)D in subjects followed over time. However, in a study by Young et al. [3], there was no association between change in adiposity and serum 25(OH)D levels in a group of 1,081 subjects followed for 5 years, although there was a significant and inverse relation at baseline.

The Tromsø health surveys have been performed regularly since 1974 [9]. In the fourth survey in 1994–1995 and in the sixth survey in 2008, body mass index (BMI) and serum 25(OH)D were measured. In addition, we have recently performed an intervention study in obese subjects with vitamin D supplementation [10]. This gave us the opportunity to evaluate both the cross-sectional and the longitudinal relation between serum 25(OH)D and BMI, and also to study the serum 25(OH)D response to vitamin D intake in obese subjects.

Methods

The Tromsø study

The Tromsø study is a longitudinal population-based multipurpose study focusing on lifestyle-related diseases [11]. In the fourth survey in 1994–1995 (1994 in the following for simplicity), 27,158 subjects participated, providing an attendance rate of 77% among eligible inhabitants. To the sixth Tromsø study in 2008, 19,762 subjects were invited and 12,984 (66%) attended.

In both surveys, the participants filled in questionnaires on lifestyle factors including use of cod liver oil and smoking. A physical activity score was calculated adding together hours of moderate and hard physical activity per week, giving hard activity double weight. In 1994, the questions included activity also during working hours, whereas the questions in 2008 were on activity in leisure time only.

Blood samples were drawn in the non-fasting state. Sera from the fourth survey were stored at −70 °C, and after a median storage time of 13 years, thawed in March 2008 and analysed for 25(OH)D, whereas sera from the sixth Tromsø study were analysed for 25(OH)D consecutively.

Intervention study

The primary end point of this study was weight reduction after supplementation with vitamin D [10]. Males and females, 21–70 years old, with BMI between 28.0 and 47.0 kg/m^2, were included. Any previous supplements with calcium and vitamin D (including cod liver oil) were discontinued and all subjects were given a daily 500 mg calcium supplement (Nycoplus Calcium®, Nycomed, Oslo, Norway) throughout the 1-year intervention period. The participants were given oral information and written recommendations on healthy diet and physical activity. The subjects were randomized to take 40,000 IU cholecalciferol per week, 20,000 IU cholecalciferol per week or placebo. Blood sample for determination of 25(OH)D was drawn at baseline and after 3, 6, 9 and 12 months and stored at −70 °C for 2–30 months before analysis. The trial was registered at ClinicalTrials.gov (NCT00243256).

Measurements

Height and weight were measured wearing light clothing and no shoes, and BMI was defined as weight (kg) divided by height squared (m^2).

Serum 25(OH)D_3 was measured by immunometry (ECLIA), using an automated clinical chemistry analyser (Modular E170, Roche Diagnostics®, Mannheim, Germany) [12]. According to the producer, the assay has, for total analytical precision, a coefficient of variation $\leq$7.8% as judged in any of three different concentrations (48.6–73.8–177.0 nmol/L). The cross-reactivity with 25(OH)D_2 was <10%, and the analytical sensitivity was 10 nmol/L. In Norway, all food fortification and ordinary supplements are vitamin D_3. Vitamin D_2 preparations are only sold by prescription and to highly selected patients. At present, the laboratory has no reference values for 25(OH)D, but the manufacturer provides a population-based reference range of 27.7–107.0 nmol/L for adults as a guideline. This analysis has been approved by the Norwegian Accreditation Authority. With this method, we have found smokers to have 15–20% higher serum 25(OH)D levels than non-smokers, which we have not found when measuring serum 25(OH)D with other immunological or LC-MSMS methods (data not shown). For this discrepancy, we have at present no explanation and have therefore decided to exclude smokers from the present analysis.

Statistics

Normal distribution was evaluated with visual inspection of histograms and determination of skewness and kurtosis,

and all variables used as dependent variables were considered normally distributed.

Linear trends across BMI groups were tested with linear regression using covariates as described in the tables. Analysis of covariance was used to calculate adjusted means of serum 25(OH)D by age, gender and physical activity. Correlations were tested with Pearson's correlation coefficient *r*.

When testing predictors for serum 25(OH)D, a linear regression model was used with gender, age, BMI, physical activity score and use of cod liver oil as covariates, and adjustment for month of blood sampling with the use of dummy variables. When testing predictors for change in serum 25(OH)D from 1994 to 2008, a similar model was used with gender, age, change in BMI and change in physical activity score and use of cod liver oil as covariates. In this model, z-scores for the serum 25(OH)D values (calculated within each month both in 1994 and 2008 to eliminate the effect of season and storage) and physical activity scores (to eliminate the effect of different mode of calculation in 1994 and 2008) were used. The values for change (delta values) were calculated as the value in 2008 minus the value in 1994.

Unless otherwise stated, all data are expressed as mean ± SD. All tests were done two sided, and $p < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 15.0 (SPSS Inc, Chicago, IL., USA).

Ethics

The study was recommended by the Regional Committee for Medical and Health Research Ethics, North Norway, and approved by the Norwegian Data Inspectorate. Each participant gave a written informed consent prior to the examinations.

Results

The sixth Tromsø study, cross-sectional analysis

Among the 12,984 subjects who participated, 12,797 had valid serum 25(OH)D and BMI measurements, 2,568 of these were smokers and excluded, leaving 10,229 for the present analysis. The distribution of serum 25(OH)D in this cohort is shown in Fig. 1. Their further characteristics are shown in Table 1 and in relation to BMI categories in Table 2. There were more women than men in the upper and lower BMI groups. There was an increase in age and a decrease in physical activity score, intake of cod liver oil, and serum 25(OH)D levels with increasing BMI. However,

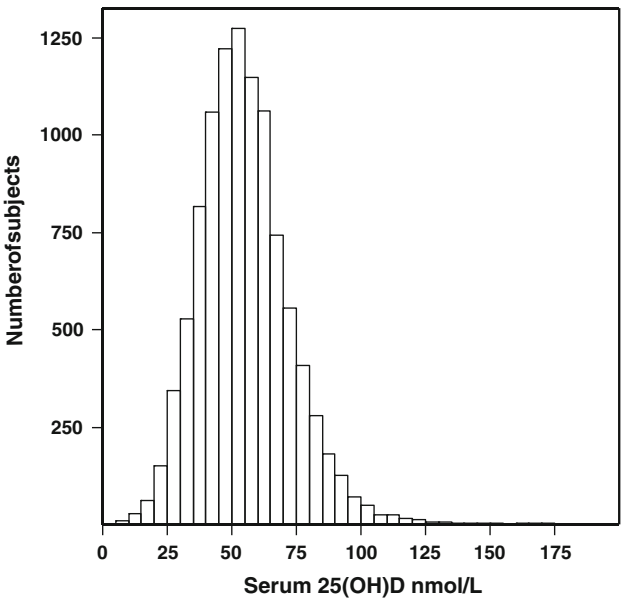

Fig. 1 Serum 25(OH)D in the 10,229 subjects from the sixth Tromsø study

Table 1 Characteristics of the 10,229 subjects included in the cross-sectional analysis from the sixth Tromsø study

Males/females	4843/5386
Age (years)	58.1 ± 12.8
BMI (kg/m^2)	27.1 ± 4.3
Physical activity score	2.4 ± 2.3
Serum 25(OH)D (nmol/L)	55.1 ± 17.8
Use of cod liver oil (%)	21.6

the relation between BMI and serum 25(OH)D was not linear, with a decrease in 25(OH)D not only in the more obese but also in those with BMI < 20.0 kg/m^2.

To examine if this pattern was due to subgroup effects, stratified analyses were performed. The fall in serum 25(OH)D in those with the higher BMI values was seen regardless of age (data not shown), in males and females, in users and non-users of cod liver oil and both during the summer and winter months (Table 3). On the other hand, the lower serum 25(OH)D in those with BMI < 20.0 kg/m^2 was only seen in the males, in non-users of cod liver oil and in those examined during the winter months (Table 3). Conversely, those at the extreme low end of the 25(OH)D range(<15 nmol/L, $n = 37$) were not particularly lean, having a mean BMI of 27.7 ± 4.1 kg/m^2.

The serum 25(OH)D levels were 60.5 ± 18.0 nmol/L during the summer months [May, June, August, September (samples not drawn in July)] and 49.8 ± 16.5 nmol/L during the winter months (November, December, January,

Table 2 Gender, age, physical activity score, unadjusted and adjusted serum 25(OH)D levels in relation to BMI group in the 10,229 subjects from the sixth Tromsø study

BMI (kg/m^2)	*N*	Gender (% males)	Age (years)	Physical activity score (hours per week)	Use of cod liver oil (%)	Serum 25(OH)D (nmol/L)	Adjusted serum 25(OH)D[a] (nmol/L)
<20.0	203	15.3	57.5 ± 15.2	2.9 ± 2.5	25.1	54.6 ± 20.5	50.4 ± 24.2
20.0–22.4	1,033	26.8	56.1 ± 13.8	3.0 ± 2.4	26.2	56.8 ± 18.6	55.8 ± 19.3
22.5–24.9	2,162	44.6	56.6 ± 13.0	2.8 ± 2.4	23.0	57.0 ± 18.3	56.8 ± 17.7
25.0–27.4	2,629	53.4	58.4 ± 12.5	2.5 ± 2.3	22.4	55.6 ± 16.8	55.4 ± 17.4
27.5–29.9	2,032	56.3	59.2 ± 12.4	2.2 ± 2.1	21.4	54.3 ± 18.2	54.3 ± 17.6
30.0–34.9	1,699	50.9	59.3 ± 12.4	1.9 ± 2.0	17.7	53.4 ± 17.2	53.8 ± 17.7
35.0–39.9	382	35.9	58.1 ± 12.5	1.6 ± 1.7	14.4	49.4 ± 16.2	50.4 ± 18.2
>39.9	89	25.8	56.6 ± 11.7	1.2 ± 1.2	16.9	45.0 ± 14.6	47.8 ± 19.8
p for trend[b]			<0.001	<0.001		<0.001	<0.001

[a] 25(OH)D adjusted for gender, age and physical activity

[b] Gender, age, physical activity score and use of cod liver oil as possible covariates

Table 3 Serum 25(OH)D levels in males and females, users and non-users of cod liver oil, and when samples drawn during the summer months and winter months in relation to BMI group

BMI groups (kg/m^2)	Gender				Use of cod liver oil				Season of blood sampling			
	Male		Female		Users		Non-users		Summer[a]		Winter[b]	
	N	Serum 25(OH)D (nmol/L)	*N*	Serum 25(OH)D (nmol/L)	*N*	Serum 25(OH)D (nmol/L)	*N*	Serum 25(OH)D (nmol/L)	*N*	Serum 25(OH)D (nmol/L)	*N*	Serum 25(OH)D (nmol/L)
<20.0	31	46.1 ± 18.0	172	56.2 ± 20.5	51	62.6 ± 16.2	152	51.9 ± 21.1	71	61.4 ± 23.9	84	47.3 ± 15.8
20.0–22.4	277	55.1 ± 19.3	756	57.4 ± 18.3	271	62.4 ± 18.3	762	54.8 ± 18.3	343	61.2 ± 19.1	411	53.0 ± 17.0
22.5–24.9	964	57.4 ± 17.8	1,198	56.7 ± 18.7	497	62.2 ± 18.6	1,664	55.5 ± 18.0	683	61.9 ± 18.3	840	52.1 ± 17.3
25.0–27.4	1,404	56.4 ± 16.4	1,225	54.7 ± 17.3	590	59.7 ± 16.1	2,039	54.4 ± 16.8	892	61.0 ± 17.4	1,018	50.5 ± 15.6
27.5–29.9	1,143	54.7 ± 17.4	889	53.8 ± 19.1	434	60.1 ± 17.7	1,598	52.8 ± 18.0	675	61.3 ± 18.4	813	48.3 ± 16.6
30.0–34.9	865	54.2 ± 18.0	834	52.6 ± 16.3	300	57.8 ± 18.1	1,399	52.5 ± 16.9	571	59.0 ± 16.8	670	47.7 ± 15.7
35.0–39.9	137	49.6 ± 15.7	245	49.4 ± 16.6	55	51.0 ± 15.9	327	49.2 ± 16.2	139	52.8 ± 15.5	139	44.7 ± 15.4
>39.9	23	48.9 ± 16.4	66	43.7 ± 13.8	15	48.9 ± 15.4	74	44.2 ± 14.4	34	49.5 ± 14.6	36	42.2 ± 14.2
p for trend[c]		<0.05		<0.001		<0.001		<0.001		<0.01		<0.001

[a] Summer months: May, June, August, September

[b] Winter months: November, December, January, February

[c] Gender, age, physical activity score and use of cod liver oil as possible covariates

February) ($p < 0.001$), whereas the summer and winter BMI values did not differ significantly (27.2 ± 4.3 and 27.1 ± 4.3 kg/m^2, respectively).

In the multiple linear regression model, gender, age, BMI, physical activity and intake of cod liver oil were all predictors of the serum 25(OH)D levels (Table 4).

Longitudinal study from 1994 to 2008

A total of 7,168 subjects had valid serum 25(OH)D and BMI measurement in the fourth survey in 1994. Among these, 3,826 subjects also had valid measurements in 2008, of whom 1,170 were smokers in 1994 and/or 2008, hence leaving 2,656 subjects for the present analysis. Their 1994 and 2008 characteristics are shown in Table 5.

In a multiple linear regression model with delta serum 25(OH)D z-score as dependent variable, change in BMI was a significant predictor together with change in physical activity and change in intake of cod liver oil. From 1994 to 2008, 407 subjects had a decrease in BMI of more than 1 kg/m^2, 920 had a change in BMI of less than 1 kg/m^2, and 1,329 subjects had an increase in BMI of more than 1 kg/m^2. Their corresponding changes (value in 2008 minus value in 1994) in serum 25(OH)D were 2.8 ± 19.9, 1.9 ± 19.9 and

Table 4 Standardized ß and *p* values in multiple regression models with serum 25(OH)D in 2008 and delta serum 25(OH)D z-score as dependent variables

	Dependent variables			
	Serum 25(OH)D in 2008 (nmol/L)		Delta serum 25(OH)D (z-score)	
	Standardized ß-coefficient	*p*-value	Standardized ß-coefficient	*p*-value
Gender (female = 0, male = 1)	0.06	>0.001	0.03	ns
Age (years)	−0.06	>0.001	−0.04	ns
BMI 2008 (kg/m^2)	−0.07	>0.001		
Physical activity score 2008 (hours per week)	0.12	>0.001		
Use of cod liver oil (non-user = 0, users = 1)	0.13	>0.001		
Delta BMI (kg/m^2)			−0.04	<0.05
Delta physical activity z-score 1994–2008			0.06	<0.01
Change in use of cod liver oil[a]			0.09	<0.001
R^2	0.14		0.02	

[a] 1 = stopped taking cod liver oil/vitamin D supplement, 2 = no change in use of cod liver oil/vitamin D supplement; 3 = started cod liver oil/vitamin D supplement

Table 5 1994 and 2008 characteristics of the 2656 subjects included in the longitudinal study

	1994	1998
Males/females	927/1729	
Age (years)	56.7 ± 9.2	
BMI (kg/m^2)	26.2 ± 3.7	27.2 ± 4.3
Physical activity score (hours per week)	3.4 ± 2.6	2.2 ± 2.1
Serum 25(OH)D (nmol/L)	53.8 ± 16.3	55.3 ± 18.2
Use of cod liver oil (%)	36.1	28.9

0.9 ± 18.2 nmol/L, respectively. This pattern was even more striking if only examining those with serum samples from the winter months both in 1994 and 2008. In these subjects, the changes in serum 25(OH)D in the aforementioned delta BMI groups were 4.6 ± 16.6 nmol/L ($n = 36$), −1.9 ± 16.0 nmol/L ($n = 120$) and −2.5 ± 15.3 nmol/L ($n = 182$), respectively.

Intervention study

There was no effect of vitamin D supplementation on weight reduction as previously described in detail [10]. A total of 445 subjects were included in the study, 347 subjects were non-smokers, and among these 93 subjects given 40,000 IU cholecalciferol per week completed the 12-month study. There was a significant correlation between BMI and serum 25(OH)D both at baseline and after 12 months ($r = -0.32$ ($p < 0.01$) and $r = -0.41$ ($p < 0.001$), respectively). There was a negative correlation between baseline serum 25(OH)D and increase in serum 25(OH)D after 3 months ($r = -0.31$, $p < 0.01$). For baseline BMI, there was no significant correlation with increase in serum 25(OH)D after 3 months ($r = -0.07$), but a negative correlation with increase in serum 25(OH)D after 12 months ($r = -0.23$, $p < 0.05$).

In Fig. 2, the serum 25(OH)D levels at baseline, 3, 6, 9 and 12 months are shown in relation to the BMI groups <30.0 kg/m^2 ($n = 8$), 30.0–34.9 kg/m^2 ($n = 51$), 35.0–39.9 kg/m^2 ($n = 26$) and >39.9 kg/m^2 ($n = 8$).

Discussion

In the present study, we have found a strong cross-sectional and longitudinal relation between serum 25(OH)D levels and BMI. The cross-sectional relation was not linear as serum 25(OH)D levels were lower both in those with low and those with high BMI values.

The lower serum 25(OH)D levels in the more obese corresponds with reports from other studies [1–3]. The serum 25(OH)D level is classically thought of as a result of intake of vitamin D, mainly from fatty fish and vitamin D supplements, and the production of vitamin D in the skin by sun exposure [5]. In the sixth Tromsø study, we did not have an accurate measure of the vitamin D intake except for intake of cod liver oil, which is usually taken as one spoonful a day giving a supplement of approximately 400 IU vitamin D. The use of cod liver oil was associated with higher serum 25(OH)D levels and was substantially lower in the obese subjects. This is in accordance with our previous findings from the fourth Tromsø study where subjects with BMI > 30 kg/m^2 had 20% lower intake of vitamin D than those with lower BMI [13]. However, the lower serum 25(OH)D levels in the more obese subjects were also seen in the cod liver oil users as well as after 12 months in the intervention study where 40,000 IU vitamin D per week were given. Accordingly, a lower

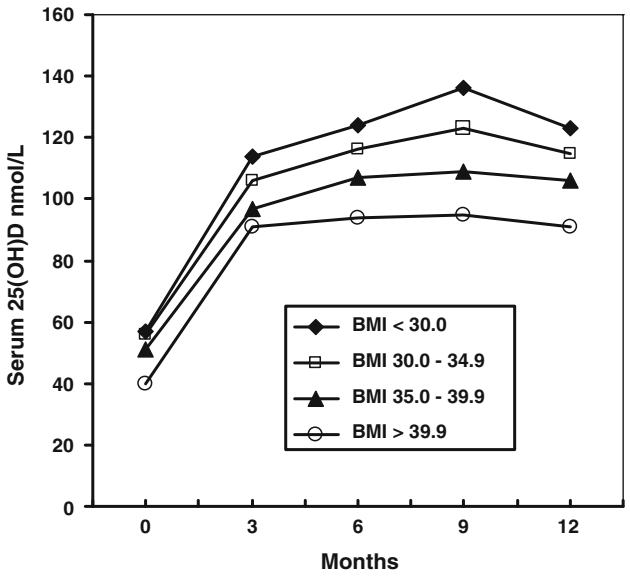

Fig. 2 Serum 25(OH)D in relation to BMI (kg/m^2) in 93 subjects given 40,000 IU vitamin D_3 per week for 12 months

intake of vitamin D cannot fully explain the low serum 25(OH)D levels in obese subjects.

The physical activity score, which can be taken as a crude measure of out-door activity and thereby sun exposure, was positively associated with serum 25(OH)D and was lower in the obese than the slimmer subjects. In addition, it has also been reported that after sun exposure obese subjects have a 57% less increase in circulating vitamin D than lean subjects, indicating that in obese subjects more of the cutaneously synthesised vitamin D is sequestered in the subcutaneous fat [14]. However, less sun exposure or less efficient cutaneous vitamin D production is unlikely to be the main cause of the lower serum 25(OH)D levels in the obese subjects, as lower levels in the obese were also seen during the winter when there is no sun at all in Northern Norway. This is in agreement with the report from Harris and Dawson-Hughes where they found no relation between per cent body fat and sunscreen use, hours spent outside per week, and skin exposure, although there was a significant association between body fat and serum 25(OH)D levels [15].

An alternative explanation could be storage of vitamin D in adipose tissue, which has been found both in animal models with radioactively labelled vitamin D [16] and in humans with radioactive labelled cholecalciferol [17]. In line with this, Wortsman et al. found that the rise in serum vitamin D_2 after ingestion of ergocalciferol was inversely correlated with BMI, and therefore suggested that not only cutaneously produced but also orally ingested vitamin D was sequestered in the larger body pool of fat in obese subjects [14]. In our intervention study, the most obese had an initial increase in serum 25(OH)D comparable to the other subjects. However, this initial increase was probably the result of their lower baseline levels, to which the response to vitamin D supplementation is directly related. This was clearly shown in a study by Aloia et al. [18], where the correlation between baseline and change in serum 25(OH)D values after 9 weeks with vitamin D supplementation was highly significant ($r = -0.46$, $p < 0.001$), as also shown in our study. After three months, the serum 25(OH)D levels in the most obese levelled off, whereas there appeared to be an increase in those with BMI $<$ 40 kg/m^2. Therefore, after 1 year with high-dose vitamin D supplementation, there was still a highly significant negative correlation between BMI and serum 25(OH)D levels. Furthermore, after 12 months, there was also a significant and inverse correlation between the increase in serum 25(OH)D and baseline BMI.

Accordingly, obese subjects need higher doses of vitamin D than lean subjects to attain the same serum 25(OH)D levels, which was also reported by Lee et al. in a study on replacement with vitamin D in subjects with severe vitamin D deficiency [19]. This is in apparent contrast to the report by Aloia et al. where they concluded that the dose needed to attain a desired serum 25(OH)D level was independent of body weight [18]. However, they made the reservation that this applied "at least in the non-obese", as their cohort did not specifically include obese subjects. In this regard, it should be noted that there was hardly any difference in serum 25(OH)D levels in the sixth Tromsø study between subjects with high and low BMI within the 20–35 kg/m^2 range, and that substantially lower serum 25(OH)D levels were only seen in the very obese subjects.

The lower serum 25(OH)D levels in subjects with BMI $<$ 20 kg/m^2 has to our knowledge not been focused on before, and was only seen in the males. Most likely this was due to life style factors as it was not seen in subjects using cod liver oil and during the summer months. On the other hand, it could also be due to chronic diseases like coeliac disease causing malabsorption, or to ill health in general. Unfortunately, we do not have detailed clinical data on these subjects with low BMI, the group was small, and the result should therefore be interpreted with caution.

In the study by Young et al. [3] that included 1,081 subjects followed for 5 years, there was no significant association between change in adiposity and serum 25(OH)D levels, probably due to lack of statistical power. However, in our longitudinal study that included 2,656 subjects, an increase in BMI from 1994 to 2008 was accompanied by a significant decrease in serum 25(OH)D, and a decrease in BMI by an increase in serum 25(OH)D. This indicates a strong association between BMI and serum 25(OH)D, but is of course no proof of causality. If a causal relation exists, the direction can in theory go both ways. However, in our intervention study where we gave high

doses of vitamin D and included 445 subjects, there was no effect on weight [10], which has subsequently been confirmed by Zitterman et al. [20]. Furthermore, there was no reduction in BMI during the summer months when the serum 25(OH)D levels were 20% higher than during the winter months. Accordingly, if there is a causal relation between BMI and serum 25(OH)D levels, it appears most likely that obesity results in low serum 25(OH)D levels, possibly because of increased storage and sequestration of vitamin D in adipose tissue [14]. However, it should be recalled the intervention studies so far published have only lasted for 1 year [10, 20], and in theory it is possible that the effect of vitamin D supplementation takes longer time before an effect is seen on body weight. Unfortunately, we do not have follow-up data from our intervention study after the 12-month study period, which could have disclosed such a long-term effect.

The present study has several weaknesses. In the cross-sectional study, we did not have a detailed food frequency questionnaire, and apart from the physical activity score we did not include questions related to sun exposure. On the other hand, our study has considerable strengths as we included a large group of subjects, and the findings were consistent in the cross-sectional and longitudinal study as well as in the intervention study.

In conclusion, we have found a strong association between BMI and serum 25(OH)D levels in obese subjects. When giving vitamin D supplements to the very obese, the dose has to be higher than in lean subjects if the same serum 25(OH)D levels are to be achieved.

Acknowledgments The superb assistance by Inger Myrnes, Astrid Lindvall and Ole Martin Ryen Sand at the Department of Medical Biochemistry, and the staff at the Clinical Research Unit at University Hospital of North Norway, is gratefully acknowledged. The present study was supported by a grant from The Northern Norway Regional Health Authority.

Conflict of interest Non-declared.

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