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ORIGINAL CONTRIBUTION

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Serum 1,25-dihydroxy vitamin D is inversely associated with body mass index

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Abstract *Background* Based on in vitro studies, it has been hypothesized that 1,25-dihydroxy vitamin D (1,25-vit D) may promote weight gain in humans, but previous studies have demonstrated conflicting results regarding the association between serum 1,25-vit D and body mass index (BMI). *Aim of the study* To evaluate the relation between serum 1,25-vit D and BMI. *Methods* Two thousand one hundred and eighty-seven subjects, recruited from a metabolic and medical lifestyle management clinic, were included in a cross-sectional study. BMI, 25-hydroxy vitamin D (25-OH-vit D) and 1,25-vit D were measured. The cohort was divided according to BMI in five groups (<25, 25–29.9, 30–34.9, 35–39.9 and >39.9 kg/m^2). Statistical analyses were performed with multiple linear regression models. Age and gender were used as explanatory covariates. *Results* With increasing BMI group, there was a significant decrease in both serum 25-OH-vit D and 1,25-vit D ($P < 0.001$). Those with BMI > 39.9 kg/m^2 had 24% lower serum 25-OH-vit D levels and 18 % lower 1,25-vit D levels than those with BMI < 25 kg/m^2. *Conclusions* There is an inverse association between BMI and the serum levels of 25-OH-vit D and 1,25-vit D. This makes it highly unlikely that high levels of circulating 1,25-vit D contribute to the development of obesity.

Key words body mass index – obesity – vitamin D

Introduction

Morbid obesity is an increasing problem in all parts of the world [11]. In 2002, 65% of the US population were overweight defined as a body mass index (BMI) between 25 and 30 kg/m^2, and 31% were obese, with a BMI above 30 kg/m^2 [14]. In Norway the prevalence of obese 40–42-year-old men increased from 7.5% in 1984–1986 to 14.0% in 1995–1997 [18].

The cause of obesity is multifactorial, and recently it has also been suggested that 1,25-dihydroxy vitamin D (1,25-vit D) may play a role in weight gain [18]. Thus, Shi et al. have shown that elevated concentrations of 1,25-vit D stimulate lipogenesis and inhibit lipolysis in cultured human adipocytes, leading to accumulation of fat [18]. Furthermore, 1,25-vit D is reported to inhibit the expression of adipocyte uncoupling protein 2 (UCP2), which would cause a decrease in the adipocyte's metabolic efficiency [17].

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If 1,25-vit D is implicated in weight gain, one would expect to find elevated levels in obese subjects, which has been reported in several older studies [3, 6, 10, 13, 20]. As secondary hyperparathyroidism is frequently found in obese subjects [3, 6, 9, 15, 20], and parathyroid hormone (PTH) stimulates the renal hydroxylation of 25-OH-vit D to form the biologically active 1,25-vit D [2], this could explain these elevated levels of serum 1,25-vit D.

On the other hand, the levels of 1,25-vit D is also dependant on availability of the substrate 25-OH-vit D [22], and 25-OH-vit D levels are known to be low in obese subjects [13]. In accordance with this, Parikh et al. found in a recent study an inverse correlation between 1,25-vit D and BMI [15].

Therefore, the association between 1,25-vit D levels and obesity is still unsettled. To clarify this, we examined the relation between serum levels of 1,25-vit D and degree of obesity in a large cohort of subjects examined in an obesity clinic.

Materials and methods

Ethics

The study was approved by the Regional Ethics Committee.

Subjects

The subjects were recruited from Dr. Fedon Lindberg's Clinic in Oslo, Norway. This is a private clinic specializing in weight loss counselling and obesity-related disorders. The data were collected between August 2001 and January 2007. At the subjects' first visit, measurment of height and weight were performed. The subjects wore light clothing and no shoes. BMI was calculated as weight (kg) divided by squared height (m^2). Fasting blood samples were drawn for measurements of 25-OH-vit D and 1,25-vit D.

Measurements

Serum 25-OH-vit D and 1,25-vit D levels were measured at the Hormone laboratory, Aker University Hospital, Oslo, Norway, using competitive radioimmunoassays (RIA) (DiaSorin, Stillwater, MN, USA) with reference ranges of 37–131 nmol/L and 42–169 pmol/L, respectively.

In the 25-OH-vit D assay, the intra-assay coefficient of variation (CV) is 6% at low serum levels (53 nmol/L), and the inter-assay CV at levels of 35, 67 and 120 nmol/L are 14, 15 and 15%, respectively. For the 1,25-vit D assay the intra-assay CV in the ranges 0–60, 60–240, and 240–480 pmol/L are 12, 7 and 8%, respectively, and the inter-assay CV at levels of 74, 140 and 340 pmol/L are 20, 17 and 20%, respectively.

Statistical analysis

Normal distribution was evaluated with visual inspection of histograms with normal curve, and determination of skewness and kurtosis. The dependent variables serum 25-OH-vit D and serum 1,25-vit D were considered normally distributed.

Comparisons between males and females were performed with Student's *t* test for unpaired samples.

The cohort was divided in five BMI groups (<25, 25–29.9, 30–34.9, 35–39.9, and >39.9 kg/m^2). In a general linear model with serum 25-OH-vit D level or serum 1,25-vit D level as dependent variable, with gender and BMI group as factors and age as covariate, there was no interaction between gender and BMI group. Males and females were therefore analysed together.

Linear trends across BMI groups for serum levels of 25-OH-vit D and 1,25-vit D were calculated with linear regression. Gender, age and BMI were used as covariates. To evaluate predictors of serum levels of 25-OH-vit D and 1,25-vit D, a similar linear regression model with gender, age and BMI as covariates was used (Model 1). In separate analyses, serum levels of 25-OH-vit D or 1,25-vit D were also included in the model (Models 2a and 2b).

The analyses were carried out using SPSS for Windows, version 11.0 (SPSS, Chicago, IL, USA). $P < 0.05$ was considered statistically significant. Unless otherwise stated, the values are means ± SD.

Results

The characteristics of the study population are shown in Table 1. The serum 25-OH-vit D levels were significantly higher in the females compared to the males.

With increasing BMI there was a significant decrease ($P < 0.001$) in serum levels of 25-OH-vit D and 1,25-vit D. Those with BMI > 39.9 kg/m^2 had

Table 1 Characteristics of the study population

	All subjects	Men	Women
N	2,187	410	1,777
Age (years)	46.8 ± 14.9	45.9 ± 16.3	47.0 ± 14.5
25-OH-vit D (nmol/L)	73.2 ± 27.4	69.5 ± 29.9	73.9 ± 26.5*
1,25-vit D (pmol/L)	108.2 ± 38.6	107.4 ± 37.1	108.1 ± 38.8
BMI (kg/m^2)	32.0 ± 6.8	32.4 ± 6.8	31.8 ± 6.6

*$P < 0.05$ versus men

Table 2 Gender, age, serum 25-OH-vit D and serum 1,25-vit D in relation to BMI groups

BMI groups (kg/m^2)	*N*	Males/ females	Age (years)	25-OH-vit D (nmol/L)	1,25-vit D (pmol/L)
<25	298	53/245	43.5 ± 18.1	83.0 ± 24.8	119.3 ± 42.2
25–29.9	592	99/493	47.0 ± 15.1	76.4 ± 24.9	113.4 ± 36.7
30–34.9	658	130/528	48.3 ± 14.2	73.3 ± 28.4	104.6 ± 37.3
35–39.9	396	72/323	47.6 ± 13.5	65.9 ± 22.0	103.6 ± 39.5
≥40	244	56/188	45.5 ± 12.9	63.9 ± 33.6	97.1 ± 34.1
Linear trend				$P < 0.001$	$P < 0.001$

Linear trend across BMI groups (linear regression with age and gender as covariates)

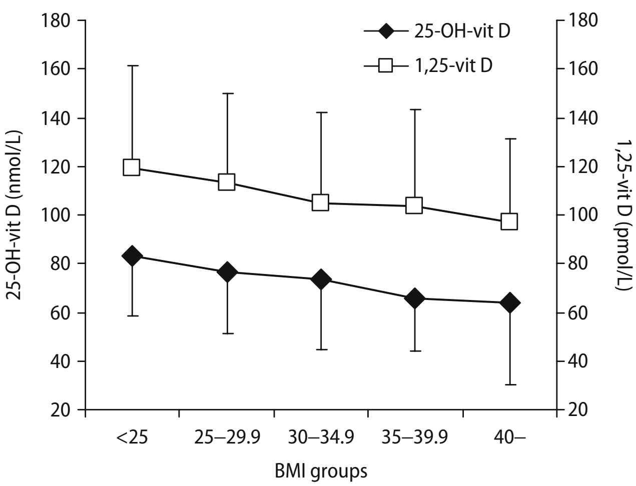

Fig. 1 Mean serum 25-OH-vit D (nmol/L) and 1,25-vit D (pmol/L) in relation to BMI (kg/m^2) category in the 2,187 subjects. The *error bars* represent the SD

24% lower serum 25-OH-vit D levels and 18% lower 1,25-vit D levels than those with BMI < 25 kg/m^2 (Table 2; Fig. 1).

In the multiple linear regression Model 1, age, gender and BMI were significant predictors of the serum 25-OH-vit D levels, and age and BMI significant predictors of the serum 1,25-vit D levels. In Model 2a and 2b, serum 1,25-vit D and 25-OH-vit D were significant predictors of each other (Table 3).

Discussion

In the present study we have found a highly significant and inverse relation between BMI and the serum levels of 25-OH-vit D and 1,25-vit D.

The finding of decreasing levels of serum 25-OH-vit D with increasing BMI is in accordance with previous reports, and it is today established that obese individuals as a group have decreased levels of 25-OH-vit D [1, 3, 5, 6, 13, 15, 20]. Several explanations for this phenomenon have been suggested. Among these are less exposure to UV radiation [5], lower intake of vitamin D and a higher distribution volume for vitamin D [8], and increased renal production of 1,25-vit D with subsequent negative feedback on the hepatic production of 25-OH-vit D [2, 3]. However, in view of our finding of significantly reduced serum levels of 1,25-vit D in obesity, the latter explanation appears unlikely. Furthermore, it has been proposed that increased metabolic clearance and enhanced uptake of vitamin D in adipose tissue accounts for the low serum levels of 25-OH-vit D in obesity [6, 13]. Thus, Wortsman et al. have demonstrated that obesity decreases the bioavailability of cutaneously synthesized vitamin D by more than 50% [19]. Because humans obtain most of their vitamin D requirements from sunlight, this could be the main reason for the consistent observations of lower 25-OH-vit D levels in obese subjects.

There is a discrepancy in the literature regarding the effect of obesity on serum levels of 1,25-vit D. In most of the older reports, higher levels of 1,25-vit D have been found in obese subjects. In a study by Hey et al. from 1982 that included 14 obese and 40 control subjects [6], in a study by Bell et al. from 1985 that included 14 obese and 14 non-obese subjects [3], in a study by Zamboni et al. from 1988 that included 16 obese children and 15 controls [20], in a study by Liel et al. from 1988 that included 13 obese and 13 non-obese subjects [13], and in a study by Kerstetter et al. from 1991 that included six obese and five lean sub-

Table 3 Standardized regression coefficient *ß* and *t* values from the linear regression models with 25-OH-vit D and 1,25-vit D as dependent variables

Independent variables	25-OH-vit D as dependent variable				1,25-vit D as dependent variable			
	Model 1		Model 2a		Model 1		Model 2b	
	ß	*t*	*ß*	*t*	*ß*	*t*	*ß*	*t*
Age (years)	0.08	3.82	0.11	5.19	−0.16	−7.41	−0.17	−8.27
Gender*	0.05	2.30	0.05	2.19	0.01	0.28	0.00	0.04
BMI (kg/m^2)	−0.02	−10.2	−0.18	−8.27	−0.16	−7.73	−0.11	−5.03
25-OH-vit D (nmol/L)							0.22	10.3
1,25-vit D (pmol/L)			0.22	10.3				
R^2	0.06		0.10		0.05		0.10	

*Males = 1, females = 2

|*t*| values >1.96, >2.58, >3.29 correspond to $P < 0.05$, $P < 0.01$, $P < 0.001$ respectively

jects [10], the 1,25-vit D levels were 20–30% higher in the obese groups. On the other hand, in the larger and more recent study by Parikh et al. from 2004 that included 154 obese and 148 non-obese subjects, the serum 1,25-vit D levels were 23% lower in the obese group [15]. In accordance with this, we found those with BMI ≥ 40 kg/m^2 to have serum 1,25-vit D levels 18% lower than those with BMI < 25 kg/m^2.

The discrepancy between the older reports [3, 6, 10, 13, 20] and the one by Parikh et al. [15] and our own findings can not be explained by differences in selection of subjects regarding age, gender and BMI. In our study and in Parikh et al.'s study [15], the subjects were included regardless of season. Liel et al. [13], however, collected their serum samples from December to May, and Hey et al. [6] and Zamboni et al. [20] in the winter months December–March. If the effect of UV exposure on the serum 25-OH-vit D levels differs between obese and non-obese subjects, the difference in time of year when the serum samples were collected could be of importance. However, season does not appear to have the same influence on the serum 1,25-vit D levels as it has on the serum 25-OH-vit D levels [16, 21], and is therefore unlikely to explain the discrepancy between the older and newer studies.

On the other hand, differences in vitamin D assay methods are a plausible explanation for this discrepancy. Thus, the older studies employed radioreceptor assays [3, 10, 13, 16], whereas we and Parikh et al. [15] used modern radioimmuno assays for determination of serum 1,25-vit D levels. The old radioreceptor assays gave widely diverging results [7] and had a problem with lipid interference in case of insufficient sample purification [4], which is not a problem with the radioimmuno assays. Since obese subjects generally have higher lipid levels than non-obese subjects, this analytic problem can explain the differences between the older and the two newer studies. In addition, the number of subjects included in the older studies were only a fraction of those included in the studies by Parikh et al. [15] and by us, and it is therefore fair to conclude that there is an inverse association between serum levels of.1,25-vit D and BMI. Accordingly, it is unlikely that high circulating levels of 1,25-vit D contribute to the development of obesity.

The serum level of 1,25-vit D depends on the renal hydroxylation of 25-OH-vit D, a process that is regulated by the serum PTH level [2]. The serum PTH level is known to be elevated in obese subjects [3, 6, 9, 15, 20], and increased levels of 1,25-vit D could therefore be expected. However, the serum 1,25-vit D level also depends on substrate availability [22], as demonstrated in our regression model where the 25-OH-vit D level appeared as the main predictor of the 1,25-vit D level.

As expected, the serum 1,25-vit D levels decreased with age. On the other hand, the serum 25-OH-vit D levels increased with age. The most likely explanation for this is the higher intake of vitamin D supplementation and cod liver oil in older Norwegian subjects [8].

Our study does have several weaknesses. We did not adjust for season, and we included only one serum sample from each subject. Although most of the blood samples were drawn at the first visit at the clinic before the start of lifestyle interventions, we do not have definite information on whether the subjects at that time were in a period of weight loss. This could be of importance as it has been reported that the serum 1,25-vit D levels are correlated to changes in caloric intake and changes in body weight [12]. Therefore, interpretation of serum 1,25-vit D levels might require multiple measurements in periods of constant body weight [12]. Furthermore, we do not have information on intakes of calcium and vitamin D, and we did not measure serum PTH. This could have shed further light on the subjects' vitamin D status. Finally, our subjects were selected from a clinical practice specializing in treatment of overweight subjects. The results must therefore be interpreted with some caution.

However, our study also has considerable strength as we have included a total of 2187 subjects, and in this large cohort the inverse relation between serum 1,25-vit D levels and BMI was highly significant.

In conclusion, we have found an inverse association between BMI and the serum levels of 25-OH-vit D and 1,25-vit D. It is therefore highly unlikely that elevated circulating levels of 1,25-vit D contribute to the development of obesity.

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