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ORIGINAL ARTICLE

The relationship between obesity and the increase in serum 25 (OH)D levels in response to vitamin D supplementation

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Abstract
Summary This study examines the relationship between obesity and the increase in serum 25(OH)D levels in response to vitamin D supplementation among adults with baseline serum 25(OH)D levels <50 nmol/L. This study revealed that the increase in serum 25(OH)D in response to vitamin D supplementation was higher in lean subjects as compared to obese subjects.
Introduction Serum 25(OH)D is lower among obese than non-obese. This study examines the relationship between obesity and the increase in serum 25(OH)D in response to vitamin D supplementation in a large sample of adults with baseline serum 25(OH)D <50 nmol/L, relatively long average treatment duration and large average daily cholecalciferol.
Methods The computerized database of the Clalit Health Services, which the largest nonprofit health maintenance organization in Israel, was retrospectively searched for all subjects aged ≥20 years who performed serum 25(OH)D test in 2011. Subjects with more than one test at different occasions in 2011 were identified and were included if the result of the first test was <50 nmol/L, and were treated with cholecalciferol between the first and the last test in 2011 (n=16,540 subjects).
Results The mean increase in serum 25(OH)D level after treatment was 28.7 (95 % confidence interval (CI), 28.0–29.4) nmol/L, 23.6 (23.0–24.2) nmol/L, and 20.1 (19.6–20.6) nmol/L in subject with BMI of <25, 25–29.9, and ≥30 kg/m^2, respectively (P<0.001). The results were similar after adjustment for the potential confounders. Similarly, the proportion of subjects who achieved serum 25(OH)D≥50 nmol/L after treatment was inversely associated with BMI; 65.1, 58.3, and 49.1 % for BMI of <25, 25–29.9, and≥30 kg/m^2, respectively. Compared to BMI of ≥30 kg/m^2, the adjusted odds ratio for achieving levels of ≥50 nmol/L were 2.12 (95 % CI, 1.94–2.31) and 1.42 (1.31–1.54) for BMI of <25 kg/m^2, and BMI of 25–29.9 kg/m^2, respectively.
Conclusions BMI is inversely associated with the increase in serum 25(OH)D levels in response to vitamin D supplementation.

Keywords 25(OH)D · BMI · Cholecalciferol · Obesity · Response to treatment · Vitamin D

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Introduction

Obesity is associated with an increased risk of lower concentrations of serum 25(OH)D [1]. The obesity epidemic is considered to be an important contributor to the increasing prevalence of low serum 25(OH)D in modern society [2]. Lower concentrations of serum 25(OH)D levels in obese subjects may be explained by enhanced uptake by adipose tissue, increased metabolic clearance, and it is suggested that the sedentary lifestyle of obese subjects could be associated with less outdoor activity and less exposure to sunlight [3, 4].

Vitamin D is important in supporting and maintaining normal mineral and bone health [5]. Accumulating data

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suggest that vitamin D may play a key role in extraskeletal health; however, this issue remains a major debate due to the lack of randomized controlled studies (RCTs). Some observational studies have shown that lower levels of serum 25 (OH)D levels were associated with increased mortality and morbidity from a variety of chronic diseases [5, 6]. Some of these diseases are more prevalent in obese individuals like diabetes mellitus [7, 8] and cardiovascular diseases [9, 10], suggesting that vitamin D supplementation may be needed in obese subjects with low serum 25(OH)D. Moreover, it has been found that the correlation of serum 25(OH)D and insulin sensitivity was stronger in overweight individuals than normal-weight individuals, suggesting that overweight subjects with low serum 25(OH)D may benefit more from vitamin D supplementation than normal-weight subjects [11].

Little is known about the response to vitamin D supplementation in obese subjects, previous studies that addressed this issue were small and showed controversial results [4, 12, 13]. This study examines the relationship between obesity and the increase in serum 25(OH)D levels in response to treatment with vitamin D supplements in a large sample of adults with relatively long average treatment duration and large average daily cholecalciferol.

Methods

Selection of the study population

We used data from the Clalit Health Services (CHS) database which is a nonprofit health maintenance organization covering more than half of the Israeli population. The computerized database includes data on laboratory tests, medications, and demographic variables. The CHS database was searched for all available serum 25(OH)D test results that were performed in 2011 (624,801 tests in 498,217 members). We included only serum 25(OH)D tests that were performed in the three largest laboratories of the CHS, together performing 84.4 % of the tests (527,475 tests). Of these, we selected tests that were performed in subjects aged ≥20 years (502,369 tests in 403,083 members). Then, we identified subjects who performed more than one test, that were analyzed by the same laboratory; in 2011 (179,361 tests in 80,075 members), the first and the last test were selected for each subject. Of these, we identified subjects in whom the first serum 25(OH)D level was <50 nmol/L (38,006 members), and then we selected only subjects who filled at least one prescription for cholecalciferol between the dates of the two tests (18,452 members). Of them, only 17,595 (95.3 %) subjects had an available body mass index (BMI) in the computerized database. In the final analyses, we included subjects in whom the treatment duration with cholecalciferol was ≥30 days (16,540 subjects).

Definitions of terms

Treatment duration is reported in days and is defined as the difference between the first and last prescription dates plus the time difference between the last prescription and the last test if the time difference was less than 30 days, or plus 30 days if the time difference was ≥30 days (the time to complete one prescription). To calculate the average daily dose of cholecalciferol (international units per day (IU/day)) we first calculated the cumulative cholecalciferol dose by summing the dose of all prescription filled in the period between the first and the last serum 25OHD tests. The average daily dose of cholecalciferol (IU/day) was calculated by dividing the cumulative cholecalciferol dose by treatment duration. As the data were collected from the pharmacy database, compliance with the filled prescriptions could not be assessed.

25OHD assay

Serum 25OHD was measured using the LIAISON® 25-OH Vitamin D Total assay (DiaSorin USA), a competitive two-step chemiluminescence assay with a measurement range of 4.0–150 ng/mL (10–375 nmol/L), analytical sensitivity of <1.0 ng/mL (2.5 nmol/L), and functional sensitivity of <4.0 ng/mL (10 nmol/L). The intra-assay precision is up to 5 % and the inter-assay precision is up to 15 %. The specificity for 25-OH vitamins D_2 and D_3 is 104 and 100 %, respectively.

Statistical analyses

Continuous data are presented as means with standard deviations or 95 % confidence intervals along with medians and interquartile range as some variables were not normally distributed. Categorical data are presented as proportions. Comparisons of continuous variables between two groups were analyzed with the Student's *t* test or Mann–Whitney test as appropriate. Comparisons of continuous variables between more than two groups were analyzed with analysis of variance or the Kruskal–Wallis test as appropriate (*P* value for the global *F* test is reported). The chi-square test was used to compare proportions between categorical variables.

The change in serum 25(OH)D after treatment was calculated by subtracting the baseline level from serum 25 (OH)D level after treatment. We used multiple linear regression model adjusting for the potential confounders in order to examine the relationship between BMI (<25, 25–29.9, and ≥30 kg/m^2) and the change in serum 25(OH)D after treatment, and to estimate the adjusted mean change in serum 25(OH)D after treatment in the BMI categories. Confounders that were included in the model were baseline

levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25(OH)D test date, and laboratory.

The recently released report on Dietary Reference Intake for calcium and vitamin D by the Institute of Medicine (IOM) suggested that serum 25(OH)D levels of 40 nmol/L meet the needs of approximately half the population, and levels of at least 50 nmol/L are practically sufficient for all the population [14, 15]. We used logistic regression to assess the association between BMI and serum 25OHD levels of ≥50 nmol/L after treatment (dependent variable) controlling for the confounders identified above. The association was estimated with odds ratio (OR) with 95 % confidence interval (CI). We performed sensitivity analyses by excluding subjects who were treated with vitamin D supplements during the last 6 months before the baseline serum 25(OH)D test.

Two-way interactions were assessed by including the product of the variables in the multivariate model. A *P* value of less than 0.05 for the two-tailed test was considered statistically significant. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Characteristic of the study subjects

Of the 16,540 study subjects, 11,850 (71.6 %) were females. The mean age was 59.8±17.1 years. Of the subjects, 13,986 (84.6 %) were Jews (Table 1). The mean BMI was 28.6±6.0 kg/m^2; the distribution of BMI categories was as follows: 29.1 % with BMI of <25 kg/m^2, 35.1 % with BMI of 25–29.9 kg/m^2, and 35.9 % with BMI of ≥30 kg/m^2. The mean serum 25(OH)D was 31.9±11.5 nmol/L at baseline and 55.7±22.4 nmol/L after treatment (<0.001).

Subjects with BMI 25–29.9 kg/m^2 were more likely to be males (34.5 %) as compared to other BMI categories, and the proportion of Arabs increased within higher BMI categories (Table 1). Subjects with BMI of <25 kg/m^2 were younger (54.7±20.2 years) as compared to subjects with higher BMI. A similar fraction of the tests after treatment were performed in summer–autumn in all BMI categories, and the mean serum 25(OH)D level at baseline was similar between all BMI categories (Table 1).

The relationship between BMI and vitamin D status

The unadjusted mean increase in serum 25(OH)D level after treatment decreased with increasing BMI; 28.7 (95 % CI, 28.0–29.4) nmol/L, 23.6 (23.0–24.2) nmol/L, and 20.1 (19.6–20.6) nmol/L in subjects with BMI of <25, 25–29.9, and ≥30 kg/m^2, respectively (Table 2). We reached similar results after adjusting for baseline levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose, and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25(OH)D test date, and laboratory. The mean increase in serum 25(OH)D level after treatment decreased with increasing BMI (*P* for trend< 0.001; Table 2, Fig. 1).

In sensitivity analyses, excluding subjects who were treated with vitamin D supplements during the last 6 months before the baseline serum 25(OH)D test, the results were very similar. The adjusted mean increase in serum 25(OH)D after treatment was 27.8 (95 % CI, 26.9–28.6) nmol/L, 23.4 (22.6–24.1) nmol/L, and 19.7 (18.9–20.5) nmol/L in subjects with BMI of <25, 25–29.9, and ≥30 kg/m^2, respectively.

Similarly, the proportion of subjects who achieved serum 25(OH)D levels of ≥50 nmol/L after treatment was inversely associated with BMI; 65.1, 58.3, and 49.1 % for BMI of <25, 25–29.9, and ≥30 kg/m^2, respectively. Compared to BMI of ≥30 kg/m^2, the adjusted ORs for achieving serum 25(OH)D levels ≥50 nmol/L were 2.12 (95 % CI 1.94–2.31) and 1.42 (1.31–1.54) for BMI of <25 and 25–29.9 kg/m^2, respectively (Table 2).

Stratified analyses

The multivariate logistic regression model revealed a significant interaction between BMI and serum 25(OH)D levels at baseline (*P*=0.031), and between BMI and age (*P*=0.034). Stratified analyses by the quartiles of baseline serum 25(OH)D levels showed that the adjusted ORs to achieve serum 25(OH)D≥50 nmol/L after treatment in normal-weight subjects as compared to obese subjects was higher in the first quartile as compared to the highest quartile of baseline serum 25(OH)D levels (Table 3). The interaction with age revealed that the adjusted ORs to achieve serum 25(OH)D≥50 nmol/L after treatment in normal weight as compared to obese subjects was higher in the first quartile of age as compared to the highest quartile of age (Table 3).

Similarly, using the multiple linear regression, we found a significant interaction between BMI and baseline serum 25(OH)D levels (*P*=0.009). The difference in the increase of serum 25(OH)D after treatment in normal-weight subjects compared to obese subjects was more pronounced at lower baseline levels than at higher levels. We also found a significant interaction between BMI and age (*P*=0.018); the difference in the increase of serum 25(OH)D after treatment in normal-weight subjects as compared to obese subjects was more pronounced in younger as compared to older subjects.

Stratified analysis of the association between BMI and achieving serum 25(OH)D≥50 nmol/L in response to vitamin D supplementation was not statistically different between the three laboratories (*P* for interaction, 0.07),

Table 1 Demographic and clinical characteristics of the study population (CHS 2011)

Variable	All (n=16,540)	Body mass index category (kg/m^2)		
		<25 (n=4,808)	25–29.9 (n=5,798)	≥30 (n=5,934)
Gender				
Males	4,690 (28.4 %)	1,190 (24.8 %)	2,002 (34.5 %)	1,498 (25.2 %)
Females	11,850 (71.6 %)	3,618 (75.2 %)	3,796 (65.5 %)	4,436 (74.8 %)
Ethnicity				
Jews	13,986 (84.6 %)	4,246 (88.3 %)	4,995 (82.6 %)	4,745 (80.0 %)
Arabs	2,554 (15.4 %)	562 (11.7 %)	803 (13.8 %)	1,189 (20.0 %)
Season[a]				
Winter–spring	4,378 (26.5 %)	1,251 (26 %)	1,534 (26.5 %)	1,593 (26.8 %)
Summer–autumn	12,162 (73.5 %)	3,557 (74.0 %)	4,264 (73.5 %)	4,341 (73.2 %)
Age (years)				
Mean±SD	59.8±17.1	54.7±20.2	62.2±16.0	61.7±14.5
Median (IQR)	61.0 (69.0–73.0)	56.0 (36.0–71.0)	63.0 (52.0–75.0)	62.0 (53.0–73.0)
Daily dose of cholecalciferol (IU)				
Mean±SD	1,763±1,220	1,803±1,240	1,728±1,164	1,765±1,257
Median (IQR)	1,333.3 (1,153.8–2,051.3)	1,333.3 (1,185.2–2,142.8)	1,333.3 (1,138.0–2,016.8)	1,333.3 (1,142.8–2,041.5)
Treatment duration (days)				
Mean±SD	97.6±76.6	91.9±75.5	100.1±79.9	99.8±77.0
Median (IQR)	72.0 (30.0–148.0)	61.0 (30.0–139.0)	77.0 (30.0–153.0)	76.0 (30.0–151.0)
Time difference[b] (days)				
Mean±SD	84.6±75.5	90.1±76.6	82.7±75.5	82.0±74.5
Median (IQR)	63.0 (22.0–129.0)	70.0 (28.0–138.0)	59.0 (21.0–126.0)	62.0 (21.0–126.0)
Baseline 25(OH)D level (nmol/L)				
Mean±SD	31.9±11.5	31.5±11.6	32.7±11.3	31.4±11.5
Median (IQR)	32.9 (22.2–41.9)	32.4 (21.5–41.5)	34.0 (23.5–42.7)	32.3 (21.6–41.3)
Laboratory[c]				
Lab. A	4,499 (27.2 %)	1,187 (24.7 %)	1,554 (26.8 %)	1,758 (29.6 %)
Lab. B	5,088 (30.8 %)	1,288 (26.8 %)	1,791 (30.9 %)	2,009 (33.9 %)
Lab. C	6,953 (42.0 %)	2,333 (48.5 %)	2,453 (42.3 %)	2,167 (36.5 %)

Percentages are column percentages

SD standard deviation, *IQR* interquartile range

[a] Season at the time of the test after treatment

[b] Time difference between the last filled prescription and last serum 25(OH)D test date

[c] Laboratory where serum 25(OH)D was tested

Table 2 The association between BMI and the increase in serum 25(OH)D in response to treatment with cholecalciferol

	Body mass index category (kg/m^2)			*P* for trend
	<25 (*n*=4,808)	25–29.9 (*n*=5,798)	≥30 (*n*=5,934)	
Mean increase in 25(OH)D[a]				
Unadjusted	28.7 (28.0–29.4)	23.6 (23.0–24.2)	20.1 (19.6–20.6)	<0.001
Adjusted[c]	25.3 (24.6–26.0)	20.9 (20.3–21.6)	16.9 (16.2–17.5)	<0.001
ORs for achieving serum 25(OH)D levels ≥50 nmol/L[b]				
Unadjusted	1.93 (1.79–2.10)	1.45 (1.35–1.56)	1.0 reference	<0.001
Adjusted[c]	2.12 (1.94–2.31)	1.42 (1.31–1.54)	1.0 reference	<0.001
Percentages of subjects who achieved 25(OH)D levels ≥50 nmol/L	65.1 %	58.3 %	49.1 %	<0.001

[a] Data are expressed as mean and (95 % confidence interval)

[b] Data are expressed as OR and (95 % confidence interval)

[c] Adjusted for baseline levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25(OH)D test date, and laboratory

between the tertiles of daily dose (*P* for interaction, 0.549), between the tertiles of treatment duration (*P* for interaction, 0.512), or between the tertiles of the time difference between the last filled prescription and last serum 25(OH)D test date (*P* for interaction 0.284; Table 4).

Discussion

This study revealed that the increase in serum 25(OH)D in response to vitamin D supplementation was higher in normal-weight individuals as compared to obese subjects. This was more prominent among subjects with low levels of circulating 25(OH)D. Whether or not these findings represent a higher intake requirement or simply a homeostatic mechanism to handle circulating levels in excess of tissue requirements cannot be answered from this study.

In line with our findings, the achieved serum 25(OH)D correlated negatively with BMI (r^2=0.63, *P*<0.01) following 1-week treatment with cholecalciferol in 17 hospital in patients with serum 25(OH)D of <15 nmol/L [12]. However, one study found that non-obese subjects, despite receiving higher input of vitamin D, did have less of an absolute change in serum 25(OH)D (2.4±7 ng/ml in non-obese versus 4±9.4 ng/ml in obese subjects, *P*=0.54), suggesting that body weight is not an important determinant for maintenance of serum 25(OH)D levels [13]. But these studies were either very short with only 1 week of treatment [12] or open label, non-randomized [13]; therefore, significant inferences cannot be drawn from these studies. BMI was inversely correlated with vitamin D2 levels after oral vitamin D2 intake (*r*=−0.56, *P*=0.007), but no significant relation was observed between BMI and serum 25(OH)D levels [4].

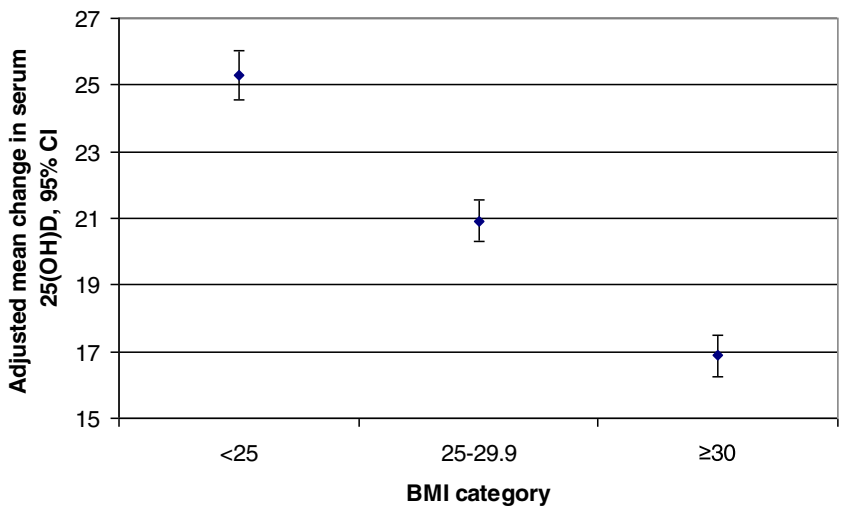

Fig. 1 Adjusted mean change in serum 25(OH)D levels after treatment (nanomoles per liter) and 95 % confidence interval by BMI category (CHS 2011). Adjusted for baseline levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25 (OH)D test date, and laboratory.

Table 3 Multivariate analysis; adjusted odds ratios (ORs) for the association of BMI with achieving serum 25(OH)D ≥50 nmol/L in response to treatment with cholecalciferol stratified by baseline serum 25(OH)D levels and age quartiles

Variables	Body mass index category (kg/m^2)			*P* for interaction
	<25 OR (95 % CI)	25–29.9 OR (95 % CI)	≥30 Reference	
Baseline serum 25(OH)D quartiles				
Q1: ≤22.2 nmol/L	2.46 (2.08–2.93)	1.66 (1.41–1.96)	1.0 Reference	0.031
Q2: >22.2–32.9 nmol/L	2.31 (1.95–2.75)	1.45 (1.24–1.69)	1.0 Reference	
Q3: >32.9–41.9 nmol/L	2.16 (1.82–2.56)	1.38 (1.18–1.61)	1.0 Reference	
Q4: >41.9 nmol/L	1.64 (1.37–1.97)	1.27 (1.08–1.48)	1.0 Reference	
Age quartiles				
Q1: ≤49.0 years	2.35 (2.00–2.76)	1.51 (1.26–1.80)	1.0 Reference	0.034
Q2: >49.0–61.0 years	2.47 (2.07–2.96)	1.50 (1.28–1.74)	1.0 Reference	
Q3: >61.0–73.0 years	2.09 (1.73–2.52)	1.37 (1.18–1.60)	1.0 Reference	
Q4: >73.0 years	1.63 (1.36–1.95)	1.31 (1.12–1.54)	1.0 Reference	

Odds ratios adjusted for baseline levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25(OH)D test date, and laboratory

Interestingly, the seasonal variation of serum 25(OH)D [peak-trough 25(OH)D concentration], was also found to be inversely associated with fat mass [3]. In an experimental setting, after exposure to UV-B irradiation, the increase in serum vitamin D3 levels was 57 % less in the obese than in the non-obese subjects 24 h after the exposure [4]. However, one study did not find a significant association between seasonal variation of serum 25(OH)D and BMI [16].

The inverse association of BMI with the increase in serum 25(OH)D in response to treatment with vitamin D supplementation may be explained by adipose tissue sequestration of circulating 25(OH)D and decreased sun exposure in obese individuals [3, 4]. Consumption of circulating 25 (OH)D by increased conversion of 25(OH)D to 1,25 (OH)2D in obese individuals may also contribute to this inverse relationship [12].

Table 4 Multivariate analysis; adjusted odds ratios (ORs) for the association of BMI with achieving serum 25(OH)D ≥50 nmol/L in response to treatment with cholecalciferol stratified by laboratory and tertiles of daily dose, treatment duration and time difference

Variables	Body mass index category (kg/m^2)			*P* for interaction
	<25 OR (95 % CI)	25–29.9 OR (95 % CI)	≥30 Reference	
Laboratory				
Lab. A	2.12 (1.78–2.51)	1.50 (1.29–1.74)	1.0 Reference	0.07
Lab. B	2.38 (2.03–2.79)	1.55 (1.35–1.78)	1.0 Reference	
Lab. C	1.96 (1.71–2.23)	1.27 (1.12–1.44)	1.0 Reference	
Daily dose of cholecalciferol				
≤1,200 IU/day	2.17 (1.88–2.50)	1.45 (1.27–1.65)	1.0 Reference	0.549
>1,200–1,624 IU/day	2.20 (1.88–2.58)	1.47 (1.27–1.71)	1.0 Reference	
>1,624 IU/day	2.05 (1.75–2.39)	1.34 (1.16–1.54)	1.0 Reference	
Treatment duration				
30–35 days	2.25 (1.92–2.64)	1.40 (1.23–1.60)	1.0 Reference	0.512
>35–104 days	1.94 (1.68–2.45)	1.39 (1.22–1.59)	1.0 Reference	
>104 days	2.15 (1.85–2.50)	1.47 (1.28–1.70)	1.0 Reference	
Time difference[a]				
≤30 days	2.05 (1.80–2.35)	1.37 (1.20–1.56)	1.0 reference	0.284
>30–121 days	2.15 (1.81–2.55)	1.50 (1.29–1.74)	1.0 reference	
>121 days	2.28 (1.95–2.68)	1.47 (1.28–1.69)	1.0 reference	

Adjusted for baseline levels of serum 25(OH)D, age, gender, ethnicity, seasonality, daily dose and treatment duration with cholecalciferol, time difference between the last filled prescription and last serum 25(OH)D test date, and laboratory.

[a] Time difference between the last filled prescription and last serum 25(OH)D test date

Another important finding of this study is that normal-weight subjects as compared to obese subjects were more likely to achieve serum 25(OH)D levels of ≥50 nmol/L especially at lower baseline serum 25(OH)D levels (Table 3). It may be suggested that at lower serum 25(OH)D, the adipose tissues are less saturated with vitamin D; hence, a greater fraction of the supplemented vitamin D will be shifted to the adipose tissues in obese subjects with lower serum 25(OH)D levels. But it is not known whether the adipose tissue stores of vitamin D are readily mobilized in times of greater vitamin D need or if once sequestered in the adipose tissue, the vitamin D is no longer available for meeting body needs. It is also possible that the increased conversion of serum 25(OH)D to 1,25(OH)2D observed in obese subjects [12] may be higher in obese subject with low serum 25(OH)D levels as compared to obese subjects with higher levels leading to more 25(OH)D consumption. Although this hypothesis seems to be plausible, it needs to be confirmed in future studies.

A significant interaction was also observed between BMI and age; the extent of increase in serum 25(OH)D after treatment in non-obese subjects as compared to obese was higher in younger as compared to older subjects. This may be explained by the fact that exposure to sunlight is likely decreased in obese subjects. Hence, the difference in sunlight exposure is expected to be more pronounced in younger subjects, because older subjects have less sun exposure irrespective of their BMI.

The major strength of this study is the large number of included subjects. Nevertheless, this study has several limitations; this study relies on a computerized database that was not specifically designed for this study. Our study may suffer from selection bias due to the reliance on blood tests that have been ordered by primary care physicians all over the country and could reflect a highly selected population. However, the study was performed in a period of increasing interest in assessing vitamin D status in the general population [17]; hence, 25(OH)D measurement was not limited to high-risk population. We did not have data about sun exposure. Although, obese subjects are usually less exposed to sun, it is unlikely that it explain all the effect. Also, we did not have data about vitamin D content of ingested food, but this is not expected to affect the results as only few foods contain natural vitamin D [18]; food fortification with vitamin D is not practiced in Israel. The inter-assay precision of the kit used to measure serum 25(OH)D is very high (15 %) and may likely result in significant misclassification of subjects. However, this misclassification is likely nondifferential because it is independent of the BMI, and therefore could be expected to bias our results toward the null.

Another limitation of this study is that the data on vitamin D supplements came from a database; therefore, the compliance with the filled prescription could not be assessed. Hence, the average daily dose of cholecalciferol may be overestimated in our study as it was calculated with the assumption that all the filled prescriptions were actually taken, but this is expected to be nondifferential. On the other hand, subjects were assumed to be without treatment 30 days after their last filled prescription according to the pharmacy database, but vitamin D supplements are available over the counter and may have been purchased in private pharmacies. Also, we could not establish whether the three laboratories are comparable; however, stratified analysis by the three laboratories revealed consistent results between the three laboratories. In addition, there was a large variability in the variable related to vitamin D supplementation including daily dose and treatment duration with cholecalciferol, and time difference between the last filled prescription and last serum 25(OH)D test date; however, stratified analysis by each of these variables revealed consistent results across levels of each variable. Also, we did not have serum PTH and 1,25 (OH)2D levels for the study participants, so we could not explain some of our findings, particularly the interaction between BMI and baseline serum 25(OH)D levels.

For instance, except for age, the IOM makes the same supplementation recommendations for all individuals regardless of any physical condition or state. Based on bone health, the IOM specify recommended daily allowances for vitamin D of 600 IU/day for ages 1–70 years and 800 IU/day for ages 71 years or older, corresponding to a serum 25(OH)D of at least 50 nmol/L, meet the requirements of most of the population [14, 15]. As regard to extraskeletal health, the IOM emphasized the need for RCTs as the current existing evidence did not meet the criteria for establishing cause and effect relationship [14, 15]. Our findings may suggest that higher requirements of vitamin D supplementations may be needed in obese individuals. However, before drawing such conclusions, it should be clarified whether or not these findings represent a higher intake requirement because the sequestered vitamin D is no longer available for meeting body needs or simply a homeostatic mechanism and the adipose tissue stores of vitamin D are readily mobilized in times of greater vitamin D need.

Conclusions

The increase in serum 25(OH)D levels in response to treatment with vitamin D supplementation is higher in non-obese compared to obese subjects. Future studies are needed to clarify the clinical implications of these findings.

Conflicts of interest None

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