Decreased bioavailability of vitamin D in obesity[1–3]

Jacobo Wortsman, Lois Y Matsuoka, Tai C Chen, Zhiren Lu, and Michael F Holick

ABSTRACT

Background: Obesity is associated with vitamin D insufficiency and secondary hyperparathyroidism.

Objective: This study assessed whether obesity alters the cutaneous production of vitamin D_3 (cholecalciferol) or the intestinal absorption of vitamin D_2 (ergocalciferol).

Design: Healthy, white, obese [body mass index (BMI; in kg/m^2) ≥ 30] and matched lean control subjects (BMI ≤ 25) received either whole-body ultraviolet radiation or a pharmacologic dose of vitamin D_2 orally.

Results: Obese subjects had significantly lower basal 25-hydroxyvitamin D concentrations and higher parathyroid hormone concentrations than did age-matched control subjects. Evaluation of blood vitamin D_3 concentrations 24 h after whole-body irradiation showed that the incremental increase in vitamin D_3 was 57% lower in obese than in nonobese subjects. The content of the vitamin D_3 precursor 7-dehydrocholesterol in the skin of obese and nonobese subjects did not differ significantly between groups nor did its conversion to previtamin D_3 after irradiation in vitro. The obese and nonobese subjects received an oral dose of 50 000 IU (1.25 mg) vitamin D_2. BMI was inversely correlated with serum vitamin D_3 concentrations after irradiation ($r = -0.55$, $P = 0.003$) and with peak serum vitamin D_2 concentrations after vitamin D_2 intake ($r = -0.56$, $P = 0.007$).

Conclusions: Obesity-associated vitamin D insufficiency is likely due to the decreased bioavailability of vitamin D_3 from cutaneous and dietary sources because of its deposition in body fat compartments. *Am J Clin Nutr* 2000;72:690–3.

KEY WORDS Vitamin D, ultraviolet radiation, tanning bed, obesity, 25-hydroxyvitamin D, parathyroid hormone, obesity, vitamin D_3, sunlight, obesity, 25-hydroxyvitamin D_3, bioavailability

INTRODUCTION

Obese individuals, as a group, have low plasma concentrations of 25-hydroxyvitamin D [25(OH)D] (1–5), which are associated with increased plasma concentrations of immunoreactive parathyroid hormone (1, 6, 7). Although the explanation for the increased risk of vitamin D deficiency in obesity is unknown, it has been postulated that obese individuals may avoid exposure to solar ultraviolet (UV) radiation, which is indispensable for the cutaneous synthesis of vitamin D_3 (3). Alternatively, it has been proposed that production of the active vitamin D metabolite 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] is enhanced and thus, its higher concentrations exert negative feedback control on the hepatic synthesis of 25(OH)D (1). It has also been suggested that the metabolic clearance of vitamin D may increase in obesity, possibly with enhanced uptake by adipose tissue (2).

Clarification of the mechanism for the subnormal concentrations of 25(OH)D in obesity is nevertheless relevant for the management of this highly prevalent condition. If, for example, the increased risk of vitamin D deficiency were the expression of a lack of exposure to sunlight, it would perhaps be only of academic interest. Conversely, if the increased risk of vitamin D deficiency in obesity were the result of a primary alteration or a direct consequence of obesity itself then a rational intervention could be instituted. We therefore performed dynamic testing to evaluate the blood concentrations of vitamin D in obese and nonobese subjects in response to UV-B irradiation or an oral dose of vitamin D_2. We also performed studies in vitro to determine whether obesity affects the cutaneous production of vitamin D_3.

SUBJECTS AND METHODS

Subjects

The experimental population was 19 healthy whites (skin types II and III) of normal body weight [body mass index (BMI; in kg/m^2) ≤ 25] and 19 healthy, obese subjects (skin types II and III; BMI > 30). Subjects were recruited among medical school personnel and had similar socioeconomic status. None of the subjects had a history of hepatic or renal disorders and none were taking vitamin D supplements, anticonvulsant medications, or corticosteroids. The study was performed during the winter (November through February) and the subjects refrained from sunlight exposure beginning 24 h before the study and during the study. All subjects gave their informed consent and the study was approved by the Jefferson Medical College (Philadelphia) Institutional Review Board.

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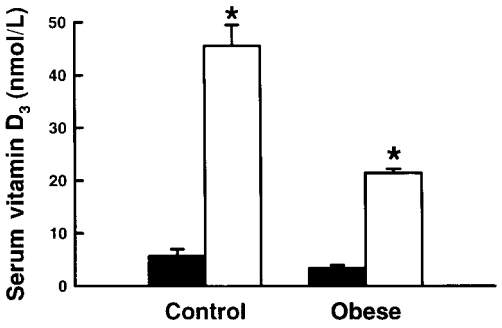

FIGURE 1. Mean (±SEM) serum vitamin D_3 (cholecalciferol) concentrations before (■) and 24 h after (□) whole-body irradiation (27 mJ/cm^2) with ultraviolet B radiation. The response of the obese subjects was attenuated when compared with that of the control group. There was a significant time-by-group interaction, $P = 0.003$. *Significantly different from before values ($P < 0.05$).

Methods

The study of cutaneous vitamin D_3 synthesis in response to UV-B irradiation consisted of submitting the subjects to whole-body irradiation in a phototherapy unit that emits wavelengths of 260–330 nm as described previously (8). The radiation delivered at these wavelengths was 0.2 mW/cm^2, determined at a distance of 30 cm from the source. A single, 27-mJ/cm^2 suberythemic dose of UV-B (290–320 nm) was delivered (one minimal erythema dose: 33–36 mJ/cm^2). Because peak serum vitamin D_3 concentrations occur 24 h after acute UV-B radiation exposure (9), blood samples were obtained 1 h before (basal determination) and 24 h after UV-B radiation exposure. Changes in serum vitamin D_3 concentrations over this period reflected the synthesis and transport of vitamin D_3 from the skin into the bloodstream (10).

The study of the response to an oral challenge with vitamin D_2 was performed ≥1 mo after the study of cutaneous vitamin D_3 photosynthesis. The oral vitamin D_2 loading test consisted of a modification of the vitamin D absorption test described previously by Lo et al (11). Subjects were instructed to avoid dairy products for 1 wk before the study and to fast from 2000 the night before the test. A basal blood sample was obtained at 0800, and immediately thereafter the subjects ingested a capsule of vitamin D_2 [50000 IU (1.25 mg) ergocalciferol] with 120 mL water. Subjects were allowed to eat 1 h later. Follow-up blood samples were obtained 6, 10, and 24 h after the intake of vitamin D_2. Serum was separated promptly and stored at −20°C until analyzed.

The serum assays for vitamin D_2 and vitamin D_3 were performed by HPLC (12). The intraassay and interassay variations for this assay were 10% and 13%, respectively. The serum assays for 25(OH)D and 1,25$(OH)_2$D were performed by using binding-protein assays as described previously (13, 14). The intraassay and interassay variations for the 25(OH)D and 1,25$(OH)_2$D assays were 8% and 10% and 10% and 12%, respectively. Parathyroid hormone concentrations (midmolecule assay; Star Corp Inc, Stillwater, MN) were measured at the Medical University of South Carolina, Charleston.

A total of 13 control (age: 34 ± 3 y; BMI: 22.2 ± 0.04) and 13 obese (age: 37 ± 2 y; BMI: 38 ± 1.7) individuals participated in the study of the cutaneous synthesis of vitamin D_3 in response to UV-B irradiation and 11 control (age: 36 ± 4 y; BMI: 21.4 ± 0.6) and 11 obese (age: 39 ± 3 y; BMI: 35.7 ± 1.8) subjects participated in the oral vitamin D_2 loading test. There was some overlap among the experimental subjects; 5 nonobese and 7 obese subjects participated in both studies. Nevertheless, characteristics of the population included in each study were similar.

In vitro studies

The direct effect of obesity on the synthetic capacity of the skin to produce vitamin D_3 was studied in whole skin (epidermis and dermis) obtained during surgery from 2 obese subjects (age: 27 and 84 y) and 2 nonobese subjects (age: 42 and 73 y) with skin type III. The skin specimens were frozen and stored at −70°C promptly after removal. Before analysis, the skin samples were thawed at room temperature and the epidermis, where most of the synthesis of vitamin D_3 takes place, was separated from the dermis (15). Individual skin pieces (1 cm^2) were exposed to simulated sunlight for the same period of time, after which the epidermis was immediately removed and analyzed for its combined vitamin D_3 content (the combination of previtamin D_3 and vitamin D_3) as described previously (15). The vitamin D_3 precursor 7-dehydrocholesterol and its photoproduct previtamin D_3 were measured in triplicate by HPLC (15).

Statistical analysis

Individual comparisons between the 2 groups were performed with Student's *t* test. Changes across the 4 time points were compared between the 2 groups in the oral study by using a two-factor repeated-measures analysis of variance. Linear relations between BMI and different variables were computed by using Pearson correlation coefficients (16). Results were considered significant if *P* values were <0.05. All results are expressed as means ± SEMs.

RESULTS

In the UV-B irradiation study, basal concentrations of vitamin D_3 were not significantly different between the obese and nonobese control groups (**Figure 1**). There was a significant increase in the circulating concentrations of vitamin D_3 in both groups 24 h after irradiation. There was also a significant difference ($P = 0.0042$) between the response of each group, with the

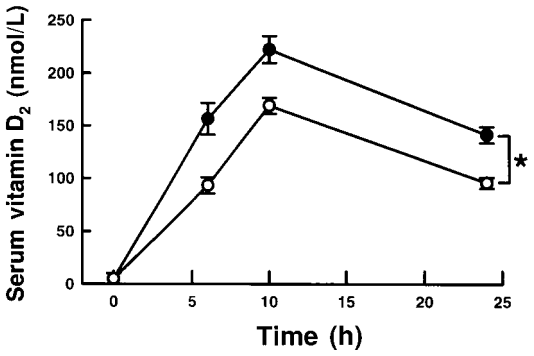

FIGURE 2. Mean (±SEM) serum vitamin D_2 (ergocalciferol) concentrations in the control (●) and obese (○) groups 0–25 h after oral intake of vitamin D_2 (50000 IU, 1.25 mg). Vitamin D_2 rose rapidly until ≈10 h after intake and then declined slightly thereafter. *Significant time and group effects by ANOVA ($P < 0.05$) but no significant time-by-group interaction. The difference in peak concentrations between the obese and nonobese control subjects was not significant.

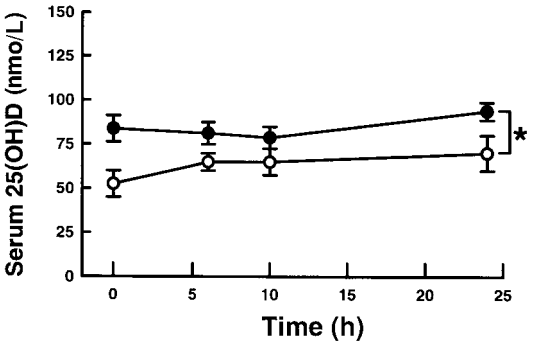

FIGURE 3. Mean (±SEM) serum 25-hydroxyvitamin D [25(OH)D] concentrations in the control (●) and obese (○) groups 0–24 h after oral intake of vitamin D_2 (ergocalciferol; 50 000 IU, 1.25 mg). The slight increase in the obese group was not significant. *Significant time-by-group interaction, $P < 0.05$ (ANOVA).

obese subjects showing an attenuated response to UV-B irradiation. When the results were recalculated as the difference between basal and postirradiation vitamin D_3 concentrations, they were still significantly different [control subjects: 38.3 ± 5.5 nmol/L (15.3 ± 2.1 ng/mL); obese subjects: 17.4 ± 3.6 nmol/L (6.7 ± 1.4 ng/mL); $P = 0.0029$].

In the oral vitamin D_2 loading test, basal serum concentrations of vitamin D_2 were not significantly different between groups [control subjects: 5.3 ± 0.2 nmol/L (2.1 ± 0.6 ng/mL); obese subjects: 3.5 ± 1.5 nmol/L (1.4 ± 0.6 ng/mL); **Figure 2**]. Additionally, there were no significant differences in basal vitamin D_3 concentrations [control subjects: 2.5 + 1.8 nmol/L (1.0 ± 0.7 ng/mL); obese subjects: 2.3 ± 2.3 nmol/L (0.9 ± 0.9 ng/mL)] or $1,25(OH)_2D$ [control subjects: 104.6 ± 14.6 pmol/L (43.5 ± 5.8 pg/mL); obese subjects: 96.6 ± 6.7 pmol/L (40.2 ± 2.8 pg/mL)]. However, 25(OH)D concentrations were significantly lower [50.0 ± 7.5 nmol/L (20.0 ± 3.4 ng/mL) compared with 84.8 ± 10.3 nmol/L (33.9 ± 4.1 ng/mL); $P = 0.017$] and parathyroid hormone concentrations were significantly higher (0.80 ± 0.05 compared with 0.63 ± 0.04 pmol/L; $P = 0.0291$) in the obese subjects than in the control subjects. After the oral intake of vitamin D_2, there was a marked increase in serum vitamin D_2 concentrations, with a significant effect of both time ($P = 0.00001$) and group ($P = 0.0186$); there was no significant time-by-group interaction (Figure 2). Peak vitamin D_2 concentrations did not differ significantly between the 2 groups [control subjects: 233.3 nmol/L (92.4 ng/mL); obese subjects: 181.6 nmol/L (71.9 ng/mL); $P = 0.0603$] nor did the difference between peak and basal vitamin D_2 concentrations [control subjects: 230.6 nmol/L (91.3 ng/mL); obese subjects: 185.4 nmol/L (73.4 ng/mL)]. There was a significant difference in the kinetics of the 25(OH)D response between groups ($P = 0.0481$, ANOVA time-by-group interaction; **Figure 3**). Follow-up analysis showed that the effect of time was significant ($P = 0.0041$), whereas the effect of group was not. Testing for changes in vitamin D_2 and $1,25(OH)_2D$ concentrations throughout the oral vitamin D_2 loading test showed that the group-by-time interaction, the time effect, and the group effect were not significant.

The effect of BMI on blood concentrations of vitamin D and its metabolites were evaluated by determining the correlation coefficients for the relations. Correlations between BMI and basal vitamin D_2, basal 25(OH)D, 25(OH)D, basal $1,25(OH)_2D$, peak 25(OH)D, and basal vitamin D were not significant. Conversely, there were 2 correlations that were highly significant: those between BMI and peak serum vitamin D_2 concentrations after the oral vitamin D_2 load (**Figure 4**) and between BMI and serum vitamin D_3 concentrations after UV-B irradiation (**Figure 5**).

The percentage conversion of provitamin D_3 (7-dehydrocholesterol) to vitamin D_3 in skin was not significantly different between the young obese and young nonobese subjects (9.4 ± 1.9% compared with 9.6 ± 1.1%) nor between the older obese and older nonobese subjects (7.6 ± 0.5% compared with 7.3 ± 0.5%).

DISCUSSION

The present study of the synthesis and processing of vitamin D confirmed that obese patients have lower basal 25(OH)D and higher serum parathyroid hormone concentrations than do nonobese persons (1–5). To determine why obese individuals are prone to vitamin D deficiency, we conducted a series of studies to determine their capability to handle vitamin D originating from either the oral route or from the skin. Because vitamin D is fat soluble and is readily stored in adipose tissue, it could be sequestered in the larger body pool of fat of obese individuals. We observed that blood vitamin D_3 concentrations increased in both the obese and nonobese subjects after exposure to an identical amount of UV-B irradiation. Moreover, the obese subjects had a larger body surface area of exposure and therefore would be expected to produce more vitamin D_3, resulting in higher blood vitamin D_3 concentrations, than would the nonobese control subjects. However, the increase in blood vitamin D_3 concentrations was 57% less in the obese than in the nonobese subjects 24 h after the exposure. The content of the vitamin D_3 precursor 7-dehydrocholesterol in the skin was not significantly different between obese and nonobese subjects, consistent with previous observations (17, 18). Furthermore, the percentage conversion to previtamin D_3 and vitamin D_3 was similar in both groups. Thus, obesity did not affect the capacity of the skin to produce vitamin D_3, but may have altered the release of vitamin D_3 from the skin into the circulation.

It is possible that the subcutaneous fat, which is known to store vitamin D_3, sequestered more of the cutaneous synthesized vitamin D_3 in the obese than in the nonobese subjects because there was more fat available for this process. To determine whether the same phenomenon occurred when vitamin D was

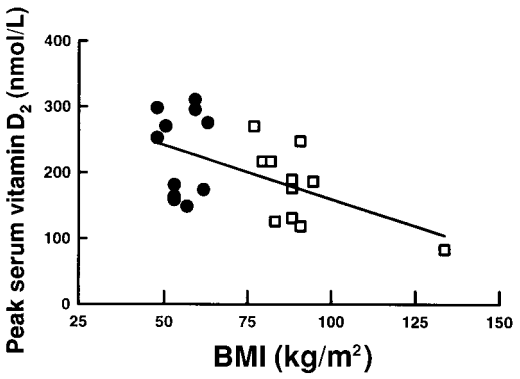

FIGURE 4. Correlation between BMI and peak serum vitamin D_2 (ergocalciferol) concentrations in the control (●) and obese (□) groups after oral intake of vitamin D_2 (50 000 IU, 1.25 mg). The correlation coefficient ($r = -0.56$) was highly significant ($P = 0.007$).

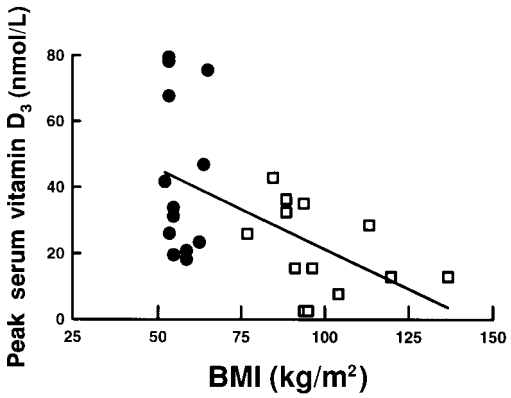

FIGURE 5. Correlation between BMI and peak serum vitamin D_3 (cholecalciferol) concentrations after whole-body irradiation (27 mJ/cm^2) with ultraviolet B radiation in control (●) and obese (□) subjects. The correlation coefficient ($r = 0.55$) was highly significant ($P = 0.003$).

ingested orally, obese and nonobese subjects were challenged with an oral dose of 50 000 IU vitamin D_2. There was no relation between basal vitamin D_2 concentrations and 25(OH)D. Peak blood concentrations of vitamin D_2 were not significantly different between the obese and nonobese subjects. However, BMI was inversely correlated with peak blood vitamin D_2 concentrations. Thus, the orally supplied vitamin D_2 was more bioavailable, probably because after absorption into the lymphatic system and transfer into the bloodstream, it is also sequestered in the large pool of body fat.

Because humans obtain most of their vitamin D requirement from casual exposure to sunlight, the >50% decreased bioavailability of cutaneously synthesized vitamin D_3 in the obese subjects could account for the consistent observation by us and others that obesity is associated with vitamin D deficiency. Oral vitamin D should be able to correct the vitamin D deficiency associated with obesity, but larger than usual doses may be required for very obese patients.

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Erratum

Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr 2000;72:690–3.

On page 692, column 2, paragraph 1, the text should read as follows: "Conversely, there were 2 correlations that were highly significant: those between body weight and peak serum vitamin D_2 concentrations after the oral vitamin D_2 load (**Figure 4**) and those between body weight and serum vitamin D_3 concentrations after UV-B irradiation (**Figure 5**)." In addition, the *x* axes of Figures 4 and 5 should read as follows: "Body weight (kg)."

Erratum

Kumanyika SK, Obarzanek E, Stevens VJ, Hebert PR, Whelton PK. Weight-loss experience of black and white participants in NHLBI-sponsored clinical trials. Am J Clin Nutr 1991;53(suppl):1631S–8S.

The first author's last name should be spelled as above and not as published in the Journal.

Am J Clin Nutr 2003;77:1342. Printed in USA.