BRIEF OBSERVATION

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Adequacy of Vitamin D Replacement in Severe Deficiency Is Dependent on Body Mass Index

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ABSTRACT

BACKGROUND: Obesity is associated with hypovitaminosis D. Whether body mass index (BMI) determines the replacement dose of vitamin D to achieve sufficiency is unclear.

OBJECTIVE: To determine the relationship between BMI and serum 25-OH vitamin D concentrations and whether the increase in serum 25-OH vitamin D concentrations with vitamin D replacement is dependent on BMI.

METHODS: Retrospective review of anthropometric data and serum 25-OH vitamin D concentrations in 95 patients attending an outpatient clinic in a tertiary hospital. In a second component of the study, 17 hospital inpatients with severe vitamin D deficiency (serum 25-OH D concentrations < 6 ng/mL [15 nmol/L]) were supplemented with 10,000 units vitamin D_3/day orally for 1 week. Biochemistry and anthropometric measurements were compared before and after vitamin D replacement.

RESULTS: Serum 25-OH vitamin D concentrations correlated negatively with BMI in the 95 outpatients ($r^2 = 0.11$, $P < .01$). In the longitudinal study, BMI correlated positively with serum intact parathyroid hormone ($r^2 = 0.84$, $P < .01$) and negatively with 1.25-$(OH)_2$ vitamin D ($r^2 = 0.19$, $P = .06$) at baseline. Serum 25-OH D concentrations achieved following 1 week of vitamin D_3 replacement correlated negatively with BMI ($r^2 = 0.63$, $P < .01$).

CONCLUSION: Efficacy of vitamin D supplementation is dependent on BMI. Overweight and obese patients with hypovitaminosis D might require higher doses of vitamin D to achieve vitamin D repletion compared with individuals with normal body weight.

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The vitamin D-parathyroid axis is influenced by body weight. Circulating 25-hydroxy vitamin D (25-OH D) levels are lower in obese subjects.[1-3] Multiple mechanisms have been proposed to explain the association of obesity with hypovitaminosis D, including lack of sunlight exposure from physical inactivity and sequestration of vitamin D in subcutaneous fat depots.[3]

The current "epidemic" of overweight and obesity is likely to increase the frequency and severity of vitamin D insufficiency encountered in clinical practice. Hypovitaminosis D is an important risk factor for osteoporosis and osteomalacia. However, vitamin D also has been increasingly recognized for its pleotropic actions. Hypovitaminosis D has been implicated in a range of conditions highly prevalent in the obese population, including diabetes, ischemic heart disease, and stroke. Although a causal link between hypovitaminosis D, obesity, and cardiovascular diseases[4] has not been established, achieving vitamin D sufficiency in obese patients is likely to improve general well-being.

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It remains unclear whether the dose of vitamin D required for repletion is related to the degree of obesity. One study reported lesser responses of vitamin D_3 to UV-irradiation and of vitamin D_2 to oral vitamin D_2 dosage in obese individuals, but no significant relationship between body mass index (BMI) and serum 25-OH D levels.[3] However, other studies have suggested that obesity may determine the therapeutic or serum 25-OH D response.[5,6] Comparison of results from these studies is difficult because of different pretreatment 25-OH D levels, and vitamin D assay variability, as well as potential variations in sunlight exposure, compliance, and diet.

CLINICAL SIGNIFICANCE

- Obesity is associated with vitamin D insufficiency.
- Adequacy of vitamin D supplementation depends on body mass index.
- Body mass index should be considered when prescribing a vitamin D supplement, and obese individuals can require a larger dose or longer duration of supplementation to achieve sufficiency.

The current study investigated the relationship between vitamin D status and BMI and whether the adequacy of vitamin D supplementations in hospital inpatients with severe vitamin D deficiency (serum 25-OH D concentration <6 ng/mL [<15 nmol/L]) was related to BMI. Unlike previous studies,[3,5,6] all subjects had severe deficiency and thus 25-OH D increments could not be attributable to any measurable difference in baseline stores. Secondly, all patients remained as hospital inpatients during the follow-up, ensuring that 25-OH D increments are independent of sunlight exposure. Thirdly, vitamin D was administered under direct nursing supervision, so compliance was 100%.

METHODS

A retrospective review of anthropometric data and vitamin D status was undertaken in 95 patients who attended the Minimal Trauma Fracture Clinic for screening of osteoporosis following a fragility fracture at Concord Hospital, Sydney, Australia, 2005-2006 (Table 1).

For the longitudinal study, data on 17 inpatients at St. Vincent's Hospital, Sydney, Australia from May to December 2007 with severe vitamin D deficiency (serum 25-OH D concentration <6 ng/mL [<15 nmol/L]) were analyzed. We reviewed demographic and biochemical variables at baseline and 1 week after initiation of oral vitamin D_3 10,000 IU/day. Patients with significant renal (eGFR <30 mL/min/1.73 m^2) and hepatic impairment and past history of malabsorption were excluded. In our practice, a loading dose of vitamin D is used routinely for patients with severe deficiency and maintenance dose determined by individual response to the loading dose.

Serum 25-OH D concentrations were measured by radioimmunoassay (RIA; DiaSorin, Stillwater, Minn; sensitivity 4 nmol/L, intra-assay precision 7.6% and interassay precision 9%). Serum 1.25-$(OH)_2$ vitamin D (1.25-$[OH]_2$D) concentrations were measured by RIA after extraction (Incstar Corporation, Stillwater, Minn), with a detection limit of 4.8 pmol/L. Serum intact parathyroid hormone (iPTH) concentrations were measured by an automated immunoassay (Roche E170; F. Hoffman-LaRoche Ltd., Basel, Switzerland) with interassay precision of 5.5% and intra-assay precision of 7.9%.

Data are expressed as mean ± standard deviation (range). Differences between groups were assessed using unpaired *t* tests. Linear regression was used to assess relationships between variables using raw data. A P value <.05 was considered statistically significant.

RESULTS

In the cohort of 95 outpatients (69 females), 89% of the patients were Caucasian, 6% were East Asian, and 5% were of Indian origin. Excluding the patients of East Asian and Indian origins did not alter the results of the analysis. In this cohort, BMI correlated negatively with serum 25-OH D ($r^2 = 0.11$, P <.01) (Figure 1a) and positively with iPTH ($r^2 = 0.23$, P <.01) (Figure 1b). Backward step-wise multiple regression was performed to determine the contribution of age, sex, BMI, serum calcium, and iPTH concentrations to 25-OH D levels. In this model, only BMI and iPTH independently predicted lower 25-OH D (adjusted $R^2 = 0.34$, P <.01). Two subjects had serum calcium levels above reference range (2.62 and 2.7 mmol/L). Excluding these 2 subjects did not alter the results of the analysis.

Table 1 Characteristics of the 95 Patients Attending Outpatient Clinic*

BMI (kg/m^2)	<25	25-29.9	≥30
Number	30	35	30
Age (years)	69 (12) [47-91]	68 (10) [47-88]	68 (10) [53-85]
Height (cm)	158 (8) [140-172]	157 (7) [141-175]	155 (7) [142-169]
Weight (kg)	58 (8) [44-74]	69 (6) [55-82]	82 (12) [67-117]
BMI (kg/m^2)	23 (2) [18-24]	28 (1) [25-30]	34 (4) [31-45]
Serum calcium (2.1-2.6 mmol/L)	2.4 (0.1) [2.2-2.6]	2.3 (0.3) [2.1-2.6]	2.2 (0.3) [2.2-2.7]
25-OH D (nmol/L)	58 (16) [30-90]	54 (19) [21-94]	43 (12) [12-66]
Serum iPTH (1-7 pmol/L)	4.8 (2.8) [2.0-12.0]	5.1 (4.1) [2-14]	7.8 (5.1) [3-20.2]

BMI = body mass index; 25-OH D = 25-hydroxy vitamin D; iPTH = intact parathyroid hormone.
*Data are Mean (SD) [Range].

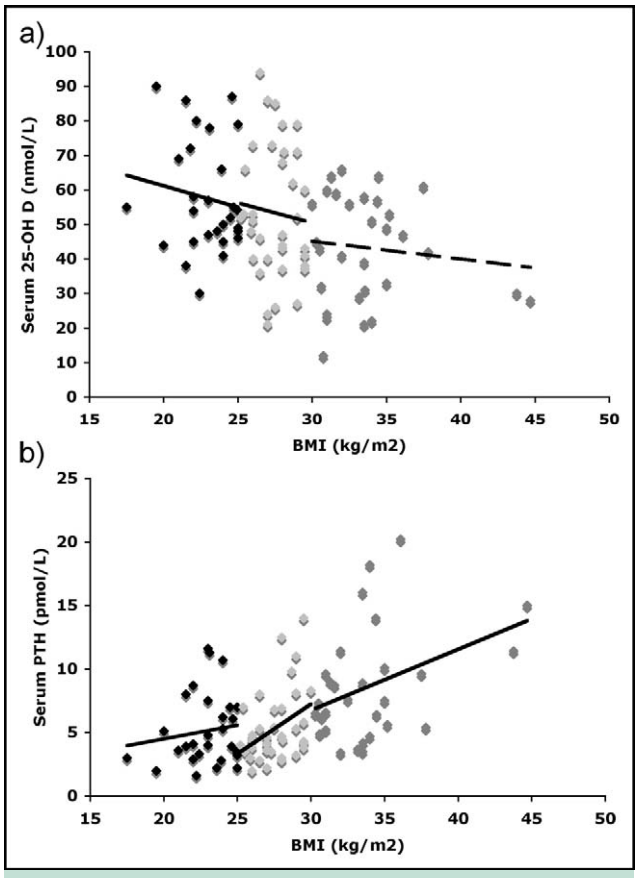

Figure 1 Relationship between serum 25-OH D (25-hydroxy vitamin D) and iPTH (intact parathyroid hormone) concentrations and BMI (body mass index) in outpatients. Fitted lines were drawn for each BMI category (black: <25 kg/m^2, light grey: 25-30 kg/m^2, dark grey: >30 kg/m^2).

In the longitudinal study (Table 2), mean duration of stay in hospital before measurement of vitamin D was 5 ± 1 day. All patients were of Caucasian origin. Admission diagnoses were falls (n = 5), delirium (n = 4), urinary tract infection (n = 2), and fractures (n = 6). Baseline serum iPTH correlated positively with BMI ($r^2 = 0.84$, $P < .01$) (Figure 2a). Baseline serum 1.25-$(OH)_2$D correlated negatively with BMI ($r^2 = 0.19$, $P = .06$). Serum 25-OH D concentration achieved following 1 week of vitamin D_3 replacement correlated negatively with baseline BMI ($r^2 = 0.63$, $P < .01$) (Figure 2b). A similar relationship was observed if BMI at 1 week was used (not shown). Consistent with the data above, baseline and final serum iPTH concentrations were significantly greater in overweight/obese patients (BMI >25 kg/m^2) (n = 9) compared with normal-weight patients (BMI <25 kg/m^2) (n = 8). This was despite the overweight/obese patients exhibiting a greater reduction in serum iPTH concentrations (Figure 2c). Baseline but not final serum 1.25-$(OH)_2$D concentrations were lower in overweight/obese patients (Figure 2d). Hence, the change in serum 1.25-$(OH)_2$D concentrations tended to be greater in the overweight/obese group (Figure 2d).

DISCUSSION

In the current study, in a cohort of 95 outpatients from a tertiary hospital, there was a negative relationship between BMI and serum 25-OH D concentrations, similar to some previous reports.[1,2] The relationship between iPTH and BMI in this cross-sectional cohort also was observed in the longitudinal component of our study conducted in 17 inpatients, with a strong positive relationship between iPTH and BMI. Importantly, the 25-OH D level achieved after a week of vitamin D replacement was highly dependent on BMI.

Although the 17 patients included in our longitudinal study had serum 25-D levels below 15 nmol/L, it is still possible that their vitamin D stores were depleted to different degrees. Given the known relationship between the severity of vitamin D deficiency and degree of hyperparathyroidism, it is possible that the overweight/obese patients were more severely deficient than normal-weight patients, as reflected by their lower baseline 1.25-$(OH)_2$D concentrations and higher baseline iPTH levels (Figure 2, c and d).

The current study has important clinical implications. Firstly, obese individuals are more likely to be vitamin D insufficient. Secondly, increments of vitamin D level are less in obese individuals, implying that a larger dose of vitamin D supplementation is required for repletion compared with normal-weight individuals. Thirdly, the increased requirement of vitamin D in deficient obese individuals is likely contributed to by a combination of substrate deficiency and increased conversion of 25-OH D to 1.25-$(OH)_2$D.

A possible causal relationship between 1.25-$(OH)_2$D and obesity has generated interest in recent years because of the stimulatory effects of 1.25-$(OH)_2$D on adipogenesis in vitro.[7] While some studies reported a positive correlation between 1.25-$(OH)_2$D and BMI,[1,8] others reported 1.25-$(OH)_2$D to be significantly lower in obese subjects,[9] arguing against 1.25-$(OH)_2$D being a significant factor for obesity. Subjects in these studies had varying initial 25-OH D levels, and it is unclear if alteration in 1.25-$(OH)_2$D was due to differences in substrate level or degrees of renal 1α-hydroxylation driven by hyperparathyroidism. In our study, baseline 1.25-$(OH)_2$D levels correlated negatively with BMI, in support of the substrate deficiency hypothesis. However, following vitamin D replacement from similar (<15 nmol/L) baseline 25-OH D levels, overweight/obese patients exhibited a greater reduction of iPTH concentrations and greater increments in 1.25-$(OH)_2$D concentrations (Figure 2, c and d), suggestive of a stimulated parathyroid-vitamin D axis with enhanced consumption of 25-OH D by its conversion to 1.25-$(OH)_2$D. Higher parathyroid hormone levels have been associated with increased cardiovascular mortality.[10] Whether the upregulated parathyroid-vitamin D axis observed in these overweight/obese subjects might contribute to the known association between obesity and cardiovascular diseases necessitates further studies.

In conclusion, the novel findings of our study challenge existing recommendations that vitamin D supplementation should be based on baseline serum 25-OH D concentrations

Table 2 Demographic and Biochemical Variables of 17 Patients with Severe Vitamin D Deficiency (Serum 25-OH D Concentration <6 ng/mL [<15 nmol/L]) at Baseline and at 1 Week Following Vitamin D_3 Supplementation of 10,000 Units/Day*

Age (years)		75 (11)	
Height (cm)		163 (10)	
Weight (kg)		68 (16)	
BMI (kg/m^2)		25.4 (4.4)	
Number of patients			
<25 kg/m^2		8	
25.0-29.9 kg/m^2		6	
≥30.0 kg/m^2		3	
Residential background (n)			
Community-dwelling		9	
Low-level care		5	
High-level care		3	
Biochemistry (at baseline, at 1 week, *P* value)			
Corrected serum calcium (2.1-2.6 mmol/L)	2.01 (0.32)	2.26 (0.13)	.005
Calculated GFR (>60 mL/min/1.73m^2)	62 (13)	60 (13)	.7
25-OH D concentration (>24 ng/mL, >60 nmol/L)	<15	46.8 (10.1)	<.00001
1.25-$(OH)_2$D concentration (36-120 pmol/L)	136 (41)	176 (21)	.001
iPTH (1-7 pmol/L)	41 (19)	27 (12)	.01

25-OH D = 25-hydroxy vitamin D; BMI = body mass index; GFR = glomerular filtration rate.
*Data are Mean (SD).

alone. Due to the small sample size of our study, further studies are required to clarify whether the larger dose requirement in obesity is due to substrate deficiency or sequestration or excessive consumption. However, irrespective of the mechanism, BMI should be considered in vitamin D supplements because overweight and obese individuals

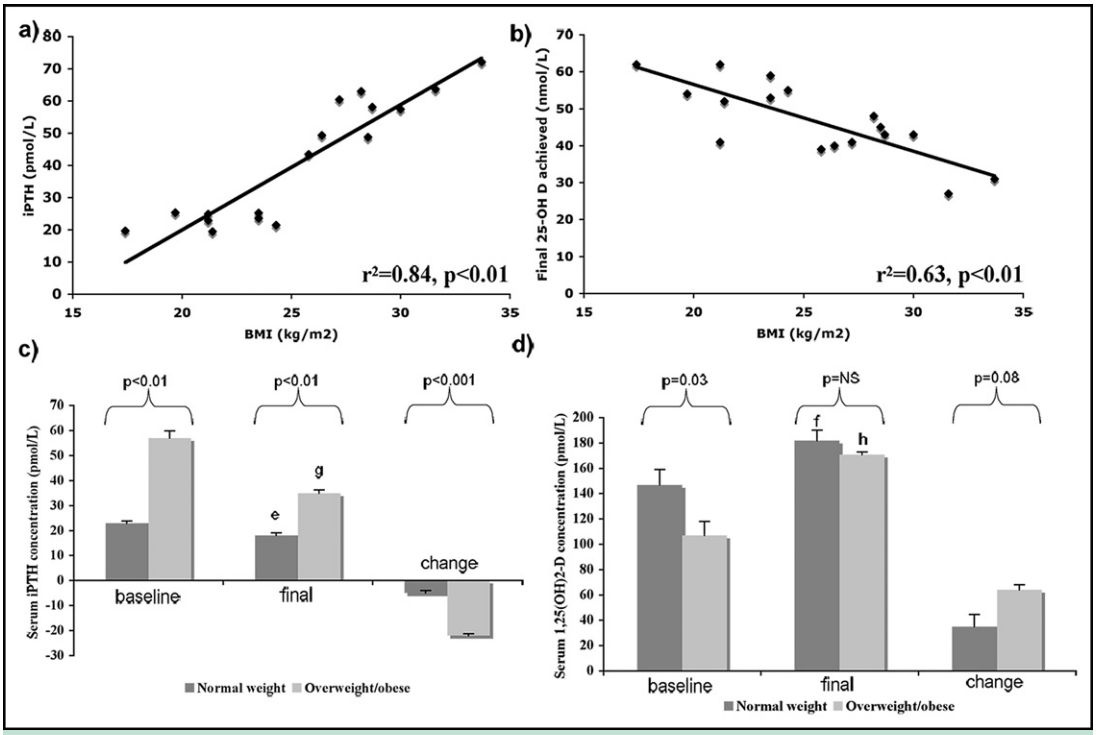

Figure 2 Relationships between BMI (body mass index) and (**a**) serum iPTH (intact parathyroid hormone) concentrations at baseline and (**b**) serum 25-OH D (25-hydroxy vitamin D) achieved following 1 week of high dose vitamin D_3 supplements (10,000 units/day) and changes in (**c**) serum iPTH and (**d**) 1.25-$(OH)_2$D concentrations in normal-weight and overweight/obese patients. (e: $p = .001$; f: $p = .007$; g: $p < .0001$; h: $p = .0008$ compared with baseline).

might require a larger dose (or longer duration) of supplementation to achieve sufficient serum 25-OH D levels.

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