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Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season

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Abstract

Low 25-hydroxyvitamin D (25[OH] D) results in hyperparathyroidism and is among the endocrine derangements of adult obesity. There are differing recommendations on defining low 25(OH) D: hypovitaminosis D (serum 25[OH] D concentration <75 nmol/L) and vitamin D deficiency (serum 25[OH] D concentration <50 nmol/L). We sought to evaluate the prevalence of low levels of 25(OH) D by examining hypovitaminosis D (<75 nmol/L), vitamin D sufficiency (≥75 nmol/L), vitamin D insufficiency (50-74.9 nmol/L), and vitamin D deficiency (<50 nmol/L) in pediatric obesity and the relationship to other calciotropic hormones and adiposity. Serum 25(OH) D, intact parathyroid hormone (iPTH), ionized calcium, glucose, and insulin levels along with hemoglobin A_{1c} (HbA_{1c}) and quantitative insulin sensitivity check index (QUICKI) were determined in 127 subjects aged 13.0 ± 3.0 years (49 Caucasian [C], 39 Hispanic [H], and 39 African American [AA]; 61.2% female; body mass index 36.4 ± 8.1 kg/m^2) during fall/winter (F/W) and spring/summer (S/S). Body composition was determined by bioelectrical impedance. Hypovitaminosis D was present in 74% of the cohort, but was more prevalent in the H (76.9%, $P < .05$) and AA (87.2%, $P < .05$) groups than in the C group (59.1%). Hypovitaminosis D corresponded to decreased vitamin D intake ($P < .005$) and was more prevalent in F/W than S/S (98.4% vs 49.2, $P < .01$). Vitamin D deficiency was identified in 32.3% of the entire cohort and was more prevalent in the H (43.6%, $P < .0001$) and AA (48.7%, $P < .0001$) groups than in the C group (10.2%) associated with decreased vitamin D intake ($P < .0001$). Vitamin D insufficiency was present in 41.7% of the cohort, with similar prevalence among C (48.9%), H (33.3%), and AA (38.5%). Vitamin D insufficiency corresponded to decreased vitamin D intake ($P < .005$), with similar prevalence in F/W and S/S (45.3% vs 38.1%), whereas vitamin D deficiency was not only accompanied by decreased vitamin D intake ($P < .0001$) but was more prevalent in F/W than S/S (53.1% vs 11.1%, $P < .0001$). Serum 25(OH) D and iPTH ($r = -0.41$, $P < .0001$) levels were negatively correlated without seasonal and ethnic/racial influences. Hypovitaminosis D and vitamin D–deficient groups had higher body mass index, fat mass (FM), and iPTH, but had lower QUICKI than vitamin D–sufficient group ($P < .01$). Whereas FM was negatively correlated with 25(OH) D ($r = -0.40$, $P < .0001$), it was positively correlated with iPTH ($r = 0.46$, $P < .0001$) without seasonal and racial/ethnic influences. Serum 25(OH) D was also positively correlated with QUICKI ($r = 0.24$, $P < .01$), but was inversely correlated with HbA_{1c} ($r = -0.23$, $P < .01$). Hypovitaminosis D was identified in 74% of obese subjects, whereas vitamin D deficiency was observed in 32.3% of our cohort. Vitamin D status was influenced by vitamin D intake, season, ethnicity/race, and adiposity. Interrelationships between 25(OH) D, iPTH, and FM were not influenced by season and race/ethnicity. Furthermore, serum 25(OH) D was positively correlated with insulin sensitivity, which was FM mediated, but negatively correlated with HbA_{1c}, implying that obese children and adolescents with low vitamin D status may be at increased risk of developing impaired glucose metabolism independent of body adiposity. Additional studies are needed to evaluate the underlying mechanisms.

1. Introduction

It has been shown that vitamin D regulates calcium metabolism through its endocrine function and its non-calciotropic effects such as cellular differentiation and replication in many organs via its paracrine and autocrine

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role [1,2]. These noncalciotropic functions comprise the immune system, endocrine pancreas, liver, skeletal muscles, and adipocytes [2]. The vitamin D endocrine system plays a role in glucose homeostasis, especially in the mechanism of insulin secretion [3-6]. Therefore, vitamin D deficiency and insufficiency (hypovitaminosis D) can adversely affect tissues that are not involved in calcium homeostasis and bone metabolism [7].

Serum 25-hydroxyvitamin D (25[OH] D) concentrations are largely determined by environmental factors, mainly through vitamin D intake (cholecalciferol and ergocalciferol) and ultraviolet radiation of 7-dehydrocholesterol in the skin (cholecalciferol) [8,9]. The serum concentration of 25(OH) D is the best marker of total body vitamin D status [10,11]; however, the definition of acceptable serum concentration of 25(OH) D is equivocal. Recently, a consensus statement for vitamin D nutritional guidelines issued by scientists and nutritional experts suggested that serum 25(OH) D ≥75 nmol/L concentration is the minimum acceptable level for maintenance of bone health and health in general [12]. There was also a general recommendation that blood concentration of 25(OH) D should at the very least meet, or exceed, a minimum desirable level of 50 nmol/L in all age groups [13]. Indeed, *vitamin D deficiency*, defined as serum 25(OH) D <50 nmol/L [13], has been shown to be common in healthy adolescent population, with a higher prevalence in African American youth and during winter months [14-16]. Indeed, low serum 25(OH) D and the resultant hyperparathyroidism are among the endocrine derangements of obesity [17]. Despite this discrepancy in proposed minimum level of acceptable serum concentration of 25(OH) D, obese adults and children have been shown to have low serum 25(OH) D and elevated intact parathyroid hormone (iPTH) levels [18-20]. Adult subjects with hypovitaminosis D are also believed to be at higher risk of insulin resistance and metabolic syndrome [6,7]. Hypovitaminosis D has been implicated in the pathogenesis of insulin resistance, β-cell dysfunction, and type 1 and type 2 diabetes mellitus [21,22].

In young children and adolescents living in the northern parts of the United States, a rise in parathyroid hormone level occurs at low-normal concentrations of vitamin D [15,23,24]. One hypothesis is that this physiologic increase in parathyroid hormone levels in response to hypovitaminosis D state is believed to increase intracellular calcium in adipocytes, which leads to increased lipogenesis and weight gain [25]. To date, the prevalence of vitamin D deficiency and hypovitaminosis D, the identification of the resultant hyperparathyroidism, and the impact on insulin sensitivity and glucose homeostasis among obese children have not been evaluated. Therefore, we evaluated the levels of fasting serum calciotropic hormones, ionized calcium (iCa^{+2}), phosphate, insulin, glucose hemoglobin A_{1c} (HbA_{1c}), and an index of insulin sensitivity and dietary intake of vitamin D and calcium in relationship to adiposity, season, and ethnicity/race in a group of obese children and adolescents residing in a northern climate (43° N).

2. Subjects and methods

2.1. Subjects and design

One hundred twenty-seven children and adolescents (age, 6.0-17.9 years) who met the criteria for obesity (body mass index [BMI] >95th percentile for age) [26] were included in the study. All subjects were evaluated at the Children's Hospital of Wisconsin (affiliated with the Medical College of Wisconsin) Endocrine Clinic for evaluation of metabolic syndrome between January 2003 and June 2004. Subjects were stratified according to season: fall/winter (F/W) (November-April) and spring/summer (S/S)(May-October). Race/ethnicity was self-assigned: Caucasian (C; n = 49, 38.6%), Mexican American (Hispanic [H]; n = 39, 30.7%), and African American (AA; n = 39, 30.7%). Children were excluded if they had hepatic or renal disease, metabolic rickets, malabsorptive disorders (Crohn disease, cystic fibrosis, and celiac disease), or cancer or if they were taking anticonvulsants or systemic glucocorticoids. The Children's Hospital of Wisconsin Institutional Review Board approved the retrospective review of patients' clinical charts; therefore, informed consent was not required.

Data were collected on patients including age, sex, self-declared ethnicity, height, weight, blood pressure, and body composition analysis that was performed by bioelectrical impedance (BIA) (TANITA-TBF-410; TANITA America, Arlington Heights, IL) [27,28]. Subjects and/or their guardians completed a questionnaire detailing their medical history and medications. Two well-trained clinicians determined pubertal maturation (Tanner stage). Fasting serum samples were obtained for glucose, iCa^{+2}, phosphate, insulin, 25(OH) D, and iPTH.

2.2. Assessment of vitamin D and calcium intake

Dietary intakes of vitamin D and calcium were estimated using 3-day food records that the parents mostly completed. The dietary and/or supplemental vitamin D and calcium contents were calculated by Nutritionist Pro (version 3.0) analysis software (Axxya Systems, Stafford, TX). *Adequate intake* (AI) of vitamin D was defined as 200 U/d as recommended by the American Academy of Pediatrics regardless of sunlight exposure, milk intake, and/or vitamin D supplement use [29].

2.3. Laboratory studies and calculations

All blood samples were obtained between 8:00 AM and 11:00 AM. Serum glucose and phosphate were measured by an autoanalyzer (Orthodiagnostics Fusion 5.1; Orthodiagnostics, Rochester, NY). Serum iCa^{+2} was measured by an ion-selective electrode method using Roche AVL 988-4

Analyzer (Roche Diagnostics, Indianapolis, IN). The intraassay coefficient of variation (CV) was 8% at 4.72 mg/dL (1.18 mmol/L), and interassay CVs were 4.08% at 1.5 mg/dL (0.338 mmol/L) and 2.85% at 2.11 mg/dL (0.527 mmol/L). Hemoglobin A_{1c} was determined by the Bayer DCA 2000 instrument (Bayer Diagnostics, Tarrytown, NY) (nondiabetic range of 4.5%-5.7%).

Serum 25(OH) D was measured using Nichols radioimmunoassay (Nichols Institute, San Clemente, CA) with intraassay and interassay CVs of 4.6% to 11.5% and 8.4% to 14.0%, respectively. Serum iPTH measurements were made using a Nichols immunochemiluminometric assay with intraassay and interassay CVs of 3.4% to 7.3% and 3.7% to 6.6%, respectively. Fasting serum insulin was measured by Nichols radioimmunoassay with intraassay and interassay CVs of 2.4% to 6.3% and 5.2% to 13.0%, respectively. The quantitative insulin sensitivity check index (QUICKI) was calculated as previously described [30,31]: QUICKI = $1/[\log(I_0) + \log(G_0)]$, where I_0 is fasting insulin (in microunits per milliliter) and G_0 is fasting glucose (in milligrams per deciliter).

2.4. Statistical analysis

Statistical analyses were carried out using SPSS (version 14.0; SPSS, Chicago, IL). Data are expressed as mean ± SD unless otherwise specified. The following definitions for vitamin D status were used for stratification of subjects: hypovitaminosis D, 25(OH) D level <75 nmol/L; vitamin D sufficiency, 25(OH) D level ≥75 nmol/L [12]; vitamin D deficiency, 25(OH) D level <50 nmol/L [13]; and vitamin D insufficiency, 25(OH) D level of 50 to 74.9 nmol/L [12]. Differences between the hypovitaminosis D and vitamin D–sufficient groups were estimated using unpaired Student *t* tests. Afterward, the differences of the multiple subgroups (ie, vitamin D sufficiency, vitamin D deficiency, and vitamin D insufficiency) were estimated by 1-way analysis of variance; Bonferroni post hoc testing was applied whenever appropriate. Because the distributions of 25 (OH) D and iPTH were skewed, we used the natural logarithmic transformation before analysis. Two multiple linear regression analyses were performed to examine the associations between fat mass (FM) and plasma 25(OH) D or iPTH while controlling for potential covariates (eg, age, sex, ethnicity, and season). Spearman correlations were used to assess the relationship between 25(OH) D and iPTH as well as the potential covariates. In addition, multiple linear regression analysis was performed to determine the associations between 25(OH) D, QUICKI, and HbA_{1c} while controlling for potential covariates (eg, age, sex, FM, ethnicity, and season). χ^2 analyses were used to compare the prevalence of hypovitaminosis D in the Caucasian subgroup with that in the Hispanic and African American subgroups. Fisher *Z* transformation was used to compare 2 correlations at a time. Multiple regression analyses were conducted using the statistical models proposed by Baron and Kenny [32] and the Sobel test [33]. $P < .05$ was considered significant.

3. Results

3.1. Findings stratified by vitamin D sufficiency and hypovitaminosis D

Table 1 summarizes the clinical and biochemical characteristics of the entire participant cohort and groups stratified according to vitamin D levels ≥75 nmol/L and <75 nmol/L. The vitamin D–sufficient and hypovitaminosis D groups were similar in age, proportion of female subjects, and Tanner stage. However, subjects in the hypovitaminosis D group had higher BMI ($P< .02$) and FM ($P < .02$) and lower ratios of fat-free mass (FFM) to FM ($P < .001$) than the vitamin D–sufficient group. Hypovitaminosis D was detected in 74% of the entire cohort. Furthermore, the hypovitaminosis D group had higher iPTH levels ($P < .001$) but had similar serum iCa^{+2} and phosphate levels compared with the vitamin D–sufficient group. In addition, serum iCa^{+2} was inversely correlated with serum iPTH ($r = -0.25$, $P < .01$) but positively correlated with 25(OH) D ($r = 0.22$, $P < .02$) in the entire cohort (data not shown). Although mean serum glucose levels and HbA_{1c} were similar in both groups, serum insulin levels were slightly higher in the hypovitaminosis D group than in the vitamin D–sufficient group; but this difference did not reach statistical significance. Nevertheless, the hypovitaminosis D group had lower QUICKI values than the vitamin D–sufficient group ($P < .005$). The hypovitaminosis D group not only reported lower intake of vitamin D and calcium than the vitamin D–sufficient group ($P < .02$), but also lower percentage of AI of vitamin D ($P < .005$).

3.2. Findings stratified by vitamin D sufficiency, vitamin D insufficiency, and vitamin D deficiency

Table 2 summarizes the clinical and biochemical characteristics of the 3 groups. Vitamin D deficiency was detected in 32.3% of the entire cohort. The vitamin D–sufficient, vitamin D–insufficient, and vitamin D–deficient groups were similar in age, proportion of female subjects, and Tanner stage. However, subjects in the vitamin D–deficient group had higher BMI ($P < .001$, $P < .01$) and FM ($P < .001$, $P < .01$) and lower FFM/FM ratios ($P < .001$, $P < .0001$) than the vitamin D–sufficient and vitamin D–insufficient groups, respectively. Furthermore, the vitamin D–deficient group had higher iPTH levels ($P < .001$) but lower serum iCa^{+2} level compared with the vitamin D–sufficient group. Although mean fasting serum glucose levels were similar, the vitamin D–deficient group had higher HbA_{1c} and serum insulin levels ($P < .05$) but lower QUICKI values than the vitamin D–sufficient group ($P < .01$). The vitamin D–deficient group not only reported lower intake of vitamin D and calcium ($P < .0001$), but also lower

Table 1
Clinical and biochemical characteristics of subjects based on hypovitaminosis D status

Parameters	All	Vitamin D sufficiency (≥75 nmol/L)	Hypovitaminosis D (<75 nmol/L)	*P*
n (%)	127	33 (26)	94 (74)	NA
Age (y)	13.0 ± 3.0	13.0 ± 3.2	12.9 ± 2.8	NS
Sex (% female)	62.2	63.6	61.7	NS
Tanner stage	3.1 ± 1.4	3.3 ± 1.4	3.1 ± 1.4	NS
BMI (kg/m^2)	37.1 ± 8.5	33.9 ± 6.0 *	38.2 ± 8.9	<.02
Fat (%)	44.6 ± 8.0	40.8 ± 8.5 **	45.8 ± 7.4	<.005
FM (kg)	43.5 ± 20.2	36.1 ± 17.3 *	46.0 ± 20.5	<.02
FFM (kg)	51.1 ± 13.9	50.1 ± 12.2	51.5 ± 14.5	NS
FFM/FM	1.32 ± 0.44	1.55 ± 0.54 ***	1.24 ± 0.36	<.001
TBW (kg)	37.3 ± 10.2	36.6 ± 8.9	37.6 ± 10.6	NS
iCa^{+2} (mmol/L)	1.24 ± 0.05	1.24 ± 0.04	1.23 ± 0.05	NS
Phosphate (mmol/L)	1.41 ± 0.19	1.39 ± 0.16	1.41 ± 0.18	NS
25(OH) D (nmol/L)	59.9 ± 23.2	89.3.4 ± 12.9 ****	49.4 ± 15.6	<.0001
iPTH (ng/L)	38.3 ± 15.0	31.4 ± 13.3 ***	40.8 ± 14.9	<.001
Glucose (mmol/L)	4.98 ± 0.44	5.00 ± 0.34	4.96 ± 0.42	NS
HbA_{1c} (%)	5.2 ± 0.4	5.04 ± 0.4	5.3 ± 0.4	NS
Insulin (pmol/L)	202.8 ± 113.9	174.5 ± 98.9	212.9 ± 117.5	NS
QUICKI	0.299 ± 0.021	0.310 ± 0.023 **	0.297 ± 0.021	<.005
Vitamin D intake (IU/d)	227 ± 121	270.9 ± 149.3 *	210.9 ± 106.1	<.02
AI of vitamin D (%)	48.1	75.8 **	36.2	<.005
Calcium intake (mmol/d)	32.1 ± 14.5	37.1 ± 17.2 *	30.2 ± 12.9	<.02

TBW indicates total body water; NA, not applicable; NS, not significant.
* $P < .02$, for comparison of vitamin D–sufficient group vs hypovitaminosis D group.
** $P < .005$, for comparison of vitamin D–sufficient group vs hypovitaminosis D group.
*** $P < .001$, for comparison of vitamin D–sufficient group vs hypovitaminosis D group.
**** $P < .0001$, for comparison of vitamin D–sufficient group vs hypovitaminosis D group.

percentage of AI of vitamin D than the vitamin D–sufficient group ($P < .005$).

In addition, vitamin D insufficiency was identified in 41.7% of our cohort. Subjects with vitamin D insufficiency had lower BMI ($P < .01$), FM ($P < .01$), FFM/FM ratios ($P < .001$), and serum insulin level ($P < .01$) than the vitamin D–deficient group. Furthermore, the vitamin D–insufficient group reported higher intake of vitamin D and calcium and percentage of AI of vitamin D ($P < .001$) than the vitamin D–deficient group. However, the vitamin D–insufficient and vitamin D–deficient groups were similar in relationship to iCa^{+2}, phosphate, iPTH, glucose, HbA_{1c}, and QUICKI values.

Finally, the vitamin D–insufficient and vitamin D–sufficient groups were similar in relationship to body adiposity; serum levels of iCa^{+2}, iPTH, glucose, insulin, and HbA_{1c}; and QUICKI values as well as reported dietary intake of vitamin D and calcium.

3.3. Findings for entire cohort

Table 1 summarizes the clinical and biochemical characteristics of the entire participant cohort. The correlations among the covariate, predictor, and dependent variables are summarized in Table 3. Two hierarchical multiple regression analyses were then performed to test whether FM was related to serum 25(OH) D and iPTH once covariates (ie, age, sex, ethnicity, and season) were taken into account. Sex was not significantly correlated with serum 25(OH) D or iPTH and was therefore not used as a covariate in either multiple regression analysis. However, because season was correlated with both serum 25(OH) D and iPTH ($r = 0.63$, $P < .0001$ and $r = -0.36$, $P < .0001$, respectively), it was used as a covariate in both regression analyses. In addition, ethnicity was correlated with serum 25(OH) D ($r = -0.35$, $P < .0001$); and age was correlated with iPTH ($r = 0.27$, $P < .001$). Therefore, each was also used in the respective multiple regression analysis. For the serum 25(OH) D regression analysis, season and ethnicity accounted for a significant proportion of the variance ($\beta = 0.55$, $t = 8.97$, $P < .0001$ and $\beta = -.33$, $t = -5.55$, $P < .0001$, respectively). However, FM emerged as a significant main effect for serum 25(OH) D ($\beta = -0.27$, $t = -4.34$, $P < .0001$). For the iPTH regression analysis, season accounted for a significant proportion of the variance ($\beta = -0.28$, $t = -3.53$, $P < .01$); but age did not ($\beta = 0.11$, $t = 1.27$, $P < .10$). However, FM emerged as a significant main effect for iPTH ($\beta = 0.35$, $t = 4.09$, $P < .001$).

Season emerged as a covariate for both serum 25(OH) D and iPTH regression analyses with FM. There were similar correlations between serum 25(OH) D and iPTH during the F/W ($r = -0.28$, $P < .03$) and S/S ($r = -0.26$, $P < .05$) seasons. The positive relationship between iPTH and FM was not significantly influenced by season (F/W: $r = 0.53$, $P < .0001$ vs S/S: $r = 0.31$, $P < .02$). The negative relationship between 25(OH) D and FM was not

Table 2
Clinical and biochemical characteristics of subjects based on vitamin D status

Parameters	All	Vitamin D sufficiency (≥75 nmol/L)	Vitamin D insufficiency (50-74.9 nmol/L)	Vitamin D deficiency (<50 nmol/L)	*P*
n (%)	127	33 (26)	53 (41.7)	41 (32.3)	NA
Age (y)	13.0 ± 3.0	13.0 ± 3.2	12.7 ± 3.1	13.3 ± 2.4	NS
Sex (% female)	62.2	63.6	60.4	65.8	NS
Tanner stage	3.1 ± 1.4	3.3 ± 1.4	2.9 ± 1.5	3.4 ± 1.3	NS
BMI (kg/m^2)	37.1 ± 8.5	33.9 ± 6.0***	35.8 ± 7.1††	41.1 ± 10.3	<.001
Fat (%)	44.6 ± 8.0	40.8 ± 8.5***	43.4 ± 6.6††	48.9 ± 7.5	<.0001
FM (kg)	43.5 ± 20.2	36.1 ± 17.3**	39.8 ± 15.8††	54.0 ± 23.1	<.0001
FFM (kg)	51.1 ± 13.9	50.1 ± 12.2	50.0 ± 14.1	53.5 ± 15.0	NS
FFM/FM	1.32 ± 0.44	1.55 ± 0.54***	1.35 ± 0.36††††	1.09 ± 0.30	<.001
TBW (kg)	37.3 ± 10.2	36.6 ± 8.9	36.5 ± 10.3	39.1 ± 10.9	NS
iCa^{+2} (mmol/L)	1.24 ± 0.05	1.25 ± 0.04**	1.24 ± 0.04	1.22 ± 0.05	<.01
Phosphate (mmol/L)	1.41 ± 0.19	1.39 ± 0.16	1.41 ± 0.19	1.39 ± 0.16	NS
25(OH) D (nmol/L)	59.9 ± 23.2	89.5 ± 12.9***	61.3 ± 7.3††††	34.2 ± 8.7	<.0001
iPTH (ng/L)	38.3 ± 15.0	31.4 ± 13.3***	38.4 ± 11.1	44.2 ± 18.5	<.005
Glucose (mmol/L)	4.98 ± 0.44	5.00 ± 0.34	5.01 ± 0.39	4.90 ± 0.46	NS
HbA_{1c} (%)	5.2 ± 0.4	5.04 ± 0.40*	5.2 ± 0.38	5.3 ± 0.40	<.02
Insulin (pmol/L)	202.8 ± 113.9	174.5 ± 98.9*	185.2 ± 86.2††	248.6 ± 140.9	<.01
QUICKI	0.299 ± 0.021	0.310 ± 0.023**	0.301 ± 0.019	0.293 ± 0.023	<.005
Vitamin D intake (IU/d)	227 ± 121	271 ± 149****	255 ± 118††††	154 ± 48	<.0001
AI of vitamin D (%)	48.1	75.8****	60.4††††	9.8	<.0001
Calcium intake (mmol/d)	32.1 ± 14.5	37.1 ± 17.2	33.1 ± 13.4	23.3 ± 5.4	<.0001

* $P < .05$, for comparison of vitamin D–sufficient group vs vitamin D–deficient group.
** $P < .01$, for comparison of vitamin D–sufficient group vs vitamin D–deficient group.
*** $P < .001$, for comparison of vitamin D–sufficient group vs vitamin D–deficient group.
**** $P < .0001$, for comparison of vitamin D–sufficient group vs vitamin D–deficient group.
†† $P < .01$, for comparison of vitamin D–insufficient group vs vitamin D–deficient group.
†††† $P < .0001$, for comparison of vitamin D–insufficient group vs vitamin D–deficient group.

affected by season (F/W: $r = -0.39$, $P < .003$ vs S/S: $r = -0.27$, $P < .04$).

Hierarchical multiple regression analyses were then conducted to test whether FM mediated the relationships between 25(OH) D and HbA_{1c} and QUICKI. The strength of the relationship between 25(OH) D and HbA_{1c} and QUICKI were reduced (HbA_{1c}: $\beta = -0.23$, $P < .01$ to $\beta = -0.19$, $P = .05$; QUICKI: $\beta = -0.24$, $P < .01$ to $\beta = 0.04$, $P = .61$) when they were controlled for FM. The reduction for 25(OH) D and QUICKI was statistically significant ($z = 4.91$, $P < .0001$), demonstrating mediation by FM; however, the reduction for 25(OH) D and HbA_{1c} was not statistically significant. Therefore, FM did not mediate the significant inverse correlation between serum 25(OH) D and HbA_{1c}.

To further examine the inverse relationship between 25 (OH) D and HbA_{1c}, a hierarchical multiple regression analysis was then conducted to test whether serum 25(OH) D and HbA_{1c} were correlated once covariates (ie, age, sex, ethnicity, and season) were taken into account. Age and sex were not significantly correlated with serum 25(OH) D or HbA_{1c} and were therefore not used as covariates in either multiple regression analysis. However, because ethnicity was correlated with both serum 25(OH) D and HbA_{1c} ($r = -0.35$, $P < .0001$ and $r = 0.27$, $P < .001$, respectively) and season was correlated with serum 25(OH) D ($r = 0.61$, $P < .0001$), they were both used as covariates in the regression analyses. For the HbA_{1c} regression analysis, ethnicity accounted for a significant proportion of the variance ($\beta = 0.22$, $t = 2.34$, $P < .05$), but not season ($\beta = -0.05$, $t = -0.46$, $P = .65$). Serum 25(OH) D did not emerge as a significant main effect for HbA_{1c} once the covariates were taken into account ($\beta = -0.13$, $t = -1.04$, $P = .30$). To further understand the significant role of the covariate ethnicity in the relationship between serum 25(OH) D and HbA_{1c}, correlations were run for the 2 variables within each of the ethnicity groups. Serum 25(OH) D and HbA_{1c} were significantly inversely correlated for Caucasians ($r = -0.31$, $P < .05$) and showed a trend toward significance for Hispanics ($r = -0.28$, $P = .085$), but was not significant for African Americans ($r = 0.13$, $P = .43$).

3.4. Findings stratified by ethnicity/race and season

3.4.1. Ethnicity/race

There were no differences in BMI, FM, and FFM/FM ratio among the ethnic/racial groups (Table 4). Hypovitaminosis D was more prevalent in H (76.9%, $P < .05$) and AA (87.2%, $P < .05$) than in C (59.1%, $P < .05$). On the other hand, vitamin D deficiency was more prevalent in H (43.6%, $P < .0001$) and AA (48.7%, $P < .0001$) than in C (10.2%) and corresponded to decreased vitamin D intake ($P < .0001$), whereas vitamin D insufficiency was observed with similar prevalence among C (48.9%), H (33.3%), and AA (38.5%). Vitamin D sufficiency was higher in C

Table 3
Bivariate correlations between covariates, predictor, and dependent variables for entire cohort

	FM (kg)	QUICKI	iPTH (ng/L)	25(OH) D (nmol/L)	HbA_{1c} (%)	Age (y)	Sex	Race/ethnicity	Season
FM (kg)	1.0	−0.49 **	0.46 **	−0.40 **	0.19 *	0.43 **	−0.12	0.04	−0.22 *
QUICKI		1.0	−0.20 *	0.24 **	−0.24 **	−0.23 *	−0.01	−0.16	0.02
iPTH (ng/L)			1.0	−0.41 **	−0.07	0.27 **	−0.12	−0.01	−0.36 **
25(0H) D (mmol/L)				1.0	−0.23 **	−0.07	−0.03	−0.35 **	0.61 **
HbA_{1c} (%)					1.0	−0.05	0.04	0.27 **	−0.13
Age (y)						1.0	−0.05	−0.13	−0.02
Sex							1.0	0.07	0.08
Race/ethnicity								1.0	−0.01
Season									1.0

* $P < .05$.
** $P < .01$.

(40.9%, $P < .05$) than AA (12.8%), but not H (23.1%). Although fasting serum glucose concentrations and HbA_{1c} were similar among ethnic/racial subgroups, Caucasians displayed lower fasting insulin concentrations (174.4 ± 98.7 vs 216.2 ± 95.9 and 234.2 ± 141.8 pmol/L, $P < .05$) but higher QUICKI value than the H and AA groups (0.306 ± 0.021 vs 0.295 ± 0.020 and 0.296 ± 0.025, $P < .05$). The Caucasian group not only reported higher intake of vitamin D (276 ± 164 vs 200 ± 67 and 192 ± 71 IU/d, $P < .0001$) and calcium (38.2 ± 18.5 vs 28.6 ± 8.9 and 28.1 ± 10.3 mmol/d, $P < .001$) than the Hispanic and African American groups, but also had higher percentage of AI of vitamin D (73.5% vs 33.3% and 30.8%, $P < .05$).

3.5. Season

The subjects in the F/W group had higher BMI (38.6 ± 9.8 vs 35.4 ± 6.6 kg/m^2, $P < .05$), percentage of fat (46.8% ± 7.5% vs 42.3% ± 8.0%, $P < .01$), and FM (47.9 ± 21.7 vs 38.9 ± 17.5, $P < .01$) but lower FFM/FM ratio (1.19 ± 0.33 vs 1.45 ± 0.49, $P < .001$) and serum 25(OH) D levels (45.3 ± 16.2 vs 74.4 ± 19.9 nmol/L, $P < .0005$) than those in the S/S group. Hypovitaminosis D was more prevalent in the F/W than in the S/S season (98.4% vs 49.2%, $P < .01$). Similarly, vitamin D deficiency was more prevalent in the F/W than in the S/S season group (53.1% vs 11.1%, $P < .0001$), corresponding to higher serum iPTH levels in the F/W

Table 4
Clinical and biochemical characteristics of all subjects according to ethnicity/race and season

Ethnicity	Caucasians			Hispanics			African Americans		
Season	F/W	S/S	*P*	F/W	S/S	*P*	F/W	S/S	*P*
n	25	24		19	20		20	19	
Age (y)	13.4 ± 2.4	13.7 ± 3.2	NS	13.0 ± 2.5	12.1 ± 2.8	NS	12.5 ± 2.8	12.9 ± 3.7	NS
Sex (% female)	48.0	66.7	NS	63.2	60.0	NS	65	68.4	NS
Tanner	3.0 ± 1.4	3.4 ± 1.4	NS	3.1 ± 1.3	3.0 ± 1.3	NS	3.0 ± 1.5	3.4 ± 1.5	NS
BMI	37.9 ± 8.1	35.3 ± 6.9	NS	38.8 ± 11.1*	32.4 ± 4.2	<.05	37.7 ± 9.6	39.1 ± 6.9	NS
Fat (%)	46.3 ± 8.6	40.9 ± 10.0	NS	46.8 ± 6.1	41.3 ± 5.9	<.01	47.5 ± 7.5	45.1 ± 7.7	NS
FM (kg)	48.6 ± 23.2	39.5 ± 20.7	NS	46.7 ± 19.5	33.4 ± 10.4	<.05	48.2 ± 22.7	44.1 ± 18.4	NS
FFM (kg)	52.6 ± 12.2	53. 4 ± 14.4	NS	51.4 ± 17.2	47.5 ± 13.2	NS	50.4 ± 15.6	50.3 ± 11.9	NS
FFM/FM	1.24 ± 0.37	1.50 ± 0.60	NS	1.17 ± 0.30	1.48 ± 0.40	<.05	1.15 ± 1.32	1.28 ± 0.41	NS
TBW (kg)	38.4 ± 8.9	39.0 ± 10.5	NS	37.5 ± 12.5	34.7 ± 9.6	NS	36.9 ± 11.4	36.7 ± 8.7	NS
iCa^{+2} (mmol/L)	1.23 ± 0.03	1.24 ± 0.04	NS	1.23 ± 0.06	1.25 ± 0.04	NS	1.24 ± 0.06	1.25 ± 0.03	NS
Phosphate (mmol/L)	1.36 ± 0.13	1.36 ± 0.16	NS	1.45 ± 0.23	1.36 ± 0.16	NS	1.45 ± 0.16	1.45 ± 0.19	NS
25(OH) D (nmol/L)	54.9 ± 15.2*	84.9 ± 18.5$^{\|}$	<.0001	41.7 ± 12.7*	73.6 ± 15.7	<.0001	37.9 ± 14.7†	62.9 ± 19.7	<.0001
Vitamin D sufficiency (%)	4.0	79.2$^{\|}$	<.0001	0.0	45.0	<.0001	0.0	26.3	<.0001
Vitamin D insufficiency (%)	76.0†	20.8$^{\|}$	<.01	21.1	45.0	<.05	30.0	47.4	NS
Vitamin D deficiency (%)	20.0†	0§	<.0005	78.9	10.0	<.0001	70.0	26.3	<.01
iPTH (ng/L)	44.8 ± 19.0	34.2 ± 12.7	<.05	38.9 ± 11.4‡	31.7 ± 9.2	<.05	46.2 ± 16.0‡	33.1 ± 13.1	<.01
Glucose (mmol/L)	4.93 ± 0.41	5.04 ± 0.34	NS	4.96 ± 0.47	5.12 ± 0.33	NS	4.88 ± 0.43	4.87 ± 0.42	NS
HbA_{1c} (%)	5.2 ± 0.4	5.0 ± 0.4	NS	5.3 ± 0.4	5.1 ± 0.3	NS	5.4 ± 0.5	5.4 ± 0.3	NS
Insulin (pmol/L)	172.2 ± 89.6	177.1 ± 109.7	NS	226.4 ± 101.4	188.2 ± 81.3	NS	238.9 ± 174.3	228.5 ± 102.8	NS
QUICKI	0.305 ± 0.017	0.307 ± 0.024	NS	0.295 ± 0.020	0.297 ± 0.019	NS	0.297 ± 0.027	0.296 ± 0.023	NS
Vitamin D (IU/d)	282 ± 157‡	271 ± 174¶	NS	203 ± 84	196 ± 47	NS	199 ± 69	189 ± 80	NS
AI of vitamin D (%)	76.0‡	70.8	NS	21.1	45.0	<.05	35.0	31.6	NS
Calcium (mmol/d)	38.6 ± 17.5‡	37.7 ± 19.9¶	NS	29.1 ± 11.3	28.2 ± 6.1	NS	29.2 ± 11.7	26.9 ± 8.8	NS

The F/W ethnic/racial subgroup comparisons: *$P < .001$, $^{\dagger}P < .001$ (Caucasian vs Hispanic or Caucasian vs African American), $^{\ddagger}P < .05$ (comparison of Caucasian F/W vs Hispanic subgroup and Caucasian vs African American). $^{\S}P < .0001$. The S/S ethnic/racial subgroup comparisons: $^{\|}P < .001$ and $^{\P}P < .05$ (Caucasian vs Hispanic or Caucasian vs African American).

group compared with the S/S group (43.5 ± 16.6 vs 33.1 ± 11.7 ng/L, $P < .0001$). However, the frequency of vitamin D insufficiency was similar in the F/W and S/S seasons (45.3% vs 38.1%). In addition, vitamin D sufficiency was decreased in the F/W compared with the S/S season (1.6% vs 50.8%, $P < .0001$). Finally, there were no seasonal differences in relationship to dietary vitamin D and calcium intake.

3.6. Ethnicity/race and season

Although the F/W Caucasian and African subgroups appeared to have higher BMI, percentage of fat, and FM compared with their respective S/S subgroups, these differences were not statistically significant. However, the F/W Hispanic subgroup had higher BMI, percentage of fat, and FM than the S/S Hispanic subgroup ($P < .05$). Although the prevalence of hypovitaminosis D was similar among the C (96%), H (100%) and AA (100%) subgroups, vitamin D deficiency was more prevalent in the H (78.9, $P < .0001$) and AA (70%, $P < .0001$) subgroups than in the C subgroup (20%) in the F/W season. However, vitamin D insufficiency was more prevalent in the C (76%, $P < .001$) compared with the H (21.1%) and AA (30%) F/W subgroups. Serum iPTH levels were higher in the F/W subgroups compared with the S/S subgroups ($P < .05$) within each ethnic/racial subgroups. The C group had lower insulin but higher QUICKI values than the H and AA groups ($P < .05$). Whereas there were no seasonal differences in reported intake of calcium and vitamin D within the C and AA subgroups, the F/W Hispanic subgroup reported lower percentage of AI of vitamin D than the S/S Hispanic subgroup ($P < .05$). Moreover, reported dietary calcium and vitamin D intakes were lower in the H and AA subgroups compared with the C subgroup in the F/W season ($P < .05$). On the other hand, hypovitaminosis D was more prevalent in H (55%, $P < .01$) and AA (73.7%, $P < .01$) than C (20.8%) in the S/S season, whereas vitamin D deficiency was present only in the H (10.0%) and AA (26.3%) subgroups but not in the C subgroup in the S/S season ($P < .0001$), corresponding to lower reported dietary calcium and vitamin D intake in the H and AA subgroups compared with the C subgroup ($P < .05$). Finally, vitamin D insufficiency was more prevalent in H (45%) and AA (47.5%) than in C (25%) in the S/S season ($P < .01$).

4. Discussion

In our study, 74% of subjects were identified with hypovitaminosis D, whereas vitamin D deficiency was observed in about one third (32.3%) of obese children and adolescents, with higher frequency in Hispanics and African Americans than in Caucasians. In addition, 41.7% met the definition of vitamin D insufficiency, whereas only 26% of the subjects had sufficient vitamin D levels. Low serum 25 (OH) D was more prevalent in the F/W than the S/S season and corresponded to suboptimal dietary intake of vitamin D. Both serum 25(OH) D and iCa^{+2} were inversely correlated with iPTH concentrations, and these relationships were not significantly affected by season and ethnicity/race. Moreover, FM was positively correlated with iPTH levels; but it was negatively correlated with 25(OH) D, even after taking covariates (eg, age, sex, ethnicity, and season) into account. Hypovitaminosis D and vitamin D–deficient subjects showed decreased insulin sensitivity compared with vitamin D–sufficient subjects, with positive relationship between serum 25(OH) D and QUICKI that was mediated by FM. However, FM did not mediate an inverse correlation between serum 25(OH) D and HbA_{1c}, which were significantly correlated for Caucasians, showed a trend toward significance for Hispanics, but were not significant for African Americans.

The prevalence of vitamin D deficiency in 2 seasonal National Health and Nutrition Examination Survey (NHANES) III subpopulations of adolescents and adults residing at median latitudes of 32° N (winter) and 39° N (summer) was previously reported to range between 8% and 29% [23] for those with serum 25(OH) D <50 nmol/L. In our study, the S/S cohort had similar prevalence of vitamin D deficiency compared with the NHANES III summer population (11.3% vs 8%-13%), whereas our F/W cohort appeared to have a higher prevalence of hypovitaminosis D than the NHANES III winter subpopulation (53.1% vs 13%-29%). The cumulative 2-season prevalence of vitamin D deficiency in our cohort was 32.3% despite living at a higher latitude (43° N), at which vitamin D is not synthesized in the skin during winter months [34], which was lower than that observed by Gordon et al [15] among healthy adolescents (42%) in Boston at a similar latitude (42° N). However, the latter study's cohort included a lower proportion of Caucasians (16.1% vs 38.6%) but a higher proportion of African American and Hispanic subjects (72.4% vs 61.4%) as compared with our study cohort; and therefore, it overrepresented racial/ethnic groups at risk for vitamin D insufficiency.

The prevalence of vitamin D deficiency was higher in African Americans and Hispanics than in Caucasians in our study [15,23,24], corresponding to significantly lower intake of calcium and vitamin D intake [15,16,35] without any seasonal difference in dietary intakes of calcium and vitamin D. Nevertheless, the F/W Hispanic subgroup had lower vitamin AI compared with the S/S Hispanic subgroup, which can, in part, explain the higher prevalence of vitamin D deficiency (78.9% vs 10.0%, $P < .0001$) during F/W in this subgroup with only a slight seasonal difference in the prevalence of hypovitaminosis D (100% vs 55%, P = not significant). Indeed, because adequate sunlight exposure cannot be precisely determined for every individual and there is growing concern regarding the hazards of ultraviolet B light exposure and risk of skin cancer in adulthood and the decreased intake of vitamin D–fortified foods among older children and adolescents, maintenance of normal serum 25 (OH) D should be achieved through dietary supplementation [36]. However, there is emerging debate that the current

recommended intake of 200 IU/d may not be enough, especially because circulating concentrations of 25(OH) D decline with growth and age, implying even higher recommended vitamin D intakes [37,38].

In addition, we observed a negative association between 25(OH) D and body fat as previously reported [11,17]. This reduction in serum 25(OH) D with increased adiposity is assumed to be due to enhanced sequestration of vitamin D in fat [39]. Consequently, lower serum 25(OH) D in our obese cohort was most likely the cause of higher iPTH concentrations; and serum iPTH levels were positively correlated with the degree of adiposity [17,20] and were higher only in the hypovitaminosis D and vitamin D–deficient groups compared with the vitamin D–sufficient subjects [17,18]. Because almost half of the hypovitaminosis D group fell in the vitamin D–deficient range, this likely influenced the significant findings between the hypovitaminosis D and vitamin D–sufficient groups.

Abnormal calcium metabolism has been associated with weight gain [40], and a high calcium intake is believed to prevent obesity [41]. In addition, low vitamin D intake and low serum calcium with the resultant hyperparathyroidism can be associated with excess weight gain [9,17,42]. In our cohort, vitamin D–insufficient and vitamin D–deficient subgroups had lower vitamin D intake corresponding to higher plasma iPTH and FM compared with the vitamin D–sufficient group. However, only vitamin D–deficient subjects demonstrated lower serum iCa^{+2} levels compared with the remainder of subjects.

Bell et al [43] reported that serum 25(OH) D is significantly lower and serum iPTH is significantly higher in African American compared with Caucasian adults, whereas serum iCa^{+2}, phosphate, and 1,25(OH)2 D were similar. However, others have observed that in African American but not Caucasian adults, serum 25(OH) D levels correlated negatively with both basal and peak iPTH responses to EDTA-induced hypocalcemia [44,45]. Indeed, basal vitamin D status appeared to be a determinant of the degree of the parathyroid response in African Americans, with peak parathyroid hormone level being inversely correlated with 25(OH) D levels. On the other hand, in our study, serum iPTH in Hispanic and African American subjects compared with Caucasians were not significantly higher despite lower 25(OH) D levels, suggesting relative resistance to vitamin D in the H and AA groups.

Hypovitaminosis D has been considered a risk factor for glucose intolerance [5,6]. Chiu et al [21] observed a positive relationship between vitamin D status and insulin sensitivity index in adults. In addition, they showed that vitamin D levels were negatively correlated with both first- and second-phase insulin responses during a hyperglycemic clamp and glucose levels during oral glucose tolerance test. Thus, they suggested that subjects with hypovitaminosis D not only displayed impaired β-cell function causing impaired glucose homeostasis, but also were at increased risk of developing insulin resistance and metabolic syndrome compared with vitamin D–sufficient adults. In our cohort, the hypovitaminosis D subjects had decreased insulin sensitivity compared with the vitamin D–sufficient subjects, corresponding to significantly higher BMI and FM in the hypovitaminosis D group as previously reported [6]. Moreover, serum 25(OH) D levels were inversely correlated with HbA_{1c} independent of body fat, implying higher ambient glucose concentrations in children with lower vitamin D concentrations [5]. However, a significant relationship between serum 25(OH) D and HbA_{1c} was only seen in Caucasians but not African Americans or Hispanics, suggesting decreased sensitivity to vitamin D and/or parathyroid hormone in these populations.

Limitations to this study include the following: retrospective design, relative overrepresentation of female subjects, and lack of oral glucose tolerance data to assess glucose homeostasis and β-cell function in relationship to 25 (OH) D and iPTH levels. In addition, the accuracy of BIA for assessment of body composition has been questioned because of larger errors in individual estimates of body fat compared with the dual-energy x-ray asorptiometry method [46]. However, BIA has been deemed accurate for assessing body composition in large groups of normal-weight or obese pediatric subjects compared with dual-energy x-ray asorptiometry [27,28]. Another limitation to the study is that there were no age- and sex-matched normal-weight controls for each racial/ethnic group. Finally, the study's cohort was broken down into multiple subgroups, which may have affected the outcomes of the statistical analyses. Therefore, a larger initial sample may have yielded stronger results when subgroups of the sample were analyzed.

In conclusion, hypovitaminosis D was present in about three quarters of obese subjects and was influenced by vitamin D intake, season, ethnicity/race, and adiposity. Despite the differential findings of the multiple vitamin D status groups, there were similarities between the vitamin D–sufficient and vitamin D–insufficient groups. These findings imply that the minimal acceptable level for vitamin D of 50 nmol/L may be the most clinically meaningful threshold for identification of insulin resistance and impaired glucose homeostasis in obese subjects. Interrelationships between 25 (OH) D, iPTH, and FM were not influenced by season and race/ethnicity. Furthermore, serum 25(OH) D was positively correlated with insulin sensitivity, which was mediated by FM, but negatively correlated with HbA_{1c}, implying that obese children and adolescents with "hypovitaminosis D" may be at increased risk of developing impaired glucose metabolism. Additional studies are needed to evaluate the underlying mechanisms.

References

[1] Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004;80(Suppl):1678S-88S.

[2] Reis AF, Hauache OM, Velho G. Vitamin D endocrine system and the genetic susceptibility to diabetes, obesity and vascular disease. A review of evidence. Diabetes Metab 2005;31:318-25.

[3] Kadowaki S, Norman AW. Time course study of insulin secretion after 1,25-dihydroxyvitamin D3 administration. Endocrinology 1985;117: 1765-71.
[4] Lee S, Clark SA, Gill RK, Christakos S. 1,25-Hydroxyvitamin D3 and pancreatic β-cell function: vitamin D receptors, gene expression, and insulin secretion. Endocrinology 1994;134:1602-10.
[5] Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, Dryson E. Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract 1995;27:181-8.
[6] Hypponen E, Power C. Vitamin D status and glucose homeostasis in the 1958 British birth cohort: the role of obesity. Diabetes Care 2006; 29:2244-6.
[7] Snijder MB, van Dam RM, Visser M, Deeg DJH, Dekker JM, Bouter LM, et al. Adiposity in relation to vitamin D status and parathyroid hormone levels: a population-based study in older men and women. J Clin Endocrinol Metab 2005;90:4119-23.
[8] DeLuca HF. The metabolism, physiology and function of vitamin D. In: Kumar R, editor. Vitamin D, basic and clinical aspects. Boston (Mass): Nijhoff Publishing; 1984. p. 259-302.
[9] Norman AW. Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. Am J Clin Nutr 1998;67:1108-10.
[10] Gloth FM, Gundberg CM, Hollis BW, Haddad JJ, Tobin JD. Vitamin D deficiency in homebound elderly persons. JAMA 1995;274:1683-6.
[11] Hollis BW. Assessment of vitamin D nutritional and hormonal status: what to measure and how to do it. Calcif Tissue Int 1996;58:4-5.
[12] Norman AW, Bouillon R, Whiting SJ, Vieth R, Lips P. 13th workshop consensus for vitamin D nutritional guidelines. J Steroid Biochem Mol Biol 2007;103:204-5.
[13] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
[14] Outila TA, Karkkainen MUM, Lamberg-Allardt CJE. Vitamin D status affects serum parathyroid hormone concentrations during winter in female adolescents: associations with forearm bone mineral density. Am J Clin Nutr 2001;74:206-10.
[15] Gordon CM, DePeter KC, Feldman HA, Grace E, Emans SJ. Prevalence of vitamin D deficiency among healthy adolescents. Arch Pediatr Adolesc Med 2004;158:531-7.
[16] Rajakumar K, Fernstrom JD, Janosky JE, Greenspan SL. Vitamin D insufficiency in preadolescent African-American children. Clin Pediatr 2005;44:683-92.
[17] Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone level is associated with body mass index. The 5th Tromso study. Eur J Endocrinol 2004;151:167-72.
[18] Parikh SJ, Edelman M, Uwaifo GI, Freedman RJ, Semega-Janneh M, Reynolds J, et al. The relationship between obesity and serum 1,25-dihydroxyvitamin D concentrations in healthy adults. J Clin Endocrinol Metab 2004;89:1196-9.
[19] Peterlik M, Cross HS. Vitamin D and calcium deficits predispose to multiple chronic diseases. Eur J Clin Invest 2005;35:290-304.
[20] Rockell JE, Green TJ, Skeaff CM, Whiting SJ, Taylor RW, Williams SM, et al. Season and ethnicity are determinants of serum 25-hydroxyvitamin D concentrations in New Zealand children aged 5-14 y. J Nutr 2005;135:2602-8.
[21] Chiu KC, Chu A, Go VLW, Saad MF. Hypovitaminosis D is associated with insulin resistance and β-cell dysfunction. Am J Clin Nutr 2004; 79:820-5.
[22] Mathieu C, Gysemans C, Giulietti A, Bouillon R. Vitamin D and diabetes. Diabetologia 2005;48:1247-57.
[23] Looker AC, Dawson-Hughes B, Calvo MS, Gunter EW, Sahyoun NR. Serum 25-hydroxyvitamin D status of adolescents and adults in two seasonal subpopulations from NHANES III. Bone 2002;30:771-7.
[24] Harkness L, Cromer B. Low levels of 25-hydroxy vitamin D are associated with elevated parathyroid hormone in healthy adolescent females. Osteoporos Int 2005;16:109-13.
[25] McCarty MF, Thomas CA. PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight. Med Hypotheses 2003;61:535-42.
[26] Cole TJ, Bellizzi MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000;320:1240-3.
[27] Lommez A, Borys JM, Ducimetiere P, Charles MA. Reliability of bioimpedance analysis compared with other adiposity measurements in children: the FLVS II study. Diabetes Metab 2005;31:534-41.
[28] Lazzer S, Boirie Y, Meyer M, Vermorel M. Which alternative method to dual-energy X-ray absorptiometry for assessing body composition in overweight and obese adolescents? Arch Pediatr 2005;12: 1094-101.
[29] Gartner LM, Greer FR, Section on Breastfeeding and Committee on Nutrition. Prevention of rickets and vitamin D deficiency: new guidelines for vitamin D intake. Pediatrics 2003;111:908-10.
[30] Katz A, Nambi SS, Mather K, Baron AD, Follmann DA, Sullivan G, et al. Quantitative insulin-sensitivity check index: a simple, accurate method for assessing insulin sensitivity in humans. J Clin Endocrinol Metab 2000;85:2402-10.
[31] Chen H, Sullivan G, Quon M. Assessing the predictive accuracy of QUICKI as a surrogate index for insulin sensitivity using a calibration model. Diabetes 2005;54:1914-25.
[32] Baron R, Kenny D. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. J Pers Soc Psychol 1986;51:1173-82.
[33] Sobel M. Asymptotic intervals for indirect effects in structural equation models. In: S. Leinhardt, ed. Sociological methodology. San Francisco (Calif): Jossey-Bass; 1982. p. 290-312.
[34] Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D3: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D3 synthesis in human skin. J Clin Endocrinol Metab 1988;67:373-8.
[35] Moore CE, Murphy MM, Holick MF. Vitamin D intakes by children and adults in the United States differ among ethnic groups. J Nutr 2005;135:2478-85.
[36] Greer FR. Issues in establishing vitamin D recommendations for infants and children. Am J Clin Nutr 2004;80:1759S-62S.
[37] Willis CM, Laing EM, Hall DB, Hausman DB, Lewis RD. A prospective analysis of plasma 25-hydroxyvitamin D concentrations in white and black prepubertal females in the southeastern United States. Am J Clin Nutr 2007;85:124-30.
[38] Vieth R, Bischoff-Ferrari H, Boucher BJ, Dawson-Hughes B, Garland CF, Heaney RP, et al. The urgent need to recommend an intake of vitamin D that is effective. Am J Clin Nutr 2007;85:649-50.
[39] Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. Calcif Tissue Int 1988;43:199-201.
[40] Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. Regulation of adiposity by dietary calcium. FASEB J 2000;14:1132-8.
[41] Heaney RP, Davies KM, Barger-Lux MJ. Calcium and weight: clinical studies. J Am Coll Nutr 2002;21:1528-58.
[42] Kamycheva E, Jokimsen RM, Jorde R. Intakes of calcium and vitamin D predict body mass index in the population of northern Norway. J Nutr 2002;132:102-6.
[43] Bell NH, Williamson BT, Hollis BW, Riggs BL. Effects of race on diurnal patterns of renal conservation of calcium and bone resorption in premenopausal women. Osteoporos Int 2001;12:43-8.
[44] Fuleihan GE, Gunberg C, Gleason R, Brwon EM, Stromski ME, Grant FD, et al. Racial differences in PTH dynamics. J Clin Endocrinol Metab 1994;79:1642-7.
[45] Cosman F, Nieves J, Morgan D, Shen V, Sherwood D, Parisien M, et al. Parathyroid hormone secretory response to EDTA-induced hypocalcemia in black and white premenopausal women. Calcif Tissue Int 1999; 65:257-61.
[46] Lazzer S, Boirie Y, Meyer M, Vermorel M. Evaluation of two foot-to-foot bioelectrical impedance analyses to assess body composition in overweight and obese adolescents. Br J Nutr 2003;90:987-92.