

Parathyroid Hormone Is Associated with Biomarkers of Insulin Resistance and Inflammation, Independent of Vitamin D Status, in Obese Adolescents

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Abstract

Background: 25-Hydroxyvitamin D [25(OH)D] and parathyroid hormone (PTH) have been shown to correlate with several markers of metabolic syndrome in adult populations. We evaluated the relationship between circulating intact parathyroid hormone (iPTH) and 25(OH)D and indices of metabolic syndrome in obese adolescents.

Methods: Body mass index (BMI), body composition, 25(OH)D, iPTH, fasting lipids, glucose, high-sensitivity C-reactive protein (hsCRP), glycosylated hemoglobin (HbA1c), insulin, and the homeostatic model assessment for insulin resistance (HOMA-IR) were evaluated in 133 obese adolescents.

Results: Vitamin D deficiency [25(OH)D < 50 nmol/L] was present in 45.1% of all patients, with higher prevalence in African-American (AA) and Hispanic (H) than Caucasian (C) subgroups (63.9% and 56.4% vs. 25.9%; $P < 0.001$). iPTH and 25(OH)D were inversely correlated ($r = -0.75$; $P < 0.0001$), with AA displaying a higher iPTH:25(OH)D ratio than H and C subgroups ($P < 0.05$). Whereas fat mass (FM) was negatively correlated with 25(OH)D ($r = -0.30$; $p < 0.001$), it was positively correlated with iPTH levels ($r = 0.38$; $P < 0.0001$). Metabolic syndrome was identified in 57.9% of the cohort with higher iPTH, iPTH:25(OH)D ratio, but lower 25(OH)D than participants without metabolic syndrome ($P < 0.02$). Whereas iPTH showed main effects for hsCRP ($\beta = 0.24$, $t = 2.61$, $P < 0.05$) and triglycerides:high-density lipoprotein cholesterol (TG:HDL-C) ($\beta = 0.21$, $t = 2.13$, $p < 0.05$), independent of serum 25(OH)D, it did not reveal a main effect for HOMA-IR.

Conclusions: Metabolic syndrome is associated with a higher iPTH:25(OH)D ratio than those without metabolic syndrome, implying greater risk of cardiovascular morbidities among AA subjects than other ethnic groups. Furthermore, the serum iPTH level is a predictor of chronic inflammation and dyslipidemia, independent of 25(OH)D.

Introduction

THE METABOLIC SYNDROME IS characterized by a collection of risk factors, including obesity, insulin resistance, hyperglycemia, dyslipidemias, and hypertension in obese adults and adolescents.^{1,2} The presence of metabolic syndrome is associated with increased risk of type 2 diabetes and cardiovascular disease.^{3,4} Several studies suggest a correlation between serum levels 25-hydroxyvitamin D [25(OH)D], calcium, insulin resistance, and metabolic syndrome.^{5,6} Furthermore, metabolic syndrome has been associated with elevated levels of intact parathyroid hormone (iPTH) and hypomagnesemia.^{7,8} Although synthesis and secretion of

iPTH are closely regulated by circulating levels of calcium and phosphate, vitamin D and magnesium also influence iPTH levels.^{9,10}

PTH and vitamin D interactively regulate calcium homeostasis¹¹ and thereby modulate insulin sensitivity and blood pressure in adults through noncalcitropic effects of vitamin D.^{12,13} Vitamin D deficiency [25(OH)D < 50 nmol/L] and resultant hyperparathyroidism are among the endocrine derangements of obesity¹⁴ and are implicated as risk factors for metabolic syndrome.⁸ McCarty et al. hypothesized that the physiologic increase of iPTH levels in response to low vitamin D state increases intracellular calcium in adipocytes, which leads to increased lipogenesis and weight gain.¹⁵

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Furthermore, iPTH has been shown to correlate with several markers of metabolic syndrome within a normocalcemic adult population.¹⁶ Although some studies suggest an association between elevated iPTH levels and metabolic syndrome, independent of vitamin D status,^{17–19} other studies have disputed these findings.^{8,20,21} Other studies suggest gender may also influence the relationship between iPTH and the presence of metabolic syndrome in adults because increasing levels of iPTH levels have been reported in older men, but not in women or younger men.^{8,22} Although mechanisms elucidating the relationship between iPTH and various indices of metabolic syndrome are not well understood, it is possible that iPTH might act as a mediator for the development of metabolic syndrome, especially through direct or indirect induction of a chronic inflammatory state.²³

We have previously reported that serum 25(OH)D was positively correlated with insulin sensitivity, which was mediated by fat mass (FM), but negatively correlated with glycosylated hemoglobin (HbA1c), implying that obese children and adolescents with low vitamin D status may be at increased risk of developing impaired glucose metabolism.²⁴ However, we did not examine the relationship between serum iPTH, vitamin D, and cardiometabolic risk factors in obese adolescents with metabolic syndrome in our earlier report. We hypothesize that circulating iPTH, independent of vitamin D level, is associated with indices of metabolic syndrome in obese adolescents. In addition, we suggest that the iPTH:25(OH)D ratio may be a mechanism through which both factors can be assessed, while also accounting for their potential confounding relationship to one another.

Subjects and Methods

Subjects and design

A total of 133 adolescents (ages 13.1–17.9 years) who met the criteria for obesity [body mass index (BMI) >95th percentile for age]²⁵ were included in the study. Participants were evaluated at the Children's Hospital of Wisconsin (CHW) Endocrine Clinic for evaluation of metabolic syndrome between July, 2005, and February, 2006. Race/ethnicity was self-assigned: Caucasian (C, $n=58$; 43.6%), Mexican American [Hispanic (H), $n=39$; 29.3%], and African American (AA, $n=36$; 27.1%). Children were excluded if they had hepatic or renal disease, metabolic rickets, malabsorptive disorders (Crohn disease, cystic fibrosis, and celiac disease), or cancer, or were taking multivitamin supplements, anticonvulsants, or systemic glucocorticoids. The CHW Institutional Review Board (IRB) approved the retrospective review of patients' clinical charts; therefore, informed consent was not required.

Data were collected on patients, including age, gender, and self-declared ethnicity, height, weight, blood pressure, and body composition analysis by bioelectrical impedance (TANITA-TBF-410, TANITA Corporation of America Inc., Arlington Heights, IL) for evaluation of FM, fat-free mass (FFM), and total body water (TBW).^{26,27} As a part of routine care, participants 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, ionized calcium (iCa^{2+}), phosphate, insulin,

HbA1c, lipid profiles, high sensitivity C-reactive protein (hsCRP), 25(OH)D, and iPTH.

Laboratory studies and calculations

All blood samples were obtained between 0800 and 1100 h after an overnight fast. Serum glucose and phosphate were measured by an autoanalyzer (Orthodiagnosics Fusion 5.1, Ortho-Diagnostics, Rochester, NY). iCa^{2+} was measured by an ion-selective electrode method using Roche AVL 988-4 Analyzer (Roche Diagnostics, Corp, Indianapolis, IN). The intraassay coefficient 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). The hsCRP assays were carried out at Quest Diagnostics (San Jose, CA) using a polystyrene particle-enhanced immunonephelometric method (Dade Behring BNII). The detection limit of this assay was 0.20 mg/L, with a measuring range of 0.18 to 1150 mg/L, and intraassay and interassay coefficients of variance were 2.65% and 3.6%, respectively. The hsCRP values >10 mg/L were excluded to avoid influence of acute infection.²⁸ HbA1c was determined by the Bayer DCA (Bayer Diagnostics Inc, Tarrytown, NY) 2000 instrument (nondiabetic range of 4.5%–5.7%).

Fasting serum insulin was measured by Nichols radioimmunoassay (RIA) (Nichols Institute, San Clemente, CA) with intraassay and interassay CV of 2.4%–6.3% and 5.2%–13.0%, respectively. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as previously described²⁹: $HOMA-IR = (\text{blood glucose mmol/L} \times \text{insulin } \mu\text{U/mL}) / 22.5$.

Serum 25(OH)D was measured using Nichols RIA with intraassay and interassay CV values of 4.6%–11.5% and 8.4%–14.0%, respectively. Serum iPTH measurements were made using a Nichols immunochemiluminometric assay with intraassay and interassay CV values of 3.4%–7.3% and 3.7%–6.6%, respectively.

Total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were determined by colorimetric methods (Beckman spectrophotometer, Fullerton, CA). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation.³⁰

Blood pressure measurements were taken twice with the patient in sitting position. Elevated systolic blood pressure (SBP) or diastolic blood pressure (DBP) was defined as a value above the 95th percentile for age and gender.³¹

Modified National Cholesterol Education Program (NCEP) criteria² for diagnosis of metabolic syndrome were defined as the presence of three or more of the following: Age-adjusted BMI \geq 95th percentile, age-adjusted SBP or DBP > 90th percentile, age-adjusted TG > 90th percentile, age-adjusted HDL-C < 5th percentile, and impaired fasting glucose > 5.6 mmol/L.

Statistical analysis

Statistical analyses were carried out using SPSS (v. 14.0). Data are expressed as mean \pm standard deviation (SD). BMI values were converted into standard deviation scores (SDS), which were normalized for age and gender based on the 2000 Centers for Disease Control (CDC) growth charts. The natural logarithmic transformation of the variables was used in the correlation and regression analyses when they were

skewed. Differences between vitamin D–deficient and –sufficient groups and those with metabolic syndrome and non–metabolic syndrome groups were estimated using unpaired Student *t*-tests. The differences among ethnic subgroups were estimated by one-way analysis of variance (ANOVA), and Bonferroni *post hoc* testing was applied whenever appropriate. Chi-squared analyses were used to compare prevalence of vitamin D deficiency and metabolic syndrome. Spearman correlations were performed to examine the associations between, iPTH, 25(OH)D, iPTH:25(OH)D, SBP, DBP, HOMA-IR, hsCRP, HbA1c, and TG:HDL ratio. Partial correlations (*i.e.*, controlling for FM) and stepwise regression analyses between the potential predictor variable [25(OH)D and iPTH] and the dependent variables (metabolic syndrome biomarkers: HOMA-IR, hsCRP, and TG:HDL ratio) were performed. $P < 0.05$ was considered significant.

Results

Findings stratified by vitamin D deficiency and vitamin D sufficiency

Vitamin D deficiency was identified in 45.1% of the entire cohort (Table 1). Vitamin D–deficient and –sufficient groups were similar in age, proportion of females, and Tanner stage. The two groups were similar on serum phosphate levels, mean serum glucose levels, and serum lipid profiles. However, the vitamin D–deficient group had higher levels on a

number of variables, including BMI, FM, iPTH, iPTH:25(OH)D ratio, serum insulin, HbA1c, HOMA-IR, hsCRP, and metabolic syndrome prevalence than the vitamin D–sufficient group. The vitamin D–deficient group also demonstrated a lower FFM:FM ratio and iCa^{2+} compared to the vitamin D–sufficient group.

Findings stratified by presence and absence of metabolic syndrome

In our cohort, 57.9% of adolescents met diagnostic criteria for metabolic syndrome displaying higher SBP, BMI SDS, FM, iPTH, iPTH:25(OH)D ratio, HOMA-IR, hsCRP, and HbA1c (Table 2). In addition, the metabolic syndrome group had higher TG levels and TG:HDL-C ratios as compared to the non–metabolic syndrome group despite similar cholesterol levels. However, the metabolic syndrome group displayed lower 25(OH)D and iCa^{2+} levels compared to the non–metabolic syndrome group without a statistically significant difference in frequency of vitamin D deficiency (53.2% vs. 33.9%).

Findings stratified by race/ethnicity

There were no differences in BMI SDS and FM and FFM:FM ratio among the ethnic/racial groups (Table 3). Vitamin D deficiency was identified in 45.1% of the cohort, but was more prevalent in the H (56.4%; $P < 0.001$) and AA (63.9%; $P < 0.001$) subgroups than in the C subgroup (25.9%). Whereas

TABLE 1. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PARTICIPANTS BASED ON VITAMIN D STATUS

Parameters	All	Vitamin D deficiency (< 50 nmol/L)	Vitamin D sufficiency (≥ 50 nmol/L)	P
N (%)	133	60 (45.1)	73 (54.9)	NA
Age (years)	14.9 ± 1.4	14.8 ± 1.3	14.9 ± 1.5	NS
Gender (% female)	78 (58.6)	40 (66.7)	38 (52.1)	NS
Tanner stage	4.2 ± 0.8	4.3 ± 0.7	4.1 ± 0.8	NS
Race/ethnicity				
Caucasians (%)	58 (43.6)	15 (25.0)	43 (58.9)	NS
Hispanics (%)	39 (29.3)	22 (36.7)	17 (23.3)	NS
African Americans (%)	36 (27.1)	23 (38.3)	13 (17.8)	NS
SBP (mmHg)	128.3 ± 13.6	126.7 ± 13.5	129.6 ± 13.6	NS
DBP (mmHg)	68.1 ± 9.5	67.8 ± 10.1	68.3 ± 8.9	NS
BMI SDS	2.4 ± 0.4	2.5 ± 0.3	2.3 ± 0.4	$< 0.01^c$
Fat mass (kg)	49.7 ± 19.4	54.2 ± 22.1	46.1 ± 16.1	$< 0.02^b$
iCa^{2+} (mmol/L)	1.24 ± 0.04	1.22 ± 0.05	1.24 ± 0.04	$P < 0.02^b$
Phosphate (mmol/L)	1.39 ± 0.2	1.38 ± 0.2	1.39 ± 0.2	NS
[25(OH)D] (nmol/L)	53.8 ± 21.6	34.7 ± 9.1	69.5 ± 15.3	$< 0.0001^d$
iPTH (ng/L)	42.1 ± 15.7	49.1 ± 16.2	36.4 ± 12.8	$< 0.0001^d$
iPTH:[25(OH)D] ratio	1.03 ± 0.8	1.6 ± 0.9	0.55 ± 0.24	$< 0.0001^d$
HbA1c (%)	5.3 ± 0.4	5.4 ± 0.4	5.2 ± 0.5	$< 0.02^b$
Insulin (pmol/L)	221.9 ± 107.7	248.2 ± 120.3	200.4 ± 91.4	$< 0.02^b$
HOMA-IR (mol μ U/mL)	7.03 ± 3.5	7.8 ± 3.8	6.4 ± 3.0	$< 0.02^b$
hsCRP (mg/L)	3.6 ± 1.5	3.9 ± 1.5	3.3 ± 1.4	$< 0.02^b$
Cholesterol (mmol/L)	4.6 ± 0.9	4.7 ± 0.9	4.6 ± 0.9	NS
TG:HDL-C ratio	4.4 ± 2.7	4.5 ± 3.0	4.2 ± 2.4	NS
Prevalence of metabolic syndrome (%)	57.9	68.3	49.3	$< 0.05^a$

^a $P < 0.05$, for comparison of vitamin D–deficient vs. vitamin D–sufficient group.

^b $P < 0.02$, for comparison of vitamin D–deficient vs. vitamin D–sufficient group.

^c $P < 0.01$, for comparison of vitamin D–deficient vs. vitamin D–sufficient group.

^d $P < 0.0001$, for comparison of vitamin D–deficient vs. vitamin D–sufficient group.

NA, not applicable; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI SDS, body mass index standard deviation score; iCa^{2+} , ionized calcium; 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

TABLE 2. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PARTICIPANTS WITH OR WITHOUT METABOLIC SYNDROME

Parameters	Metabolic syndrome	Non-metabolic syndrome	P
N (%)	77 (57.9)	56 (42.1)	NA
Age (years)	14.9±1.5	14.8±1.2	NS
Gender (% female)	47 (61%)	31 (55.4)	NS
Tanner stage	4.3±0.8	4.0±0.7	NS
Ethnicity			
Caucasians (%)	32 (41.6)	26 (46.4)	NS
Hispanics (%)	25 (32.5)	14 (25.0)	NS
African Americans (%)	20 (25.9)	16 (28.6)	NS
SBP (mmHg)	131.2±13.7	124.3±12.4	<0.01 ^c
DBP (mmHg)	68.9±9.7	66.8±9.1	NS
BMI SDS	2.5±0.3	2.3±0.4	<0.01 ^c
Fat mass (kg)	53.3±19.6	44.7±18.2	<0.01 ^c
iCa ²⁺ (mmol/L)	1.23±0.04	1.25±0.04	<0.01 ^c
Phosphate (mmol/L)	1.38±0.2	1.39±0.2	NS
[25(OH)D] (nmol/L)	49.8±21.3	59.2±20.9	<0.02 ^b
[25(OH)D] deficiency (%)	53.2	33.9	NS
iPTH (ng/L)	48.9±13.9	32.8±12.4	<0.0001 ^d
iPTH:[25(OH)D] ratio	1.27±0.9	0.71±0.60	<0.0001 ^d
HbA1c (%)	5.4±0.5	5.2±0.4	<0.02 ^b
Insulin (pmol/L)	239.2±86.2	198.2±128.7	<0.05 ^a
HOMA-IR	7.7±2.9	6.1±3.9	<0.01 ^c
hsCRP (mg/L)	4.2±1.3	2.7±1.3	<0.0001 ^d
Cholesterol (mmol/L)	4.8±0.9	4.5±1.0	NS
TG:HDL-C ratio	5.6±2.8	2.7±1.2	<0.0001 ^d

^a $P < 0.05$, for comparison of metabolic syndrome and non-metabolic syndrome groups.

^b $P < 0.02$, for comparison of metabolic syndrome and non-metabolic syndrome groups.

^c $P < 0.01$, for comparison of metabolic syndrome and non-metabolic syndrome groups.

^d $P < 0.0001$, for comparison of metabolic syndrome and non-metabolic syndrome groups.

NA, not applicable; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI SDS, body mass index standard deviation score; iCa²⁺, ionized calcium; 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

serum 25(OH)D was significantly lower among the AA and H groups compared with the C group, there was no difference in serum iPTH among ethnic subgroups. However, the iPTH:25(OH) D ratio was significantly higher in the AA group compared to the H and C groups. Also, HbA1c values were higher among the AA and H groups as compared to the C group. However, all groups displayed similar fasting glucose, insulin, HOMA-IR, hsCRP, and lipid profiles.

Findings in the entire cohort

Table 4 provides a summary of the bivariate correlations among the clinical and biochemical variables for the entire cohort. Both iPTH and 25(OH)D levels demonstrated significant relationships with biomarkers of metabolic syndrome as well as an inverse relationship with each other. Therefore, three hierarchical multiple regression analyses were conducted to examine whether the significant relationship between iPTH and each of the three biomarkers of metabolic syndrome (e.g., HOMA-IR, hsCRP, and TG:HDL-C ratio) was maintained beyond the main effects of serum 25(OH)D alone.³² To demonstrate this, the predictor variables were entered into the regression analyses in two steps: (1) Serum 25(OH)D and (2) iPTH, with each of the biomarkers of metabolic syndrome as the dependent variable separately (HOMA-IR, hsCRP, and TG:HDL-C ratio). For the first regression, iPTH did not emerge as having an association with HOMA-IR beyond the significant main effects of serum 25(OH)D ($\beta = -0.21$, $t = -2.24$, $P < 0.05$). For the second re-

gression, iPTH showed an association with hsCRP ($\beta = 0.24$, $t = 2.61$, $P < 0.05$), and although the serum 25(OH)D initially demonstrated a significant relationship to hsCRP, it was no longer a significant main effect once iPTH was taken into account in the regression. In the third regression, iPTH emerged as having an association with the TG:HDL-C ratio ($\beta = 0.21$, $t = 2.13$, $P < 0.05$), but not serum 25(OH)D. Thus, iPTH demonstrated a significant relationship with two of the three biomarkers of metabolic syndrome (hsCRP and TG:HDL-C) independent of the role of serum 25(OH)D levels.

To determine whether FM was a potential mechanism through which iPTH and serum 25(OH)D are related to the biomarkers of metabolic syndrome, subsequent partial correlation analyses that controlled for FM were conducted. Specifically, iPTH continued to display a positive correlation with hsCRP ($r = 0.18$; $P < 0.05$) and the TG:HDL-C ratio ($r = 0.22$; $P < 0.025$) and a negative correlation with HbA1c ($r = -0.179$; $P < 0.05$), whereas serum 25(OH)D only had an inverse correlation with HbA1c ($r = -0.19$; $P < 0.025$). Finally, the partial correlation analyses also indicated that the iPTH:25(OH)D ratio was positively correlated with HOMA-IR and hsCRP ($P < 0.01$).

Discussion

Consistent with the previous literature, we observed that serum 25(OH)D was inversely correlated with iPTH in a group of obese adolescents. Both iPTH and 25(OH)D variables were also significantly related to metabolic syndrome

TABLE 3. CLINICAL AND BIOCHEMICAL CHARACTERISTICS OF PARTICIPANTS ACCORDING TO ETHNICITY/RACE

Ethnicity	Caucasians	Hispanics	African Americans	P
N (%)	58 (43.6)	39 (29.3)	36 (27.1)	NA
Age	14.7±1.5	14.7±1.2	15.4±1.4	NS
Gender (% female)	37 (63.8)	22 (56.4)	19 (52.8)	NS
Tanner	4.2±0.8	4.2±0.7	4.3±0.8	NS
SBP (mmHg)	129.1±15.2	125.5±10.9	130.1±13.2	NS
DBP (mmHg)	68.1±9.7	66.0±9.3	70.1±9.0	NS
BMI SDS	2.4±0.4	2.4±0.3	2.6±0.3 ^b	<0.025 ^b
Fat mass (kg)	48.9±20.3	45.2±15.3	56.0±20.6 ^a	<0.05 ^a
iCa ²⁺ (mmol/L)	1.25±0.04	1.24±0.04	1.22±0.04 ^b	<0.025 ^b
Phosphate (mmol/L)	1.38±0.1	1.39±0.2	1.39±0.1	NS
25(OH)D (nmol/L)	61.5±20.7	49.8±20.6 ^c	45.6±20.4 ^c	<0.01 ^c
Vitamin D deficiency (%)	25.9 ^d	56.4	63.9	<0.001 ^d
iPTH (ng/L)	41.3±18.9	42.7±11.1	42.8±14.5	NS
iPTH:[25(OH)D] ratio	0.84±0.70	1.12±0.9	1.22±0.8 ^a	<0.05 ^a
HbA1c (%)	5.2±0.4 ^c	5.4±0.4	5.5±0.5	<0.01 ^c
Insulin (pmol/L)	205.9±95.3	217.8±98.4	252.3±130.6	NS
HOMA-IR	6.4±3.1	7.0±3.3	7.9±4.0	NS
hsCRP (mg/L)	3.5±1.2	3.9±1.5	3.4±1.9	NS
Cholesterol (mmol/L)	4.7±0.9	4.6±1.0	4.7±1.0	NS
TG:HDL-C ratio	4.5±2.6	4.7±2.6	3.7±2.9	NS

^aP<0.05, African Americans vs. Hispanics and Caucasians.

^bP<0.025, African Americans vs. Hispanics and Caucasians.

^cP<0.01, Caucasians vs. Hispanics and African Americans.

^dP<0.001, Caucasians vs. Hispanic and African Americans.

NA, not applicable; NS, not significant; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI SDS, body mass index standard deviation score; iCa²⁺, ionized calcium; 25(OH)D, 25-hydroxyvitamin D; iPTH, intact parathyroid hormone; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

indices (e.g., chronic inflammation, insulin resistance, and dyslipidemia). However, iPTH level remained a predictor of chronic inflammation and dyslipidemia, even after the main effects of vitamin D level were taken into account. These findings indicate the importance of assessing parathyroid hormone in addition to 25(OH)D levels in obese adolescents at risk for metabolic syndrome.

One mechanism through which both iPTH and 25(OH)D can be assessed, while still accounting for their inverse relationship, is through the iPTH:25(OH)D ratio. In the present study, the iPTH:25(OH)D ratio was higher among obese adolescents with metabolic syndrome than those without metabolic syndrome. Furthermore, AA adolescents displayed a higher iPTH:25(OH)D ratio than other ethnic/racial groups, suggesting increased risk of chronic inflammation and cardiovascular morbidity among this group. Richart et al. also suggested that expressing the physiologic interaction between iPTH and 25(OH)D as a ratio instead of mutual adjustment for both calciotropic hormones clarifies the associations between these hormones and metabolic syndrome and its components.¹⁸

Recent studies examining the association of cardiovascular risk factors with vitamin D deficiency,^{33,34} elevated parathyroid hormone,^{16,17} or both²² have found that there is a relationship between these factors and hypertension,^{34,35} obesity,¹⁷ metabolic syndrome,^{16,17,22,33} and diabetes mellitus.³⁶ Although some studies have shown an inverse relationship between 25(OH)D level and blood pressure after adjusting for iPTH,^{37,38} others have not.^{39,40} In our study, there was a positive correlation between blood pressure and iPTH, but not with serum 25(OH)D. Kayaniyil et al. suggested that serum 25(OH)D, but not iPTH, was significantly

associated with metabolic syndrome components such as waist circumference, TG, and fasting insulin.²¹ However, Grethen et al. observed that major determinant of both 25(OH)D and iPTH was weight.⁴¹ In our cohort, we observed that iPTH was only positively correlated with biomarkers of inflammation (hsCRP and TG:HDL-C ratio), when controlled for FM. However, 25(OH)D was only inversely correlated with HbA1c, when adjusted for adiposity.

Obesity is associated with increased iPTH and hypovitaminosis D in the general population.²² However, weight reduction and increased calcium intake decreases the risk for obesity-related cardiometabolic disease^{17,42} and suppresses iPTH secretion in children and adults.^{43,44} Although direct effects of calcium and vitamin D on metabolic syndrome are not believed to be significant, they may be clinically beneficial, due to their indirect effects on iPTH.^{8,13,17,22} Our study findings imply that iPTH is related to blood pressure, insulin sensitivity, and development of chronic inflammation and dyslipidemia.

Enhanced renal activation of 25(OH)D to active 1,25(OH)₂D inhibits the activity of the rennin-angiotensin-aldosterone system, which can beneficially lower blood pressure.⁴⁵ In our cohort, serum ionized calcium was positively correlated with 25(OH)D, but was negatively correlated with body adiposity, blood pressure, and iPTH levels. These findings underline the role of calciotropic hormones and calcium homeostasis in the pathogenesis of metabolic syndrome. On the other hand, extrarenal activation of circulating 25(OH)D by activated macrophages in the vascular wall opens calcium channels on vascular smooth muscle cells and thus accelerates arterial calcification⁴⁵ and is accompanied by lowered circulating concentrations of 25(OH)D and increased iPTH:(25(OH)D) ratio.

TABLE 4. BIVARIATE CORRELATIONS FOR BIOMARKERS OF METABOLIC SYNDROME

	Fat mass (kg)	SBP (mmHg)	DBP (mmHg)	iCa ²⁺ (mmol/L)	iPTH (ng/mL)	25(OH)D (nmol/L)	iPTH:25(OH)D ratio	HbA1c (%)	HOMA-IR (mol μU/mL)	hsCRP (mg/L)	TG:HDL-C ratio
Fat mass (kg)	1.0										
SBP (mmHg)		1.0									
DBP (mmHg)			1.0								
iCa ²⁺ (mmol/L)				1.0							
iPTH (ng/mL)					1.0						
25(OH)D (nmol/L)						1.0					
iPTH:25(OH)D Ratio							1.0				
HbA1c (%)								1.0			
HOMA-IR (mol μU/mL)									1.0		
hsCRP (mg/mL)										1.0	
TG:HDL-C ratio											1.0

^aP < 0.05.
^bP < 0.01.
^cP < 0.001.
^dP < 0.0001.

SBP, systolic blood pressure; DBP, diastolic blood pressure; iCa²⁺, ionized calcium; iPTH, intact parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; hsCRP, high-sensitivity C-reactive protein; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol.

Furthermore, inflammation is believed to accelerate the pathogenesis of metabolic syndrome and some of its components through local activation of 25(OH)D to its active form by tissue macrophages,⁴⁵ which can open calcium channels and lead to calcification in vascular smooth muscle cells. Additionally, it has been shown that increased iPTH:25(OH)D is associated with increased abdominal obesity, impaired glucose tolerance, increased prevalence of metabolic syndrome and its components, and increased carotid intima media thickness, a surrogate marker of coronary calcification.¹⁸ In our cohort, the iPTH:25(OH)D ratio was associated with adiposity, insulin resistance, and chronic inflammation, suggesting an interaction among these variables, but we did not observe a significant association between the iPTH:25(OH)D ratio and HbA1c. Recently, it has been observed that there are racial differences in the relationship between iPTH and 25(OH)D.⁴⁶ Aloia et al. demonstrated that African-American women had an increase in serum iPTH at a lower 25(OH)D level than Caucasian women.⁴⁷ In our cohort, the AA subgroup had higher iPTH:25(OH)D ratios than H and C subgroups despite similar serum iPTH levels. Because higher iPTH levels appear to have adverse extraskeletal health implications,⁴⁸ AA adolescents may be at greater risk of negative cardiovascular health outcomes than other racial groups.

Limitations to this study include retrospective design and lack of oral glucose tolerance data to assess glucose homeostasis and β-cell function in relationship to 25(OH)D and iPTH levels. Also, the accuracy of bioelectrical impedance (BIA) for assessment of body composition has been questioned because of larger errors in individual estimates of body fat compared to the dual-energy X-ray absorptiometry (DXA) method.⁴⁹ However, BIA has been deemed accurate for assessing body composition in large groups of normal weight or obese pediatric subjects compared to DXA.⁵⁰ Another limitation to the study is that there were no age- and sex-matched normal weight controls for each racial/ethnic group.

In conclusion, despite the intercorrelation between iPTH and 25(OH)D, serum iPTH level is an independent predictor of chronic inflammation and dyslipidemia, beyond the role of 25(OH)D levels alone. Metabolic syndrome is associated with higher iPTH:25(OH)D ratios than those without metabolic syndrome, especially in AA subjects, implying greater risk of cardiovascular morbidities among AA subjects than other ethnic groups. Additional studies are needed to evaluate the relationship between serum iPTH and the iPTH:25(OH)D ratio and development of vascular inflammation and endothelial dysfunction in obese adolescents with and without metabolic syndrome.

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Author Disclosure Statement

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