Circulating 25-Hydroxyvitamin D Concentrations Are Correlated With Cardiometabolic Risk Among American Black and White Adolescents Living in a Year-Round Sunny Climate

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OBJECTIVE—Low vitamin D status is common among healthy black and white adolescents residing at southern U.S. latitudes with a year-round sunny climate. Thus we aimed to study the relationships between circulating 25-hydroxyvitamin D [25(OH)D] and cardiometabolic risk factors in this population.

RESEARCH DESIGN AND METHODS—25(OH)D concentrations were measured with liquid chromatography tandem mass spectroscopy in 701 girls and boys (14–18 years old, 54% blacks, 49% females). Cardiometabolic risk was indexed by adipokines, inflammatory markers, fasting glucose, homeostatic model assessment-insulin resistance (HOMA-IR), lipid profile, and blood pressure (BP).

RESULTS—Controlling for age, sex, race, sexual maturation, season, physical activity, and percent body fat, 25(OH)D concentrations were significantly correlated with adiponectin ($r = 0.06$, $P = 0.05$), leptin ($r = -0.32$, $P < 0.01$), fibrinogen ($r = -0.05$, $P = 0.03$), glucose ($r = -0.16$, $P = 0.02$), HOMA-IR ($r = -0.17$, $P < 0.01$), HDL cholesterol ($r = 0.14$, $P = 0.02$), systolic BP ($r = -0.10$, $P = 0.02$), and diastolic BP ($r = -0.21$, $P < 0.01$). When 25(OH)D concentrations were stratified into increasing tertiles, there were significant linear upward trends for adiponectin ($P = 0.01$) and HDL cholesterol ($P = 0.04$), but significant linear down trends for glucose ($P < 0.01$), HOMA-IR ($P < 0.01$), and systolic BP ($P < 0.01$), after adjusting for the above covariates.

CONCLUSIONS—Circulating 25(OH)D concentrations are associated with various adverse cardiometabolic risk factors, independent of adiposity. Clinical trials addressing the effects of vitamin D supplementation on cardiometabolic risk are warranted in adolescents irrespective of their geographical regions.

Diabetes Care **35:1133–1138, 2012**

Low vitamin D status as indicated by circulating 25-hydroxyvitamin D [25(OH)D] is linked to cardiometabolic risk factors such as inflammation, insulin resistance, abnormal lipid profile, and high blood pressure (BP) in adults (1–4). However, few studies have evaluated the relationship between 25(OH)D concentrations and these cardiometabolic risk factors in children and adolescents. In this regard, there are at least three studies using the nationally representative sample of children and adolescents from the National Health and Nutrition Examination Survey (NHANES) (5–7). First, in 2009, Reis et al. (5) conducted a cross-sectional analysis of 3,577 fasting nondiabetic youth aged 12 to 19 years (65% whites, 14% blacks, and 11% Mexicans) who participated in the 2001–2004 NHANES. After adjustment for age, sex, race, BMI, and physical activity by self-report, 25(OH)D concentrations were found to be inversely associated with systolic BP and plasma glucose concentrations. Second, Kumar et al. (6) demonstrated that in 6,257 children and adolescents aged 1 to 21 years from the 2001–2004 NHANES sample, vitamin D deficiency (<15 ng/mL) compared with 25(OH)D sufficiency (>30 ng/mL) was associated with increased systolic BP, and lower HDL cholesterol, after multivariable adjustment. Third, in 2011, using the newly updated serum 25(OH)D data released by the National Center for Health Statistics, Ganji et al. (7) studied 5,867 adolescents aged 12–19 years from three cycles of NHANES (2001 to 2002, 2003 to 2004, and 2005 to 2006). They found that serum 25(OH)D was related to homeostatic model assessment–insulin resistance index (HOMA-IR), systolic BP, and HDL cholesterol, but not to C-reactive protein (CRP).

Although the aforementioned NHANES studies in children and adolescents have been valuable, there are still questions unaddressed. First, data collection from the south U.S. regions by the study design were limited to the winter season (5–7). Second, most of the data were collected in the geographical regions with relatively high latitudes, such that it is unclear whether low vitamin D status affects cardiometabolic factors in adolescents residing in low latitudes (5–7). Finally, CRP has been the only inflammatory factor used in the analyses in relation to 25(OH)D (7). Other inflammatory factors and, perhaps more noteworthy, adipokines are not yet included.

The southeastern region of the U.S. has a sunny climate and relative proximity

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Received 6 October 2011 and accepted 3 February 2012.
DOI: 10.2337/dc11-1944
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to the equator, which should favor plentiful cutaneous production of vitamin D. However, we have recently reported that low vitamin D status is common in black and white adolescents (14–18 years of age) residing in Augusta, GA (33° North latitude) (8). Furthermore, plasma 25(OH)D concentrations were consistently and inversely related to the degree of adiposity. Thus the current study aimed to evaluate whether 25(OH)D concentrations were correlated with cardiometabolic risk factors including adipokines, inflammatory markers, fasting glucose, HOMA-IR, lipid profile, and BP independent of adiposity in this adolescent population.

RESEARCH DESIGN AND METHODS

Study population

Adolescents of 14 to 18 years of age (n = 701) were recruited from high schools in the Augusta area, GA (latitude 33°N). Subjects were generally healthy, normotensive, nondiabetic, and had no contraindications to any of the study procedures. Adolescents were excluded if they used any prescription medications or had any chronic medical conditions that might affect growth and development. Written informed parental consent and subject assent were obtained before testing. All procedures were approved by the Human Assurance Committee at the Medical College of Georgia. Data collection took place between 2001 and 2009, and enrollment was conducted throughout all seasons: winter (December–February), spring (March–May), summer (June–August), and fall (September–November).

Anthropometry and blood sample collection

Height and body weight measurements were collected to calculate sex- and age-specific BMI percentiles. Dual-emission X-ray absorptiometry total body scans (QDR-4500 W DXA; Hologic Waltham, MA) were performed to measure percent body fat (%BF). Spine and anthropomorphic phantoms were scanned daily for quality assurance. Blood samples were obtained from subjects between 0800 and 0900 after a 12-h fast, and samples were then centrifuged and frozen at −80°C until analysis.

Sexual maturation

Sexual maturation by self-report was determined using a sex-specific questionnaire including a five-stage scale, ranging from I (prepubertal) to V (fully mature) as described by Tanner (9). Using a sex-specific questionnaire, the subjects reported their Tanner stage by comparing their own physical development to the five stages in standard sets of diagrams. When an individual reported discordant stages of pubic hair and breast or genital development, the higher of the two stages was used.

Physical activity

The amount of minutes per day spent in moderate and vigorous physical activities was assessed using MTI Actigraph monitors (model 7164; MTI Health Services, Fort Walton Beach, FL). With epoch length set at 1 min and expressed as counts per minute, the accelerometers were to begin recording when the subject left our laboratory after the first day of testing. The subjects were instructed to wear the monitor for a period of 7 days. Daily and total movement counts per day were converted as minutes per day spent in moderate (3–6 METs) and vigorous (>6 METs) physical activity by the software accompanying the device (10).

Plasma 25(OH)D concentrations

Liquid chromatography tandem mass spectroscopy was used to measure plasma concentrations of 25(OH)D as described previously (11). The detection limit was 10 nmol/L. The intra-assay coefficient of variation was 7–11%, and the interassay coefficient of variation was 8–13%.

Inflammatory factors and adipokines

Serum adipokines and inflammatory factors were measured by ELISA kit (R&D Systems, Minneapolis, MN). The assay sensitivity for leptin, adiponectin, and resistin were 7.8 pg/mL, 0.246 ng/mL, and 26 pg/mL, respectively. The intra-assay coefficient of variation for leptin, adiponectin, and resistin were 3.0, 3.4, and 5.3%, respectively. The interassay coefficient of variation for leptin, adiponectin, and resistin were 4.2, 5.8, and 9.2%, respectively. The assay sensitivity for tumor necrosis factor-α (TNF-α), intracellular adhesion molecule (ICAM)-1, and high-sensitivity CRP (hs-CRP) were 1.6 pg/mL, 0.096 ng/mL, and 0.010 ng/mL, respectively. The intra-assay coefficient of variation for TNF-α, ICAM-1, and CRP were 4.3, 5.2, and 3.8%, respectively. The interassay precision for TNF-α, ICAM-1, and CRP were 7.3, 5.3, and 7.0%, respectively. Fibrinogen was measured using citrated plasma and was assayed in duplicate using a BBL Fibrometer and reagents purchased from Biomerieux (St. Louis, MO).

Fasting glucose, insulin, HOMA-IR, and lipid profile

Fasting glucose was measured in 10-μL sera using an Ektachem DT II System (Johnson and Johnson Clinical Diagnostics, Rochester, NY). The intra-assay coefficient of variation was 0.61%; mean interassay coefficient of variation was 1.45%. Insulin was assayed in duplicate 100-μL aliquots of sera by specific radioimmunoassay (Linco Research, St. Charles, MO); cross-reactivity with proinsulin was less than 0.2%. Assay sensitivity was 3.41 μU/mL; intra-assay coefficient of variation was 3.7%. HOMA-IR was calculated through a computer-solved model. Plasma concentrations of triglycerides, total cholesterol, LDL cholesterol, and HDL cholesterol were measured at the Emory Lipid Research Laboratory using homogeneous enzymatic assays (Equal Diagnostics, Exton, PA).

Statistical analyses

Descriptive statistics for raw variables are presented as mean ± SD. Normal distribution and homogeneity of variances were confirmed by Shapiro-Wilks W and Levene's tests, respectively. Group differences for anthropometric, body composition, biochemical measures, BP, and physical activity were determined using independent samples two-tailed t tests if data were distributed normally and Mann-Whitney U tests otherwise. Partial Pearson's correlation coefficients were used to examine the associations of plasma 25(OH)D concentrations with cardiometabolic risk factors. Potential confounding variables that were included in the analyses were age, sex, race, season, sexual maturation, physical activity, and %BF. We further explored the 25(OH)D-cardiometabolic risk factor relationship by comparing the cardiometabolic risk factor variables across increasing tertiles of plasma 25(OH)D concentrations (Tertile 1 = ≤54.8 nmol/L, Tertile 2 = 55.5–85.9 nmol/L, and Tertile 3 = ≥87.2 nmol/L). For the comparison of the primary dependent variables (i.e., adiponectin, leptin, resistin, hs-CRP, fibrinogen, ICAM, TNF-α, glucose, HOMA-IR, triglycerides, LDL cholesterol, HDL cholesterol, total cholesterol, systolic BP, and diastolic BP), F test was performed to test the assumption of homogeneity of regression slopes for the interactions between the independent variable

[i.e., 25(OH)D] and covariates (age, sex, race, season, sexual maturation, physical activity, and %BF). Because there were no interactions, ANCOVA was used to compare the primary dependent variables across tertile groups of plasma 25(OH)D after adjusting for the same covariates. Because adiponectin, leptin, hs-CRP, TNF, HOMA-IR, and triglycerides had skewed distributions, they were transformed to their natural logarithm for analyses. Data were analyzed using SPSS version 18.02 (PASW Statistics, Chicago, IL), and statistical significance was set at P value < 0.05.

RESULTS

Clinical characteristics of the participants

Clinical characteristics of the participants are shown in Table 1. Participants were 701 black and white adolescents aged 14–19 years (54% blacks, and 49% females). Seasons of subject visits of white adolescents were distributed as 19% in winter, 28% in spring, 18% in summer, and 35% in fall, whereas seasons of subject visits of black adolescents were distributed as 20% in winter, 36% in spring, 21% in summer, and 23% in fall. There were statistically significant differences between blacks and whites with respect to BMI, BMI percentiles, %BF, adiponectin, fibrinogen, ICAM, HOMA-IR, triglycerides, total cholesterol, HDL cholesterol, systolic BP, and diastolic BP. All the variables, except adiponectin and ICAM, were higher in whites than blacks.

Correlations

Correlations are shown in Table 2. With control for age, sex, race, sexual maturation, season, physical activity, and %BF, 25(OH)D concentrations were correlated with adiponectin ($r = 0.06$, $P = 0.05$), leptin ($r = -0.32$, $P < 0.01$), fibrinogen ($r = -0.05$, $P = 0.03$), fasting glucose ($r = -0.16$, $P = 0.02$), HOMA-IR ($r = -0.17$, $P < 0.001$), HDL cholesterol ($r = 0.14$, $P = 0.02$), systolic BP ($r = -0.10$, $P = 0.02$), and diastolic BP ($r = -0.21$, $P < 0.01$).

Multivariate linear regression

Multivariate linear regression analyses were conducted to examine the contributions of plasma 25(OH)D concentrations to cardiometabolic factors. After multivariable adjustment, 25(OH)D concentrations significantly explained the variances in adiponectin ($R^2 = 0.008$, $P = 0.05$), leptin ($R^2 = 0.022$, $P < 0.01$), fibrinogen ($R^2 = 0.009$, $P = 0.03$), fasting glucose ($R^2 = 0.012$, $P = 0.04$), HOMA-IR ($R^2 = 0.039$, $P < 0.01$), HDL cholesterol ($R^2 = 0.007$, $P = 0.02$), systolic BP ($R^2 = 0.012$, $P = 0.04$), and diastolic BP ($R^2 = 0.055$, $P < 0.01$).

Table 1—*Clinical characteristics of participants*

Variables	Total sample	Whites	Blacks	*P* value
N (female %)	701 (49)	321 (45)	380 (54)	
Age (years)	16.2 ± 1.2	16.1 ± 1.2	16.2 ± 1.2	0.97
BMI (kg/m^2)	23.0 ± 4.7	22.2 ± 3.9	24.0 ± 5.2	<0.01
BMI percentile	61.6 ± 27.8	58.0 ± 27.5	66.1 ± 27.5	<0.01
Percent BF (%)	23.8 ± 9.8	24.2 ± 9.2	23.3 ± 10.6	0.89
Physical activities (min/day)				
Moderate	38.6 ± 24.2	39.3 ± 17.5	39.5 ± 16.5	0.83
Vigorous	4.6 ± 6.8	4.5 ± 4.6	4.7 ± 4.5	0.81
Adiponectin (mg/L)	8.3 ± 5.7	9.3 ± 5.4	7.2 ± 4.4	<0.01
Leptin (μg/L)	11.8 ± 12.5	10.2 ± 10.7	13.9 ± 14.3	0.19
Resistin (μg/L)	11.9 ± 6.1	12.0 ± 5.1	11.8 ± 7.1	0.69
hs-CRP (mg/L)	1.2 ± 2.8	0.4 ± 1.8	1.5 ± 2.1	0.19
Fibrinogen (g/L)	2.8 ± 0.5	2.7 ± 0.5	2.9 ± 0.6	<0.01
ICAM (ng/mL)	220.2 ± 74.2	231.9 ± 71.6	209.0 ± 75.9	<0.01
TNF-α (pg/mL)	0.9 ± 0.9	1.0 ± 0.7	0.9 ± 1.0	0.99
Glucose (mmol/L)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	0.76
HOMA-IR	3.7 ± 2.1	3.4 ± 1.9	4.1 ± 2.2	<0.01
Cholesterol (mmol/L)				
Total	3.8 ± 0.7	3.7 ± 0.8	3.9 ± 0.7	0.02
HDL	1.2 ± 0.3	1.2 ± 0.3	1.3 ± 0.3	0.01
LDL	2.4 ± 0.7	2.3 ± 0.7	2.4 ± 0.7	0.89
Triglycerides (mmol/L)	0.8 ± 0.5	0.8 ± 0.5	0.7 ± 0.4	<0.01
BP (mmHg)				
Systolic	112 ± 10	110 ± 11	113 ± 10	<0.01
Diastolic	60 ± 6	58 ± 6	61 ± 6	<0.01
25(OH)D (nmol/L)	72.5 ± 37.8	93.7 ± 35.4	46.7 ± 20.8	<0.01

Data are presented as means ± SD.

Table 2—*Correlations between plasma 25(OH)D and cardiometabolic risk factors*

Variable	*r*	*P* value
Adiponectin#	0.06	0.05*
Leptin#	−0.32	<0.01*
Resistin	−0.01	0.72
hs-CRP#	−0.04	0.18
Fibrinogen	−0.05	0.03*
ICAM	−0.02	0.32
TNF-α#	−0.08	0.46
Glucose	−0.16	0.02*
HOMA-IR#	−0.17	<0.01*
Triglycerides#	−0.1	0.09
Cholesterol		
Total	−0.05	0.52
LDL	−0.06	0.18
HDL	0.14	0.02*
BP		
Systolic	−0.1	0.02*
Diastolic	−0.21	<0.01*

All the tests were adjusted for age, sex, race, sexual maturation, season, physical activity, and percent BF. *Statistically significant. #Log-transformed values used.

Tertile analysis

When we examined the cardiometabolic risk factor variables across tertiles of plasma 25(OH)D concentrations, our findings were quite similar to the correlational data. For instance, the same covariates (age, sex, race, season, sexual maturation, physical activity, and %BF) were adjusted, there were significant linear upward trends for adiponectin and HDL cholesterol across tertiles of plasma 25(OH)D concentrations (both P trend < 0.04). Conversely, significant linear down trends across tertiles of plasma 25(OH)D concentrations were observed for fasting glucose, HOMA-IR, and systolic BP (all P trend < 0.01) (Table 3).

CONCLUSIONS—We reported previously that black and white adolescents residing in the southeastern region of the U.S. were not ensured adequate vitamin D, possibly because of sedentary lifestyle,

Table 3—*Cardiometabolic risk factors across the tertiles of plasma 25(OH)D concentrations*

	Plasma 25(OH)D			
	Tertile 1 (≤54.8 nmol/L)	Tertile 2 (55.5–85.9 nmol/L)	Tertile 3 (≥87.2 nmol/L)	*P* trend
N	233	226	238	
Adiponectin (mg/L)	7.3 ± 0.6	8.5 ± 0.5	9.4 ± 0.5	0.01
Leptin (μg/L)	11.8 ± 12.2	12.1 ± 0.6	10.9 ± 0.6	0.51
Resistin (μg/L)	12.0 ± 10.7	11.7 ± 0.6	11.4 ± 0.6	0.66
hs-CRP (mg/L)	1.1 ± 0.2	0.9 ± 0.2	0.7 ± 0.1	0.08
Fibrinogen (g/L)	2.8 ± 0.1	2.7 ± 0.0	2.8 ± 0.1	0.19
ICAM (ng/mL)	217.1 ± 8.2	224.2 ± 6.4	224.3 ± 6.6	0.74
TNF-α (pg/mL)	0.9 ± 1.0	1.0 ± 0.7	1.0 ± 0.7	0.62
Glucose (mmol/L)	5.1 ± 0.1	4.9 ± 0.0	4.9 ± 0.0	<0.01
HOMA-IR	4.6 ± 0.2	3.6 ± 0.2	3.0 ± 0.2	<0.01
Cholesterol (mmol/L)				
Total	3.8 ± 0.1	3.8 ± 0.1	3.8 ± 0.1	0.45
HDL	1.2 ± 0.0	1.2 ± 0.0	1.3 ± 0.0	0.04
LDL	2.4 ± 0.1	2.3 ± 0.1	2.3 ± 0.1	0.08
Triglycerides (mmol/L)	0.8 ± 0.1	0.8 ± 0.0	0.7 ± 0.0	0.34
BP (mmHg)				
Systolic	115 ± 1	110 ± 1	108 ± 1	<0.01
Diastolic	60 ± 1	60 ± 0	60 ± 1	0.75

Data are means ± SE. Values were adjusted for age, sex, race, sexual maturation, season, physical activity, and percent.

insufficient outdoor activity, lack of adequate sun exposure, adiposity, poor diet, or skin pigmentation (in blacks). The major finding of this study was that independent of adiposity (%BF), circulating 25(OH)D concentrations were associated with various cardiometabolic risk factors including adiponectin, leptin, fibrinogen, fasting glucose, HOMA-IR, HDL cholesterol, systolic BP, and diastolic BP in adolescents living in a year-round sunny climate. To our knowledge, apart from the NHANES studies, this is the only large study addressing relationships between vitamin D status and cardiometabolic risk factors in adolescents and the first study to explore these relationships in subjects residing in sunny locations within lower latitudes of the U.S.

Adipokines and inflammatory factors

This study is the first study to examine the relationship of 25(OH)D with numerous adipokines (leptin, adiponectin, and resistin) and inflammatory markers (hsCRP, fibrinogen, ICAM, and TNF-α). Adipose tissue is recognized to function as an endocrine tissue, capable of producing cytokines that influence metabolic processes in different tissues. Adipose tissue has also been considered as a storage depot for vitamin D, although the role of vitamin D in the regulation of adipokine secretion deserves investigations. Vitamin D has known immunomodulatory effects on a wide range of immune cells. Each of these immune cell types expresses vitamin D receptors (VDRs) and produces the enzyme 1α-hydroxylase (CYP27B1) and 24-hydroxylase (CYP24A1). These cells are therefore capable of locally producing active $1,25(OH)_2D$ (12). The expression of nuclear VDRs in most cells of the immune system, including activated CD4 and CD8 T lymphocytes, B lymphocytes, and macrophages as well as dendritic cells, triggers the hypothesis that vitamin D may act as an immune modulator and interfere with systemic inflammation (13). Vitamin D supplementation has been shown to downregulate nuclear factor-κB activity, increase the anti-inflammatory levels, and decrease the proinflammatory cytokines (14,15). We found that independent of %BF, 25(OH)D concentrations were correlated with adiponectin, leptin, and fibrinogen, but not with resistin, hs-CRP, ICAM, or TNF-α. The lack of a relation of 25(OH)D with CRP was also found in the recent adolescent NHANES study (7). Maetani et al. (16) demonstrated that low vitamin D concentrations were associated with increased leptin levels in adult females. In 147 extremely obese adults, serum 25(OH)D levels were inversely associated with levels of hs-CRP, interleukin-6, and TNF-α (17). However, the associations of 25(OH)D with a panel of inflammatory markers including CRP, interleukin-6, ICAM-1, TNF-α, and fibrinogen were inconsistent in the Framingham adult subjects (18). Therefore, vitamin D supplementation studies are required to establish the causal role of vitamin D on adipokines and inflammatory factors in both adolescents and adults.

Glucose and insulin resistance

Based on the 25(OH)D assay–adjusted NHANES 2001–2006 data, adolescents in the lowest 25(OH)D tertile had significantly higher HOMA-IR scores than did those in the highest 25(OH)D tertile (7). The association of 25(OH)D with insulin resistance was also found in other smaller pediatric populations (19,20). Possible mechanisms driving the relationship between 25(OH)D and fasting glucose and insulin resistance are not fully understood, but one hypothesis is that 25(OH)D directly stimulates insulin secretion (21). Vitamin D may directly influence pancreatic β-cell secretory function through nuclear VDRs and may influence insulin sensitivity through insulin-receptor expression regulation of intracellular calcium (22). Insulin secretion was increased in vitamin D–deficient rats in vivo (23), and more recently in adult human subjects treated with vitamin D (24,25). Another explanation is that insulin sensitivity may increase with increased 25(OH)D levels, supported by findings that diabetic patients demonstrate improved insulin secretion and glucose tolerance when administered vitamin D (26). Finally, in the context of low vitamin D status, parathyroid hormone (PTH) activity increased with reduced insulin sensitivity, leading to the speculation that PTH may mediate the effects of vitamin D on insulin sensitivity and glucose tolerance (27).

HDL cholesterol

The NHANES 2001–2004 analyses including children and adolescents aged 1 to 21 years showed that 25(OD)D deficiency (<15 ng/mL) was associated with HDL cholesterol levels as compared with 25(OH)D levels ≥30 ng/mL (6). The assay-adjusted 25(OH)D data from NHANES 2001–2006 in adolescents aged 12–19 years found that 25(OH)D was directly related to HDL cholesterol (7). In addition,

Rajakumar et al. (28) reported that in 237 black and white children (mean ± SD: 12.7 ± 2.2 years), plasma 25(OH)D was positively associated with HDL cholesterol. In theory, vitamin D could affect lipid levels directly, e.g., vitamin D is thought to be essential for maintaining adequate levels of apolipoprotein A-I, a major component of HDL cholesterol (29,30). In addition, the indirect effects of vitamin D on lipids could be through PTH or calcium balance. Furthermore, vitamin D might improve insulin secretion and insulin sensitivity, thereby indirectly influencing lipid metabolism (31). Our results demonstrated that 25(OH)D was positively correlated with HDL cholesterol independent of adiposity (i.e., %BF), which requires carefully controlled interventional and other experimental studies to further understand the observation.

BP

All the NHANES studies consistently observe the negative correlation between 25(OH)D and BP in children and adolescents. The NHANES 2001–2004 data demonstrated that in adolescents (12–19 years of age) including blacks, Mexican Americans, and whites, 25(OH)D concentrations were lower in those with hypertension. The NHANES 2001–2004 data also demonstrated that in children and adolescents aged 1 to 21 years, after multivariable adjustment, vitamin D insufficiency (15–29 ng/mL) and deficiency (<15 ng/mL) were associated with increased systolic BP and diastolic BP, respectively (3,4). The NHANES 2001–2006 data using the assay-adjusted 25(OH)D found that 25(OH)D was related to systolic BP in adolescents aged 12–19 years. In our adolescents aged 14–19 years, 25(OH)D was associated with systolic and diastolic BP. The antihypertensive and vasculoprotective function of vitamin D may include several pathways. The first pathway could be the direct effects of vitamin D on the vessel wall. Endothelial cells, vascular smooth muscle cells, and macrophages express the VDR as well as 1α-hydroxylase (32–34). In spontaneously hypertensive rats, $1,25(OH)_2D$ reduced endothelium-dependent contractions of the aorta by decreasing cytosolic-free calcium concentrations in endothelial cells (35). A $1,25(OH)_2D$-mediated increase in prostacyclin production in vascular smooth muscle cells has been reported (36). The second pathway may involve renoprotective effects. The function of vitamin D in kidneys such as decreasing podocyte loss and podocyte hypertrophy, or suppression of mesangial cell proliferation, might counteract the development of arterial hypertension (37). Additionally, the antihypertensive and vasculoprotective function of vitamin D could also result from suppression of the renin-angiotensin-aldosterone system (4,38), effects on calcium metabolism, prevention of secondary hyperparathyroidism, counterbalance of inflammation and oxidative stress, and improvement of glucose metabolism and insulin sensitivity (4,39,40).

Strengths and weaknesses

There are several strengths in the current study. The uniqueness of this study is that the vitamin D and cardiometabolic risk relations were, for the first time, evaluated in a large adolescent cohort living at Southern U.S. latitudes. Our findings indicate that vitamin D might be involved in cardiometabolic risk in adolescents, irrespective of geographic locations. Second, our blood samples were collected throughout all seasons, and the seasonality was considered as a confounding factor for the outcomes of interest. Third, to delineate adiposity in the relations between 25(OH)D and cardiometabolic risk, we used %BF, which is a more accurate and robust indicator for adiposity as compared with BMI or BMI percentiles. Finally, a panel of adipokines and inflammatory markers versus a single marker was included in such a large study.

Nonetheless, the limitations should be acknowledged. First, the cross-sectional study design limited causal inference about the effects of low vitamin D status on those risk factors in adolescents. Longitudinal studies are underway to address this issue. Second, there were no availability of data of sun exposure and time spent outdoors. However, the low levels of moderate (38.6 ± 24.2 min/day) and vigorous (4.6 ± 6.8 min/day) physical activity in our adolescents may indicate sedentary lifestyles associated with limited outdoor activities and subsequent inadequate sun exposure. Third, we did not have more robust measures for some of the cardiometabolic risk factors such as ambulatory BP and oral glucose tolerance tests. Finally, lack of measurements of serum PTH is another limitation, because serum PTH data might help to elucidate the relationship between vitamin D metabolism and cardiometabolic regulation.

In conclusion, we found that lower 25(OH)D was related with various adverse cardiometabolic risk factors in black and white adolescents living in a year-round sunny climate of the U.S., findings that were not attributable to season and adiposity. Because adolescence is a critical period for growth and development, well-designed randomized clinical trials of vitamin D supplementation in relation to cardiometabolic risk as well as outcomes such as type 2 diabetes and hypertension are urgently needed in adolescents despite their geographic locations.

Acknowledgments—This study was supported by an intramural grant of the Diabetes and Obesity Discovery Institute at the Georgia Health Sciences University. Y.D. is supported by National Heart, Lung, and Blood Institute Grant HL-077230.

No potential conflicts of interest relevant to this article were reported.

S.P., N.K.P., H.Z., and Y.D. contributed to the study concept and design. S.P., N.K.P., and Y.D. analyzed and interpreted the data. B.G., H.Z., and Y.D. acquired the data. S.P., D.-h.G., and Y.D. drafted the manuscript. S.P., D.-h.G., K.P., J.B., C.H., and H.Z. critically revised the manuscript for important intellectual content. Y.D. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

The authors thank the study staff and the participants who made this study possible.

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