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Original Research

Associations of 25-hydroxyvitamin D with markers of inflammation, insulin resistance and obesity in black and white community-dwelling adults

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ABSTRACT

Aims: Vitamin D is a fat-soluble vitamin classically known for its role in calcium absorption and bone health. Growing evidence indicates that vitamin D deficiency may be associated with inflammation, insulin resistance, and obesity. However, prior studies examining the association of vitamin D with metabolic risk factors had relatively low representation of individuals of black race, limiting their ability to characterize associations of vitamin D and parameters of metabolic health in black vs. white individuals.
Methods: We examined associations of 25-hydroxyvitamin D (25(OH)D) concentrations with markers of inflammation (interleukin [IL]-6, IL-10, high sensitivity C-reactive protein [hsCRP]), insulin sensitivity (adiponectin, resistin, HOMA-IR), and obesity (body mass index [BMI], waist circumference) in 1042 participants from the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a large national cohort of black and white adults 45 years or older.
Results: In unadjusted analyses, lower 25(OH)D concentrations were associated with higher IL-6 and hsCRP concentrations; lower adiponectin concentrations; higher HOMA-IR; and higher BMI and waist circumference ($P < 0.05$ for all). After adjustment for sociodemographic, clinical, lifestyle, and laboratory variables, lower 25(OH) D concentrations remained associated with lower adiponectin concentrations, higher IL–6 concentrations, higher HOMA-IR, and higher BMI and waist circumference ($P < 0.05$ for all). The magnitude of these associations did not differ by race ($P_{interaction} > 0.1$).
Conclusions: Lower 25(OH)D concentrations are associated with disturbances in metabolic health in both blacks and whites. Whether correcting vitamin D deficiency could offer a beneficial therapy for disease prevention requires further study.

Introduction

Vitamin D is a fat-soluble vitamin and hormone essential for calcium absorption and bone health. Vitamin D status is most commonly determined by serum concentrations of 25-hydroxyvitamin D (25(OH)D), the storage form of vitamin D. Epidemiologic data have established that a large portion of the population has vitamin D deficiency, generally defined as 25(OH)D concentrations <20 ng/ml. Though vitamin D is classically known for its function in skeletal health, studies have shown that low 25(OH)D concentrations are associated with obesity, insulin resistance, and inflammation [1–6], suggesting that vitamin D has pleiotropic actions which impact numerous physiologic systems involved in metabolic health.

Prior studies that examined the associations of 25(OH)D with markers of metabolic health have been limited by relatively low representation from black individuals. This is important in that both vitamin D deficiency and established metabolic risk factors such as visceral adiposity, hypertension and inflammation are more common in black individuals than in white individuals. Further, prior studies have shown racial differences in the association of 25(OH)D with markers of insulin resistance [7,8], suggesting that the association of 25(OH)D with other metabolic risk factors may differ by race. Few studies have examined associations of 25(OH)D with markers of insulin resistance, obesity and inflammation in a large sample of black and white adults. Accordingly, we examined the association of 25(OH)D with markers of inflammation, insulin resistance, and obesity in

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participants of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a prospective cohort of community-dwelling black and white adults living throughout the United States (US).

Methods

Study participants

The REGARDS study is a population-based investigation of stroke incidence in black and white US adults ≥45 years of age. Details of the study design have been reviewed elsewhere [9]. Briefly, participants were recruited from the 48 contiguous US states and the District of Columbia. The study was designed to provide approximately equal representation of men and women, and oversampled black individuals and persons living in the "stroke belt/buckle" of the US (Georgia, Alabama, North Carolina, South Carolina, Tennessee, Arkansas, Mississippi, and Louisiana). Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants' socio-demographics, cardiovascular risk factors, tobacco usage, physical activity, and use of medications. Following this interview, an in-home study visit was conducted that included an electrocardiograph (ECG) recording, inventory of medications and collection of blood and urine samples.

Overall, 30,239 black and white adults were enrolled between January 2003 and October 2007 (42% black, 55% women). For this study, we used a subset of participants with measured plasma 25(OH)D concentrations (n = 1042) who were randomly selected from the REGARDS Study population using a stratified sampling procedure to ensure sufficient representation of participants from high risk categories (e.g., black individuals and older participants), as previously described [10]. Briefly, all participants with at least one follow-up contact (n = 29,653) were categorized into 20 strata based on age (45–54, 55–64, 65–74, 75–84, ≥85 years), race (black or white), and sex (male or female). In each stratum, participants were randomly selected to fulfill the desired distribution: 50% black, 50% white, 50% female, 50% male, 20% age 45–54, 20% age 55–64, 25% age 65–74, 25% age 75–84, and 10% age ≥85. Each individual was assigned a weight that was calculated as the inverse of their sampling fraction, with the sample weight representing the number of individuals in the full REGARDS cohort represented by that one person in the subcohort. All analyses were performed using this weight, which effectively makes the results reflect the original sample (as indicated by the weighted N).

The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided written informed consent.

Data collection

Plasma 25(OH)D was measured in baseline samples using a commercially-available ELISA (Immunodetection Systems, Fountain Hills, AZ). The assay range was 5–150 ng/ml. Intra-assay coefficients of variation (CVs) were 8.82–12.49%. Interleukin (IL) 6 was measured by ultra-sensitive ELISA (Quantikine HS Human IL-6 Immunoassay; R&D Systems, Minneapolis, MN), with an inter-assay CV range of 6.8–7.3%. IL-10 was measured using the Milliplex MAP Human Cardiovascular Disease (CVD) Panel 3 (Millipore Corporation; Billerica, MA) run as a single-plex assay with an inter-assay CV range of 8.3–12.1%. High sensitivity C-reactive protein (hsCRP) was measured by particle enhanced immunonephelometry using the BNII nephelometer (N High Sensitivity CRP; Dade Behring, Deerfield, IL) with inter-assay CVs of 2.1–5.7% [11]. Serum glucose and insulin were measured using the Ortho Vitros 950 IRC Clinical Analyzer (Johnson & Johnson Clinical Diagnostics, Raritan, NJ) and Roche Elecsys 2010 System (Roche Diagnostics, Indianapolis, IN), respectively. Insulin resistance was assessed using the homeostasis model assessment [HOMA-IR = insulin [mg/dL] × glucose [mg/dL]/405] [12]. Fasting insulin was only obtained in participants without a history of diabetes, so calculations of HOMA-IR were only available for those without diabetes (n = 810). Resistin and adiponectin were measured using Human Serum Adipokine Panel A LINCOplex Kit (Linco Research, Inc.; St. Charles, MO). Inter-assay CVs ranges from 8.0–13.2% and 6.1–10.4%, respectively.

Age, race, sex, annual family income, educational attainment, and tobacco use history were determined by self-report. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared measured during the in-home visit. Waist circumference (in centimeters) was measured during the in-home visit using a tape measure positioned midway between the lowest rib and the iliac crest with the participant standing. Systolic and diastolic blood pressure BP were defined as the average of two measurements taken by a trained technician using a standard protocol, after the participant was seated for 5 minutes. Physical activity was assessed through a single question: "How many times per week do you engage in intense physical activity, enough to work up a sweat," with response options of: none, 1–3 times/week or >4 times/week. History of coronary heart disease (CHD) was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous angioplasty), or self-reported history of myocardial infarction. History of stroke was ascertained by self-report. Diabetes was defined as self-reported use of insulin or oral hypoglycemic agents, fasting blood glucose concentration of 126 mg/dL or higher, or a non-fasting blood glucose concentration of 200 mg/dL or higher. Dyslipidemia was defined as a serum total cholesterol concentration ≥240 mg/dL, low-density lipoprotein concentration ≥160 mg/dL or high-density lipoprotein concentration <40 mg/dL, or a self-reported prior diagnosis of high cholesterol or current use of cholesterol-lowering medications. Phosphorus and calcium concentrations were measured using standard assays. Serum intact parathyroid hormone concentrations (PTH) were measured using a commercially available ELISA (Roche Elecsys 2010, Roche Diagnostics, Indianapolis, IN) with intra- and inter-assay CVs range from 2 to 4% and 3 to 6%, respectively.

Serum creatinine was calibrated to an international isotope dilution mass spectroscopic (IDMS)-traceable standard, measured by colorimetric reflectance spectrophotometry. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation [13]. Albumin and creatinine were measured in a random spot urine specimen by nephelometry (BN ProSpec Nephelometer, Dade Behring, Marburg, Germany) and Modular-P chemistry analyzer (Roche/Hitachi, Indianapolis, IN), respectively. Spot urine albumin-to-creatinine ratio (UACR) was calculated in mg/g. Prevalent CKD was defined as an eGFR <60 ml/min/1.73 m^2 or a UACR ≥30 mg/g.

Statistical analyses

Standard descriptive statistics were used to examine demographic, clinical and laboratory characteristics of the participants in the overall sample across clinically-relevant categories of 25(OH)D (<20 ng/ml, 20–29 ng/ml, ≥30 ng/ml). To account for the stratified sampling design of the subcohort, all analyses were weighted by the inverse probability of the random cohort sampling fraction. Linear regression models were used to examine the association of 25(OH)D as the primary independent variable with markers of inflammation (IL-6, IL-10, hsCRP), insulin resistance (resistin, adiponectin, HOMA-IR) and BMI and waist circumference as the dependent variables of interest. The initial models were adjusted for age, sex, race, and region of residence. The second model was adjusted for parameters in Model 1 plus indices of socioeconomic status (annual household income, educational achievement), history of diabetes