Relation of 25-hydroxyvitamin D and parathyroid hormone levels with metabolic syndrome among US adults

Jared P Reis 1,2, Denise von Mühlen 3 and Edgar R Miller III 1,2

1Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins Medical Institutions, Baltimore, Maryland 21205, USA; 2Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland 21205, USA and 3Department of Family and Preventive Medicine, University of California, San Diego, California 92093, USA

(Correspondence should be addressed to J P Reis who is now at Department of Epidemiology and the Welch Center for Prevention, Epidemiology, and Clinical Research, 2024 E. Monument Street, Suite 2-602, Baltimore, Maryland 21205, USA; Email: jreis@jhsph.edu)

Abstract

Objective: Previous research on the combined association of 25-hydroxyvitamin D (25(OH)D) and parathyroid hormone (PTH) with metabolic syndrome may have been limited by restricted age variability and a lack of representation of the general population. This study examined the combined association of 25(OH)D and PTH with Adult Treatment Panel III-defined MetSyn among a nationally representative sample of US adults.

Design and methods: This population-based cross-sectional study included 834 men and 820 women aged ≥20 years without diagnosed diabetes who completed a physical examination as part of the 2003–2004 US National Health and Nutrition Examination Survey.

Results: After adjusting for age, sex, race/ethnicity, income, lifestyle factors, total calcium, and energy intake, the odds ratio (OR) for MetSyn in the highest quintile of 25(OH)D (median 88.0 nmol/l) compared with the lowest quintile (median 26.8 nmol/l) was 0.27 (0.15, 0.46; \( P_{\text{trend}} < 0.001 \)). This relation was unchanged after additional adjustment for PTH level (OR, 0.26; 0.15; 0.44; \( P_{\text{trend}} < 0.001 \)) and did not differ by sex (interaction 0.6) or age (\( < \) or \( \geq 50 \) years; interaction 0.2).

In contrast, the multivariable-adjusted odds for MetSyn increased with increasing PTH among older men (\( P_{\text{trend}} 0.004 \)), but not younger men (\( P_{\text{trend}} 0.4 \)) or women regardless of age (\( P_{\text{trend}} 0.4 \) in younger and older women).

Conclusions: These data suggest an inverse association of 25(OH)D with MetSyn, independent of potential confounding factors, calcium intake, and PTH, and a positive association of PTH with MetSyn among older men.

Introduction

The most well-known function of the vitamin D/parathyroid hormone (PTH) axis is to maintain extracellular calcium homeostasis (1). Vitamin D, obtained largely from exposure to u.v. B radiation and to a lesser extent from dietary and supplemental sources, increases the efficiency of intestinal calcium absorption, while PTH is released in response to low circulating calcium concentrations. The release of PTH stimulates the reabsorption of calcium in the kidney, the resorption of calcium from the skeleton, and enhances the production of 1,25-dihydroxvitamin D or 1,25(OH)₂D, the physiologically active molecule of vitamin D. Hypovitaminosis D is associated with increased PTH secretion, increased bone turnover, osteoporosis, osteomalacia, and an increased risk of fracture (2–5). More recent evidence from several lines of research has suggested nontraditional roles for vitamin D and PTH in conditions which are frequently observed with metabolic syndrome, including reduced insulin secretion and sensitivity (6–8), obesity (9, 10), diabetes (11–17), and hypertension (18–22).

Decreased vitamin D status (as measured by serum 25-hydroxyvitamin D or 25(OH)D) and a dietary intake low in dairy products have been implicated as risk factors for metabolic syndrome (6, 23, 24), including an analysis of the third National Health and Nutrition Examination Survey (NHANES III) (25). However, previous studies have been limited by the failure to account for PTH level, which may at least partly explain the inverse association observed between vitamin D and metabolic syndrome, since vitamin D deficiency is accompanied by enhanced PTH synthesis and secretion in order to maintain extracellular calcium homeostasis. In a recent report, we documented increased odds for metabolic syndrome with increasing PTH concentration among community-dwelling older men, but not women (26). This association was independent of 25(OH)D level, and no association of 25(OH)D with metabolic syndrome...
syndrome was observed in either sex. However, it is unknown whether those findings of the combined association of 25(OH)D and PTH with metabolic syndrome are representative of younger populations or those who reside in geographic locations that do not experience a sunny and temperate year-round climate. The purpose of the present study was to examine the individual and combined associations of 25(OH)D and PTH levels with metabolic syndrome in a nationally representative sample of US adults.

Research design and methods

The present study utilized data from NHANES conducted from 2003–2004 by the National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention. NHANES is an ongoing data collection initiative which employs a complex, multi-stage, stratified probability sampling design to select participants representative of the civilian, noninstitutionalized US population. Data collection occurs during a home interview and a physical examination conducted within a mobile examination center. The Institutional Review Board at NCHS approved the overall design of NHANES and all participants provided written informed consent.

A total of 1977 adults aged ≥20 years completed a morning physical examination after at least an 8-h fast as part of NHANES 2003–2004. For our purposes, we excluded pregnant women (n=90), those with diagnosed diabetes (based upon a physician diagnosed history of type 1 or type 2, or use of diabetes medications; n=194), individuals who were missing information regarding 25(OH)D (n=2), PTH (n=12), or those in whom we could not confirm the presence of metabolic syndrome (n=25). The remaining 834 men and 820 women formed the sample population for analyses.

Data collection

Information on age, sex, race/ethnicity, smoking, alcohol use, physical activity, household income, dietary intake, and supplement use was obtained by self-report. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic African American, Mexican American, and others. Current, former, or never smoking was based upon the use of cigarettes, cigars, or pipe tobacco. Individuals who smoked at least 100 cigarettes, 20 cigars, or 20 pipes of tobacco in their lifetime, but no longer smoked were considered former smokers. Long-term consumption frequency of alcoholic beverages (beer, wine, liquor) over the past year was assessed. The frequency and duration of walking/bicycling for transportation, home or yard work, and moderate and vigorous intensity leisure-time physical activities performed for at least 10 min at a time during the past month was requested. Responses to these questions were incorporated into a single summary variable expressed in metabolic equivalent-min/week (MET-min/week) using intensity values recommended by NCHS (27, 28).

Total energy and dietary calcium intakes were estimated from 24-h dietary recalls completed in-person during the physical examination and a follow-up telephone interview 3–10 days later (29, 30). The average intake from both assessments, available for ~90% of participants, was used in analyses. For remaining participants, information from a single assessment was used. Data on the use of individual and multivitamin supplements over the past month were used to assess intake of supplemental calcium and vitamin D. Total calcium intake was calculated from dietary and supplemental sources.

A certified technician measured blood pressure a maximum of four times in seated subjects after a 5-min rest with a mercury sphygmomanometer. The average of all available readings was used in analyses. Body weight to the nearest 0.1 kg and standing height to the nearest 0.1 cm were measured using a Toledo electronic scale and Seca stadiometer. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Trained technicians measured waist circumference to the nearest 0.1 cm using a steel measuring tape at the level of the iliac crest at the end of a normal expiration.

Blood samples were obtained by venipuncture and immediately centrifuged, aliquoted, and frozen to −70 °C at the mobile examination center. The frozen serum and plasma samples were then shipped on dry ice to central laboratories and stored at −70 °C until analysis. Serum 25(OH)D (25(OH)D$_3$ + 25(OH)D$_2$) levels were measured by RIA (Diasorin Inc., Stillwater, MN, USA). Intra-assay coefficients of variation ranged from 6.3 to 13.2%, the limit of detection was 7.5 nmol/l, and the reference range was 25–137 nmol/l. Serum intact PTH levels were measured by the Elcsys PTH immunoassay (Elecsys 1010 System, Roche); intra-assay coefficients of variation ranged from 2.3 to 4.8%, the limit of detection of was 9.3 ng/l, and the reference range was 18–74 ng/l. Vitamin D and PTH levels were classified into quintiles using cutting points defined by the weighted distribution of these variables in the population.

Serum HDL cholesterol was measured by heparin–manganese precipitation methods. Triglycerides were measured enzymatically using coupled reactions in which triglycerides are hydrolyzed to produce glycerol. Serum creatinine was measured with the Jaffe rate reaction (Beckman Astra, Brea, CA, USA). Glomerular filtration rate, a measure of kidney filtration function, was estimated with the abbreviated Modification of Diet in Renal Disease Study equation, calculated as 175×(serum creatinine, mg/dl)$^{-1.154}$×(age, years)$^{-0.203}$×0.742 (if female) or×1.212 (if African American) (31).
Plasma insulin was measured by ELISA (AIA-PACK IRI, Tosoh, Tokyo, Japan). Plasma resistance was measured using standard hexokinase enzymatic assays. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) equation, calculated as ((fasting glucose, mmol/l)×(fasting insulin, μU/ml))/22.5. The NHANES quality control and assurance protocols meet the 1988 Clinical Laboratory Improvement Act mandates.

Metabolic syndrome was defined according to the National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATP III)(32). Participants were classified as having prevalent metabolic syndrome if they had three or more of the following five components: 1) waist circumference >102 cm in men, >88 cm in women; 2) triglycerides ≥1.69 mmol/l (150 mg/dl); 3) HDL <1.04 mmol/l (40 mg/dl) in men, <1.3 mmol/l (50 mg/dl) in women; 4) systolic blood pressure ≥130 mmHg or diastolic blood pressure >85 mmHg or use of antihypertensive medication; or 5) fasting glucose ≥6.1 mmol/l (110 mg/dl).

Statistical analysis

All analyses were weighted to the US population to provide nationally representative estimates. SAS-callable SUDAAN statistical software, release 9.0 (Research Triangle Institute, Research Triangle Park, NC, USA) was used to account for the complex survey design, a stratified multistage cluster sample. PTH as well as several other variables were positively skewed and therefore were log transformed or categorized depending upon the type of analysis conducted; untransformed means are reported throughout for ease of interpretation. Weighted Pearson correlations and a one-way ANOVA were used to examine the relation of 25(OH)D and log-transformed PTH with covariates. Participant characteristics were compared by metabolic syndrome status using independent sample t-tests for continuous measures and χ² tests for categorical measures. Multivariable logistic regression models were fit to examine the individual and combined associations of 25(OH)D and PTH with metabolic syndrome while adjusting for potential confounding factors. The combined association of 25(OH)D and PTH with metabolic syndrome was determined by entering both variables into the model simultaneously. Analysis of covariance was used to determine the association of 25(OH)D and PTH with metabolic syndrome components after adjustment for potential confounders. Tests for a linear trend were performed by creating an ordinal variable from the medians of the quintile categories of 25(OH)D and PTH. Effect modification of the association of 25(OH)D or PTH with metabolic syndrome by sex and age (< and ≥ 50 years, n=757 and 857 respectively) was tested with multiplicative interaction terms, and the threshold for significance was set at P<0.1. All other tests of hypotheses were based upon a type I error rate of 0.05 using two-sided tests.

Results

Weighted mean (±S.E.M.) age of the sample was 45.2±0.7 years (44.1±0.7 years for men and 46.2±0.9 years for women). Overall weighted prevalence (±S.E.M.) of metabolic syndrome was 24.8±1.8% (24.1±2.2% and 25.4±2.3% of men and women respectively; P=0.6). Mean 25(OH)D and PTH concentrations were 62.4±1.5 nmol/l and 42.3±0.6 ng/l respectively, and did not differ by sex (63.7±1.4 nmol/l and 41.7±0.9 ng/l in men; 61.2±1.8 nmol/l and 42.9±0.9 ng/l in women; P<0.05 for 25(OH)D and 0.4 for PTH).

25(OH)D levels decreased with increasing PTH concentration (r=−0.30), BMI (r=−0.20), HOMA-IR (r=−0.19), and glomerular filtration rate (r=−0.16), and increased with increasing physical activity (r=0.11), total energy intake (r=0.08), calcium intake (r=0.17), and vitamin D intake (r=0.12) (all P<0.001). PTH increased with age (r=0.27), BMI (r=0.20), and HOMA-IR (r=0.15), and decreased with increasing alcohol (r=−0.09), total energy intake (r=−0.09), calcium intake (r=−0.15), and glomerular filtration rate (r=−0.14) (all P<0.005). 25(OH)D was highest and PTH was lowest among white adults and those with a higher income level. Former smokers had the highest vitamin D levels, while current smokers had the lowest PTH levels. No associations of 25(OH)D with age (r=0.03) or alcohol use (r=0.05), or of PTH with physical activity (r=−0.01) or vitamin D intake (r=−0.04) were observed (all P>0.05).

Those with metabolic syndrome were older, had a higher BMI, lower glomerular filtration rate, and were less physically active than those without metabolic syndrome (Table 1). Mean 25(OH)D and PTH concentrations were significantly lower and higher respectively, among those with metabolic syndrome. As expected, each component of metabolic syndrome was higher among those with the syndrome. Alcohol use, household income, smoking, and total energy and calcium intakes were similar between those with and without metabolic syndrome.

Multivariable-adjusted odds ratios (ORs) for metabolic syndrome decreased significantly across increasing quintiles of 25(OH)D (P<0.001) (Table 2). Additional adjustment for PTH level had little influence on the strength of this association (P<0.001). Likewise, adjustment for estimated glomerular filtration rate did not appreciably alter the results (P<0.001). The observed inverse association remained statistically significant after additional adjustment for HOMA-IR. However, the OR in the top quintile of 25(OH)D was attenuated from 0.27 to 0.40 (Table 2). After inclusion of BMI in the model, multivariable-adjusted ORs (95% confidence intervals, CIs) for metabolic syndrome across increasing quintiles of 25(OH)D were 1.00 (referent), 0.62 (0.29, 1.33), 0.56 (0.30, 1.04), 0.48 (0.25, 0.90), and 0.38 (0.19, 0.76);
Furthermore, the inverse association of vitamin D and metabolic syndrome persisted among those who were under/normal weight, overweight, and obese (data not shown). No association of PTH level with metabolic syndrome was observed among all subjects (Table 2).

There was no evidence to suggest that the association of 25(OH)D with metabolic syndrome differed by sex ($P_{\text{interaction}}$ 0.6) or age ($P_{\text{interaction}}$ 0.2). However, age appeared to modify the association of PTH with metabolic syndrome ($P_{\text{interaction}}$ 0.03). Furthermore, the PTH-metabolic syndrome association differed by sex ($P_{\text{interaction}}$ 0.6) and age ($P_{\text{interaction}}$ 0.2). There was no evidence to suggest that the association of 25(OH)D with metabolic syndrome differed by sex ($P_{\text{interaction}}$ 0.6) or age ($P_{\text{interaction}}$ 0.2). However, age appeared to modify the association of PTH with metabolic syndrome ($P_{\text{interaction}}$ 0.03). Furthermore, the PTH-metabolic syndrome association differed by sex ($P_{\text{interaction}}$ 0.6) and age ($P_{\text{interaction}}$ 0.2). 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significantly by sex among older (P_{interaction} 0.06), but not younger adults (P_{interaction} 0.9). Among older men (n=449), multivariable-adjusted ORs (95% CIs) across increasing quintiles of PTH were 1.00 (referent), 1.75 (0.50, 6.14), 3.17 (1.00, 10.12), 2.52 (0.87, 7.28), and 3.70 (1.16, 11.74); \( P_{trend} \text{0.004}. \) Adjustment for HOMA-IR (OR comparing the top quintile of PTH with the bottom: 1.94, 95% CI: 0.37, 10.22; \( P_{trend} \text{0.4} \), but not 25(OH)D (\( P_{trend} \text{0.02} \)) appeared to largely explain this association. ORs (95% CIs) for older women (n=408) were 1.00 (referent), 0.56 (0.16, 1.92), 1.41 (0.56, 3.53), 1.49 (0.46, 4.83), and 1.13 (0.28, 4.46); \( P_{trend} \text{0.4}. \) No relation of PTH level with metabolic syndrome was observed among younger men (n=412) (\( P_{trend} \text{0.4} \) for both sexes).

Waist circumference and systolic blood pressure decreased, while HDL cholesterol increased with increasing vitamin D (Table 3). Waist circumference increased with increasing PTH. These associations persisted after simultaneous adjustment for either 25(OH)D or PTH level (data not shown). No association of 25(OH)D with diastolic blood pressure, triglycerides or glucose, or PTH with blood pressure, triglycerides, glucose, or HDL cholesterol was observed (Table 3). Evaluation of the association of PTH with components of metabolic syndrome among older men revealed a positive association with waist circumference and HDL cholesterol (\( P_{trend} \text{0.04} \) and < 0.001 respectively).

### Discussion

In this nationally representative cross-sectional sample of US adults, we observed a strong inverse association of 25(OH)D level with metabolic syndrome that was not explained by numerous potential confounding factors, including calcium intake, PTH, BMI, or renal function. This association did not differ between men and women or younger and older adults (< or ≥ 50 years respectively). In contrast, we found a positive association of PTH level with metabolic syndrome among older men, but no relation in older women or young adults, regardless of sex.

Lower 25(OH)D levels and a dietary intake low in dairy products have been associated with metabolic syndrome in clinical studies (6, 23), and most (24, 25), but not all, population-based studies (26). In an analysis of NHANES III, Ford et al. (25) documented a strong inverse association of 25(OH)D level with metabolic syndrome. However, major limitations of that study included the inability to simultaneously account for PTH level and the failure to adjust specifically for calcium intake. The former is a concern since PTH and vitamin D are together responsible for maintaining extracellular calcium homeostasis (33), and the latter is a problem as calcium is frequently accompanied with the oral ingestion of vitamin D (34). Our results provide support for an inverse association of 25(OH)D with metabolic syndrome, independent of PTH and total calcium intake, and further suggest a positive-independent association of PTH with metabolic syndrome among older men.

It is intriguing to speculate as to the reasons for the discrepancy in results between the studies that have demonstrated an inverse association between 25(OH)D level or dairy intake and metabolic syndrome, and our previous study with participants in the Rancho Bernardo cohort that contradicted this finding (26). The most obvious difference in these studies is that the latter investigation included participants with a suspected high exposure to u.v. B radiation due to their residence in a southern California community, which has a sunny and temperate year-round climate. Skin exposure to sunlight...
is the predominant source of vitamin D and latitude of residence has been shown to be a strong determinant of 25(OH)D production, with declining concentrations observed with increasing distance from the equator (35). In fact, weighted mean 25(OH)D levels among men and women in the present study (64 and 61 nmol/l respectively) were nearly 45% lower than mean levels observed among participants in the Rancho Bernardo study (109 and 102 nmol/l). These findings suggest that a threshold may exist, whereby vitamin D deficiency may influence the development of metabolic syndrome, whereas higher levels may not.

We found that the inverse association of vitamin D and metabolic syndrome was independent of BMI, and was consistent among under/normal weight, overweight, and obese adults, suggesting that this association may not be explained or moderated by adiposity. However, many have questioned the usefulness of BMI as an anthropometric indicator of body composition (36, 37). Preliminary evidence from weight loss studies suggests that vitamin D may be a consequence of excess adiposity (38, 39), since vitamin D is largely stored in adipose tissue and those who are obese may have reduced cutaneous vitamin D production resulting from restricted mobility or clothing habits. In addition, increased vitamin D levels among those without metabolic syndrome may be a surrogate parameter for healthy nutrition. Additional research is needed to confirm our findings.

Our findings of a positive association of PTH with metabolic syndrome among older men and not older women confirm those of the Rancho Bernardo cohort (26). In that study, odds of metabolic syndrome among men increased with increasing PTH concentration, while no evidence of an association was observed in women (26). We are unable to explain why the association of PTH level with metabolic syndrome appears to be limited to older men. Dietary calcium intake, especially in the form of supplemental calcium, has been shown to be higher in women compared with men (26). In addition, evidence suggests that estrogen is a potent stimulator of intestinal calcium absorption (40) and that the menopausal transition without supplemental estrogen is associated with a decrease in bone mineral density and an increased risk of fracture (41). We speculate that differences in the bioavailability and absorption of calcium between men and women may result in significant differences in regard to circulating calcium homeostasis. Further research is necessary to confirm our findings and evaluate the mechanisms underlying this association.

The biological mechanism by which 25(OH)D and PTH may influence metabolic syndrome has not been established. However, there is accumulating evidence from clinical and experimental studies that vitamin D and PTH may influence glucose homeostasis. Decreased vitamin D and increased PTH levels have both been associated with insulin resistance, including an additional effect for 25(OH)D in optimizing β-cell function (6, 7). Pancreatic β-cells and skeletal muscle have been shown to contain vitamin D receptors (42, 43) and β-cells are capable of expressing the 1α-hydroxylase enzyme (44), required to convert 25(OH)D to its active form. Supplementation with vitamin D restores insulin release in vitamin D-deficient animal models (8, 45, 46). Furthermore, vitamin D increases both insulin receptor capacity and responsiveness for glucose transport (47). Insulin resistance is a suspected precursor of metabolic syndrome (48). In the present study, the adjustment for insulin resistance with the use of HOMA-IR partly attenuated the relation of 25(OH)D and PTH with metabolic syndrome, suggesting at least one potential mediating pathway. Our findings await the results of the future studies to examine whether 25(OH)D or PTH level influence the development of metabolic syndrome.

The external validity of these results is enhanced by the nationally representative sample of US adults. However, the present study is limited by its cross-sectional design, which impairs causal inference due to the absence of a temporal sequence. Furthermore, an indication of long-term exposure to 25(OH)D or PTH may have been reduced, since only a single baseline measurement was obtained. However, this measurement error is unlikely to be associated with any of the factors assessed in the present study and therefore the significance of the associations reported here may be conservative. In addition, our analyses were limited by the inability to account for the season during which blood samples were obtained. However, Ford et al. (25) showed that the 25(OH)D-metabolic syndrome association was independent of season of study participation.

In conclusion, our results suggest that decreased 25(OH)D status may increase odds for metabolic syndrome. This association appears independent of numerous potentially confounding factors including calcium intake, BMI, PTH level, and renal function. In addition, an increased PTH level may increase odds for metabolic syndrome among older men. These relations may be mediated, at least in part, through insulin resistance. Further studies are necessary to confirm these findings, including prospective research to determine whether decreased 25(OH)D or increased PTH is a cause or consequence of metabolic syndrome.

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References


5 Trivedi DP, Doll R & Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003 326 469.


7 Chiu KC, Chuang LM, Lee NP, Ryu JM, McMullin JL, Tsai GP & Saad ME. Insulin sensitivity is inversely correlated with plasma intact parathyroid hormone level. Metabolism 2000 49 1501–1505.


46 Cade C & Norman AW. Vitamin D₃ improves impaired glucose tolerance and insulin secretion in the vitamin D-deficient rat *in vivo*. *Endocrinology* 1986 **119** 84–90.


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