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Journal of Health Disparities Research and Practice

Volume 3 | Issue 1 Article 4

2009

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Sreenivasa R. Chandana , *Michigan State University*
Lakshmi P. Kocharla , *University of Cincinnati*
Susan S. Harris , *Tufts University*

See next page for additional authors

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Keywords

Deficiency; Hypertension; Medically uninsured women; Uninsured; Vitamin D; Vitamin D deficiency; Women

Cover Page Footnote

We would like to thank Dr. Rima Kudish, Carolyn Fitzpatrick and the staff at Genesee county free medical clinic for all their support.

Authors

Sreenivasa R. Chandana, Lakshmi P. Kocharla, Susan S. Harris, and Radhika R. Kakarala

JOURNAL OF HDRP

Journal of Health Disparities Research and Practice
Volume 3, Number 1, Spring 2009 , pp. 43–52

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Sreenivasa R. Chandana, Michigan State University

Lakshmi P. Kocharla, University of Cincinnati

Susan S. Harris, Tufts University

Radhika R. Kakarala, Michigan State University

Abstract

Vitamin D deficiency is an epidemic in the United States. Uninsured women are at high risk due to a lower intake of vitamin D and limited sun exposure. We examined the association between vitamin D deficiency and hypertension in 96 uninsured women at a County Free Medical Clinic in urban Michigan. Questionnaires were used to obtain information about demographics, medical history including hypertension, and dietary habits. Measurements including blood pressure and serum 25(OH)D level were also collected. Prevalence of hypertension was higher in subjects with 25(OH)D less than 50nmol/l compared with others (85% vs. 27.3%, p = 0.014). For every 1 nmol/L decrease in serum 25(OH)D, there was an increase in the systolic and diastolic blood pressure by 0.20 (p =0.006) and 0.13 (p =0.003) mm of Hg respectively. These results demonstrate a high prevalence of hypertension in the vitamin D deficient, uninsured female population

Key Words: Vitamin D; Deficiency; Hypertension; uninsured; women

INTRODUCTION

According to the 2006 U.S. Census, there are now 47 million American citizens who do not have health insurance and the number is steadily increasing (www.urban.org). Uninsured adults are more likely than others to have untreated or uncontrolled hypertension (Ostchega, et al, 2008; Duru et al, 2007) and stroke (Fowler-Brown et al, 2007). Among stroke sufferers, those without health insurance experience more neurological impairment, longer hospital stays and higher mortality than others (Shen et al, 2007).

We recently reported a high prevalence of vitamin D deficiency in a group of uninsured women living in the northern United States of America (Kakarala et al, 2007). Several lines of evidence suggest that poor vitamin D status may be a risk factor for hypertension and stroke. People living at higher latitudes throughout the world, where skin production of vitamin D is limited, are at higher risk of developing hypertension than others (Rostand SG, 1997). Several observational studies have shown inverse correlations of vitamin D status, as determined from blood levels of 25-hydroxyvitamin D [25(OH) D], with blood pressure or hypertension (Lind et al, 1995; Martins et al, 2007; Forman et al, 2007). Two independent cross sectional studies from the third National Health and Nutrition Examination Survey, reported this association across different ethnic groups (Scragg et al, 2007; Judd et al, 2008). In one intervention study, supplementation with calcium and vitamin D resulted in a substantial (9%) decrease in systolic blood pressure in elderly women (Pfeifer et al, 2001). Evidence from animal studies suggests that vitamin D may affect blood pressure through regulation of the renin-angiotensin system (Li et al, 2004).

We conducted the present analysis to determine whether vitamin D status in our population of uninsured women receiving their health care at a community based free clinic is associated with blood pressure or hypertension status. If so, this study would provide preliminary evidence that addressing the poor vitamin D status of uninsured adults might reduce morbidity and mortality from hypertension and stroke.

METHODS

Subjects and study design

The design and data-collection methods for this study have been reported previously (Kakarala et al, 2007). The study was approved by the Institutional Review Board for human subjects, and all patients gave written informed consent to participate in the study. This is a cross-sectional study of uninsured women aged 18 to 64 years receiving medical care from a County Free Clinic in urban Michigan during the period of 2005 to 2006. The exclusion criteria included known significant renal or hepatic dysfunction, diseases associated with significant malabsorption, use of prescription vitamin D, pregnancy, treatment with medications that interfere with vitamin D metabolism, or substantial discrepancies between self-reported medical status and medical record information.

Two investigators recruited the subjects three days a week using a standardized case report form. Of the 155 eligible patients, 145 women, all uninsured, provided written informed consent and were enrolled. Assessment of vitamin D status required a separate laboratory visit, and 49 of the 145 enrolled patients were unwilling or unable to return for that visit. The 96 patients with known vitamin D status were included in this analysis. As previously reported (Kakarala et al, 2007), there were no significant differences

between the 49 women who were unwilling to return for the laboratory visit and the 96 who were eventually enrolled with respect to race, vitamin D intake, sun exposure and body mass index. However the enrolled subjects were an average of 5 years older than those women that were excluded.

Measurements

Hypertension diagnosis was defined as a positive response by the patients to a question on an administered health questionnaire. This question asked patients whether a clinician had diagnosed hypertension in them. The reliability of self-reported hypertension has been shown in previous epidemiological studies (Vargas et al, 1999), but we nevertheless verified hypertension diagnosis and treatment by review of the medical records. All the subjects with hypertension were prescribed anti-hypertensive medications as confirmed by chart review. They obtain their medication monthly at the free clinic, after consultation with a physician, for proper control of their blood pressure. Blood pressure was measured with a sphygmomanometer with an appropriate sized cuff, after asking the subjects to sit quietly for a few minutes. Systolic and diastolic blood pressures were taken at Korotkov sounds I and V. Information about demographics including age, height, weight, body mass index (BMI: calculated as weight in kilograms divided by height in meters squared) race, health status, multivitamin, vitamin D supplementation, sunlight exposure and dietary habits were ascertained from the health questionnaire. Height was self-reported. A validated short food frequency screening instrument was used to assess dietary vitamin D and calcium intakes (Blalock et al, 2003). Serum 25(OH)D levels were measured with direct radioimmunoassay (using a Diasorin radioimmunoassay kit) and reported as nmol/l (multiply nmol/L by a conversion factor of 2.496 to obtain ng/ml). Vitamin D deficiency was defined as a serum 25(OH)D concentration less than 50 nmol/L (20 ng/ml) for consistency with a prior study in the same subjects (Kakarala et al, 2007) and to allow for comparison of our subjects with the representative NHANES III population (Looker et al, 2002). Serum total calcium level was measured using standard automated calorimetric method.

Data Analysis

The biostatistical evaluation was carried out using the SPSS 14.0 statistical package (SPSS Inc., Chicago, IL). A descriptive statistical analysis was made, including measurements of central tendency and spread for quantitative variables. Chi-square and student "t" tests were used to compare the variables between different groups. Pearson correlation coefficients were calculated to assess simple linear associations of 25(OH)D with other variables. A series of multiple linear regression analyses were performed to describe the association between serum 25(OH)D levels and blood pressure and to adjust for other determinants of blood pressure (age, BMI, race, calcium intake and vitamin D intake). A multiple logistic regression analysis was performed in order to describe the association of 25(OH)D with hypertension after adjustment for other variables. Statistical significance was established as a P value of 0.05.

RESULTS

Characteristics of the study subjects

Characteristics of the 96 subjects are shown in Table 1. Subjects with lower serum 25(OH)D levels tended to be older and have a higher BMI than those who are non-deficient, however there was no statistically significant difference between the groups. Vitamin D deficiency was more prevalent in African- American women than in others, and subjects with higher serum 25(OH)D levels were consuming more calcium and vitamin D through their diet.

Association of serum 25(OH)D with hypertension

Hypertension was present in 65% (62 out of 96) of the subjects and its prevalence decreased across categories of increasing 25(OH)D (Table 1). Similarly, 25(OH)D was significantly lower among hypertensive than normotensive subjects (59.4±33.2 vs. 38.9±20.8 nmol/l, P<0.001).

Table 1. Characteristics of participants (N = 96) according to the serum 25 (OH)D status. Variable values are shown as mean±SD

Variable	Serum 25(OH)D (nmol/L)					P-value
	≤22.5 (n=20)	22.6 - 37.5 (n=25)	37.6 - 50.0 (n=19)	50.1 - 79.9 (n=21)	≥80.0 (n=11)	
25 (OH)D*	18.4±4.4	30.1±3.8	45.3±5.7	60.5±8.4	107.2±16.0	<0.001
Age (Yrs)	51.7±9.2	47.5±8.9	51.1±9.4	46.2±13.7	46.2±13.7	0.145
BMI (Kg/m2)	34.4±6.6	31.9±9.0	35.7±7.4	31.2±9.6	30.2±7.8	0.186
SBP**	139.3±21.2	132.2±16.0	131.7±15.3	123.2±15.9	115.6±14.8	0.002
DBP**	80.1±12.4	82.5±10.4	78.2±9.7	76.3±13.2	70.7±7.7	0.053
Vitamin D¶	72±56	116±111	142±102	174±131	166±119	0.029
Calcium§	402±174	591±373	825±595	741±420	701±382	0.019
Race (n, (%))						<0.001
Caucasian	4 (20.0)	15 (60.0)	15 (79.0)	19 (90.4)	11 (100.0)	
AA	13 (65.0)	6 (24.0)	2 (10.5)	0 (0.0)	0 (0.0)	
Hispanic	1 (5.0)	2 (8.0)	0 (0.0)	1 (4.8)	0 (0.0)	
NA	1 (5.0)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	
Other	1 (5.0)	2 (8.0)	2 (10.5)	0 (0.0)	0 (0.0)	
Hypertension	17 (85.0)	17 (68.0)	14 (73.7)	11 (52.4)	3 (27.3)	0.014

*Serum 25(OH)D levels in nmol/L; BMI = Body mass index; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; **Blood pressure in mm of Hg; ¶Vitamin D intake in IU/day; §Calcium intake in mg/day; Vitamin D and calcium intake were calculated from food questionnaires; AA = African American; NA = Native American

We performed logistic regression analyses in order to determine whether this association remained after adjustment for potential confounders including age, race, BMI and calcium intake. In this analysis, (Table 2) the odds ratio for 25(OH)D (included as a continuous variable) was 0.96, indicating a 4% reduction in risk of hypertension for each 1 nmol/L increase in serum 25(OH)D.

Table 2. Independent predictors of hypertension in 96 women

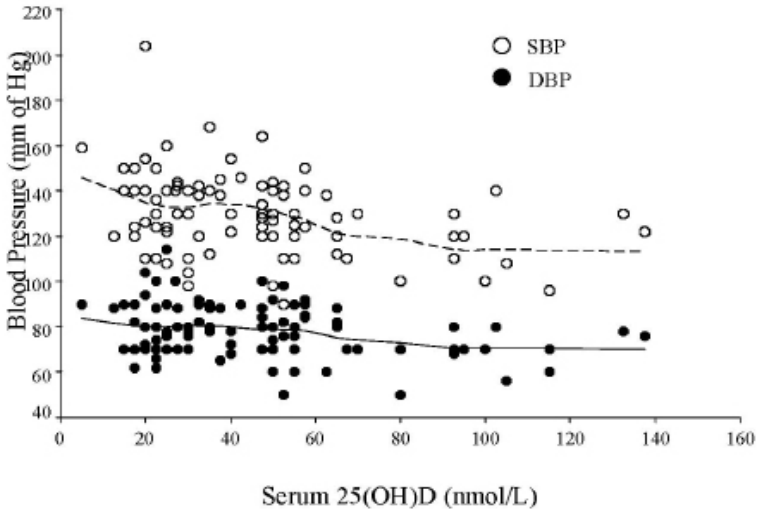
Variable	Odds Ratio	95% CI	P-Value
Serum 25(OH)D*	0.963	0.937 - 0.989	0.006
Age (years)	1.127	1.054 - 1.205	<0.001
BMI (Kg/m2)	1.192	1.087 - 1.307	<0.001
Race			
Non-Caucasian	1.720	0.397 - 7.450	0.469
Caucasian (Reference Group)			
Calcium Intake (mg/d)	0.999	0.998 - 1.001	0.447

*Serum 25(OH)D level in nmol/L, BMI = Body Mass Index

Association of serum 25(OH)D levels with blood pressure

Both systolic and diastolic blood pressure decreased across categories of increasing serum 25(OH)D level (Table 1). There was a negative correlation between serum 25(OH)D and blood pressure [systolic ($r= -0.40$, $p < 0.001$) and diastolic ($r= -0.31$, $P= 0.002$)] (Figure 1). Although all the hypertensives in this study were being treated for their condition their blood pressure remained significantly higher than that of the normotensive subjects (136±16 vs. 117±1, $P<0.001$ for systolic blood pressure and 80±12 vs. 75±10, $P= 0.036$ for diastolic blood pressure). In order to determine whether the association of 25(OH)D with blood pressure differed between normotensives and treated hypertensives, we included a 25(OH)D by hypertension status interaction term in regressions of 25(OH)D on systolic and diastolic blood pressure while also controlling for age, race, BMI and calcium intake. The interaction terms were not statistically significant for systolic ($P=0.695$) or diastolic ($P=0.598$) blood pressure and were removed in subsequent regressions. The effects of adding potential confounders as independent variables in regressions of systolic and diastolic blood pressure on 25(OH)D are shown in table 3. Regression coefficients for 25(OH)D in relation to systolic blood pressure and diastolic blood pressure were -0.20 ($P= 0.006$) and -0.13 ($p = 0.003$) respectively, after adjustment for age, BMI, race and calcium intake. In other words, for every 1 nmol/L decrease in serum 25(OH)D, there is an increase in the systolic and diastolic blood pressure by 0.20 and 0.13 mm of Hg respectively.

Figure 1. Systolic (SBP) and diastolic (DBP) by 25(OH)D in 96 women.



The correlation between the blood pressure and serum 25(OH)D level was shown in the lowess scatter plots. SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

Table 3. Association of serum 25(OH)D level with systolic and diastolic blood pressure (BP) in 96 women

	25(OH)D (nmol/L)		
	RC (SE)	95% CI	P value
Systolic BP			
Model 1	-0.26 (0.06)	-0.39 to -0.13	<0.001
Model 2	-0.22 (0.06)	-0.34 to -0.10	<0.001
Model 3	-0.21 (0.06)	-0.33 to -0.09	0.001
Model 4	-0.20 (0.07)	-0.34 to -0.07	0.004
Model 5	-0.20 (0.07)	-0.34 to -0.07	0.003
Model 6	-0.20 (0.07)	-0.34 to -0.06	0.006
Diastolic BP			
Model 1	-0.13 (0.04)	-0.21 to -0.05	0.002
Model 2	-0.13 (0.04)	-0.21 to -0.04	0.004
Model 3	-0.12 (0.04)	-0.20 to -0.03	0.006
Model 4	-0.16 (0.05)	-0.26 to -0.07	0.001
Model 5	-0.16 (0.05)	-0.25 to -0.07	0.001
Model 6	-0.14 (0.05)	-0.24 to -0.05	0.003

Model 1: Un-adjusted; Model 2: Adjusted for age; Model 3: Adjusted for age, BMI; Model 4: Adjusted for age, BMI and race; Model 5: Adjusted for age, BMI, race and calcium intake, Model 6: age, BMI, race and calcium intake and vitamin D intake. BMI = Body Mass Index, Calcium and vitamin D intake are calculated form food questionnaire. RC = Regression Coefficient; SE = standard Error; CI = Confidence Interval; P value is considered significant, if ≤ 0.05; Race is a categorical variable, with values 0 (Caucasian) and 1 (Non-Caucasian).

DISCUSSION

In our earlier paper (Kakarala et al, 2007), we reported that two thirds of the uninsured women in our study population were vitamin D deficient as defined by a serum 25(OH)D level less than 50 nmol/L. In the present analysis we found that both blood pressure and the prevalence of hypertension decreased with increasing 25(OH)D levels in this group, and these associations were independent of age, BMI, and race. Although this association has been observed in other populations (Foreman et al, 2007; Sowers et al, 1987), it may be of particular importance among uninsured adults because it suggests a potential route for preventing hypertension that is inexpensive and not dependent on formal medical care. As we reported previously, the non-Caucasian women in this study, most of whom were African-American, were three times more likely than Caucasian women to have 25(OH)D levels under 50 nmol/L (Kakarala et al, 2007). Scragg et al (2007), recently reported that racial differences in 25(OH)D explained about half the increased hypertension prevalence of black compared with white participants in NHANES III. Judd et al (2008), analyzed the NHANES III data somewhat differently and reported a significant interaction of race with 25(OH)D indicating no association of 25(OH)D with blood pressure in blacks (Judd et al 2008). More work is needed to fully understand the contribution of poor vitamin D status to increased hypertension in blacks, particularly because most observational studies, including ours, lacked sufficient numbers of black participants with high 25(OH)D concentrations to fully explore the benefit of vitamin D repletion in this group. However, given the mounting evidence of a role for vitamin D in preventing numerous chronic and infectious diseases, many of which are more prevalent in persons of color (Harris et al 2006), improving the poor vitamin D status of African-Americans should be an important public health priority.

The finding of an inverse association between 25(OH) D and blood pressure, in our study, supports the cumulative evidence of various epidemiological and clinical data from the past decade. Animal model studies demonstrate that vitamin D is a negative endocrine inhibitor of the renin-angiotensin II system and plays a role in the regulation of blood pressure and volume homeostasis (Li et al, 2004). A recent study by Zhou et al also showed that 1,25(OH)2D might play an important role in cardiovasular health by repressing the renin-angiotensin system, independent of extracellular calcium or phosphorus (Zhou C et al, 2008).

Intervention studies are needed to establish a firm causal link between vitamin D status and hypertension. However, given the growing evidence of widespread vitamin D deficiency (Looker et al, 2002) and its association with numerous chronic conditions (Holick et al, 2007) and increased mortality (Melamed et al, 2008), it is not premature to encourage uninsured individuals, like others, to increase their vitamin D intake. Although the optimal 25(OH) D concentration to prevent hypertension is unknown, a level of at least 75-

80 nmol/L is considered optimal for multiple health outcomes (Holick et al, 2007; Bischoff-Ferrari HA et al, 2008). Most experts now feel that 1000 IU/d or more are needed for adults in northern areas to maintain adequate vitamin D levels year round (Dawson-Hughes et al, 2005; Holick et al, 2008), much more than the 100-200 IU/d consumed by most of our subjects. The safety of doses as high as or higher than 1000 IU/d is well established (Vieth et al, 2007). In summary, the prevention and treatment of vitamin D deficiency may be one way to reduce the risk for and consequences of hypertension in the vulnerable uninsured population.

CONCLUSIONS

These results demonstrate a high prevalence of hypertension in a vitamin D deficient, uninsured, medically underserved female population. Uninsured women should be strongly encouraged to increase their vitamin D intake to control their hypertension, along with therapeutic lifestyle changes and medications.

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ACKNOWLEDGEMENTS

We would like to thank Dr. Rima Kudish, Carolyn Fitzpatrick and the staff at Genesee county free medical clinic for all their support.

Sreenivasa R. Chandana, MD, PhD, Department of Internal Medicine, Division of Hematology and Oncology, Michigan State University, Lansing, MI

Lakshmi P. Kocharla, MD, Division of Immunology and Rheumatology, Department of Medicine, University of Cincinnati, Cincinnati, OH

Susan S. Harris DSc, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, MA

Radhika R. Kakarala, MD, MS, Department of Internal Medicine, McLaren Regional Medical Center, Michigan State University, Flint, MI

Address for correspondence and reprint request to Dr. Radhika Kakarala, 3230 Beecher Road, Suite # 2, Flint, MI 48532, USA (e-mail: radhikak@mclaren.org), Phone: 810-342-5800, Fax: 810-342-5810