Dietary Magnesium Intake Modifies the Association Between Vitamin D and Systolic Blood Pressure: Results From NHANES 2007-2014.

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Abstract

Introduction

Although the association between blood pressure and vitamin D has been well studied, the effects of dietary magnesium intake on this relationship are still unclear. Thus, this study aimed to determine the effects of dietary magnesium intake on the association between vitamin D and blood pressure.

Research design and methods

The present study analyzed data from the continuous NHANES 2007-2014. We included 8799 participants aged 20 years or older. Multivariable linear regression was performed to assess the association between vitamin D and systolic blood pressure (SBP), diastolic blood pressure (DBP). Dietary magnesium intake was stratified by low magnesium intake (<299mg/d), high magnesium intake ($\geq$ 299mg/d). Effect modification by dietary magnesium intake was assessed through interaction tests between vitamin D and SBP in the multivariable linear regression.

Results

In this cross-sectional study, we found vitamin D was negatively related to SBP, but not to DBP. The relationship between vitamin D and SBP was different in the low and high magnesium intake group (β : -0.18 95%CI: -0.35-0 vs β : -0.3 95%CI: -0.51- -0.1). Furthermore, magnesium intake significantly modified the negative relationship between vitamin D and SBP (P value for interaction: 0.026).

Conclusion

Our research showed that magnesium and vitamin D have an interactive effect in reducing SBP, which may have great importance for clinical medication.

Introduction:

Hypertension is a global public health problem with the prevalence of nearly 40% in adults over 25 years of age worldwide [1]. It can be the risk factor of some cardiovascular diseases, including stroke and heart failure [2]. However, the underlying mechanism of hypertension is not clear, and it cannot be cured so far [3].

Vitamin D deficiency (VDD) is highly prevalent worldwide [4]. It is associated with pre-eclampsia, childhood dental caries, periodontitis, cardiovascular diseases, and so on [5]. Recent studies have pointed out the relationship between vitamin D and blood pressure (BP). [6 7]. Observational studies in Meta-analysis have also shown that VDD is associated with higher BP [8]. Studies in animals and humans suggested that VDD can activate the renin-angiotensin system (RAS), which promotes the development of hypertension [9]. In addition, Sakamoto R found that 25(OH)D levels were negatively correlated with systolic blood pressure, but the relationship between serum 25(OH)D and diastolic blood pressure was

non-significant[10]. However, a prospective cohort study by Myriam Abboud showed no association between vitamin D and BP [11]. The differences in results of the studies may be attributed to potential confounding factors which have not been fully considered, such as dietary magnesium intake.

Previous studies have shown the enzymes that synthesize and metabolize vitamin D depend on magnesium [12]. Recent observational studies have shown that magnesium and vitamin D have a significant interaction, and vitamin D is related to the risk of death from colorectal cancer. [12]. However, limited clinical studies have assessed the effect of magnesium intake on vitamin D and BP [13]. Therefore, we hypothesized that magnesium has an interaction between vitamin D and BP. This cross-sectional study aims to explore the association between serum vitamin D and BP and the effect of magnesium intake on this association.

Methods:

Data source

Four stages of The National Health and Nutrition Examination Survey (NHANES) 2007–2008, 2009–2010, 2011–2012, and 2013–2014 were used in the present study. NHANES is a health-related program that includes a nationally representative cross-sectional survey of the non-institutionalized civilian population of the United States. Demographic, socioeconomic, and health-related information was obtained through questionnaires, physical and laboratory examination. Health interviews were conducted at the participants' homes, while extensive physical examinations, including blood sample collection, were conducted at the Mobile Inspection Center (MEC). The serum specimens were then tested at the Division of Laboratory Sciences. Before participating, all participants provided written informed consent, and the study was approved by the NCHS Research Ethics Review Board (<https://wwwn.cdc.gov/nchs/nhanes/default.aspx>).

Measurement of Vitamin D status

Laboratory specimens for measurement of 25(OH)D status collected during the MEC examination were centrifuged, aliquoted, and transported in cold storage to the CDC Environment Health Laboratory, where 25-hydroxyvitamin D3[25(OH)D3], 25-hydroxyvitamin D2[25(OH)D2], and 3-epi-25-hydroxyvitamin D3[3-epi-25(OH)D3] concentrations were examined using ultra-high-performance liquid chromatography-tandem mass spectrometric method (UHPLC-MS/MS). Serum 25(OH)D3 and 25(OH)D2, the major circulating forms of vitamin D, were summed and defined as total serum 25(OH)D.

Magnesium intake

Dietary data regarding magnesium intake was obtained via a precise list of all foods consumed by an individual during the former period of 24 hour. The daily magnesium intake was defined based on the average value of the overall population as high (> 299mg/d) or low intake (< = 299mg/d).

Blood pressure measurement

BP, the main outcome variable, was measured with a mercury sphygmomanometer by trained staff according to standardized protocols [14] with the participant in a seated position. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) are respectively defined as the point where the first Korotkoff sound is heard and the mercury level 2 mm below the point where the last sound is heard. In the present study, we calculated the average of up to 3 brachial systolic and diastolic BP readings for further analyses.

Covariates

Since several factors may affect the outcomes, the participants' age, gender, race/ethnicity, the season of examination, physical activity, educational level, alcohol consumption, smoking status, calcium intake, body mass index (BMI), family income, and biochemical indexes including triglyceride, cholesterol, and HDL-cholesterol were selected as the potential covariates in our analysis models. Race/ethnicity was categorized as Mexican America, other Hispanic, Non-Hispanic white, Non-Hispanic black, and other races. Educational level was categorized as less than high school, high school graduation, and college or above. According to the time of NHANES survey, the season of examination was classified as winter months (November to April) or summer months (May to October). Data on alcohol drinking (yes = at least 12 alcohol drinks per year vs. no = less than 12 alcohol drinks per year) was obtained by questionnaire interviews. Smoking status is divided into current smokers (who have smoked more than 100 cigarettes in a lifetime and currently smoke), former smokers (who have smoked more than 100 cigarettes in a lifetime but have not smoked), and never smokers (who have never smoked more than 100 cigarettes). Physical activity is defined as Vigorous work activity, Moderate work activity, Walk or bicycle, Vigorous recreational activities, and Moderate recreational activities according to the level of activity intensity. To assess family income, we selected the poverty income ratio (PIR), which was calculated by the family size-specific threshold. PIR was categorized as < 1 (below the poverty line), 1 to 3, and ≥3. Information on vitamin D and calcium intake was obtained through 24-hour dietary recalls as well. Moreover, the specific information concerning serum contents of triglyceride, cholesterol, HDL-cholesterol was extracted from the NHANES laboratory detection data.

Statistical analysis

All the analyses were conducted using the statistical software packages R (<http://www.R-project.org>, The R Foundation) and Free Statistics software version 1.3[15]. The complex multistage stratified sampling design of NHANES was illustrated by the use of appropriate strata, clusters, and weights in the statistical analysis process. To examine the association between vitamin D and BP, multivariate linear regression procedures were performed. SBP and DBP means were respectively evaluated across strata of magnesium intake. Interaction among subgroups was inspected by the likelihood ratio test.

95% confidence intervals (CIs) were calculated. The level of statistical significance was set at $p < 0.05$. Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), and categorical variables are expressed as weighted percentages (%) in descriptive analysis.

Chi-square tests (categorical variables) and t-test (normal distribution), Kruskal-Wallis (skewed distribution) test are respectively performed to evaluate continuous variables and categorical variables.

Results

Baseline characteristics of the study participants

This study used four cycles of NHANES 2007–2008, 2009–2010, 2011–2012, and 2013–2014. We enrolled 4,0617 participants, 2,2673 adults (≥ 20 years old) who completed the interview, and MEC examination was enrolled in our study. Participants with missing data on serum 25-hydroxyvitamin D concentration ($n = 2,018$) and blood pressure ($n = 2257$) were excluded. After excluding participants with missing data for covariates, our analysis included 8,779 participants in total. The flowchart of the exclusion criteria is summarized in Fig. 1. The descriptive characteristics of participants were displayed in Table 1 based on dietary magnesium intake. Compared with the low magnesium intake ($< 299\text{mg/d}$), participants with high magnesium intake ($\geq 299\text{mg/d}$) were more likely to be younger, male, non-Hispanic white, had lower BMI, received a good education, PIR > 3 , higher intake of alcohol, dietary vitamin D, dietary calcium, dietary magnesium and higher value of triglycerides. No statistically significant differences were detected in the season of examination, smoking status, physical activity, cholesterol, and direct HDL-cholesterol (all p values > 0.05).

Table 1
Characteristics of participants

Variables	Dietary magnesium intake(mg/d)			
	Total (n = 8779)	< 299mg/d (n = 5077)	> 299mg/d (n = 3702)	p-value
Age(years), Mean $\pm$ SD	49.1 $\pm$ 17.7	50.0 $\pm$ 18.3	47.8 $\pm$ 16.8	< 0.001
Gender,n(%)				< 0.001
male	4413 (50.3)	2095 (41.3)	2318 (62.6)	
female	4366 (49.7)	2982 (58.7)	1384 (37.4)	
Race/Ethnicity, n (%)				< 0.001
Mexican America	1253 (14.3)	647 (12.7)	606 (16.4)	
Other Hispanic	862 (9.8)	509 (10)	353 (9.5)	
Non-Hispanic white	4145 (47.2)	2337 (46)	1808 (48.8)	
Non-Hispanic black	1741 (19.8)	1161 (22.9)	580 (15.7)	
Other races	778 (8.9)	423 (8.3)	355 (9.6)	
Season of examination, n (%)				0.563
Winter	4046 (46.1)	2326 (45.8)	1720 (46.5)	
Summer	4733 (53.9)	2751 (54.2)	1982 (53.5)	
BMI(kg/m**2), Mean $\pm$ SD	29.0 $\pm$ 6.6	29.3 $\pm$ 6.8	28.6 $\pm$ 6.4	< 0.001
Education level, n (%)				< 0.001
Did not graduate from high school	2155 (24.6)	1398 (27.6)	757 (20.5)	
Graduated from high school	1974 (22.5)	1246 (24.6)	728 (19.7)	
College education or above	4644 (52.9)	2428 (47.9)	2216 (59.9)	
PIR, n (%)				< 0.001
<1	1847 (21.0)	1183 (23.3)	664 (17.9)	
1–3	3651 (41.6)	2232 (44)	1419 (38.3)	

Variables	Dietary magnesium intake(mg/d)			
	Total (n = 8779)	< 299mg/d (n = 5077)	> 299mg/d (n = 3702)	p-value
>3	3281 (37.4)	1662 (32.7)	1619 (43.7)	
Smoking status, n (%)				0.354
current smoker	1883 (21.4)	1112 (21.9)	771 (20.8)	
former smoker	2098 (23.9)	1221 (24)	877 (23.7)	
never smoker	4798 (54.7)	2744 (54)	2054 (55.5)	
Physical activity, n (%)				0.489
Vigorous work activity	1575 (17.9)	910 (17.9)	665 (18)	
Moderate work activity	1829 (20.8)	1051 (20.7)	778 (21)	
Walk or bicycle	1249 (14.2)	717 (14.1)	532 (14.4)	
Vigorous recreational activities	596 (6.8)	327 (6.4)	269 (7.3)	
Moderate recreational activities	3530 (40.2)	2072 (40.8)	1458 (39.4)	
Had at least 12 alcohol drinks/lifetime, n (%)				< 0.001
Yes	6478 (73.8)	3533 (69.6)	2945 (79.6)	
No	2291 (26.1)	1537 (30.3)	754 (20.4)	
Don't know	10 (0.1)	7 (0.1)	3 (0.1)	
Dietary vitamin D (D2 + D3) intake(mcg),Median (IQR)	3.1 (1.2, 6.0)	2.2 (0.8, 4.4)	4.9 (2.3, 8.3)	< 0.001
Dietary calcium intake(mg),Median (IQR)	815.0 (535.0, 1188.0)	631.0 (421.0, 892.0)	1128.0 (823.0, 1552.0)	< 0.001
Dietary magnesium intake(mg),Median (IQR)	270.0 (195.0, 367.0)	207.0 (161.0, 249.0)	389.0 (336.2, 480.0)	< 0.001
Cholesterol (mmol/L), Mean $\pm$ SD	5.0 $\pm$ 1.1	5.0 $\pm$ 1.1	5.0 $\pm$ 1.1	0.664
Triglycerides (mmol/L), Mean $\pm$ SD	1.4 (0.9, 2.1)	1.4 (0.9, 2.1)	1.4 (0.9, 2.2)	0.003
Direct HDL-Cholesterol (mmol/L), Mean $\pm$ SD	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	1.4 $\pm$ 0.4	0.401
PIR: poverty income ratio; BMI: body mass index				

Table 2
Association between serum vitamin D and blood pressure

Models	n	DBP		SBP	
		β _95CI	P_value	β _95CI	P_value
model 1	8779	-0.23 (-0.33~-0.14)	< 0.001	0 (-0.14 ~ 0.13)	0.976
model 2	8779	-0.12 (-0.22~-0.02)	0.024	-0.36 (-0.49~-0.23)	< 0.001
model 3	8779	-0.05 (-0.15 ~ 0.06)	0.401	-0.21 (-0.34~-0.07)	0.002
model 4	8779	-0.05 (-0.16 ~ 0.05)	0.328	-0.19 (-0.33~-0.06)	0.005
model 5	8779	-0.06 (-0.17 ~ 0.05)	0.263	-0.22 (-0.35~-0.08)	0.002
model1:not adjusted; model2;adjusted for age,sex,race/ethnicity; model3:model2 + BMI,PIR,education level,smoking status,physical activity,alcohol use,season of examination; model4:model3 + dietary magnesium intake,dietary calcium intake,dietary vitamin D intake; model5:model4 + cholesterol,triglycerides, HDL-Cholesterol; DBP:diastolic blood pressure; SBP:systolic blood pressure; PIR:poverty income ratio; BMI:body mass index					

Table 3
Interactive effect of vitamin D and dietary magnesium intake on SBP

models	low-magnesium intake (n = 5077)		high-magnesium intake (n = 3702)		p for interaction
	β (95%CI)	P-value	β (95%CI)	P-value	
model 1	0.18 (0 ~ 0.36)	0.044	-0.24 (-0.45~-0.04)	0.021	0.003
model 2	-0.28 (-0.45~-0.1)	0.002	-0.46 (-0.67~-0.26)	< 0.001	0.017
model 3	-0.15 (-0.32 ~ 0.03)	0.102	-0.29 (-0.5~-0.08)	0.006	0.02
model 4	-0.15 (-0.33 ~ 0.03)	0.093	-0.28 (-0.49~-0.07)	0.008	0.024
model 5	-0.18 (-0.35 ~ 0)	0.052	-0.3 (-0.51~-0.1)	0.004	0.026
model1:not adjusted; model2;adjusted for age, sex, race/ethnicity; model3:model2 + BMI,PIR,education level, smoking status, physical activity, alcohol use, season of examination; model4:model3 + dietary magnesium intake, dietary calcium intake, dietary vitamin D intake; model5:model4 + cholesterol,triglycerides, HDL-Cholesterol; DBP: diastolic blood pressure; SBP :systolic blood pressure; PIR: poverty income ratio; BMI: body mass index					

Association between serum vitamin D and BP

In the unadjusted model and model2, vitamin D was negatively associated with DBP. But in turn after adjustment of confounding factors in the fully adjusted model, vitamin D was not associated with DBP(p-values > 0.05). In the fully adjusted model, vitamin D was negatively associated with SBP (β :-0.22, CI:-0.35,-0.08).

Magnesium intake affects the association between vitamin D and SBP

In the fully adjusted models (model 5), the association between vitamin D and SBP was significant in the high magnesium intake group but not in the low magnesium group ($p > 0.05$). In the high magnesium intake group, when vitamin D increased by 0.1nmol/L, the value of SBP dropped by 0.3mmHg (β :-0.3 95%CI:-0.51~-0.1). In addition, the interaction between magnesium intake and vitamin D and SBP was significant (P-value for interaction likelihood ratio test was < 0.05).

Discussion

Analyzing the nationally representative adult population data in the United States, this study showed that vitamin D was negatively related to SBP, and has no significant relationship with DBP. Besides, it was found that dietary magnesium intake and vitamin D had an interactive effect on reducing SBP, which indicates that vitamin D sufficiency and magnesium intake are greater than the sum of the individual effects.

To the best of our knowledge, this is the first large-scale study to assess the interaction of dietary magnesium intake on the association of vitamin D and SBP. Similar to our study, Karani S Vimalaswaran [7] used a Mendelian randomization study to evaluate whether BP and hypertension risk can be modified by 25(OH) D concentration. In this study, a higher 25(OH) D concentration was associated with decreased SBP and reduced risk of hypertension, but not with decreased DBP. Sheng Hui Wu also gave the same conclusion in his study [16]. A meta-analysis suggested that vitamin D supplementation slightly reduced SBP by 1.964 mmHg, but did not reduce DBP, and the decrease in SBP was not dependent on the dose. [17]. Joukar F conducted a prospective cohort study that found the relationship between vitamin D levels and SBP was weak but statistically negative, and there was no significant relationship between vitamin D levels and DBP [18].

However, a randomized trial showed that vitamin D treatment did not affect the blood pressure of the patients compared to placebo [19]. A review [20] and a meta-analysis [21] revealed that vitamin D supplementation did not reduce blood pressure. These conclusions may be that the study population happens to be a low-magnesium population. Magnesium is necessary to activate vitamin D and it is a cofactor of vitamin D binding protein [22]. Moreover, vitamin D is metabolized into 1, 25 (OH)₂D active form through liver 25-hydroxylation and kidney 1 α -hydroxylation, which is a magnesium-dependent process[22]. Therefore, high magnesium intake is conducive to the enhancement of vitamin D activity. This mechanism can explain the interaction effect found in the present study. A review suggests that magnesium supplementation may reduce the risk of vitamin D deficiency-related complications [22]. Deng X [23] claims that serum 25(OH)D will increase significantly only when supplemented with vitamin D and magnesium. For diseases treated with vitamin D, adequate magnesium supplementation should be considered at the same time, which requires further clinical trials to prove.

Some limitations exist in our research. First, we cannot prove causality or directionality because of the cross-sectional design. And the results might be confounded by some other unmeasured variables even after multiple adjustments. However, some potential confounding factors including some dietary factors were adjusted in the logistic regression model. Second, there is no simple and accurate method to determine the total magnesium status of the human body [13 26]. We obtain the magnesium intake of participants through questionnaire surveys. Recall bias may occur because the dietary data comes from self-reported 24-hour dietary recall. Third, although a large number of samples were included, the study population was limited to U.S. residents. Therefore, consideration is necessary when inferring other populations. As a result, well-designed multi-center controlled trials are needed to verify our findings.

Conclusion

In conclusion, our results indicate that vitamin D and SBP are negatively correlated. And this correlation was significant in the high magnesium intake group. The interaction of magnesium on the association between vitamin D and BP may be of great significance to the clinical use of drugs for the prevention of hypertension.

Declarations

Ethics approval and consent to participate

The survey protocol for the NHANES was approved by CDC's National Center for Health Statistics Institutional Research Ethics Review Board. All participants provided written informed consent, and the study was approved by the NCHS Research Ethics Review Board (<https://wwwn.cdc.gov/nchs/nhanes/default.aspx>).

Consent for publication

Not applicable

Availability of data and materials

NHANES data sets are publicly available through the Centers for Disease Control and Prevention website at [https:// wwwn. cdc. gov/ nchs/nhanes/ Default. aspx](https://wwwn.cdc.gov/nchs/nhanes/Default.aspx).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Weichao Huang conducted data collection, analysis. Xiaoman Ma wrote the manuscript. Weichao Huang and Xiaoman Ma modified the manuscript. Yue Chen conducted data interpretation. Jiayi Zheng drew the figure. Haojia Li conducted data collection. Ayinigaer Nizhamu made the table. Xuguang Guo designed the study and reviewed the manuscript.

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Figures

Figure 1

Flowchart of participants enrollment