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Prevalence of Thrombocytopenia and Its Association with Serum Magnesium

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Abstract The present study aimed to investigate the prevalence of thrombocytopenia and its association with serum magnesium in a nationally representative cohort. A total of 8478 participants aged 18 years and over were recruited in a cross-sectional survey. Thrombocytopenia was defined as platelet count less than 150×10^9/L. Multivariable logistic regression models were applied to examine the association between serum magnesium and thrombocytopenia. The prevalence of thrombocytopenia in total was 16.5 % with 18.8 % for men and 14.4 % for women ($P < 0.0001$), respectively. Compared with men in the first quartile of serum magnesium, the odds ratios (ORs) and 95 % confidence intervals (CIs) for those in the second, third, and fourth quartiles of serum magnesium were 0.96 (0.75, 1.21), 0.78 (0.62, 0.98), and 0.82 (0.65, 1.04), respectively, after adjusting for multiple confounders. Likewise, the corresponding ORs (95 % CIs) were 0.80 (0.63, 1.01), 0.79 (0.62, 0.99), and 0.65 (0.51, 0.84) in women. When serum magnesium was treated as a continuous variable, each one standard deviation increase of magnesium was associated with 12 and 8 % lower risk of thrombocytopenia in men and women, respectively. Serum magnesium was inversely associated with thrombocytopenia, and the association was slightly different in men compared with that in women.

Keywords Magnesium · Thrombocytopenia · Platelet

Introduction

Platelets are colorless blood cells that play a vital role in blood clotting by clumping and forming plugs in blood vessel holes. The average life span of a platelet in the blood is around 10 days [1]. Thrombocytopenia, also called low platelet count, occurs when platelets are losing from the circulation faster than that they can be replenished from the bone marrow [2]. Although thrombocytopenia is a rare disease in the general population, it could result in severe conditions due to extra bleeding or hemorrhage. Some of the complications might be fetal if spontaneous bleeding occurs in the gastrointestinal or intracranial [3, 4].

Causes of thrombocytopenia vary and depend on specific situations of specific patients [5]. Congenital thrombocytopenia usually follows inherited diseases. For instance, patients with Bernard-Soulier syndrome have abnormal platelet functions, and sometimes they suffer lifelong bleeding symptoms [6]. Other causes, such as deficient platelet production or diminished platelet survival duration, also account for a large proportion of thrombocytopenia cases. Although infection [7], vitamin B12, as well as folic acid deficiency [8] can partially contribute to additional explanations, the reasons and mechanisms of acquired thrombocytopenia remain to be examined.

For the past decades, serum magnesium has been reported to be associated with systemic diseases, such as cardiovascular diseases (CVD) and anemia [9–11]. Magnesium deficiency occurs more frequently in patients with diabetes and CVD, in whom platelet hyperactivity is a common influencing factor

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[12–14]. Diabetic patients also showed an increased platelet reactivity that can increase the risk of CVD [13, 15]. However, studies examining the relationship between serum magnesium and thrombocytopenia are scarce. In the present study, we aimed to investigate the prevalence of thrombocytopenia and explore its association with serum magnesium in a nationally representative cohort in China.

Materials and Methods

Participants

The China Health and Nutrition Survey (CHNS) was initiated in 1989 and aimed to understand the changes of health status with the follow-up interval of 2 or 3 years. The CHNS selected individuals from 228 communities and was designed to represent 56 % of China's population from nine provinces. A multistage, random cluster sampling design was applied for recruiting participants. This survey was approved by the institutional review committees of the University of North Carolina at Chapel Hill, the National Institute of Nutrition and Food Safety, the Chinese Center for Disease Control and Prevention, and the China-Japan Friendship Hospital, Ministry of Health. All participants provided written informed consent. Details about the study design were reported elsewhere [16]. In our study, we excluded those with missing information on interested variables. Altogether, 8478 adults were included in the present analysis. Of these participants, 199 had cardiovascular diseases and 662 had diabetes. High-sensitivity C-reactive protein (hs-CRP) was analyzed by an automatic clinical chemistry analyzer (Hitachi 7600 model, Japan). Dietary intake data were collected by asking each household member to report regarding all food consumed away from home and at home on a 24-h recall basis. Using food models and picture probes, trained field interviewers recorded the types, amounts, and place of consumption of all food during the previous day. The latest Food Composition Table for China was utilized to calculate nutrient values for the dietary data, such as energy and protein intake.

Data Collection

All participants were interviewed by trained physicians and nutritionists using a questionnaire to collect demographic, anthropometric, and lifestyle data. Height and weight were measured by physicians following a standard protocol similar to that developed by the National Center for Health Statistics for the National Health and Nutrition Examination Survey in the USA. Height was measured without shoes and rounded to the nearest 0.1 cm. Weight was recorded in light clothing to the nearest 0.1 kg.

Serum Magnesium and Thrombocytopenia Assessment

Blood samples were collected by venipuncture after an overnight fasting. Plasma and serum samples were then frozen and stored at −86 °C for laboratory analysis. The samples were analyzed in a national central laboratory in Beijing (medical laboratory accreditation certificate ISO 15189:2007) with strict quality control. Serum magnesium was assessed by xylidyl blue colorimetric method (Reagent manufacturer: Randox, UK) in Hitachi 7600 Automatic Analyzer. Platelet count was measured by fluorescence flow cytometry method (Reagent manufacturer: Beckman Coulter, USA) in Beckman Coulter LH753. Thrombocytopenia was defined as platelet less than 150×10^9/L.

Covariates

Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters. Education level was classified into 0–9 years, 10–12 years, and ≥13 years. Smoking status was categorized as never smoker, former smoker, and current smoker. Drinking status was categorized as currently drinking alcohol or not. Physical activity was measured as metabolic equivalents per week and categorized into quartiles. Residence area was divided into urban and rural.

Statistical Analysis

In the descriptive analysis, we presented the basic characteristics of the study participants as mean (standard deviation) for continuous variables and number (percentage) for category variables. We used *t* test to examine the difference in platelet count according to reference level of serum magnesium (0.70 mmol/L) and found that platelet count was lower in those with lower magnesium ($P = 0.0065$). In order to explore if there is a linear trend relationship between serum magnesium and platelet count and thrombocytopenia, we reported the results by categorizing magnesium to quartiles. Chi-square test was applied to compare thrombocytopenia prevalence between men and women. Cochran-Armitage trend test was applied to examine the trend of prevalence of thrombocytopenia across quartiles of serum magnesium. Then, we performed multivariable logistic regression analysis to examine the association between serum magnesium and thrombocytopenia. Three models were used in the present study. The first model included serum magnesium as an independent variable followed by the second model adjusted for age (plus sex for both sexes). The third model was additionally adjusted for BMI, energy intake, protein intake, education, smoking status, drinking status, physical activity, and residence area. Additionally, because a linear trend between serum magnesium and prevalence of thrombocytopenia was observed, serum

magnesium was treated as a continuous variable and odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated with one standard deviation increase of serum magnesium. We also did more analyses when treating platelet count as a continuous variable using multiple linear regression models. *P* values were two-tailed and $P < 0.05$ was considered as statistical significance. All analyses were performed using *R* 3.0.

Results

Table 1 presents the basic characteristics of the study participants by quartiles of serum magnesium. The cutoff values of serum magnesium quartiles were 0.88, 0.94, and 0.99 mmol/L, respectively. In total, the average platelet counts were 207.3×10^9/L, 213.0×10^9/L, 214.6×10^9/L, and 215.9×10^9/L for those in the four magnesium quartiles groups, respectively.

The prevalence of thrombocytopenia by quartiles of serum magnesium is shown in Table 2. Overall, 16.4 % of the participants in this study were with thrombocytopenia and men had a higher prevalence than women (18.8 vs. 14.4 %, $P < 0.0001$). Participants with lower levels of serum magnesium were more likely to have thrombocytopenia. Cochran-Armitage trend test showed that the prevalence of thrombocytopenia decreased with increasing levels of serum magnesium and results were consistent in both men and women ($P < 0.05$).

The association of serum magnesium and thrombocytopenia in all participants is described in Table 3. The ORs (95 % CI) for the second to fourth quartiles of serum magnesium were 0.96 (0.75, 1.21), 0.78 (0.62, 0.98), and 0.82 (0.65, 1.04) compared with the first quartile in men after adjusting

Table 1 Basic characteristics of study participants by quartiles of serum magnesium

Variables		Q1	Q2	Q3	Q4
Age(years)		49.6 ± 15.6	49.9 ± 14.6	51.4 ± 15.1	52.5 ± 14.6
BMI(kg/m^2)		23.3 ± 3.5	23.3 ± 3.4	23.4 ± 3.4	23.7 ± 3.4
Energy(kcal)		2142.2 ± 954.5	2222.9 ± 1086.1	2257.3 ± 1578.2	2167.8 ± 794.5
Protein(g)		64.3 ± 23.8	67.1 ± 26.3	67.3 ± 26.1	67.6 ± 25.5
Platelet(10^9/L)		207.3 ± 66.8	213.0 ± 66.5	214.6 ± 70.0	215.9 ± 69.0
Magnesium(mmol/L)		0.82 ± 0.07	0.91 ± 0.01	0.96 ± 0.02	1.05 ± 0.1
hs-CRP					
	<3 mg/L	1649 (76.8)	1503 (76.7)	1762 (76.3)	1497 (73.2)
	3–10 mg/L	410 (19.1)	389 (19.8)	454 (19.7)	438 (21.4)
	>10 mg/L	87 (4.1)	68 (3.5)	93 (4.0)	111 (5.4)
Education					
	0–9 years	1690 (78.2)	1485 (75.8)	1777 (77.0)	1532 (74.8)
	10–12 years	391 (18.1)	369 (18.8)	406 (17.6)	410 (20.0)
	13 years	81 (3.7)	106 (5.4)	126 (5.5)	105 (5.1)
Smoking status					
	Never	1572 (72.7)	1394 (71.1)	1548 (67.0)	1343 (65.6)
	Former	64 (3.0)	56 (2.9)	80 (3.5)	82 (4.0)
	Current	526 (24.3)	510 (26.0)	681 (29.5)	622 (30.4)
Drinking alcohol					
	Never	1534 (71.0)	1345 (68.6)	1545 (66.9)	1288 (62.9)
	Current	628 (29.0)	615 (31.4)	764 (33.1)	759 (37.1)
Physical activity					
	Q1	251 (11.6)	207 (10.6)	253 (11.0)	227 (11.1)
	Q2	674 (31.2)	579 (29.5)	709 (30.7)	629 (30.7)
	Q3	636 (29.4)	570 (29.1)	649 (28.1)	587 (28.7)
	Q4	601 (27.8)	604 (30.8)	698 (30.2)	604 (29.5)
Residence area					
	Urban	662 (30.6)	664 (33.9)	757 (32.8)	711 (34.7)
	Rural	1500 (69.4)	1296 (66.1)	1552 (67.2)	1336 (65.3)

Q quartile, *BMI* body mass index, *hs-CRP* high-sensitivity C-reactive protein

Table 2 Prevalence of thrombocytopenia by quartiles of serum magnesium

	All	Men	Women
Q1	398 (18.4)	193 (21.8)	205 (16.1)
Q2	324 (16.5)	171 (19.6)	153 (14.0)
Q3	362 (15.7)	192 (17.2)	170 (14.3)
Q4	311 (15.2)	189 (17.3)	122 (12.8)
P for trend test	0.003	0.005	0.038

Q quartile

for multiple confounders. Likewise, the respective ORs (95 % CIs) for serum magnesium in women were 0.80 (0.63, 1.01), 0.79 (0.62, 0.99), and 0.65 (0.51, 0.84). Participants with higher levels of serum magnesium were less likely to suffer low platelet count compared with those in the first quartile group.

Table 4 shows the association between magnesium and platelet count when treating platelet count as a continuous variable using multiple linear regression models. Similar to the results in Table 3, the associations were significant in both men and women. The platelet counts were 2.78 (−3.28, 8.83), 8.86 (3.15, 14.58), and 9.78 (3.99, 15.57) higher (unit 10^9/L) for the second to fourth quartiles compared with the first quartile of serum magnesium in men. Likewise, platelet counts were 10.12, 10.06, and 14.71 × 10^9/L higher for participants in the second to fourth quartiles in women.

Table 3 Association between serum magnesium and thrombocytopenia using logistic regression models [OR (95 % CI)]

	Model 1	Model 2	Model 3
All			
Q1	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	0.88 (0.75,1.03)	0.87 (0.74,1.02)	0.87 (0.73,1.02)
Q3	0.82 (0.70,0.96)	0.78 (0.66,0.91)	0.77 (0.66,0.91)
Q4	0.79 (0.67,0.93)	0.72 (0.61,0.85)	0.73 (0.62,0.87)
1 SD increase	0.91 (0.86,0.97)	0.88 (0.83,0.94)	0.91 (0.86,0.97)
Men			
Q1	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	0.88 (0.70,1.11)	0.94 (0.74,1.18)	0.96 (0.75,1.21)
Q3	0.75 (0.60,0.93)	0.78 (0.62,0.98)	0.78 (0.62,0.98)
Q4	0.75 (0.60,0.94)	0.79 (0.63,0.99)	0.82 (0.65,1.04)
1 SD increase	0.88 (0.81,0.96)	0.89 (0.82,0.97)	0.88 (0.81,0.96)
Women			
Q1	1.0 (ref.)	1.0 (ref.)	1.0 (ref.)
Q2	0.85 (0.68,1.07)	0.82 (0.65,1.03)	0.80 (0.63,1.01)
Q3	0.87 (0.70,1.08)	0.80 (0.64,1.00)	0.79 (0.62,0.99)
Q4	0.76 (0.60,0.97)	0.67 (0.53,0.86)	0.65 (0.51,0.84)
1 SD increase	0.92 (0.84,1.00)	0.88 (0.80,0.96)	0.92 (0.84,1.00)

OR odds ratio, *CI* confidence interval, *Q* quartile, *SD* standard deviation

Discussion

In the present study, we found a significant association between serum magnesium and thrombocytopenia in a large community-based cohort. A dose-response relationship showed that higher serum magnesium was associated with higher platelet count and conferred a lower risk of thrombocytopenia. In addition to that, the effect was stronger in women compared with that in men. These findings were suggestive of the significance of serum magnesium involved in the biological function of platelet.

The prevalence of thrombocytopenia was seldom reported in the general community-based populations [17, 18]. The reasons may lie in the fact that thrombocytopenia in the general population usually has few symptoms and has not attracted too much attention in the scientific community. However, some special patients may experience extra bleeding during injury, surgery, or menstruation. The consequences of these experiences may be fetal if they occur in the gastrointestinal or intracranial [19, 20]. Thus, exploring the possible risk factors of thrombocytopenia might shed light on its treatment and prevention.

The exact biological mechanisms between serum magnesium and thrombocytopenia remain unclear; several possible explanations could be proposed to clarify the statistically significant findings. Firstly, magnesium deficiency has been linked to platelet hyperactivity and adhesiveness, and intravenous magnesium supplementation was found to be able to reverse these changes [21]. Thus, more platelets could be released back to blood during the reversible platelet aggregation phase provided there was sufficient serum magnesium. Secondly, thrombocytopenia is usually accompanied by varying degrees of anemia, which is one of the symptoms for impaired marrow production. Higher serum magnesium has been reported to be associated with lower prevalence of anemia [11]. Thus, it might also be possible that serum magnesium is related to better bone marrow function as well as more platelet production. Thirdly, magnesium deficiency was related to inflammation and oxidative stress [22], both of which could promote accelerated platelet adhesiveness and aggregation [23]. Higher magnesium also reduces vulnerability to oxygen-derived free radicals and improves endothelial function and inhibits platelet aggregation [24]. In our multivariable analysis, the effect size of serum magnesium on platelet did not change too much even after further adjusting for hs-CRP. Thus, other possible biological mechanisms might still be accountable for our

Table 4 Association between serum magnesium and platelet count using linear regression models [β (95 % CI)]

	Model 1	Model 2	Model 3
All			
Q1	0 (ref.)	0 (ref.)	0 (ref.)
Q2	5.71 (1.54, 9.88)	6.40 (2.29,10.51)	6.98 (2.85,11.10)
Q3	7.36 (3.36,11.36)	9.54 (5.58,13.49)	9.70 (5.72,13.68)
Q4	8.62 (4.49,12.74)	12.24 (8.15,16.33)	12.60 (8.47,16.73)
1 SD increase	3.24 (1.78, 4.70)	4.57 (3.12, 6.01)	3.24 (1.78, 4.70)
Men			
Q1	0 (ref.)	0 (ref.)	0 (ref.)
Q2	4.11 (−1.93,10.16)	2.54 (−3.45, 8.54)	2.78 (−3.28, 8.83)
Q3	9.79 (4.10,15.49)	8.56 (2.91,14.21)	8.86 (3.15,14.58)
Q4	10.88 (5.16,16.61)	9.64 (3.96,15.32)	9.78 (3.99,15.57)
1 SD increase	3.65 (1.74, 5.56)	3.40 (1.51, 5.29)	3.65 (1.74, 5.56)
Women			
Q1	0 (ref.)	0 (ref.)	0 (ref.)
Q2	7.99 (2.31,13.68)	9.09 (3.42,14.75)	10.12 (4.46,15.78)
Q3	7.42 (1.86,12.97)	9.73 (4.16,15.29)	10.06 (4.49,15.64)
Q4	10.34 (4.44,16.24)	13.99 (8.04,19.94)	14.71 (8.76,20.67)
1 SD increase	4.37 (2.18, 6.57)	5.74 (3.52, 7.96)	4.37 (2.18, 6.57)

CI confidence interval, *Q* quartile, *SD* standard deviation

findings, and these mechanisms need to be clarified in future studies.

The strength of the present study is its population-based sampling with a large sample size, which enables us to perform sex-stratified analysis with sufficient statistical power. To the best of our knowledge, this is the largest cohort to date looking at serum magnesium and platelet count. The major limitation of our analysis was its cross-sectional study design. A causal association between magnesium and platelet count, therefore, cannot be established merely on the basis of the present analysis and results. Moreover, serum magnesium concentrations assessed at a single time point in this study did not reflect the overall average life-course serum magnesium status, which probably could lead to a non-differential bias. The true effect size may be stronger than the association reported here.

In summary, our results suggest that higher serum magnesium concentrations are associated with lower risks of thrombocytopenia. The associations appear to be independent of several confounders. Future observational or interventional prospective cohort studies are warranted to examine the beneficial effects of magnesium intake on platelet count. Confirmation of our results would have important public health and clinical implications.

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Conflict of Interest The authors declare that they have no competing interests.

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