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Dose-response relationship between higher serum calcium level and higher prevalence of hyperuricemia

A cross-sectional study

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Abstract

The aim of the study was to examine the relationship between serum calcium (Ca) levels and the prevalence of hyperuricemia (HU).

The data included in this analysis were extracted from a population-based study conducted at the Xiangya Hospital Health Management Centre. Serum Ca levels were measured using the Arsenazo III method. HU was defined as the uric acid ≥416 μmol/L for male subjects, and ≥360 μmol/L for female subjects. The association between serum Ca levels and the prevalence of HU was evaluated using logistic and spline regression.

The present study included a total of 6337 subjects. The overall prevalence of HU for the target population was 17.5%. Compared with the lowest quintile, the odds ratios adjusted by age, sex, body mass index, smoking, and drinking for HU were 1.51 [95% confidence interval (CI): 1.20–1.91], 1.43 (95% CI: 1.13–1.82), 2.02 (95% CI: 1.61–2.54), and 2.54 (95% CI: 2.02–3.18) for the second, third, fourth, and fifth quintiles of serum Ca levels, respectively (*P* for trend <.001), and a positive dose-response relationship was observed. Similar results were observed for men and women, respectively. The findings were not materially altered by the adjustment for further potential confounders.

Subjects with higher serum Ca levels are subject to a higher prevalence of HU in a dose-response relationship manner.

Abbreviations: BMI = body mass index, Ca = calcium, CI = confidence interval, HU = hyperuricemia, OR = odds ratio.

Keywords: calcium, hyperuricemia, cross-sectional

1. Introduction

Hyperuricemia (HU), which is generally defined as the serum uric acid level exceeding the normal range, is increasingly considered as a potential pathogenic factor for gout and several other chronic diseases, such as hypertension, diabetes, atherosclerosis, cardiovascular disease, and chronic kidney disease.[1–5] According to the recent epidemiological data, approximately 21% of adults in the United States suffered from HU[6]; and the prevalence of HU ranged between 13% and 25.8% in some countries in Asia.[7–10] Thereby, HU has become not only a medical but also a social issue, and is currently drawing great concern worldwide.[1] Unfortunately, the pathophysiology of HU has not been thoroughly elaborated.

Calcium (Ca) is a critical constituent in a number of cellular processes, such as muscle contraction, hormone secretion, exocytosis, nerve conduction, and activation and inactivation of abundant enzymes.[11] In addition to oxalate, Ca and uric acid are another 2 important components of urine that support the genesis of urinary stones.[12] There were also some studies that investigated the association between Ca concentration and uric acid in the serum sample,[13–17] which, however, lacks support by conclusive evidence and remain controversial.[13,16,17]

A better understanding of the association between serum Ca and the prevalence of HU in the general population is still warranted, because it can probably provide valuable information for disease monitoring and clarification of specific mechanisms. To fill this knowledge gap, data were collected from a large population-based study in this research work to examine the relationship between the 2. It was hypothesized that the serum Ca concentration is positively associated with the prevalence of HU.

2. Methods

2.1. Study population

The present cross-sectional study was conducted at the Department of Health Examination Center Xiangya Hospital, Central South University in Changsha, Hunan Province, China. Approval had been granted by the ethics committee of Xiangya Hospital, Central South University (reference numbers: 201312459) before the research work. Nowadays, routine

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health examinations have become very common in China, as the central government is encouraging people to perform regular medical checkups. The overall design of this study is the same as some earlier works.[18–21] The subjects were selected according to the following inclusion criteria: 40 years old or above; undergoing serum uric acid and serum Ca measurement; availability of all basic characteristics, including age, sex, and body mass index (BMI), availability of information on health-related habits, such as smoking status, alcohol-consumption status, activity level, and so on. After preliminary screening, a total of 31,259 subjects who received routine medical examinations including measurement of serum uric acid and serum Ca between October 2013 and December 2015 were included in this cross-sectional study. Among them, 6337 subjects provided details of demographic characteristics and health-related habits, and were eventually included for final analysis.

2.2. Assessment of hyperuricemia

All subjects were requested to go through a 12-hour overnight fast before drawing their blood samples. The samples were stored under the condition of 4°C before analysis. The uric acid was measured using the Beckman Coulter AU 5800 (Beckman Coulter Inc, Brea, CA). HU was defined as uric acid ≥416 μmol/L for men, ≥360 μmol/L for women.[22]

2.3. Assessment of exposures

The serum Ca concentration was detected using the Arsenazo III method. The interassay coefficients of variation were 1.03% (3.01 mmol/L) and 0.858% (2.33 mmol/L), and the intra-assay coefficients of variation were 0.86% (2.35 mmol/L) and 0.58% (3.56 mmol/L) for serum Ca. The concentration of fasting plasma glucose was detected by the glucose oxidase enzyme method. Laboratory tests were undertaken using the Beckman Coulter AU 5800 (Beckman Coulter Inc, Brea, CA). The blood pressure was detected by an electronic sphygmomanometer. Subjects having a fasting glucose level ≥7.0 mmol/L or receiving medicine treatment for blood glucose control were classified as diabetic patients; subjects having a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or currently receiving antihypertensive medication were classified as hypertensive patients. The BMI of each subject was calculated based on the height and weight measurement. All subjects were requested to describe their average frequency of physical activity and average duration of each physical activity in a quantitative way (frequency: never, 1–2 times per week, 3–4 times per week, ≥5 times per week; duration: 30 min, 30–60 min, 60–120 min, >120 min), as well as the current smoking and alcohol drinking status (yes or no for each).

2.4. Statistical analysis

Before analysis, the data were collected and expressed in appropriate formats (quantitative data as mean ± standard deviation; qualitative data as percentage). The serum Ca concentration was categorized into 5 groups on the basis of the quintile distribution of the study population: ≤2.27, 2.28–2.33, 2.34–2.38, 2.39–2.44, and ≥2.45 mmol/L. The difference in the continuous data was evaluated using the 1-way classification analysis of variance (normally distributed data) or the Kruskal-Wallis H test (non-normally distributed data). The difference in the qualitative data was evaluated using the χ^2 test. The age- and sex-adjusted odds ratios (ORs) with 95% confidence intervals (CIs) for the association between the serum Ca and the prevalence of HU were computed for each quintile of serum Ca. The quintile with the smallest value was taken as the reference (model 1). In addition, 2 multivariable models (models 2 and 3) were employed in the logistic analysis of the overall population, the male population and the female population, respectively. The covariant variables of model 2 included sex, age, BMI, smoking, and drinking status (age, BMI, smoking status, and drinking status for the sex subgroup). Model 3 further included the variables of educational level, activity level, hypertension, and diabetes on the basis of model 2. Then, based on logistic regression, tests for linear trends were performed by utilizing the median variable of the serum Ca concentrations of all groups. The dose-response relationship between levels of serum Ca and the prevalence of HU was evaluated by restricted cubic splines regression with 4 knots defined by the tertile distribution of serum Ca.[23]

SPSS version 21.0 (SPSS Inc, Chicago, IL) and STATA 12.0 (StataCorp LP, College Station, TX) were used to perform the data analyses. $P < .05$ was considered to represent statistical significance.

3. Results

This cross-sectional study included a total of 6337 subjects. Table 1 presents the characteristics of the study population in

Table 1

Basic characteristics of 6337 participants according to quintiles of serum calcium.

Basic characteristics	Quintiles of serum calcium, mmol/L					P
	Q1 (≤2.27)	Q2 (2.28–2.33)	Q3 (2.34–2.38)	Q4 (2.39–2.44)	Q5 (≥2.45)	
Number	1299	1411	1255	1221	1151	–
Median calcium concentration, mmol/L	2.23	2.31	2.36	2.41	2.49	–
Age, y	52.56 ± 7.61	52.44 ± 7.56	51.96 ± 7.19	51.73 ± 7.13	51.40 ± 7.04	.007
Sex (% female)	47.3	42.4	38.8	35.5	37.3	<.001
Smoking (%)	24.7	26.5	24.4	26.2	26.1	.646
Drinking (%)	35.3	39.1	43.0	45.5	43.4	<.001
Education level (% with or above high school background)	44.6	47.2	49.4	50.2	47.2	.047
Activity level, h/wk	1.89 ± 3.20	1.96 ± 3.15	2.23 ± 3.40	2.12 ± 3.25	2.17 ± 3.32	.023
BMI, kg/m^2	24.48 ± 3.31	24.65 ± 3.33	24.66 ± 3.16	24.56 ± 3.07	24.44 ± 3.27	.033
Hypertension, %	31.6	31.5	30.7	32.5	35.9	.064
Diabetes, %	8.2	9.4	10.2	10.8	13.2	.001

Data are mean ± standard deviation, unless otherwise indicated. *P* values are for test of difference across all quintiles of serum calcium.
BMI = body mass index.

Table 2

Multivariable-adjusted relationship between serum calcium and hyperuricemia.

	Quintiles of serum calcium, mmol/L					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	*P* for trend
Median calcium concentration (mmol/L)	2.23	2.31	2.36	2.41	2.49	–
Total						
Model 1 (95% CI)	1.00 (reference)	1.52 (1.21, 1.91)	1.47 (1.16, 1.86)	2.02 (1.61, 2.53)	2.51 (2.01, 3.15)	<.001
Model 2 (95% CI)	1.00 (reference)	1.51 (1.20, 1.91)	1.43 (1.13, 1.82)	2.02 (1.61, 2.54)	2.54 (2.02, 3.18)	<.001
Model 3 (95% CI)	1.00 (reference)	1.53 (1.21, 1.94)	1.46 (1.15, 1.86)	2.04 (1.62, 2.57)	2.53 (2.01, 3.19)	<.001
Male						
Model 1 (95% CI)	1.00 (reference)	1.41 (1.08, 1.83)	1.38 (1.06, 1.80)	1.80 (1.39, 2.33)	2.19 (1.69, 2.83)	<.001
Model 2 (95% CI)	1.00 (reference)	1.39 (1.06, 1.81)	1.33 (1.02, 1.74)	1.77 (1.36, 2.30)	2.16 (1.67, 2.81)	<.001
Model 3 (95% CI)	1.00 (reference)	1.41 (1.08, 1.85)	1.36 (1.04, 1.79)	1.80 (1.39, 2.34)	2.21 (1.69, 2.88)	<.001
Female						
Model 1 (95% CI)	1.00 (reference)	1.84 (1.14, 2.98)	1.56 (0.93, 2.60)	2.61 (1.61, 4.23)	3.23 (2.02, 5.17)	<.001
Model 2 (95% CI)	1.00 (reference)	1.99 (1.22, 3.24)	1.58 (0.94, 2.66)	2.93 (1.79, 4.80)	3.56 (2.21, 5.74)	<.001
Model 3 (95% CI)	1.00 (reference)	1.95 (1.20, 3.19)	1.62 (0.96, 2.74)	2.94 (1.79, 4.84)	3.32 (2.05, 5.38)	<.001

Values are adjusted OR (95% CI) unless otherwise indicated.

Model 1 included age (continuous data), sex (male, female).

Model 2 included age (continuous data), sex (male, female), BMI (≥28 kg/m^2, <28 kg/m^2), smoking status (yes/no), and drinking status (yes/no) (age, BMI, smoking status and drinking status for the sex subgroup).

Model 3 added education level (with or above high school background or not), activity level (quintiles), hypertension (yes/no), diabetes (yes/no), on the basis of model 2.

CI = confidence interval, OR = odds ratio, HU = hyperuricemia.

terms of the quintiles of serum Ca. It can be seen that the differences across all quintiles of serum Ca for age, sex, BMI, education level, activity level, drinking status, and diabetes are significant in the target population.

The prevalence of HU was 17.5% in the overall sample of this cross-sectional study. A positive relationship between the serum Ca concentration and the prevalence of HU was observed in all the 3 multivariable models (Table 2). As shown in model 1, the ORs (95% CIs) for HU, with adjustment for age and sex, were 1.52 (95% CI: 1.21–1.91), 1.47 (95% CI: 1.16–1.86), 2.02 (95% CI: 1.61–2.53), and 2.51 (95% CI: 2.01–3.15) from the second to the highest serum Ca quintile, respectively (*P* for trend <.001), compared with the lowest quintile. With further adjustment for BMI, smoking, and drinking status (model 2), the multivariable-adjusted ORs (95% CIs) for HU were higher than that for the lowest quintile in the second (1.51, 95%CI: 1.20–1.91), third (1.43, 95% CI: 1.13–1.82), fourth (2.02, 95%CI: 1.61–2.54), and fifth (2.54, 95% CI: 2.02–3.18) quintiles of serum Ca (*P* for trend <.001). On the basis of model 2, an additional model including education level, activity level, hypertension, and diabetes (model 3) did not materially alter the results (*P* for trends <.001, respectively) (Table 2). Similar results were obtained for men and women, respectively. Furthermore, as shown in Figure 1, serum Ca concentration was approximately associated with the OR for HU in a dose-response relationship manner (*P* for trend = .06).

4. Discussions

The present cross-sectional study demonstrated a positive association between the concentration of serum Ca and the prevalence of HU in the general population, with adjustment of several major confounding factors. Such association remained valid in both the male and female population according to the sex

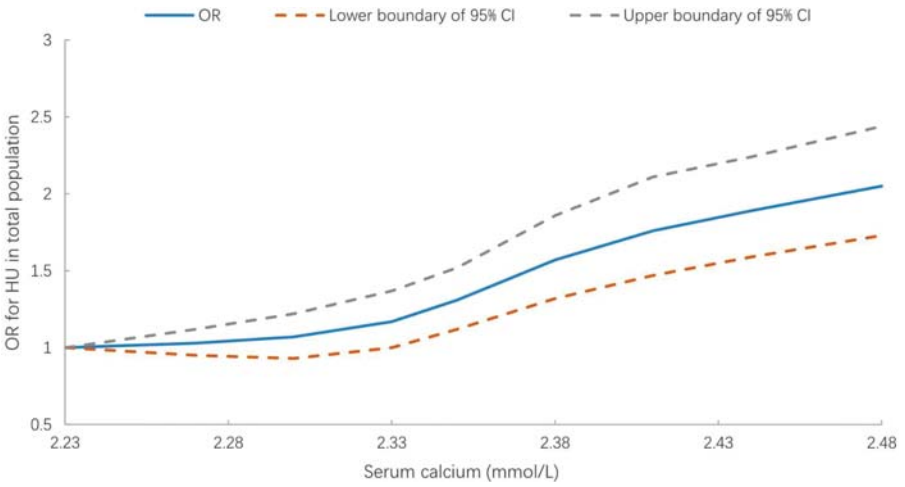

Figure 1. Dose-response relationship between serum calcium and the odds ratio for HU in total population (n = 6337). CI = confidence interval, HU = hyperuricemia, OR = odds ratio.

subgroup analysis. Meanwhile, an approximate dose-response relationship manner was also observed in such association.

The increased production of endogenous uric acid and the increased intake of purine-rich foods are suspected potential factors for HU, but it is more commonly caused by the decreased excretion of uric acid. HU often predisposes the affected individuals to gout,[7] and increases the risks of developing certain diseases such as hypertension, diabetes, chronic kidney disease, atherosclerosis, and cardiovascular disease.[1–5,24] In addition, some common diseases, such as obesity, insulin resistance, hyperglycemia, and dyslipidemia are also deemed to be associated with a high level of serum uric acid.[10,25–28]

As a vital element in the maintenance of health and growth of human body, Ca plays a critical role in a variety of metabolic processes.[11] The serum Ca concentration is maintained within a narrow range by the regulation mechanism of Ca metabolism in the kidney, intestine, and bones. Some studies that investigated the association between Ca concentration and uric acid in the serum sample could be retried form literature research.[13–17] For example, Coates and Raiment[14] examined the serum Ca concentration in 8 patients with gout and found that the serum Ca concentration in gout patients was generally above the normal upper limit. Guessous et al[17] also found that the serum Ca concentration was positively associated with the serum uric acid level. Moreover, compared with non-HU subjects, Kumar et al[16] showed that serum Ca concentration was significantly increased in HU patients. Nevertheless, a latest study suggested that serum Ca concentration was not associated with the serum uric acid level in patients with stroke,[15] and Gouri et al[13] also showed that increased serum Ca was associated with a lower level of serum uric acid.

Previous works suggested that the patients with gouty diathesis might develop calcium oxalate stones,[29,30] and the allopurinol could significantly decrease the recurrence of Ca oxalate lithiasis.[31–33] It therefore implies that uric acid plays a certain role in the formation of Ca stone,[34,35] and may act as an anti-inhibitor by reducing the level of free urinary glycosaminoglycans, which in turn blocks the inhibitory effect on Ca oxalate crystallization.[36–38] Meanwhile, it has also been postulated that the effect of urate on Ca oxalate crystallization is attributed to its ability of salting out Ca oxalate from the solution.[39–42] Consistent with aforementioned studies, the present cross-sectional study suggested a positive association between serum Ca and HU with a sample of 6337 subjects.

The inflammatory mechanism also plays a potential role in the association between serum Ca and HU. On the one hand, an elevated level of serum uric acid may contribute to inflammatory arthritis when it crystalizes in joints.[43,44] Some important inflammatory cytokines, such as IL-6 and TNF-α, are positively associated with the serum uric acid.[45–47] It has also been established that the degree of HU strongly predicts the occurrence of acute inflammation in gout.[44,48,49] On the other hand, there is also a positive association between serum Ca concentration and inflammation. Hypercalcemia is well-recognized to be associated with a number of inflammatory diseases.[50,51] Meanwhile, IL-1β, IL-6, and some other important inflammatory cytokines have been demonstrated to upregulate the Ca sensing receptor, which functions in controlling the blood Ca homeostasis and has been proved to be both a promoter and responder to inflammation.[52–54] From the analysis above, the inflammatory mechanism may contribute to the positive association between serum Ca concentration and HU, which however needs further exploration.

Several strengths are noteworthy in the present study. First of all, this is the first study that directly investigated the dose-response relationship between levels of serum Ca and the prevalence of HU based on a large sample (6337 subjects). Meanwhile, the multivariable model used in this study has been adjusted for a considerable number of potential confounding factors, such as sex, age, BMI, smoking status, drinking status, education level, activity level, hypertension, and diabetes, which greatly improved the reliability of the results. However, the findings of this study are also subject to some limitations. First of all, sensitivity analyses were failed to be conducted to eliminate the impact of some medications use. For example, as a common treatment for hypertension, diuretics have been reported to have an influence on both the serum calcium and uric acid level.[55,56] In addition, since the cross-sectional design precludes causal relations, further prospective studies and intervention trials should be included to build a causal relationship between serum Ca and HU.

5. Conclusions

Subjects with higher serum Ca levels are subject to a higher prevalence of HU in a dose-response relationship manner.

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