

Increased risk for hyperuricemia in adults sensitized to cow milk allergen

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Abstract Several studies indicated the beneficial role of milk or dairy intake in protecting against gout or lowering rate levels. The elimination of milk or other dairy products due to cow milk allergies might increase the risk for gout and hyperuricemia. We investigated the potential risk of hyperuricemia in adults in the USAs according to the presence of milk allergen sensitization. We analyzed the data from the 2005–2006 National Health and Nutrition Examination. A total of 3893 adults with available data from specific IgE tests for milk allergen, serum uric acid levels, and no other missing information on their questionnaires were included in this study. Hyperuricemia was defined as serum uric acid levels >7.0 mg/dL. Overall, 151 (4.0 %) subjects were sensitive to milk allergen. The mean uric acid level in the sensitized subjects was higher than that in their non-sensitized counterparts. A significant difference in the rate of hyperuricemia between the two groups was found. Compared with subjects who were not sensitized to milk allergen (reference), subjects sensitized to milk allergen exhibited a significant increase in uric acid ($\beta = 0.29$; 95 % CI = 0.09–0.48) after adjusting for all potential covariates. In addition, the sensitized subjects, compared with the non-sensitized subjects, showed an increased risk of hyperuricemia (OR = 1.72; 95 % CI = 1.17–2.53). Adults who showed sensitivity to cow milk allergen were at a higher risk of hyperuricemia than those who were not sensitized,

suggesting that restricted intake of milk or dairy products may be a possible risk factor for hyperuricemia.

Keywords Dairy intake · Epidemiology · General population · Gout · Immune response

Introduction

Gout is a disorder associated with abnormalities in purine metabolism and is characterized by hyperuricemia and the deposition of uric acid crystals (monosodium urate) in the joints and other tissues [1]. Gout causes severe pain and suffering, leading to a poor health-related quality of life [2]. People with gout or hyperuricemia are at increased risk for several conditions, such as insulin resistance syndrome, cardiovascular events, and premature death [3–5]. The known risk factors for gout and hyperuricemia include alcohol consumption (beer and hard liquor), obesity, hypertension, diabetes, and diuretics use [6]. Dietary factors are considered key to developing gout and hyperuricemia [7]. A higher intake of purine-rich foods (i.e., meat and seafood), sugar-sweetened soft drinks, and fructose was shown to increase the incidence of disease, whereas a higher consumption of folate and coffee was inversely associated with disease risk [6, 8–12].

Dairy products are of particular interest in this condition. Several studies from epidemiologic observation to a randomized control trial have indicated the beneficial role of dairy intake as gout-protective or urate-lowering [7–9, 13, 14]. Although the exact cause remains unclear, recent research has suggested that certain dairy fractions and components, such as casein, lactalbumin, calcium, and lactose, are involved in preventing and managing gout and blood rate levels [7, 8, 13]. Based on these findings, the elimination of milk or other dairy products due to cow milk allergies might result in

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adverse health outcomes, in terms of gout and hyperuricemia. However, there has been no evidence to support this assumption.

This study hypothesized that adults who were allergic to cow milk would show higher uric acid levels than their non-allergic counterparts. We estimated the potential risk of hyperuricemia in adults in the USA according to the presence of milk allergen sensitization based on immunoglobulin E (IgE)-mediated sensitivity to milk.

Materials and methods

Study population

We used the data from the 2005–2006 National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention, which is a nationally representative survey of the non-institutionalized civilian population of the USA. For the current study, we included 4425 participants who were aged ≥ 20 years and were available for specific IgE tests for milk allergen in the initial survey. We excluded 532 adults for whom serum uric acid levels were unavailable ($n = 32$) or who had missing data for other variables ($n = 500$). Therefore, a final study population of 3893 adults was included in the analyses.

Variables of interest

For specific IgE tests for milk allergy, serum samples were collected and analyzed using the Pharmacia Diagnostics Immuno CAP 1000 System (Pharmacia Diagnostics, Kalamazoo, MI). The lower limits of detection were 2.00 kU/L for total IgE and 0.35 kU/L for each of the allergen-specific IgE antibody tests. A specific IgE level of 0.35 kUA/L or greater indicated a milk allergy. Details of the laboratory methods and quality control procedures were previously described [15].

Uric acid was measured using the Beckman Synchron LX20 system [16]. Hyperuricemia was defined as a serum uric acid levels >7.0 mg/dL [17].

The following covariates were obtained via questionnaire: age (20–29, 30–39, 40–49, 50–59, 60–69, 70–79, or ≥ 80 years); sex (male or female); race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, or other); smoking status (current, former, or never); and alcohol consumption (drinker or non-drinker). Body mass index (BMI) was categorized into four groups: underweight (<18.5 kg/m²), normal weight (18.5–24.9 kg/m²), overweight (25–29.9 kg/m²), and obese (≥ 30.0 kg/m²). History of diseases included type 2 diabetes mellitus, hypertension, and allergic disease. Total energy intake was organized as quartiles, and the use of diuretics was categorized as “yes” or “no.”

Statistical analysis

The uric acid value was treated both continuously and categorically based on the cut-off of hyperuricemia (>7.0 mg/dL in males and females). To assess the association between uric acid and milk allergen sensitization, we performed linear regression analysis, and calculated the beta coefficient (β) and corresponding 95 % confidence intervals (95 % CIs) for a 1-unit increases in uric acid in adults sensitized to milk allergen, compared with non-sensitized adults as the reference group. In addition, logistic regression analysis was conducted and provided odds ratios (ORs) and 95 % CIs for hyperuricemia in adults sensitized to milk allergen, compared to those without milk allergen sensitization. All of the analyses were performed using the PROC SURVEY procedures in SAS 9.2 (SAS Institute, Cary, NC, USA). Statistical significance was set at $\alpha = 0.05$ (two-sided).

Results

Table 1 shows the general characteristics of the study subjects according to sensitization to milk allergen. Overall, 151 (4.0 %) subjects were sensitive to milk allergen. Subjects with sensitization to milk allergen were more likely to be young, male, and White. The presence of sensitization to milk allergen differed significantly by disease history of diabetes, hypertension, and allergic disease but did not differ significantly according to cigarette smoking, alcohol consumption, BMI, total energy intake, and the use of diuretics.

We compared the mean value of uric acid and the percentages of hyperuricemia between the sensitized and the non-sensitized subjects (Fig. 1). The mean uric acid level in the sensitized subjects was higher than that in the non-sensitized subjects (5.8 vs. 5.3 mg/dL, p value < 0.0001). After adjusting for age, gender, ethnicity, smoking, alcohol intake, BMI, history of diabetes, hypertension, or allergic diseases, total energy intake, and diuretics use, the uric acid levels were still higher in the sensitized subjects (5.7 vs. 5.4 mg/dL, p value = 0.0116). A significant difference in the rate of hyperuricemia between the two groups was found (31.1 vs. 19.1 %, p value = 0.0002).

Table 2 shows the linear regression coefficients (95 % CI) of uric acid associated with sensitization to milk allergen. Compared with subjects who were not sensitized to milk allergen (reference), subjects sensitized to milk allergen showed a significant increase in uric acid ($\beta = 0.29$; 95 % CI = 0.09–0.48) after adjusting for age, gender, ethnicity, smoking, alcohol intake, BMI, history of diabetes, hypertension, or allergic diseases, total energy intake, and diuretics use. Subjects sensitized to milk allergen, compared to their counterparts, showed a significantly increased risk of hyperuricemia (OR = 2.08; 95 % CI = 1.18–3.68).

Table 1 General characteristics of the study subjects according to sensitization to milk allergen

	Subjects sensitized to milk allergen (<i>n</i> = 151)		Subjects not sensitized to milk allergen (<i>n</i> = 3742)		<i>p</i> -value*
Age, years					
20–29	32	(4.0)	763	(96.0)	0.0319
30–39	15	(2.3)	651	(97.8)	
40–49	24	(3.6)	652	(96.5)	
50–59	28	(5.2)	513	(94.8)	
60–69	19	(3.3)	553	(96.7)	
70–79	16	(4.1)	379	(96.0)	
≥80	17	(6.9)	231	(93.2)	
Gender					
Male	87	(4.7)	1782	(95.4)	0.0160
Female	64	(3.2)	1960	(96.8)	
Ethnicity					
White	94	(4.7)	1929	(95.4)	0.0010
Black	38	(4.6)	786	(95.4)	
Hispanic	16	(1.8)	884	(98.2)	
Others	3	(2.1)	143	(98.0)	
Cigarette smoking					
Current smoker	31	(3.6)	822	(96.4)	0.8307
Past smoker	38	(3.7)	981	(96.3)	
Never smoker	82	(4.1)	1939	(95.9)	
Alcohol consumption					
Yes	109	(4.1)	2575	(95.9)	0.3800
No	42	(3.5)	1167	(96.5)	
Body mass index, kg/m ²					
Underweight (<18.5)	4	(6.5)	58	(93.6)	0.1259
Normal (18.5–24.9)	31	(2.8)	1068	(97.2)	
Overweight (25.0–29.9)	55	(4.0)	1309	(96.0)	
Obesity (≥30)	61	(4.5)	1307	(95.5)	
History of diabetes					
Yes	30	(6.6)	428	(93.5)	0.0016
No	121	(3.5)	3314	(96.5)	
History of hypertension					
Yes	64	(4.9)	1247	(95.1)	0.0209
No	87	(3.4)	2495	(96.6)	
History of allergic disease					
Yes	66	(5.3)	1172	(94.7)	0.0014
No	85	(3.2)	2570	(96.8)	
Total energy intake, kcal					
Q1 (≤1452)	33	(3.4)	927	(96.6)	0.6604
Q2 (1453–1982)	38	(4.0)	925	(96.1)	
Q3 (1983–2644)	44	(4.5)	939	(95.5)	
Q4 (≥2645)	36	(3.7)	951	(96.4)	
Diuretics use					
Yes	18	(5.1)	336	(94.9)	0.2178
No	133	(3.8)	3406	(96.2)	

**p* value was based on the chi-square test

Discussion

We found that adults with sensitization to milk allergen were at higher risk for increased uric acid ($\beta = 0.29$; 95 %

CI = 0.09–0.48) and hyperuricemia (OR = 2.08; 95 % CI = 1.18–3.68) compared with adults not sensitized to milk allergen, after adjustment for age, gender, ethnicity, smoking, alcohol intake, BMI, history of diabetes, hypertension, or

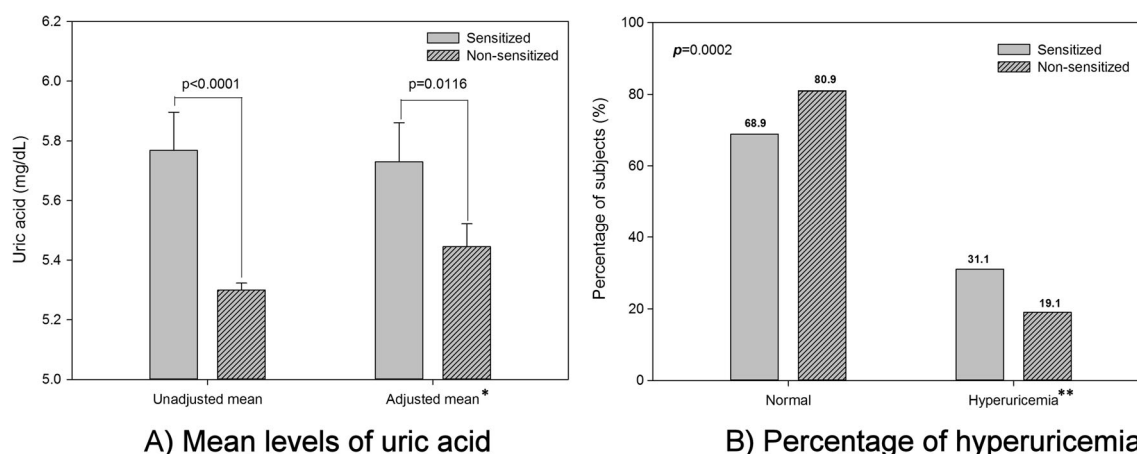


Fig. 1 Comparisons of uric acid levels between sensitized and non-sensitized subjects. **a** Mean levels of uric acid. **b** Percentages of hyperuricemia. Error bars represent standard error. Adjusted mean levels of uric acid were adjusted by age, gender, ethnicity, smoking,

alcohol intake, BMI, history of diabetes, hypertension, or allergic diseases, total energy intake, and diuretics use. Hyperuricemia was defined as averaging above 7.0 mg/dl.

allergic diseases, total energy intake, and diuretics use. Our results provide the first data showing the risk of hyperuricemia among milk allergen-sensitized persons, and our results support the existing evidence on the potential beneficial effect of dairy ingestion on lower serum urate levels and a decreased risk of gout.

No previous studies have evaluated the risk of hyperuricemia with respect to milk allergen sensitization, although many studies have suggested the possibility that the intake of dairy products has a role in protecting against gout or hyperuricemia [8, 9, 14, 18]. The Health Professionals Follow-up Study reported a strong inverse association between the consumption of dairy products (assessed by a food-frequency questionnaire) and the incidence of gout. The authors observed that compared with men in the lowest quintile of low-fat dairy consumption or dairy protein intake, the relative risk of gout in those with the highest quintile was lowered 44 and 48 %, respectively [8]. Similar to men, milk product consumption was associated with a lowered risk of gout among women [9].

A study showed that milk ingestion was associated with the prevention of gout flares [19]; in that study, the group treated with skim milk powder (SMP) enriched with glycomacro peptide and G600 milk fat extract over the 3-month study period showed a significantly greater reduction of the frequency of gout flares, pain, and fractional excretion of uric acid compared to the lactose powder control group or SMP control group.

Consistent with the link between gout and dairy products, the serum uric acid level was also found to be significantly associated with dairy consumption [14, 18]. Choi et al. [18] analyzed a representative US sample data from the NHANES III (1984–1999) and observed that adults with a daily intake of milk had a lower serum uric acid than those without a daily intake of milk, with a the multivariate difference per unit increase of -0.25 [95 % CI $-0.40, -0.09$] [18]. Adults with an every other day intake of yogurt also showed a lower serum uric acid level than those who did not consume yogurt (multivariate difference -0.26 [95 % CI $-0.41, -0.12$]). In a

Table 2 Results from linear and logistic regression for uric acid and hyperuricemia associated with sensitization to milk allergen

	Subjects sensitized to milk allergen		Subjects not sensitized to milk allergen
Uric acid	β	(95 % CI)	
Crude	0.52	(0.19–0.85)	Reference
Model 1	0.39	(0.15–0.62)	Reference
Model 2	0.29	(0.09–0.48)	Reference
Hyperuricemia	OR	(95 % CI)	
Crude	2.40	(1.45–3.97)	Reference
Model 1	2.33	(1.43–3.78)	Reference
Model 2	2.08	(1.18–3.68)	Reference

Model 1 was adjusted by age, gender, and ethnicity. Model 2 was further adjusted by smoking, alcohol intake, BMI, history of diabetes, hypertension, or allergic diseases, total energy intake, and diuretics use

population-based case-control study in Scotland, skim milk and low-calorie yogurt intake were inversely associated with plasma urate levels ($\beta = -4.4$ mmol/dL per serving, p value = 0.02 and $\beta = -11.7$ mmol/dL per serving, p value = 0.04, respectively) [14]. These findings indicated the protective effect of dairy food intake, especially low-fat dairy products, against the development of gout and in favor of the suppression of serum uric acid levels.

Notably, cow milk may be involved in lowering urate levels without the concomitant purine load, unlike any other protein sources (i.e., meat and seafood) [8]. Garrel et al. [20] investigated changes in serum and urinary uric acid levels before and after milk- and soy-protein ingestion [20]. Soy proteins increased serum uric acid, while serum uric acid was significantly reduced after ingestion of lactalbumin and casein originating from milk because these two purine-free proteins increased urinary uric acid excretion. Dalbeth et al. [13] conducted a short-term randomized controlled cross over trial assigning 16 participants to the four following products: soy control, early-season skim milk, late-season skim milk, and MPC 85 skim milk [13]. These authors found that participants who ingested all milks, in comparison with the soy control, showed a significant reduction in serum urate of approximately 10 % ($p < 0.0001$) over the 3-h follow-up period; however, the intensity of the urate-lowering effect did not differ among the three milks. Conversely, a 4-week randomized clinical trial indicated significant increases in serum uric acid in dairy-free diet subjects [21]. This line of evidence suggests that milk ingestion might affect several stages in gout pathogenesis by reducing serum uric acid levels, which ultimately leads to the dissolution of needle-like urate crystals from the joints, implying the potential for an increased risk of hyperuricemia associated with an absence or lack of milk intake, as our findings show.

The mechanism for the inverse association between milk ingestion and the risk of gout or hyperuricemia is not fully understood, but nutrients present in milk are likely responsible for the uricosuric effect [7]. The possible mediators include casein, lactalbumin, orotic acid, calcium, and lactose, which might promote renal urate excretion and thus might decrease blood uric acid [14, 20–22]. Moreover, a high consumption of milk or dairy products might be a good surrogate for an overall healthier diet and lifestyle [14], leading to their protective effect regarding the risk of gout.

To our knowledge, our finding provided the first evidence indicating that adults who are sensitized to milk allergen have an increased risk of hyperuricemia compared with those who are not sensitive to milk. Our findings were based on the large-scale, high-power, representative sample data of the NHANES and were likely to be generalizable to the US adult population. The presence of milk sensitization was assessed using the IgE-mediated allergy test as an objective tool. Admittedly, the present study used a cross-sectional design

that did not allow one to make a causal inference with the observed association; even so, it is unlikely that individuals with hyperuricemia over react to the IgE-allergic test. Although we included potential covariates to establish the independence of the association between them, because of the observational nature of this investigation, we cannot rule out the possibility of residual confounding effects due to unmeasured confounders. This study is also not free from bias because several variables were dependent on self-reported data.

In conclusion, we found that adults who had sensitivity to cow milk allergen were at a higher risk of hyperuricemia than those who were not sensitized. Our findings suggest that sensitization to cows' milk allergen might be a risk factor for increased serum uric acid, and strategies to intervene and prevent hyperuricemia or gout are needed for people who are restricted in their intake of milk or dairy products.

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Compliance with ethical standards

Disclosures None.

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