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Randomized Controlled Trial

Urate-lowering effect of calcium supplementation: Analyses of a randomized controlled trial

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SUMMARY

Objective: To investigate if the gout-protective effect of low-fat dairy products could be attributed to the urate-lowering effect of calcium.

Methods: This is a placebo-controlled trial in which thirty-five adult (aged 18–42 years) female low-calcium consumers (<800 mg/d) were randomized to one of three treatment groups: low calcium breakfast (control, ~70 mg of calcium/d) –C or high-calcium breakfast (~770 mg/d) from calcium citrate – CIT or from skim milk – SM, during 45 consecutive days. Breakfasts were matched for potential confounders and were provided as part of an energy-restricted normoprotein diet containing an additional 800 mg of calcium/d. Dual-energy X-ray absorptiometry measurements (body fat assessment) and fasting blood samples (urate, ionic calcium, PTH, and 1,25-(OH)2-D3) were taken at baseline and the end of the experiment. Clinical trial registration: http://www.ensaiosclinicos.gov.br/ (RBR-7Q2N33).

Results: Despite no significant changes in total body weight/fat, CIT and SM led to a significant reduction in serum urate and ionic calcium, but did not affect PTH and vitamin D concentrations compared to C. CIT and SM reduced baseline serum urate by ~14% and ~17%, respectively. There was a trend to a positive correlation between changes in serum urate and changes in ionic calcium on day 45 ($r = 0.327$, $P = 0.055$).

Conclusions: Calcium supplementation (770 mg/d from dairy or calcium citrate) reduced serum urate concentrations, suggesting that the gout-protective effect of low-fat dairy consumption is at least partly due to a urate-lowering effect of calcium.

1. Introduction

Hyperuricemia is characterized by elevated concentrations of serum uric acid and is traditionally related to gout. Over the past decade, interest in new approaches to promote uricemia control increased dramatically since hyperuricemia is also associated with obesity-related comorbidities including hypertension, kidney disease, metabolic syndrome, type 2 diabetes, and heart disease [1,2].

The excess of uric acid could be resulted from: 1) urate overproduction due to the consumption of purine rich diets, purine metabolism errors, or cell breakdown and turnover; 2) decreased uric acid excretion, mainly due to renal dysfunction; or a combination of both [3]. The most common complication of hyperuricemia is gout but evidence also suggests that hyperuricemia is linked to acute and chronic kidney disease, diabetes, metabolic syndrome, cardiovascular disease, hypertension, and dyslipidemia [3,4].

Longitudinal observational studies and meta-analysis of population based cohorts have shown a clear inverse relationship between low-fat dairy intake and hyperuricemia/gout risk [6–8]. An acute study demonstrated that while different skim milk types reduced uricemia, non-calcium soy drink consumption increased serum urate concentrations in the same magnitude [9], suggesting the urate-lowering effect of calcium.

Dairy products are the main dietary calcium source. Nevertheless, as far as we know, there is a lack of clinical studies assessing the long-term protective effect of dairy consumption on uricemia,

Abbreviations: LC, low calcium breakfast; CIT, calcium citrate; SM, skim milk.

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as well as the role of calcium in this approach. Chronic consumption of calcium citrate pills (600 mg/d or 1200 mg/d) did not reduce uricemia in men with high-calcium dietary intake at baseline [10]. Since then, the gout-protective effect of low-fat dairy products has been mainly attributed to their low purine protein content, but the possible urate-lowering effect of dietary calcium has been neglected. However, intravenous calcium chloride administration increased uric acid excretion in idiopathic urolithiasis patients [11], which may in the long term exert a gout protective effect. Furthermore, low habitual calcium consumption and the presence of dairy protein may improve intestinal calcium uptake and could be required to detect the urate-lowering effect of calcium [12]. Therefore, low habitual calcium consumption of enrolled subjects and the inclusion of dairy proteins seems to be critical methodological aspects in conducting clinical trials about the role of calcium on uricemia.

Calcium could also has an indirect role in decreasing uricemia by downregulation of parathyroid hormone (PTH), with or without Vitamin D influence. PTH could decreases urate excretion, via downregulation of renal and intestinal plasma ABCG2 expression, leading to increased uric acid concentrations and hyperuricemia [13–16]. On the other hand, vitamin D (1,25-dihydroxyvitamin D) could inhibit PTH secretion by stimulating intestinal calcium absorption, leading to a transient increase in serum ionized calcium [17]. Therefore, it would be interesting to investigate if the documented gout-protective effects of low-fat dairy consumption is partly due to a urate-lowering effect of calcium, monitoring confounding factors that may affect urate concentrations, such as the presence of chronic diseases, and the serum concentrations of vitamin D, ionic calcium, and PTH. Thus, we explored the effect of calcium supplementation from low-fat dairy (~770 mg/d) or calcium citrate (~770 mg/d), in the presence of dairy protein, in comparison to a control (~70 mg of calcium/d) in low-calcium consumers.

2. Materials and methods

2.1. Study design and eligibility

The study occurred at the Laboratory of Energy Metabolism and Body Composition (LAMECC) of the Department of Nutrition and Health at Universidade Federal de Viçosa-MG, Brazil. Participants were recruited between January and December 2012. Recruitment was completed when the number of individuals previously calculated to compose the sample was reached with an addition of 20% for losses. One hundred fifty-seven women were recruited through local advertising to participate in this single-blind placebo-controlled Latin square design study.

The inclusion of the participants in the study was made considering the following criteria: having more than 31% of body fat [18]; usual low calcium intake (<800 mg/day) [19,20]; weight loss of less than 3 kg in the last 12 weeks, level of physical activity between irregularly active and active [21]; and responses to food inhibition/disinhibition and hunger $\leq$12 [22]; aged between 19 and 40 years. The exclusion criteria adopted in the study were: pregnancy; lactation; lactose intolerance; primary hyperparathyroidism or other chronic diseases; familial dyslipidemia; endocrine disorders, including diabetes mellitus type 2 (defined as fasting blood glucose $\geq$7.0 mmol/L or 126 mg/dL); renal dysfunction; hepatic disease or malabsorption syndrome; caffeine intake more than 350 mg/day; excessive alcohol intake (ingestion of more than 50 g/day of ethanol); excessive caffeine intake (>1250 mg/day); smoking; drug treatment to control lipemia or obesity; use of vitamin/mineral supplements; use of medications that alter body composition and food intake or that interfere with energy, calcium and/or vitamin D metabolism.

2.2. Randomization and study groups

After screening, 35 healthy female low-calcium consumers (<800 mg/d), aged 18–42 y, and total body fat >38% were randomly assigned to participated of one of the study groups during 45 ± 2 consecutive days. Study groups were classified according to the study breakfasts as followed: a) low calcium or placebo breakfast (control group – C, with ~70 mg of calcium/d; $n = 11$); b) high calcium breakfast from calcium citrate (CIT, ~770 mg of calcium/d; $n = 11$); c) high calcium breakfast from skim milk (SM, ~770 mg of calcium/d; $n = 13$).

Breakfasts were composed by strawberry flavored shakes (300 mL, which varied in calcium content according to the study group) and bakery products (non-calcium bread or cookies). Whey protein (18.0 g), sucrose (23.5 g), sodium chloride (0.7 g), and Vitamin D (3.53 μg) was added to C and CIT shakes in order to reach identical SM shake nutrients content except for calcium in C. Elemental calcium citrate was added to CIT shake to reach calcium content of SM shake. The offered shakes were masked and served with identical sensory aspects. There was blinding of those responsible for data analysis, which was guaranteed employing codes for designating participants and groups.

During the intervention, breakfasts were daily provided in the laboratory as part of an energy-restricted normoprotein diet (−2,092 kJ/d; total of 800 mg of calcium/d for C and 1500 mg of calcium/d for CIT and SM). Breakfasts and prescribed diets were matched on carbohydrate, protein, fat, fiber, sodium, and vitamin D contents. Prescribed diets contained similar amounts of foods containing moderate amounts of purine (meat, poultry, fish, and beans) to match purine consumption among groups. High-purine foods were not prescribed, and the intake of high-fructose beverages was discouraged during the study.

At baseline and at the end of the experiment, subjects reported to the laboratory after a 12-h overnight fast for blood sampling, body weight, and body composition assessment. The intervention had a continuous framework with participants from all groups being included consecutively according to the recruitment order.

The pre-established primary outcomes are changes in blood uric acid concentrations as assessed by enzymatic colorimetric testing, while the secondary are total body fat loss assessed by dual energy X-ray absorptiometry (DEXA) measurements. Body composition was assessed by DEXA (GE Lunar Prodigy, General Electric Medical Systems, Milwaukee, WI, USA) according to manufacture instructions in order to verify changes in body fat due to energy restriction. Fasting serum urate (enzymatic-colorimetric method, Cobas Mira Plus, Roche Diagnostic Systems), ionic calcium (calcium arsenazo assay, Cobas Mira Plus, Roche Diagnostic Systems), PTH (electrochemiluminescence, Elecsys-Modular E-170, Roche Diagnostics Systems), and vitamin D (1,25-(OH)2-D3) (chemiluminescent microparticle immunoassay – CMIA, Architect i2000, Abbott Diagnostics) concentrations were evaluated.

Compliance was based the participants' attendance at the laboratory to consume breakfasts and by dietary records filled out in the first, third, and last intervention week (3 non-consecutive days 24-h dietary records in each assessment period). Subjects were instructed to maintain their physical activity and to avoid alcohol during the study.

2.3. Statistical analysis and power analysis

Sample size calculations indicated that 11 subjects would be required per group, considering a 95% confidence interval, and a 20% reduction in the baseline uricemia mean and standard deviation values [23]. Data were expressed as mean (SEM) or median (percentile 25–75). Delta values were compared using one-way

ANOVA or Kruskal–Wallis followed by Tukey's or Dunn's test, respectively, and Pearson's correlation was used to evaluate the association between variables (SAS v 9.2, SAS Institute, Cary, NC, USA). An α level of 5% was maintained throughout. Study power was calculated considering serum urate concentrations as the main variable.

2.4. Ethics

The study protocol was approved by the Ethics Committee of the Universidade Federal de Viçosa, Brazil, conducted in accordance with the Helsinki declaration and registered in the database at http://www.ensaiosclinicos.gov.br/ (RBR-7Q2N33). Written informed consent was obtained from all subjects.

3. Results

A total of 35 subjects were consented to and enrolled in the study. Among participants who completed the study, there were $n = 11$ participants in C; $n = 11$ in CIT; and $n = 13$ in SM (Fig. 1). According to the assessments, these participants were in compliance with the research protocol. Two participants in the SM group reported undesirable effects, such as increased intestinal flow and gases, but the symptoms were tolerable and they remained in the experiment. The exclusion of these two participants did not affect the results. For that reason, we kept them in the analyses.

There were no differences between groups with respect to clinical characteristics at baseline (Table 1). Dietary treatments did not affect body weight (C: −1.29 (0.28) kg; CIT: −1.15 (−1.35/−0.80) kg; SM: −2.20 (0.34) kg) and total body fat (C: −1.97 (−2.33/0.19) kg; CIT: −1.13 (0.42) kg; SM: −1.64 (0.35) kg) reductions due to energy restriction.

CIT and SM significantly reduced serum urate (C: 0.04 (0.15) mg/dL; CIT: −0.57 (0.18) mg/dL; SM: −0.68 (0.15) mg/dL) and ionic calcium (C: 0.03 (0.08) mg/dL; CIT: −0.35 (0.09) mg/dL; −0.30 (0.11) mg/dL), but did not affect PTH (C: 0.97 (4.11) ng/mL; CIT: 0.80 (2.97) ng/mL; SM: 1.12 (2.76) ng/mL) and vitamin D (C: 2.10 (2.83) ng/mL; CIT: 2.63 (2.31) ng/mL; SM: 2.15 (2.60) ng/mL) concentrations (Fig. 2). CIT and SM reduced baseline serum urate by ~14% and ~17%, respectively. There was a trend for positive correlation between changes in serum urate and changes in ionic calcium on day 45 ($r = 0.327$, $P = 0.055$) (Fig. 2).

4. Discussion

As far as we know, this randomized controlled trial demonstrates for the first time that consumption of calcium from low-fat dairy (~770 mg of calcium/d) or calcium citrate supplementation (~770 mg of calcium/d) reduced serum urate concentration in healthy female low-calcium consumers. The results were evidenced in the presence of dairy proteins. Serum urate reduction was followed by a reduction in ionic calcium, but not in vitamin D or PTH, indicating a direct effect of calcium on uricemia.

Although the urate-lowering effect of dairy products has been well reported in observational studies [10,24,25], the mechanism involved remains poorly explored in randomized clinical trials. As previously mentioned, consumption of purine-rich foods and consequent increase in endogenous urate production are well known potential factors for hyperuricemia [26]. Therefore, low purine content of milk has been related to its urate-lowering effect [27]. In our study, we evidenced urate-lowering effect of calcium even after matching study groups for purine content. Besides urate overproduction, hyperuricemia is most related to decreased uric acid excretion [26]. It has been proposed that the urate-lowering effect of calcium supplementation is due to PTH suppression, since PTH reduces renal urate excretion [1]. Our results showed reduction in uricemia after calcium supplementation despite changes in serum PTH. The difference between the result obtained in that study and the one we obtained may be associated with the fact that our subjects had normal PTH values at the baseline. Hyperparathyroidism seems to be required to detect the indirect effect of calcium supplementation over PTH suppression [28].

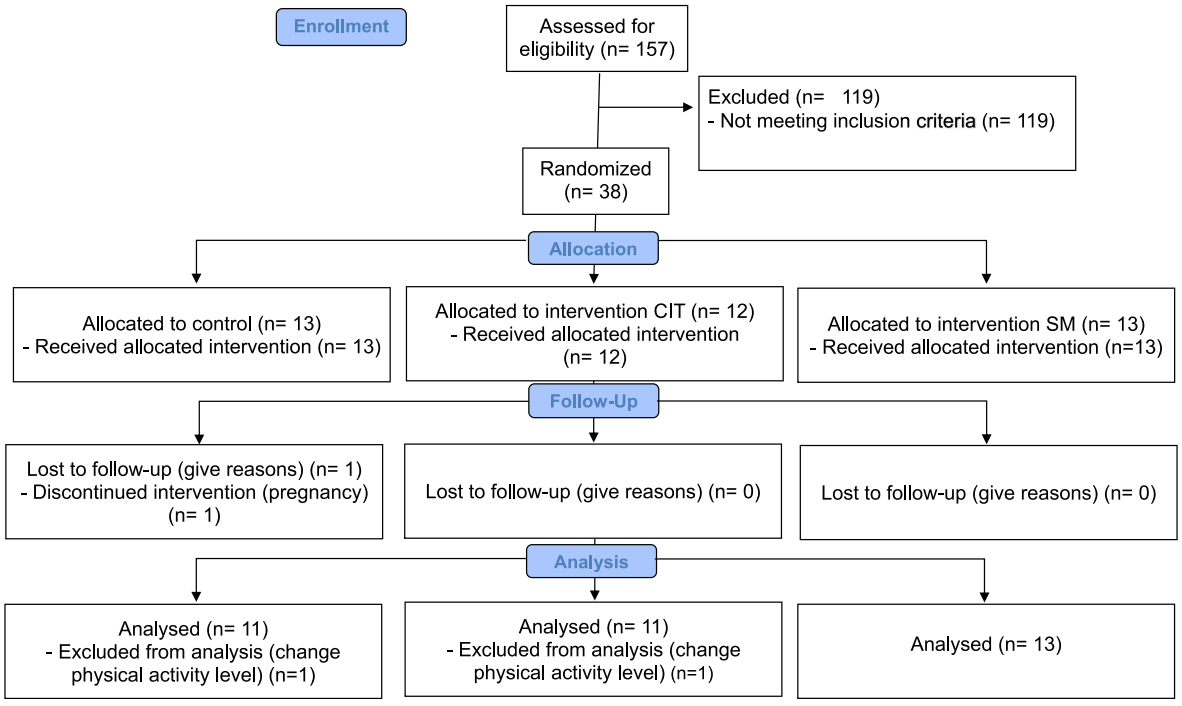

Fig. 1. The CONSORT diagram.

Table 1
Baseline characteristics of the study subjects according to experimental groups [mean (SEM); median (25/75%)].

	C (~70 mg of calcium/d)	CIT (~770 mg of calcium/d)	SM (~770 mg of calcium/d)	*P*-value
n	11	11	13	–
Age (y)	25.5 (2.5)	26.4 (1.6)	31.2 (1.6)	0.08
Weight (kg)	74.7 (69.6/77.5)	73.2 (69.4/82.1)	73.3 (71.6/75.3)	0.90
BMI (kg/m^2)	27.5 (0.3)	28.9 (0.4)	28.6 (0.4)	0.17
Total body fat (kg)	32.4 (0.7)	32.3 (0.8)	30.8 (0.6)	0.67
Lean mass (kg)	38.9 (0.6)	41.2 (0.7)	39.2 (0.4)	0.32
Energy intake (kcal/d)	2385.0 (2266.0/3114.0)	2332.0 (1906.0/3084.0)	2243.0 (2143.0/2704.0)	0.16
Calcium intake (mg/d)	615.6 (58.5)	616.1 (58.2)	616.3 (73.6)	1.00
Glycemia (mmol/L)	4.9 (0.2)	4.7 (0.2)	4.7 (0.2)	0.22
HOMA-IR	1.9 (1.5/3.2)	2.3 (1.9/2.4)	2.0 (1.6/2.8)	0.64
Triglycerides (mg/dL)	104.0 (79.3/147.5)	102.0 (69.5/129.5)	113.0 (75.0/141.0)	0.89
Total cholesterol (mg/dL)	192.0 (1.8)	174.4 (1.5)	180.9 (1.6)	0.44
HDL-c (mg/dL)	51.0 (42.0/54.8)	57.0 (39.5/66.5)	50.0 (45.0/57.0)	0.70
LDL-c (mg/dL)	119.2 (1.8)	101.9 (1.4)	107.8 (1.7)	0.44
Serum urate (mg/dL)	3.9 (0.2)	4.0 (0.3)	4.0 (0.2)	0.84
Ionic calcium (mg/dL)	5.1 (0.2)	5.3 (0.2)	5.2 (0.2)	0.18
1,25-$(OH)_2$-D_3 (ng/mL)	24.18 (0.,88)	26.5 (0.9)	30.3 (0.7)	0.16
PTH (ng/mL)	29.90 (1.08)	26.8 (0.8)	29.5 (0.9)	0.72

CIT: calcium citrate group. SM: skim milk group. HOMA-IR: homeostatic model assessment of insulin resistance. There were no significantly differences between experimental groups (one-way ANOVA or Kruskal–Wallis, $P > 0.05$).

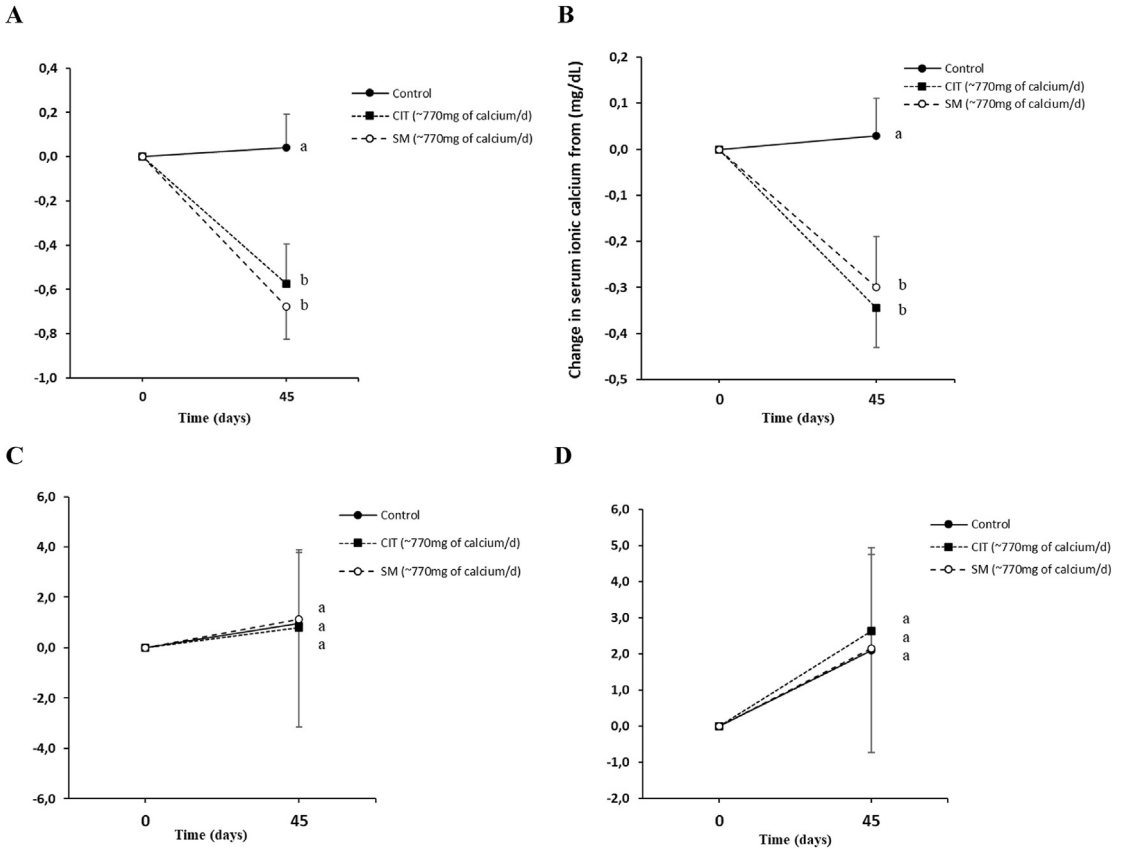

Fig. 2. Mean (S.E.) changes in serum urate (A), ionic calcium (B), PTH (C), and vitamin D (D) concentrations in response to the consumption of low calcium breakfast (control, ~70 mg of calcium/d) or high-calcium breakfast (~770 mg/d) from calcium citrate – CIT or from skim milk – SM, during 45 consecutive days. For the sake of clarity, error bars are only given for the maximum and minimum values at each time point. Lines followed by different letters differ from each other by One-way ANOVA, followed by Tukey's test, $P < 0.05$.

Our results suggest a possible direct effect of calcium on urate regulation. Interestingly, the consumption of dairy, particularly low-fat dairy products, were inversely related to uric acid concentrations [5,29] and to a substantial reduction in gout risk [5]. Although higher serum calcium concentration was positively associated with hyperuricemia in a dose response way [27], dietary calcium has also been suggested as a possible mediator of the urate-lowering effect of dairy products. The inverse association of dietary calcium and serum uric acid concentrations were observed for minimum consumption of 1000 mg/d of calcium for men and 650 mg/d for women [25]. This apparently contradictory relationship was also evidenced in our study, since calcium supplementation reduced uricemia and serum ionic calcium, and there are a trend to a positive relationship. There was a trend to a

positive correlation between changes in serum urate and changes in ionic calcium during experiment. Whether calcium intake has a direct effect on uric acid excretion is unknown. Nevertheless, supplemental calcium from dairy and some calcium salts may reduce urinary pH [30] and low pH can increase urinary urate excretion [31]. Besides, it is also speculated that increased calcium excretion and thus reabsorption of phosphate and upregulation of renal sodium–phosphate cotransporters could be related to the inverse association between calcium intake and serum uric acid [25].

Our study has several strengths. We enrolled only low-calcium consumers in general presenting good health and we monitored changes in serum ionic calcium, PTH and vitamin D concentrations during the experiment. In addition, we used a placebo and we matched study breakfasts for several dietary confounders including protein content. Supplement consumptions were attested in the laboratory, and we controlled diet adherence, purine consumption, and changes in physical activity. Potential limitations of our results are the fact that dairy products naturally contain many uricosuric factors, like specific protein fractions, orotic acid, and lactose [12]. C and CIT breakfasts were not matched to SM breakfast in terms of all these components, which could be confounding factors. However, CIT breakfast had the same protein content as the C breakfast, except for CIT calcium citrate content, and CIT showed comparable results to SM. Therefore, this result reinforces the role of calcium in the process and suggests that, if SM had a higher content of other uricosuric factors, they didn't have a relevant impact on uricemia. While CIT breakfast contained only whey protein, SM contained whey protein and casein as protein sources, which could be considered as a limitation of our study. However, according to some authors, whey protein and casein have the same urate-lowering impact [32]. Therefore, the differences in protein types between the experimental groups are not a limitation of the study. Another confounding factor not evaluated was the production of endogenous purines. Also, although we excluded individuals with chronic disease, we did not assess renal function, which could affect urate excretion. Future studies are now needed to elucidate the mechanisms enrolled in urate regulation mediated by increased calcium intake.

5. Conclusion

In conclusion, these 45 consecutive days randomized crossover trial showed that calcium supplementation (770 mg/d) from low-fat dairy products or calcium citrate reduced serum urate concentrations. Our results suggested that the gout-protective effect of low-fat dairy consumption is at least partly due to a urate-lowering effect of calcium.

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Declaration of competing interest

The authors declare no conflicts of interest.

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Statement of authorship: FGC, DMO, and RCGA designed the research study, drafted the manuscript, wrote sections of the manuscript, conducted the research study, analyzed the data and performed statistical analyzes. RDMA conceived, designed, and performed statistical analyzes. JMB and DMUPR wrote sections of the manuscript. All authors had full access to data and revised and approved the manuscript for publication.

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