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ORIGINAL ARTICLE

Potential renal acid load and the risk of renal stone formation in a case–control study

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OBJECTIVE: The potential renal acid load (PRAL) in diet may have a key role in renal stone formation through its effect on calcium and citrate metabolism. We examined the association between calcium renal stone formation and the PRAL in a population-based case–control study.

METHODS: A group of 123 calcium renal stone formers was compared with an equal number of age- and sex-matched controls. Dietary history was obtained by 24-h recall. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated across quartiles of dietary intakes of PRAL.

RESULTS: Compared with those in the lowest quartiles of PRAL, we found an increased risk of renal stone formation for those in the highest quartile (Q4 OR = 2.51, 95% CI 1.218–5.172). Regarding individual food patterns, we found a significant protection for a high consumption of vegetables (two or more servings/day; OR = 0.526, 95% CI 0.288–0.962).

CONCLUSIONS: A PRAL in diet and a reduced consumption of vegetables are associated with an increased risk of calcium renal stone formation. In renal stone formers consumption of plant foods should be encouraged in order to counterbalance the acid load derived from animal-derived foods.

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INTRODUCTION

The diet of the inhabitants of Western industrialized countries is characterized by a high dietary acid load that may be the cause of several chronic diseases affecting these populations, including arterial hypertension, osteoporosis and recurrent nephrolithiasis.

Not surprisingly, the major dietary risk factors for kidney stones overlap with the determinants of the acid load in diet which are dietary intakes of protein, calcium and potassium.

In fact, Curhan *et al.*[1] demonstrated not only an inverse correlation between the risk of incident kidney stones and dietary intake of calcium but also the finding that the risk of incident kidney stones is directly related to dietary protein intake and inversely related to dietary potassium intake.

These observations followed the results of previous studies that showed an increase of dietary protein intake in renal stone formers (RSFs) compared with controls, but they were unable to demonstrate differences in the intake of dietary calcium and potassium between the two groups.[2]

The assessment of potential renal acid load (PRAL) in the diet[3] can be included in the more general paradigm of studying whole dietary patterns, which is becoming increasingly popular in nutritional epidemiology.[4]

The aim of the study was to assess the association between the PRAL in diet and calcium renal stone formation by an analysis conducted with 123 control-matched pairs.

MATERIALS AND METHODS

In a population-based case–control study carried out in the area of Milan, Italy, the diets of 123 calcium RSFs were compared with the diets of 123 community controls.

Cases included 123 consecutive patients with renal calcium oxalate stones who presented for dietary and metabolic evaluation 1 month after spontaneous passage or extracorporeal or endoscopic treatment.

Out of them, 28 were first-stone formers and 95 were recurrent stone formers. At metabolic evaluation 39 (32%) (28 M, 11 F) were hypercalciuric (M > 7.5 mmol/day, F > 6.2 mmol/day), 38 (31%) (20 M, 18 F) hypocitraturic (< 1.7 mmol/day), 13 (11%) (10 M, 3 F) hyperoxaluric (> 0.45 mmol/day) and 14 (11%) (10 M, 4 F) hyperuricosuric (M > 5 mmol/day, F > 4 mmol/day). No metabolic defect was demonstrated in 48 patients (39%) (15 M, 33 F), whereas more than one metabolic defect was observed in 22 (18%).

Infrared spectrometry of stones confirmed calcium oxalate stone composition. Patients with mixed stones of calcium oxalate and uric acid were excluded from the study, whereas patients with mixed calcium oxalate and calcium phosphate stones were included if the calcium phosphate content was less than 10%.

Cases were frequency matched by gender and 10-year age group to controls randomly selected from the file of a general practitioner who practiced in the same area.

Patients and controls gave consent for scientific research on their data.

Detailed data including anthropometric measurements and dietary histories by 24-h recall were collected during in-person interview. Participants were also asked to report their average frequency of consumption of specific groups of foods. Food groups included grains (pasta, rice and cereals), meats (meats, poultry and fish), cured meats, eggs, cheeses, legumes, potatoes, vegetables, fruit and fruit juices, milk and dairies, bread. Portion size was included as a part of the question or of the response.

The PRAL in the diet was estimated according to the equation of Remer and Manz[3] without taking into account sodium and chloride intakes, whose evaluation is more difficult and less reliable, in particular with respect to the evaluation of salt added to food. The net acid excretion (NAE) was assessed by the sum of PRAL plus an anthropometric-based measure of organic acid (OA) production (Table 1).

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Table 1. Equations used to evaluate potential renal acid load (PRAL), organic acid production (OA) and body surface area (BSA)

PRAL (mEq/day)	$0.49 \times$ dietary protein (g) $+ 0.037 \times$ dietary phosphate (mg) $- 0.021 \times$ dietary potassium (mg) $- 0.02 \times$ dietary magnesium $- 0.013 \times$ dietary calcium (mg)
OA (mEq/day)	Body surface area (m^2) $\times$ 41 (mEq/day per 1.73 m^2)/1.73 (m^2)
BSA (m^2)	$0.007184 \times \text{weight}^{0.425} \times \text{height}^{0.725}$

Cases were compared with controls in terms of estimated acid load in the diet and of frequency of individual food items consumed. For purposes of this analysis, the daily PRAL intake was categorized in quartiles, and the intake of individual food items was dichotomized in two categories. We identified four major food items named animal products (meat + cured meat + egg + cheese), vegetables, fruits and grains. The upper category of food intake was defined by the cut-off of the upper quartile and was set as two or more servings/day for vegetable, fruit and grains consumption and as more than two servings/day for animal product consumption.

We determined descriptive statistics (means and s.d.) for all variables and calculated the significant differences between the control and patient groups using independent *t*-tests. All reported *P*-values were two-tailed. A *P*-value less than 0.05 was considered as statistically significant.

We evaluated the association between quartiles of PRAL intake and categories of individual food item intake and the risk of renal stone formation. Odds ratios (ORs) and 95% confidence intervals (CI) were used as estimates of the relative risk of stone formation.

All analyses were performed by using the SPSS statistical software package (version 11.5).

RESULTS

The age, gender distribution, anthropometric data and estimates of PRAL, OA and NEA for controls and RSFs are given in Table 2.

The estimated values of daily PRAL and NEA were higher ($P = 0.033$ and 0.048, respectively) in the RSFs group compared with controls. Dietary sodium intake in renal stone formers was not significantly different than in controls (2245 ± 3466 vs 2484 ± 3522: $P = 0.593$).

The mean daily PRAL and NAE values were significantly lower in women than in men ($P = 0.003$ and $P = 0.000$, respectively) and the mean daily PRAL and NAE values were significantly lower in class age >65 years (31–40 group vs >65 group, $P = 0.015$ and $P = 0.015$, respectively) (Tables 3 and 4).

Compared with the lowest quartile, those with the highest quartile of PRAL had an increased risk of renal stone formation (Q4 OR = 2.51, 95% CI 1.218–5.172; Table 5).

The high-vegetable pattern was negatively associated with renal stone formation (36/123 controls vs 22/123 RSFs, 29% vs 19%, $P = 0.035$; OR = 0.526, 95% CI 0.288–0.962; Table 6). No significant association with renal stone formation was found for high-animal product (23/123 vs 17/123; 19% vs 14% $P = 0.174$; OR = 0.661, 95% CI 0.363–1.209), high-fruit (36/123 vs 41/123; 29% vs 33%, $P = 0.492$; OR = 1.208, 95% CI 0.704–2.073) and high-grains patterns (32/123 vs 26/123; 26% vs 21%, $P = 0.349$; OR = 0.754, 95% CI 0.417–1.362).

DISCUSSION

The dietary intakes of protein, calcium and potassium are among the main determinants of endogenous acid production. The formula for the computation of net endogenous acid production proposed by Frassetto *et al.*[5] is based on the relationship between dietary intakes of calcium and potassium, whereas the most complex equation of Remer and Manz[3] for the calculation of the PRAL includes the intake of phosphate, magnesium, sodium and chloride, although usually it is used in a simplified version that does not take into account sodium and chloride intakes, whose measurement may be unreliable. In brief, a dietary intake high in protein and low in potassium, calcium and magnesium results

Table 2. Demographics and estimated acid production of 123 calcium renal stone formers (RSFs) and 123 matched controls

	Controls	*RSFs*	*Sig*
Age (years)	40.8 ± 13.2	41.4 ± 12.6	0.697
M/F	60/63	60/63	
Weight (kg)	66 ± 12	66 ± 14	0.601
Height (cm)	167 ± 9	168 ± 9	0.740
Body surface area (m^2)	1.74 ± 0.18	1.73 ± 0.20	0.726
Potential renal acid load (mEq/day)	14.8 ± 18.9	20.4 ± 21.9	0.033
Organic acid (mEq/day)	41.4 ± 4.4	41.2 ± 4.8	0.726
Net acid excretion (mEq/day)	56.2 ± 19.8	61.6 ± 22.6	0.048

Table 3. Potential renal acid load (PRAL), organic acid (OA) and net acid excretion (NAE) by gender

	PRAL	*OA*	*NAE*
M ($n = 120$)	21.6 ± 21.4	44 ± 3	66 ± 21
F ($n = 126$)	13.8 ± 19.2	38 ± 3	51 ± 19
Sig	$P = 0.003$	$P = 0.000$	$P = 0.000$

Table 4. Potential renal acid load (PRAL), organic acid (OA) and net acid excretion (NAE) by class ages

Class age (years)	*PRAL*	*OA*	*NAE*
<30 ($n = 60$)	19.2 ± 17.5	40 ± 5	59 ± 18
31–40 ($n = 78$)	21.3 ± 22.0	41 ± 5	62 ± 24
41–50 ($n = 47$)	16.7 ± 20.4	41 ± 5	58 ± 21
51–60 ($n = 39$)	15.7 ± 20.4	42 ± 4	58 ± 20
>65 ($n = 22$)	5.4 ± 21.1[a]	40 ± 5	46 ± 20[a]
Total	17.6 ± 20.6	41 ± 5	59 ± 21
Sig	$P = 0.027$	$P = 0.312$	$P = 0.036$

[a]PRAL and NEA 31–40 group vs >65 group $P = 0.015$.

Table 5. Risk of symptomatic renal stones according to potential renal acid load (PRAL) in the diets of controls and renal stone formers (RSFs)

	Q1	*Q2*	*Q3*	*Q4*
PRAL	<3.13	3.13–16	16–31	>31
Controls	39	28	31	25
RSFs	23	33	30	37
Total	62	61	61	62
χ^2		0.058	0.176	0.012
OR		1.998	1.641	2.510
95% Confidence interval		0.972–4.108	0.799–3.369	1.218–5.172

Table 6. Relative risk (RR) of stone formation by intake of vegetables (= or >2 servings/day) in controls and renal stone formers (RSFs)

Vegetables	*Low 0–1*	*= or >2*
Controls	87	36
RSFs	101	22
Total	188	58
χ^2		0.035
OR		0.526
95% Confidence interval		0.288–0.962

in an increase of the renal acid load in the diet. In particular, variations in dietary potassium can modify bicarbonate reabsorption by the proximal tubule and alter acidification by the distal nephron by modifying both proton transport and renal ammonia production.[6] Additionally, potassium is contained in plant foods (vegetables and fruits) as salts of organic anions (malate, citrate, galacturonate, tartrate) which exert alkalinizing effects through bicarbonate generation.[7]

The data of this study demonstrate that the PRAL of RSFs is higher than that of healthy controls and that high PRAL values are associated with an increased risk of renal stone formation.

In addition, the estimation of NEA values is higher in RSFs than that in the controls as a consequence of the high values of PRAL in the first group, whereas the estimates of the production of OAs on the basis of the anthropometric data are not different in the two groups. In fact, in this series, the body mass index was not higher in RSFs compared with controls, unlike what was previously described by other authors.[8] Elevated body mass indexes may be a further cause of high NAE in obese RSFs.

The effect of the oral acid load on calcium metabolism is well known from the studies of Lemann *et al*.[9] and others,[9,10] and the urinary excretion of citrates is inversely correlated with the acid load in the diet of RSFs.[11] In fact RSFs may be genetically more susceptible to the metabolic effects of an increased acid load of the diet. Incomplete distal renal tubular acidosis (dRTA) may be associated with hypocitraturia of renal stone formers.[12] Gene polymorphisms of vitamin D receptor VDR have been demonstrated with higher frequency in hypocitraturic stone formers when compared with both normocitraturic stone formers and normal controls[13] and a single nucleotide polymorphism in the gene encoding renal sodium citrate cotransporter h-NaDC-1 has been associated with reduced urinary citrate excretion in recurrent stone formers.[14] The acid load in the diet therefore constitutes an effective index of dietary lithogenic risk that unifies the effect of the intakes of protein, potassium, calcium and magnesium. The present study demonstrates that the reduction in protein intake may be an insufficient prescription for the prevention of kidney stone formation. In fact, our RSFs have not shown an increased consumption of meat, sausages, cheese and eggs with respect to controls as they are rather characterized by a low consumption of vegetables. The effect of these dietary patterns produces a cumulative dietary pattern that increases the risk of forming kidney stones. In contrast, the appropriate diet suggested by Borghi *et al.*[15] in their successful trial for the prevention of recurrent calcium stones allowed for a moderate intake of food of animal origin but was associated to a very high intake of vegetables. A nutritional analysis of the diet suggested in that study shows a negative PRAL despite a moderate protein restriction.

A similar dietary pattern is recommended for the prevention of high blood pressure by the DASH (Dietary Approaches to Stop Hypertension) diet, based on seven components: a high intake of fruits, vegetables, nuts and legumes, dairy products and whole grains and a low intake of sweetened beverages and red and processed meats. Higher DASH scores were associated with a marked decrease in kidney stone risk[16] and a DASH-style diet may reduce stone risk by increasing urinary citrate and volume.[17]

Finally, the supplementation of fruits and vegetables to the diet of hypocitraturic RSFs significantly increased citrate excretion without affecting oxalate excretion and decreased calcium oxalate and uric acid relative saturation. In contrast, the complete restriction of fruits and vegetables in normal subjects adversely modifies the urinary stone risk profile despite the reduction in urinary oxalate.[18] The consumption of vegetables should be preferred to that of fruits because of their high content of fructose. In fact, fructose intake is associated with an increased risk of incident kidney stones that is related to the increase in the urinary excretion of calcium, oxalate, uric acid and other factors associated with kidney stone risk.[19]

In conclusion, a high consumption of vegetables should be included in the advice for dietary prevention of calcium renal stones in order to counterbalance the acid load derived from animal-derived foods, although consumption of vegetables with high oxalate content (spinach, Swiss chard, beet greens, collards, okra, parsley, leeks and quinoa) should be discouraged. However, the results of our study, as all case–control study, can be biased by recall bias (RSFs may be more aware of their dietary intake by being aware of their possibly diet-related disease) and by reverse causality (RSFs may have their dietary pattern changed secondary to the stone diagnosis). For this reason, confirmation by a prospective study of incident stones or by an interventional dietary controlled trial[20] could be advisable to confirm this finding.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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