Published in final edited form as:
Urol Res. 2009 April ; 37(2): 63–68. doi:10.1007/s00240-009-0170-z.

Increased protein intake on controlled oxalate diets does not increase urinary oxalate excretion

John Knight[1], **Linda H. Easter**[2], **Rebecca Neiberg**[3], **Dean G. Assimos**[1], and **Ross P. Holmes**[1]

1 *Department of Urology, Wake Forest University School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA, e-mail: jknight@wfubmc.edu*

2 *GCRC Bionutrition Unit, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*

3 *Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, NC 27157, USA*

Abstract

High animal protein intake is a risk factor for calcium oxalate stone disease. The effect of dietary protein on the urinary excretion of calcium, acid and citrate is well established. However, its effect on oxalate excretion is unclear, due in part to an inadequate control of dietary oxalate intake in previous studies. This relationship warrants clarification due to the proposed important role of the metabolism of amino acids in endogenous oxalate synthesis. In this study, 11 normal subjects consumed controlled oxalate diets containing 0.6, 1.2 and 1.8 g protein/kg body weight/day. The analysis of 24 h urine collections confirmed that as protein intake increased, urinary calcium and glycolate increased and urinary pH and citrate decreased. The increased glycolate excretion was due in part to an increased hydroxyproline, but not glycolate consumption. Total daily urinary oxalate excretion did not change. When indexed to creatinine there was a small but significant decrease in oxalate excretion. This is most likely due to hyperfiltration. These results indicate that as dietary protein intake increases, the catabolism of diet-derived amino acids is not associated with an increased endogenous oxalate synthesis in normal subjects.

Keywords

Dietary protein; Oxalate excretion; Oxalate synthesis; Glycolate; Hydroxyproline

Introduction

Both dietary and genetic factors play an important role in the onset of calcium oxalate stone disease [1]. The ingestion of excessive amounts of protein, sodium, vitamin C, fructose or oxalate have all been reported to increase the risk of stone disease as well as inadequate intake of fluids, calcium or potassium [2–4]. An increase in dietary protein has consistently been reported to increase calcium and uric acid excretion, decrease citrate excretion and lower urine pH; all risk factors for stone formation [5,6]. Increased oxalate excretion is also a stone risk factor. However, the impact of dietary protein on urinary oxalate excretion has not been clearly delineated. Some studies reported that urinary oxalate excretion increased with increased protein intake and decreased with protein restriction [6–10], whereas others noted no change [11–14]. A limitation of these studies is a lack of dietary oxalate control. An effect of dietary

Correspondence to: John Knight.

protein on urinary oxalate excretion might be expected due to the increased utilization of amino acids as an energy source when protein intake increases. The metabolism of hydroxyproline, glycine, phenylalanine, tyrosine and tryptophan has been observed to result in oxalate synthesis [15]. The oxidation of hydroxyproline and glycine generates glyoxylate, the majority of which should be converted to glycine by alanine:glyoxylate aminotransferase (AGT) and glycolate by glyoxylate reductase (GR). Some glyoxylate produced however, is converted to oxalate by lactate dehydrogenase (LDH), and this has been observed in the metabolism of these amino acids, both in humans and in experimental animals [16–18]. Aromatic amino acids may also form unstable enol tautomers after deamination and this could generate oxalate [19].

Reliable estimates of the oxalate contents of a large range of foods are now available permitting a more accurate determination of the relationship of protein intake to oxalate excretion. In this report, we have re-examined the relationship between dietary protein and urinary oxalate excretion in normal subjects consuming diets in which oxalate and other nutrients are controlled.

Materials and methods

Subjects

A total of 11 healthy human subjects (6 males and 5 females) of mean age, 32.0 ± 9.4 years, and mean BMI, 23.5 ± 3.0, completed the study. Their health status was judged from a medical history. The subjects denied ever having kidney stones or any condition that may affect the intestinal or renal transport of ions or the metabolism of nutrients. Comprehensive metabolic profiles of serum samples obtained from all subjects before the study commenced were normal. Subjects provided informed consent before participating in this study, which was approved by the Institutional Review Board.

Dietary protocol

Subjects consumed controlled, eucaloric diets that contained 0.6, 1.2 or 1.8 g of protein/kg body wt/day. These protein levels are considered to be low, normal and high, respectively [20]. While the amounts of vegetable protein were the same for all three phases, animal protein consumption varied for each sequence. Milk products, eggs, beef, chicken, turkey and pork were the sources of animal protein. Individual energy needs were calculated to the nearest 100 kcal using the Harris–Benedict equation with an added activity factor based on self-reported daily activity. Each protein diet was consumed for 6 days in random order and consisted of a 3 day menu cycle. There was a 3–5 days washout period between protein phases. Twenty-four hour urines were collected on each of the last 3 days of each diet. The nutrients that were controlled are shown in Table 1 for diets containing 2,500 kcal. The contents of ascorbate, magnesium, and potassium ranged from 178, 163 and 1,664 to 76, 234 and 2,402 mg/day, respectively, on the low and high protein diets. Fluids were provided at 1 ml/kcal daily. Diets were prepared in the metabolic kitchen of the GCRC using ProNutra/ProNESSy menu planning, analysis, and production software (Viocare Technologies Inc., 2000–2007). The oxalate content of the foods used in the diets was measured by capillary electrophoresis, as previously described [21]. The subjects were asked to refrain from vigorous exercise and the use of supplements including calcium and vitamin C. The subjects consumed diets obtained from the GCRC at their location of choice.

Assays

Creatinine, calcium, magnesium, sodium, potassium, urea-N, uric acid, oxalate and citrate were measured on a Beckman C5E Analyzer. Sodium and potassium were measured by ion specific electrodes, oxalate using a kit provided by Trinity Biotech (St Louis, MO, USA), citrate using a kit provided by Boehringer Mannheim (Darmstadt, DE), and other analytes using kits

provided by the manufacturer. Sulfate was measured by ion chromatography (IC) and glycolate by IC/MS as previously described [18]. Foods were prepared for hydroxyproline and glycolate analysis by homogenization with either 2 or 3 volumes of water in a blender for 1 min. An aliquot (1.5 ml) was centrifuged at 15,000×*g* in a microfuge and the supernatant filtered through a 0.2 μm pore size polysulfone filter (Pall Corp., Ann Arbor, MI, USA) before analysis. Hydroxyproline was estimated in samples following acid digestion by AAA Laboratories (Mercer Island, WA).

Statistical analyses

Results for self-selected diets are presented as raw means ± SEM. The effects of dietary protein on urinary excretions were determined by a mixed model ANOVA using SAS version 9.1 (SAS Institute, Cary, NC). Correlation between multiple observations on a subject over time was accounted for using an autoregressive [AR (1)] correlation structure in PROC MIXED. LSMEANS ± SEM of protein levels (low, medium and high) from these models are shown in Table 2. Models were also adjusted for age, gender and order of administration of protein level. Probabilities of <0.05 were taken as being statistically significant.

Results

The urinary excretions on self-selected diets shown in Table 2 suggest that the subjects had a normal protein intake and consumed more oxalate, sodium and potassium when providing their own foods than they did on the controlled diets. Notably, urinary oxalate excretion decreased by 25–30% and sodium excretion by 34–46% on the low oxalate, moderate sodium diets. The mean 24 h urinary excretions observed on the last 3 days of controlled protein diets are also shown in Table 2. With increasing protein intake, significant increases in the urinary excretion of urea, uric acid, creatinine, sulfate, calcium, potassium, sodium, glycolate and the Tiselius Index [22] occurred. A lack of control of dietary potassium may have made a contribution to the urinary potassium increase. A significant negative correlation with protein intake and urine pH was present ($P < 0.01$), but the results on the medium and high protein diets were similar. A similar trend was seen with citrate excretion, but this did not reach statistical significance ($P = 0.088$). When indexed to creatinine excretion, there was a small (5.6%) but significant ($P = 0.023$) decrease in oxalate excretion as protein intake increased. This decrease relative to creatinine was apparently due to the increased creatinine excretion and a presumed increase in glomerular filtration rate known to occur with the consumption of high protein diets [23]. There was no significant gender effect on urinary oxalate excretion when indexed to urinary creatinine ($P = 0.76$). The mean urinary oxalate ± SEM (mg/g creatinine) for females was 16.1 ± 0.5 and for males 16.5 ± 0.5 on the low protein diet, 15.2 ± 0.3 for females and 14.4 ± 0.2 for males on medium protein consumption, and 14.9 ± 0.5 for females and 14.7 ± 0.3 for males on the high protein diet. However, firm conclusions cannot be made regarding gender influence because of the small group sizes.

The increase in urinary glycolate excretion with increasing protein intake could be due to increased glycolate or hydroxyproline consumption. To test this possibility, meals from a representative day on the low and high protein diets were homogenized and assayed for glycolate and hydroxyproline. The low protein diet contained 13.0 mg glycolate and 12.8 mg hydroxyproline/day/2,500 kcal and the high protein diet 8.6 mg glycolate and 238 mg hydroxyproline/day/2,500 kcal. These results suggest that hydroxyproline, but not glycolate ingestion, contributes to increases in glycolate excretion with increased protein intake.

Discussion

Dietary protein is used by the body as a source of amino acids for protein synthesis, as an energy source, and as an energy store following its conversion to glycogen and fat. The

distribution of dietary protein between these different metabolic pathways in healthy individuals depends on the amount of protein ingested, its composition, and other nutrients ingested. The main purpose of our study was to determine whether the metabolism of increasing amounts of protein results in increased endogenous oxalate synthesis, and to determine whether it contributes to stone risk. Dietary oxalate intake was restricted to 51 mg/2,500 kcal/day so that the contribution of dietary oxalate to urinary oxalate excretion would be limited. This level is much lower than the average daily intake, which is estimated to be 101–214 mg/day [3,21, 24]. This lower dietary oxalate content coupled with other dietary control measures, decreased urinary oxalate excretion by 25–30% compared to self-selected diets and provides an insight into the magnitude of the effect of dietary oxalate absorption on urinary oxalate excretion. The dietary control used in this study also limited the variability in urinary oxalate excretion of study subjects. The mean coefficient of variation in excretions of subjects on the low protein diet was 7.8 and 4.7% on the high protein diet.

The results of this study show that increasing dietary protein from 0.6 to 1.8 g/kg body wt/day results in a small but significant decrease (6%) in urinary oxalate excretion when indexed to urinary creatinine in normal subjects of either sex. Glomerular hyperfiltration known to occur with increasing protein consumption is a potential explanation of these findings. This could have also been impacted by the increased amount of creatine and phosphocreatine known to be present in a high animal protein diet, which could augment creatinine production. Other potential influences are the increased carbohydrate and ascorbate consumption on the low protein diet. The increased carbohydrate consumption could have resulted in an increased fructose intake, which may increase endogenous oxalate synthesis [25,26].

Previous studies examining the relationship between dietary protein and urinary oxalate excretion did not control dietary oxalate, a major limitation of these investigations [6–9,11–14]. Such dietary control is essential when urinary oxalate excretion is an endpoint in any investigation due to the important contribution that dietary oxalate makes to urinary oxalate excretion [27]. It is possible that higher intakes of protein than those used in this study might affect oxalate synthesis, such as would occur with an Atkins-type diet. However, Reddy et al. [28] did not observe this when protein intake was increased from 16.5 to 35.7% of calories. It is also possible that some stone formers may differ from normal subjects and synthesize more oxalate from protein catabolism, as suggested by Nguyen et al. [6]. They reported that in stone forming individuals with a mean oxalate excretion above 40 mg/day, in three collections on self-selected diets, oxalate excretion increased by 18% when protein intake was raised from 15 to 35% of energy intake. Nguyen et al. observed variable responses to dietary protein in their experimental groups. We also observed a variable response with oxalate excretion, decreasing by a mean of 14.1% in eight subjects when comparing excretions on the low and high protein diets, and increasing by a mean of 5.6% in the other three individuals.

The term “mild metabolic hyperoxaluria” was conceived over two decades ago to identify a sub-group of calcium oxalate stone formers who had mildly elevated excretions of both oxalate and glycolate [29]. Such a relationship could be considered logical as glyoxylate is an immediate precursor of both glycolate and oxalate synthesis [15]. Prior studies have shown that glycolate excretion increases substantially as dietary protein increases [6,7]. In this study, glycolate excretion on a high protein diet (mg/g creatinine) increased 70% compared to that observed on a low protein diet. As an increase in oxalate synthesis was not observed in our studies, this does not support a strong link between glycolate and oxalate synthesis. Potential sources of increased glycolate excretion are increased glycolate ingestion, amino acid catabolism, or the catabolism of another nutrient carried by the high protein diet. Increased glycolate ingestion is unlikely as the high and low protein diets we tested had similar glycolate contents, <13 mg/day. Harris and Richardson [30] estimated that glycolate intake averaged 33 mg/day. We previously reported that their values were over-estimated based on the use of mass

spectrometry to determine the glycolate content of foods [18]. Furthermore, how much of the ingested glycolate is absorbed is not known, but is likely to be incomplete.

Glycine and hydroxyproline are two amino acids that are potentially metabolized to glyoxylate, glycolate and oxalate [15]. Ongoing studies in our laboratory infusing normal subjects intravenously with $^{13}C_2$-glycine suggest that glycine metabolism contributes very little to the endogenous production of either glycolate or oxalate (unpublished results). Hydroxyproline metabolism, however, is a potential contributor. We have previously reported that in normal subjects the addition of 2.75 g of hydroxyproline/day in the form of gelatin to a controlled oxalate diet resulted in a 63.4 mg/g creatinine increase in glycolate excretion and a 7.2 mg/g creatinine increase in oxalate excretion [18]. We predict based on these relationships that the ingestion of 238 mg of hydroxyproline on the high protein diet in our current study would result in an increased excretion of 5.3 mg glycolate/g creatinine and 0.6 mg oxalate/g creatinine. However, our results showed a decrease in oxalate excretion suggesting that the impact of increased hydroxyproline ingestion was masked by other factors such as glomerular hyperfiltration and differences in the carbohydrate and ascorbate contents of the diets.

The amount of vegetable protein in diets was within a narrow range in this study whereas the amount of animal protein increased with protein content. Animal proteins compared to plant proteins are enriched in sulfur amino acids and the metabolism of these amino acids results in acid production as sulfate is formed [5]. The results in this study confirmed this as increasing animal protein intake resulted in increased sulfate and acid excretion. Also consistent with other studies, urinary calcium excretion increased and urinary citrate decreased as dietary protein intake increased [5]. There was also a significant increase in the Tiselius stone risk index for calcium oxalate due to these urinary changes. The significant increase in sodium excretion as protein intake increased may partly be due to hyperfiltration. These associations have been previously reported [23]. However, the strengths of the association with potassium excretion may not be as firm as that for sodium as dietary potassium was not tightly controlled. The lack of tight control of potassium intake may have also influenced the associations observed with urinary pH and citrate excretion.

There are several limitations in the interpretation of the results. Urinary oxalate excretion is used as a surrogate marker of endogenous oxalate synthesis. Oxalate is derived from the diet as well as from endogenous synthesis, but the low oxalate content of the diets should limit its contribution to oxalate excretion. A second limitation is the lack of dietary control of some nutrients including potassium, ascorbate and carbohydrates, which may have influenced urinary excretions. A further limitation is that a small number of subjects were studied. It is possible that if the cohort size were expanded and included stone formers, a positive relationship between protein consumption and oxalate excretion may be detected in a subset.

Acknowledgements

This research was supported by NIH grants RO1 DK73732 and MO1 RR07122. We gratefully acknowledge the skilled assistance of Martha Kennedy, Diane Dezern and the staff of the GCRC with these experiments.

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Table 1

Composition of controlled nutrients in study diets (per 2,500 kcal)

Protein level	Total protein (g)	Vegetable protein (g)	Oxalate (mg)	Ca (mg)	Na (mg)	Protein (% kcal)	Fat (% kcal)	Carb (% kcal)
Low	35.4	26.9	51.7	995	2,988	5.9	30.3	63.7
Medium	70.3	27.7	51.8	1,002	3,000	11.8	30.3	57.9
High	105.0	24.9	51.3	1,007	2,985	17.4	30.6	52.0

Table 2

The effect of the amount of protein in the diet on 24 h urinary excretions

	Self-selected diet	Protein level			*P* value*
		Low	Medium	High	
Oxalate (mg)	33.4 ± 2.0	23.3 ± 0.8	23.3 ± 0.8	24.8 ± 0.8	0.158
Oxalate (mg/g creatinine)	21.5 ± 1.3	16.0 ± 0.4	14.8 ± 0.4	15.1 ± 0.4	0.023
Glycolate (mg)	40.7 ± 4.5	24.8 ± 2.6	33.2 ± 2.8	45.9 ± 2.7	<0.0001
Glycolate (mg/g creatinine)	26.7 ± 2.2	16.5 ± 1.6	21.0 ± 1.7	28.1 ± 1.6	<0.0001
Calcium (mg)	192 ± 16	130 ± 20	159 ± 20	182 ± 20	<0.0001
Citrate (mg)	542 ± 54	494 ± 49	424 ± 51	410 ± 49	0.088
Creatinine (mg)	1,583 ± 62	1,468 ± 43	1,583 ± 46	1,651 ± 44	0.0007
Magnesium (mg)	94.9 ± 6.3	81.2 ± 4.1	78.9 ± 4.4	83.4 ± 4.2	0.720
Potassium (mmol)	80.6 ± 16.8	41.6 ± 2.8	47.4 ± 3.0	62.5 ± 2.9	<0.0001
Sodium (mmol)	173.7 ± 13.7	93.8 ± 5.6	109.1 ± 5.9	115.4 ± 5.8	0.017
Sulfate (g)	2.03 ± 0.2	1.07 ± 0.13	1.91 ± 0.13	2.90 ± 0.13	<0.0001
Urea nitrogen (g)	10.9 ± 0.7	6.6 ± 0.5	10.5 ± 0.5	16.0 ± 0.5	<0.0001
Uric acid (mg)	624 ± 48	393 ± 45	544 ± 48	627 ± 46	<0.0001
pH	6.02 ± 0.1	6.01 ± 0.08	5.76 ± 0.08	5.77 ± 0.08	0.0076
Tiselius index (CaOx)	ND	0.49 ± 0.05	0.65 ± 0.05	0.72 ± 0.07	0.0021
Urine volume (ml)	2,196 ± 991	2,039 ± 73	1,979 ± 77	2,076 ± 77	0.6913

ND not determined

*Test for difference in response to protein level where type 1 error rate is 0.05. Excretions on the self-selected diets were not included in the model and are presented for comparative purposes only. The model was adjusted for repeated measures on subject, gender, age and diet order. The results presented are the means ± SEM of the 11 individuals

Urol Res. Author manuscript; available in PMC 2009 May 18.