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ORIGINAL PAPER

Calciuria, oxaluria and phosphaturia after ingestion of glucose, xylitol and sorbitol in two population groups with different stone-risk profiles

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Abstract The effects of glucose, sorbitol and xylitol ingestion on calciuria, oxaluria and phosphaturia in healthy black and white males on a standardized diet were investigated. After ingestion, they collected urine hourly for 3 h. Glucose decreased phosphaturia in blacks. Sorbitol decreased phosphaturia in both groups and increased oxaluria in whites. Xylitol increased oxaluria in blacks. Decreases in phosphaturia are attributed to penetration by phosphate into cells leading to decreases in phosphatemia and the renal filtered load. We suggest that this mechanism is more sensitive in blacks. We speculate that the increase in oxaluria after sorbitol ingestion occurs via its conversion to glyoxylate and that this pathway may be blocked in blacks. For the increase in oxaluria after xylitol ingestion, it is hypothesized that ketohexokinase and aldolase may be more active in blacks. Our results demonstrate, for the first time, a urinary effect due to sorbitol ingestion and an ethnic dependency of these and other effects.

Keywords Sugar alcohols · Polyols · Glucose · Sorbitol · Xylitol · Kidney stones · Calciuria · Phosphaturia · Oxaluria

Introduction

Several previous studies have addressed the question of whether carbohydrate ingestion influences the urinary risk factors for calcium oxalate (CaOx) urolithiasis. In particular, attention has been focused on the excretion of calcium, oxalate and phosphorus. Of the carbohydrates which have been investigated, glucose has been shown to cause an increase in calciuria [1–6] and oxaluria [3–5] and a decrease in phosphaturia [6]. Sucrose has also been reported to increase calciuria and decrease phosphaturia, but no effect was found on oxaluria [1, 7]. Similarly, fructose has been found to increase calciuria, but to decrease oxaluria [5]. In addition, fructose is the only carbohydrate known to increase the production of uric acid [8]. These effects, particularly those which pertain to increases in urinary calcium and oxalate, are of interest in the context of urolithiasis as they may increase the risk of this disease. In an attempt to circumvent this potential problem and to decrease the risk of other diseases related to diets rich in refined carbohydrates such as tooth decay, obesity and diabetes mellitus, artificial sweeteners in the form of sugar alcohols (polyols) have been advocated as substitutes for sucrose and glucose. Common examples include sorbitol and xylitol [6]. Whilst the former has not had any effect on the urinary risk factors for CaOx urolithiasis [6], the latter has been found to increase calciuria, oxaluria and phosphaturia [6, 9].

Previous studies in our laboratory have demonstrated that subjects from South Africa's black population, in which urolithiasis is extremely rare, display different renal responses to various lithogenic and antilithogenic dietary challenges compared to their compatriots in the stone-prone white population [10–12]. Thus, investigation of the handling mechanisms of polyols, particularly xylitol, in the two population groups is an obvious area of interest and provides the motivation for the present study.

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Methods

Subjects

Ten healthy males (ages 18-30 years) from each of the black and white student cohorts at the University of Cape Town volunteered for the study which was approved by the Research and Ethics Committee of the University. All of the subjects signed informed consent documents prior to participation. Studies were performed in accordance with the ethical standards as originally laid down in the 1964 Declaration of Helsinki and updated in October 2001. Each subject underwent a medical examination to exclude kidney stone disease and diabetes mellitus. Subjects were not allowed to ingest any drugs or supplements which affect calcium, oxalate or phosphorus metabolism.

Test sugars

Three sugars were administered randomly to each subject. These were glucose (Tongaat Hulett Starch, Germiston, South Africa, 99% purity), sorbitol (Sigma Aldrich, Steinheim, Germany, 97% purity) and xylitol (Sigma Aldrich, Steinheim, Germany, 99% purity).

Protocol

A double-blind design was adopted for the study. The protocol, with some minor modifications, was modeled as described by Nguyen and co-workers [6]. Subjects followed a dietary advice sheet for 1 week, whilst on a self-selected diet which controlled for calcium (1 g/day) and carbohydrate (300 g/day) intake. In the second week on day 1, subjects consumed a strict standardized diet and collected urine for 24 h. They then fasted overnight for 12 h and drank 250 ml of Caledon Natural Spring Water (Quindrink Pty Ltd, Cape Town) on waking (corresponding to time 0 on day 2). The composition (mg/l) of this water is Ca 6.1, Mg 1.0, Na 17.0, K 5.0, Cl 23.0, SO_4 1.7, bicarbonate 32.0, Fe 0.01, pH 6.4. Baseline urines and blood samples were collected 1 h later. Solutions of each test sugar (20 g in 250 ml Caledon water) were randomly assigned to each subject and were then ingested. A further blood sample was drawn 30 min after ingestion of the test solution. Urine was collected hourly for the next 3 h. The standardized diet was then resumed and urine was collected over the remaining 20 h of the 24 h test period. All blood and urine samples were stored at 4°C until analysis. A washout period of 7 days was observed between each protocol. No dietary restrictions were imposed during this period.

Table 1 Nutrient content of the standardized diet

Variable	Amount
Energy (kJ)	1,434
Total protein (g)	109.5
Total fat (g)	112
Carbohydrate (g)	302
Calcium (mg)	1,001
Magnesium (mg)	415
Phosphorus (mg)	1,781
Citric acid (mg)	1,509
Oxalic acid (mg)	66

Analytical methods

The fractional urines (1, 2 and 3 h) were analysed for Na, K, Ca and Mg using flame atomic absorption spectrometry. Oxalate was determined using oxalate decarboxylase. Citrate was determined by conversion to oxaloacetate using citrate lyase. Inorganic phosphorus was determined using ammonium molybdate, creatinine using picric acid, uric acid using uricase and chloride using an ion-selective electrode. Serum glucose was determined using an oxygen rate method employing a Beckman oxygen electrode [13].

Statistical methods

Data were analysed using one-way analysis of variance (ANOVA) and considered statistically significant at $P \leq 0.05$.

Results

No side effects were observed in any subject for any of the protocols. The nutrient content of the standardized diet is given in Table 1. Blood glucose concentrations at baseline and 30 min after ingestion of each sugar are given in Table 2. As expected, blood glucose concentrations increased significantly in both groups after glucose ingestion. Glucose concentrations remained unchanged after sorbitol and xylitol ingestion.

The mean calcium, oxalate and phosphate excretions for the fractional urine collections (1, 2 and 3 h) following ingestion of each sugar are given in Tables 3, 4 and 5. Results have been normalized against creatinine as a reference standard as this serves as a more accurate index of excretion in urine samples which have been collected randomly [14]. The normalized values are expressed as (Ca/Cr) × 100, (Ox/Cr) × 100 and (P/Cr) × 100, respectively, and lie within the same ranges as those previously reported [6]. It is noted that the intake of glucose resulted in a decrease in urinary phosphate excretion (at 2 and 3 h) in black subjects but not in whites. The ingestion of sorbitol also induced significant decreases in phosphaturia, but

Table 2 Mean blood glucose concentrations ± SE (mmol/l) at baseline and 30 min after sugar ingestion

Sugar ingested	Blacks			Whites		
	Baseline	30 min	*P*	Baseline	30 min	*P*
Glucose	4.67 ± 0.48	6.02 ± 0.83	0.002*	4.60 ± 0.50	6.32 ± 0.96	0.004*
Sorbitol	4.67 ± 0.48	4.68 ± 0.54	0.806	4.60 ± 0.50	4.70 ± 0.76	0.849
Xylitol	4.67 ± 0.48	4.62 ± 0.57	0.704	4.60 ± 0.50	4.90 ± 0.65	0.169

* Statistically significant, $P \leq 0.05$

these occurred in both groups and were more prominent in blacks in whom the decreases were observed in two of the urinary fractions (1 and 2 h), unlike in whites where the decrease was observed in only one fraction (2 h). Sorbitol also caused an increase in oxaluria in whites (3 h). After the ingestion of xylitol, oxaluria increased significantly in blacks (3 h).

Discussion

As stated earlier, previous studies in humans have demonstrated increases in calciuria and oxaluria and a decrease in phosphaturia, following administration of an oral glucose load. In the present study, changes in calciuria and oxaluria were not observed. We attribute this to a dose-dependency effect arising from our administration of only 20 g glucose compared to 75 g and 100 g loads which were used in other studies. Justification for the smaller load in the present study is based on unfavourable side effects which have been reported following ingestion of sorbitol [15] and xylitol [9] in dosages of 35 and 29 g, respectively, coupled with our protocol-motivated requirement to standardize the mass concentrations of the test substances. The dose dependency relationship between oral glucose ingestion and urinary calcium excretion has been described by Nguyen and co-workers [6] who showed a greater increase in insulinemia and calciuria after a 75 g dose than after a 20 g dose. This is expected, since an increase in serum concentration of insulin causes an increase in calciuria [16]. The increase in oxaluria observed in other studies has been ascribed to the concomitant decrease in the tubular reabsorption of oxalate which is likely to accompany the rise in calciuria [5]. Thus, any increase in oxaluria following an oral glucose load is also likely to be dose-dependent. Indeed, increases in oxaluria were observed after administration of 75 g glucose [3, 5] and 100 g glucose [4], but were absent after administration of only 20 g glucose[6]. This is consistent with our result. Nevertheless, despite the aforementioned argument, an increase in calciuria following the administration of only 20 g glucose has indeed been previously observed [6] so the absence of this effect in the present study is puzzling.

Table 3 Mean (Ca/Cr) × 100 excretion values ± SE in black and white subjects

Time	Blacks		Whites	
	(Ca/Cr) × 100	*P**	(Ca/Cr) × 100	*P**
Glucose				
0 h	8.49 ± 1.21		16.3 ± 3.47	
1 h	9.75 ± 2.07	0.6469	16.7 ± 3.04	0.9304
2 h	12.2 ± 2.81	0.3133	16.9 ± 2.72	0.8956
3 h	9.46 ± 2.29	0.7356	17.8 ± 2.80	0.7484
Sorbitol				
0 h	11.9 ± 2.32		13.3 ± 2.05	
1 h	9.05 ± 2.46	0.4225	16.1 ± 3.31	0.4421
2 h	14.5 ± 3.58	0.5735	16.0 ± 2.60	0.5127
3 h	18.0 ± 4.95	0.2910	17.5 ± 3.42	0.3821
Xylitol				
0 h	8.50 ± 1.46		16.1 ± 3.15	
1 h	8.62 ± 2.01	0.5185	18.3 ± 3.47	0.7221
2 h	12.2 ± 2.61	0.2869	20.7 ± 3.91	0.3043
3 h	8.45 ± 4.31	0.0646	20.3 ± 4.12	0.3531

* *P* values represent statistical comparisons with the excretion ratio at 0 h

Notwithstanding that in our study the glucose load was insufficient to induce any changes in calcium and oxalate excretions; it was nevertheless large enough to provoke a decrease in phosphate excretion. Of interest is that this occurred only in black subjects. It has been proposed that a decrease in urinary phosphate excretion is consequential to penetration by phosphate into cells after glucose ingestion [6]. This leads to a decrease in phosphatemia which reduces the renal filtered load of phosphate, thereby causing a decrease in its urinary excretion [6]. The observation of an effect in black subjects, but not in whites, suggests that this mechanism is more sensitive in the former group. Comparison of phosphatemia levels in the two groups (not measured in the present study) would allow this hypothesis to be tested.

Our results for sorbitol ingestion are noteworthy for several reasons. First, the only other controlled study investigating the effects of sorbitol ingestion on urinary

Table 4 Mean (Ox/Cr) × 100 excretion values ± SE in black and white subjects

Time	Blacks		Whites	
	(Ox/Cr) × 100	*P**	(Ox/Cr) × 100	*P**
Glucose				
0 h	2.67 ± 0.73		5.21 ± 1.29	
1 h	2.95 ± 0.74	0.7779	3.23 ± 0.70	0.1946
2 h	3.69 ± 0.57	0.3074	4.61 ± 1.24	0.7425
3 h	3.15 ± 0.50	0.5782	2.85 ± 0.41	0.0973
Sorbitol				
0 h	3.56 ± 0.89		1.85 ± 0.53	
1 h	3.05 ± 1.33	0.7581	2.77 ± 0.66	0.3318
2 h	4.34 ± 1.74	0.7076	2.92 ± 0.77	0.2983
3 h	5.54 ± 0.88	0.1417	5.50 ± 1.37	0.0347**
Xylitol				
0 h	1.84 ± 0.54		2.84 ± 0.78	
1 h	1.78 ± 0.56	0.9371	2.50 ± 0.52	0.7425
2 h	2.68 ± 0.52	0.2970	4.97 ± 0.93	0.0583
3 h	6.61 ± 1.12	0.0024**	3.47 ± 0.43	0.3040

* *P* values represent statistical comparisons with the excretion ratio at 0 h

** Statistically significant, $P \leq 0.05$

risk factors for urolithiasis did not find any changes at all [6]. Second, our observation of an increase in oxaluria (in white subjects) is intriguing and warrants an attempt to explain the mechanisms by which this could occur. We are able to advance two possibilities. The first of these invokes the metabolic conversion of sorbitol into glucose via the following pathway [17]:

sorbitol → fructose → fructose-6-phosphate
→ glucose-6-phosphate → glucose

We suggest that since glucose ingestion has been shown in other studies to increase oxalate excretion (as described earlier), sorbitol ingestion might do the same via its conversion to glucose. However, since the subjects of the present study failed to demonstrate either a calciuric or oxaluric response to the administration of glucose itself, it is unlikely that this mechanism can account for the observed increase in oxaluria. The second possibility involves the hepatic transformation of sorbitol into glyoxylate and then into oxalate. Such a conversion has been proposed for xylitol but the authors did not provide details of the mechanistic steps to demonstrate how this occurs [6]. Consideration of the generalized scheme of metabolic pathways linking sugars, polyols and other glycols to oxalate production [18] allows us to propose the following pathway for the conversion of sorbitol to oxalate:

sorbitol → fructose → fructose-1-phosphate
→ glyceraldehyde → hydroxypyruvate
→ glycoaldehyde → glycolate → glyoxylate
→ oxalate

It is our contention that the increase in oxaluria which occurred in our white subjects after ingestion of sorbitol occurred via this hepatic mechanism.

The observation of an increase in oxaluria in our white subjects but not in our black subjects suggests that this metabolic pathway is retarded or inhibited in the latter group. This might occur as a consequence of lower enzymatic activities of polyol dehydrogenase (conversion of sorbitol to fructose) or ketohexokinase (conversion of fructose to fructose-1-phosphate) or aldolase (conversion of fructose-1-phosphate to glyceraldehyde) or glyoxylate reductase (conversion of glyceraldehyde to hydroxypyruvate) in black subjects. However, irrespective of what these reasons might be, our results support our general hypothesis, formulated in other studies, that renal handling of some nutrients may proceed via different mechanisms in the two groups.

The third and final noteworthy result obtained after ingestion of sorbitol is the decrease in urinary phosphate excretion in both groups. We propose that the decrease in phosphaturia might occur via the same mechanism by which glucose ingestion is thought to induce this effect, namely cell penetration by phosphorus leading to a decrease in phosphatemia and a reduction in the renal filtered load of phosphate. Moreover, since the decrease in phosphaturia

Table 5 Mean (P/Cr) × 100 excretion values ± SE

Time	Blacks		Whites	
	(P/Cr) × 100	*P**	(P/Cr) × 100	*P**
Glucose				
0 h	121 ± 19.9		122 ± 8.90	
1 h	107 ± 14.5	0.9440	94.3 ± 8.30	0.4023
2 h	56.6 ± 11.4	0.0153**	76.3 ± 6.45	0.1205
3 h	60.9 ± 12.1	0.0269**	94.6 ± 7.66	0.3787
Sorbitol				
0 h	109 ± 9.52		103 ± 20.5	
1 h	61.2 ± 14.0	0.0181**	78.1 ± 28.9	0.5378
2 h	47.6 ± 7.24	0.0002**	44.4 ± 10.2	0.0367**
3 h	78.6 ± 15.2	0.1469	83.7 ± 17.2	0.5385
Xylitol				
0 h	105 ± 16.8		148 ± 24.0	
1 h	65.4 ± 14.2	0.1085	96.4 ± 15.5	0.1582
2 h	65.0 ± 12.6	0.0795	98.8 ± 21.3	0.3201
3 h	105 ± 10.8	1.0000	143 ± 24.2	0.7787

* *P* values represent statistical comparisons with the excretion ratio at 0 h

** Statistically significant, $P \leq 0.05$

appears to have been more prominent in the black group, we speculate that this effect occurs to a greater extent in this group than in the white group. As stated earlier, this hypothesis could not be tested since phosphatemia values were not determined. This parameter was also not measured in a previous study which investigated the effects of sorbitol on blood metabolites [19]. Thus, although changes in phosphatemia levels after sorbitol ingestion were not observed in a previous study [6], the notion of sorbitol affecting urinary phosphorus excretion remains a possibility.

The increase in oxaluria (in black subjects) after xylitol ingestion warrants comment. This result agrees with that reported for persons consuming this polyol in their diets [6, 9]. A metabolic pathway to explain the production of oxalate from xylitol has been proposed by Conyers and co-workers [18].

xylitol → D-xylulose → xylulose-1-phosphate
→ glycolaldehyde → glycolate → glyoxylate
→ oxalate

These researchers have shown that ketohexokinase and aldolase purified from human liver can metabolize D-xylulose to glycoaldehyde. Since an increase in oxaluria occurred in black subjects but not in whites in the present study, we hypothesize that these enzymes might be more active in the former group. This is surprising and counterintuitive, given that whilst our previous studies have demonstrated different renal handling mechanisms in the two ethnic groups in response to different lithogenic agents, these mechanisms have tended to decrease the risk of stone formation rather than to increase it. Nevertheless, the observation of different responses is again in support of our general hypothesis.

In summary, we have demonstrated, for the first time that sorbitol ingestion favourably alters key urinary risk factors for urolithiasis. Our results also provide evidence in support of our general hypothesis that the black and white population groups in South Africa invoke different renal handling mechanisms when lithogenic and anti-lithogenic nutrients are administered. These results, and the proposed hypotheses, deserve further attention in future studies.

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