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Glucocorticoids and body fat associated with renal uric acid and oxalate, but not calcium excretion, in healthy children

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Abstract

In patients with hypercortisolism, who are frequently obese, the prevalence of elevated urinary excretion rates of the potential lithogenic factors (calcium, oxalate, and uric acid) is increased. We examined whether the 24-hour urinary excretion rates of calcium, oxalate, and uric acid are already associated with body fat and endogenous glucocorticoids in healthy free-living children, taking relevant nutritional and acid-base factors into account. Urinary analyte excretions were determined in 24-hour urine samples of 300 healthy children aged 4 to 14 years. Potentially bioactive free glucocorticoids were assessed as urinary free cortisol + urinary free cortisone. Associations of glucocorticoids and percentage body fat with the outcome variables were examined in regression models adjusted for sex, height, growth velocity, urinary volume, net acid excretion, and relevant nutritional factors. Percentage body fat and urinary free cortisol + urinary free cortisone explained most of the growth-independent variation of urinary uric acid and also a relevant part of oxalate, but none of calcium. Net acid excretion, an indicator of endogenous acid production, and dietary protein, salt, and fiber intakes were also variably associated with the outcomes urinary calcium, oxalate, and uric acid. In conclusion, body fatness and potentially bioactive free glucocorticoids (even in the physiologic range) appear to affect urinary excretion rates of oxalate and uric acid, whereas urinary calcium output is more strongly related to dietary factors in healthy children. Our data provide the first in vivo–based evidence that the obesity- or hypercortisolism-associated urolithiasis may be a pathophysiologic continuation of the corresponding endocrine metabolic variations in healthy children.

1. Introduction

Overweight and obesity are strongly associated with an elevated risk of kidney stone formation (urolithiasis) [1]. This may be due to an increased urinary excretion of potential lithogenic factors, such as calcium, oxalate, and/or uric acid, which has been observed in people with greater body mass index (BMI) [1,2]. However, the mechanisms for these changes in urinary output are still not clear. Obesity-associated particular dietary patterns (eg, high-protein, high-salt, or high–acid-forming diet) [3] or other related metabolic alterations (eg, insulin resistance [4,5]) may be relevant. In fact, increased body fatness and excessive excretion of urinary potential lithogenic factors were both observed in patients with Cushing syndrome [6], which is characterized by persistent, inappropriate glucocorticoid excess. Thus, it is worthy to generally examine the association of body fat, glucocorticoid, and urinary excretion of potential lithogenic factors.

Although kidney stones are relatively uncommon in children, metabolic alterations or abnormalities in the growing years may portend relevant long-term consequences. Persistently increased urinary excretion of calcium and/or uric acid in children not only can increase the risk for stone forming, but may also be indicative of an impairment of calcium homeostasis and/or uric acid metabolism. Disorders of uric acid metabolism often coexist with metabolic syndrome [7] and are considered to be a critical health problem.

The examination of normal physiologic ranges of potentially lithogenic factors can help identify the initially underlying metabolic, hormonal, and nutritional causes, which may in the long run lead to urolithiasis. Based on this background, we examined to what extent 24-hour urinary excretion of calcium, oxalate, and uric acid is associated with body fat as well as endogenous glucocorticoids in free-living

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children, taking relevant nutritional and acid-base factors into account.

2. Subjects and methods

2.1. Study design and subjects

This cross-sectional study was carried out in 300 healthy children from the ongoing Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study [8], on whom an analysis of their urinary glucocorticoid metabolites had been previously performed. This study was approved by the Ethics Committee of the University of Bonn, and all assessments are performed with parental consent. A preschool, a late-prepuberty, and a puberty group with 50 boys and 50 girls each were randomly selected from the DONALD cohort. The corresponding age ranges were 4 to 5, 8 to 9, and 12 to 14 years, with girls in the last group being 12 to 13 years old and boys being 13 to 14 years old. Stage of their pubertal development was determined by a pediatrician with the use of the grading system defined by Tanner.

For the 24-hour urine collection, the children and their caregivers received personal and written instructions on how to collect complete samples. The children were instructed to void their bladder in the morning after arising. This micturition was completely discarded, and the time was noted as the start time of urine collection. For the next 24 hours, all micturitions were collected, including the first void of the following morning. The samples were immediately stored in preservative-free, Extran-cleaned (Extran, MA03; Merck, Darmstadt, Germany) 1-L plastic containers at less than −12°C before transfer by a dietitian to the research institute. A dietitian reviewed the child's compliance with the family and discussed the completeness of the urine collection. Completeness was also checked by creatinine measurements. All children with urinary creatinine less than 0.1 mmol kg^{-1} d^{-1} were excluded. At the institute, the urine samples were stored at −20°C until analyzed [9].

2.2. Measurements

2.2.1. Anthropometry and anthropometrics-derived parameters

Body weight was measured to the nearest 0.1 kg with an electronic scale (Seca 753, Hamburg, Germany). Height was measured in standing position to the nearest 0.1 cm with a digital telescopic wall-mounted stadiometer (Harpenden, Crosswell, United Kingdom). Skinfold thickness measurements were taken on the right side of the body at the biceps, triceps, subscapular, and suprailiac sites to the nearest 0.1 mm using a skinfold caliper (Holtain, Crosswell, Dyfeld, United Kingdom). Equation of Deurenberg et al [10] was used to estimate percentage body fat (%BF).

2.2.2. Urinary measurements

Urinary free cortisol (UFF) and urinary free cortisone (UFE) were measured by specific radioimmunoassays with the use of tritiated steroids (Amersham Pharmacia Biotech, Freiburg, Germany) and specific antibodies raised and characterized in the steroid laboratory in the department of pharmacology (University of Heidelberg, Germany), as described elsewhere [11]. Before radioimmunoassay, UFF and UFE were extracted from the urine with dichloromethane and chromatographically purified using Celite columns (Celite columns 545 AW; Sigma-Aldrich Chemie, Steinheim, Germany). Intra- and interassay coefficients of variation were less than 10% and less than 13%, respectively. Potentially bioactive free glucocorticoids were assessed by the sum of UFF and UFE [12,13].

Creatinine was measured by the Jaffé method with the use of a creatinine analyzer (Beckman-2; Beckman Instruments, Fullerton, CA). Urinary calcium and sodium (the latter as a marker of salt intake) were quantified by flame atomic absorption spectrometry (Perkin Elmer 1100 Spectrometer; Perkin Elmer, Überlingen, Germany); urinary oxalate, with a Dionex 2000 i/SP ion chromatograph with an ion Pac AS4A column (Dionex, Idstein, Germany); and urinary uric acid, by the uricase method using a spectral photometer (PM2DL Zeiss, Oberkochen, Germany). Titratable acidity, ammonium, and bicarbonate were measured according to the method of Lüthy et al [14]. Renal net acid excretion (NAE), an indicator of daily net endogenous acid production, was determined conventionally with titratable acidity + ammonium − bicarbonate.

2.2.3. Dietary parameters

All foods and beverages before consumption as well as leftovers were weighed and recorded by the parents of the children or by the older subjects themselves on 3 consecutive days (3-day weighed-diet records). Nutrient intakes were calculated from the weighed dietary record of the day, on which the 24-hour urine was collected, using our in-house nutrient database LEBTAB, which contains detailed data on the energy and nutrients content of all recorded food items and is continuously updated. Because we could not calculate the dietary oxalate intake, fiber intake was used as a crude indicator for dietary oxalate intake, which is usually found in fiber-rich food [15].

2.3. Statistical analysis

All statistical analyses were carried out with SAS procedures (Version 8.2; Statistical Analysis System, Cary, NC). Data were presented as means ± SD. $P < .05$ was considered statistically significant. Overall effects of age and sex were tested by using 2-way analysis of variance. Covariance analyses were used to check for hormone by sex, %BF by sex, hormone by age group, and %BF by age group interactions. No interaction was observed for the dependent variables. Thus, the subsequent analyses were performed in the total samples with boys and girls combined.

Associations of independent variables with outcome variables were examined in multiple regression models. The 24-hour urinary excretion rates of calcium, oxalate, and

Table 1
Subject characteristics according to age group (n = 300; mean ± SD)

Characteristics	Group 1 (4-5 y)	Group 2 (8-9 y)	Group 3 (12-14 y)
Basic demographics			
n (male/female)	100 (50/50)	100 (50/50)	100 (50/50)
Age (y)	4.5 ± 0.5	8.5 ± 0.5	13.0 ± 0.7
Anthropometrics			
Weight (kg)	18.2 ± 2.2	29.6 ± 5.7	51.7 ± 9.6
Height (cm)	108.0 ± 4.9	133.6 ± 6.4	162.7 ± 8.0
%BF	18.1 ± 3.7	18.2 ± 6.0	17.9 ± 4.1
Growth velocity (cm/y)	6.8 ± 1.3	5.9 ± 1.8	7.3 ± 3.0
Body surface area (m^2)	0.73 ± 0.06	1.05 ± 0.11	1.54 ± 0.16
BMI (kg/m^2)	15.6 ± 1.2	16.5 ± 2.3	19.4 ± 2.7
BMI-SDS	−0.01 ± 0.88	0.02 ± 1.05	0.34 ± 1.01
Dietary			
Protein intake (g/d)	39.8 ± 10.3	51.9 ± 13.0	67.6 ± 18.6
Sodium (mmol/d)[a]	57.1 ± 22.9	82.5 ± 30.7	113.3 ± 43.7
Calcium intake (mg/d)	628 ± 224	738 ± 290	948 ± 441
Fiber intake(g/d)	12.9 ± 5.1	16.7 ± 5.1	20.3 ± 6.9
Total energy intake (MJ/d)	5.4 ± 1.2	7.0 ± 1.5	8.5 ± 2.0
Urinary parameters			
Calcium (mmol/d)	1.0 ± 0.8	1.4 ± 1.0	1.8 ± 1.5
Oxalate (mmol/d)	0.38 ± 0.24	0.59 ± 0.34	0.64 ± 0.32
Uric acid (mmol/d)	1.4 ± 0.4	1.9 ± 0.6	2.7 ± 1.0
NAE (mEq/d)	23.5 ± 11.0	34.5 ± 16.1	51.7 ± 19.8
UFF (μg/d)	8.5 ± 3.8	12.1 ± 6.0	15.8 ± 7.6
UFE (μg/d)	15.0 ± 5.8	21.8 ± 8.9	33.2 ± 12.3
UFF + UFE (μg/d)	23.6 ± 8.9	33.8 ± 13.5	49.1 ± 18.7
Volume (mL)	508.4 ± 208.9	657.0 ± 226.5	932.8 ± 361.4
Creatinine (mmol/d)	2.7 ± 0.5	4.9 ± 1.2	9.0 ± 2.5
pH	6.4 ± 0.4	6.3 ± 0.5	6.1 ± 0.5

SDS indicates standard deviation score.
[a] Data were measured in 24-hour urine samples and used as an indicator for dietary sodium intake.

uric acid served as the dependent variables. The %BF and UFF + UFE were our major independent variables. Dietary intakes of salt (indexed by 24-hour urinary sodium excretion) and protein as well as NAE were considered as confounding factors for all the 3 outcomes and were included in all the models. Dietary calcium intake was included in the models for the urinary outcomes calcium and oxalate. Fiber intake, as proxy for oxalate intake, was included only in the model for urinary oxalate. Furthermore, all the models were a priori adjusted for sex, height, and growth velocity. Because UFF + UFE is influenced by water intake as suggested by several studies [16-18], urine volume was also a priori adjusted.

Statistical interfering dependence of the variables was ruled out with multicollinearity test. All variables used were also checked for normality; and where required, log or square root transformation was undertaken before entering the variables into the models. In addition, to avoid correlated measurement errors, which may occur if both the dependent and the major independent variables are renal excretion rates measured in the same urine samples, the daily excretion rates were not determined conventionally. Instead, they were determined as follows: each individually calculated 24-hour analyte-creatinine ratio was multiplied by individual body weight and by published constant sex-and age-specific body weight–related creatinine reference values [9], and this yields the corresponding creatinine-standardized 24-hour analyte excretion rate [12,13].

3. Results

Demographic, anthropometric, dietary, and urinary data of the 300 healthy subjects are shown in Table 1 according to age groups. Group means were significantly different between the age groups for nearly all variables ($P < .05$), except for %BF and BMI-SDS (standard deviation score). For most variables, mean values increased with increasing age, except for urinary pH, which decreased. Age group 2 had the lowest growth velocity, and 3 had the highest.

Table 2 reports the results for the prediction of urinary calcium, oxalate, and uric acid in a regression model a priori adjusted for sex, height, growth velocity, and urinary volume. Higher dietary intakes of protein, sodium chloride, and calcium as well as higher NAE were all predictors of higher renal calcium excretion levels. Glucocorticoid and body fat effects were not discernible for urinary calcium excretion. However, %BF and the renal marker for functional glucocorticoid activity, UFF + UFE, were both positively associated with urinary oxalate output. In addition, NAE was negatively associated and fiber intake was positively associated with urinary oxalate excretion.

With regard to urinary uric acid, all significant predictors showed positive associations. Of all the predictors, %BF and

Table 2
Prediction models for urinary excretion of calcium, oxalate, and uric acid in 300 healthy children

Outcome variables	Predictors	β	R^2	P
Calcium excretion	A priori adjusted variables[a]		0.13	
	Protein intake	0.28	0.07	<.0001
	Sodium[b]	0.50	0.04	<.0001
	Calcium intake	0.31	0.02	.0094
	NAE	0.08	0.01	.0371
	Model R^2		0.27	
Oxalate excretion	A priori adjusted variables[a]		0.20	
	%BF	**0.02**	**0.04**	**.0007**
	UFF + UFE	**0.23**	**0.02**	**.0295**
	Fiber intake	0.23	0.02	.0150
	NAE	−0.15	0.05	.0004
	Model R^2		0.33	
Uric acid excretion	A priori adjusted variable[a]		0.49	
	%BF	**0.02**	**0.06**	**<.0001**
	UFF + UFE	**0.24**	**0.04**	**<.0001**
	Sodium[b]	0.17	0.03	<.0001
	Protein intake	0.17	0.01	.0317
	Model R^2		0.63	

Only %BF was close to normal distribution; NAE was transformed with square root method; other parameters shown in this table were log-transformed. Boldface indicates the variables of primary interest.
[a] All models were a priori adjusted for sex, height, growth velocity, and urinary volume, for which the sum of partial R^2 is shown.
[b] Data were measured in 24-hour urine samples and used as an indicator for dietary sodium intake.

UFF + UFE explained most of the variation of urinary excretion levels of uric acid. The remaining variations were explained by dietary protein and salt intake. Net acid excretion is not significant for outcome urinary uric acid.

4. Discussion

In this study, we examined the associations of body fatness and an index of functional glucocorticoid activity with potential lithogenic factors in 24-hour urine samples of healthy children, taking relevant nutritional and acid-base factors into account. Until now, no such combined data are available for free-living children. We identified %BF and potentially bioactive free glucocorticoids (determined as UFF + UFE) as 2 factors affecting daily renal excretions of uric acid and oxalate. Percentage body fat even proved to be the strongest predictor of uric acid and the second strongest of oxalate excretion. However, neither body fat nor UFF + UFE were associated with urinary calcium excretion.

Several studies have demonstrated that overweight and obesity may result in increased urinary excretion of calcium, oxalate, and uric acid [1,2]. However, such examinations in healthy children have been lacking so far. Our data show that %BF is a predictor for uric acid and oxalate excretion, but not for calcium excretion, in healthy children after adjustment for known nutritional determinants. In healthy adults with higher body fat, both serum levels and urinary excretion rates of uric acid increase [19]. This suggests that it is not the decline in uric acid clearance, regularly occurring with increasing fatness [20], which is solely responsible for the uric acid rise in the circulation. Rather, uric acid production itself is increased in subjects with higher body fatness [21], who also usually show elevated blood leptin. Whether leptin is involved in an enhancement of uric acid production is currently under discussion [22], and it should be mentioned that associations of increased serum uric acid and higher body fatness are even apparent in adolescents [23]. The positive association between urinary oxalate and %BF in our children is in line with recent findings in healthy adults [1,2]. The underlying mechanism for an enhanced oxalate excretion among persons with higher levels of body fat is still unclear, but it is likely due to an increased intestinal absorption and/or endogenous production induced by higher insulin levels. Insulin has been shown to be positively correlated with body fat ($r = 0.4$) in healthy adolescents [24]. Insulin was suggested as a candidate hormone that can promote endogenous oxalate synthesis [25]. In addition, Conyers et al [26] have presented preliminary evidence to show that, in humans, the 24-hour urinary oxalate excretion correlates with fasting serum insulin. Finally, similar to the results reported by Taylor and Curhan [1] for stone-forming and non–stone-forming adults, no relationship between body fatness and urinary calcium excretion was observed in our study once other parameters were adjusted for. It appears likely that the positive association between body fatness and urinary calcium observed in some studies [27,28] may be due to a lack of adjustment for the known dietary determinants of urinary calcium excretion.

Our results confirm that, with higher dietary intakes of protein and salt as well as higher net endogenous acid production, more calcium is excreted in the urine. Regarding oxalate excretion, several studies [29,30] have shown that it can be influenced by dietary calcium intake because intraluminal calcium could form complexes with oxalate in small intestine and reduce the amount of oxalate absorbed. However, we did not find any association between them. This could be due to the fact that other dietary components such as phytic acid, which is usually contained in vegetarian food, can also bind calcium and lead to a decrease in intestinal calcium concentration [31], potentially affecting renal oxalate output. Therefore, the dietary calcium of mixed diets, as consumed by our children, may not reflect the intraluminal calcium available for complexation with oxalate. The positive association seen between dietary fiber intake and oxalate excretion is obviously due to the high oxalate content in foods rich in fiber. Clear dietary effects were also observed for the outcome urinary uric acid excretion. We observed that, apart from dietary protein, which is considered as the most common contributor of uric acid output, dietary salt intake may also influence uric acid excretion in healthy children. Nevertheless, only few data are available on the possible effects of high sodium chloride intakes on daily uric acid excretions [32].

Although diet is an important factor that affects urinary excretion of uric acid, some hyperuricosuria patients are unable to lower their urinary uric acid excretion on low-purine and low-salt diet [33]. Other metabolic changes may also contribute to uric acid excretion. Our study in healthy children provides the first evidence that endogenous glucocorticoids are positively associated with uric acid excretion even under physiologic conditions. Uric acid excretion has been shown to increase also after corticotropin or glucocorticoid administration in subjects with normal adrenal function [34,35]. A recent study in Cushing disease patients strongly suggests that excessive endogenous glucocorticoids stimulate uric acid excretion [6]. There are several potential mechanisms how glucocorticoids could promote uric acid excretion. It may be a direct effect of glucocorticoids on uric acid transport in the renal tubule [34,36] or a potential contribution of glucocorticoids to de novo uric acid biosynthesis directly in the tubular cells [35,37]. In addition, glucocorticoids, as partially catabolic hormones, might increase degradation of fibrillar muscle protein and thereby increase urinary nitrogen and uric acid excretion [6,38].

Increased glucocorticoids may also yield increased oxalate excretion as suggested by a recent case-control study [6] that found significantly increased urinary oxalate levels in patients with Cushing disease compared with controls. Interestingly, we observed that, even in our healthy children, endogenous glucocorticoids were already positively associated with oxalate excretion. It has been proposed

that glucocorticoids might induce oxalate synthesis via activation of the enzymes involved in the synthesis pathway of oxalate [25]. Whether such a mechanism is already effective with moderate glucocorticoid variations is unknown. Finally, increased glucocorticoids are also frequently associated with persistent calcium losses. This is commonly explained by decreased net renal tubular reabsorption [39] and/or enhanced bone mobilization [38]. However, our data suggested that modest increases in glucocorticoids within the physiologic range do not play any role in renal calcium excretion.

Limitations of our study lie on its cross-sectional design and the fact that no plasma samples were available to analyze the relevant metabolites in the circulation. Because no blood withdrawal is carried out in DONALD children before the age of 18 years, we could not identify whether the increased urinary uric acid and oxalate excretion is due to increased production or diminished renal reabsorption. It remains to be elucidated whether the positive association of functional glucocorticoid status (in the physiologic range) seen with the urinary excretion of uric acid can also be confirmed for uric acid plasma levels. This is of particular relevance because increased serum uric acid concentrations appear to already play an important role in the pathogenesis of the metabolic syndrome in the growing years [7].

In conclusion, body fatness and potentially bioactive free glucocorticoids (even in the physiologic range) appear to affect urinary excretion rates of oxalate and uric acid, but not calcium. Urinary calcium is obviously more related to dietary factors and net endogenous acid production in healthy children. Our data provide the first in vivo–based evidence that the overweight- or Cushing syndrome–associated urolithiasis may be a pathophysiologic continuation of the corresponding endocrine metabolic variations in healthy children.

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