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Prospective Evaluation of Urinary Metabolic Indices in Severely Obese Adolescents after Weight Loss Surgery

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Abstract

BACKGROUND—Observational studies in obese adults have shown abnormal urinary metabolic indices that predispose to nephrolithiasis. Few studies have been performed in severely obese adolescents.

OBJECTIVES—To assess urinary stone risk factors in severely obese adolescents and in those undergoing two types of weight loss surgery.

SETTING—Children's Hospital, United States

METHODS—A prospective cross-sectional study was performed to assess urinary metabolic profiles in severely obese adolescents who have either not undergone any gastrointestinal surgery or who have undergone Roux-en-Y gastric bypass (RYGB) or vertical sleeve gastrectomy (SG). 24-hour urine collections were performed at home and evaluated at a central laboratory. Established normal reference ranges for adults were used in the analysis. A linear regression analysis was performed assessing the relationship of the study group with each of the outcomes.

RESULTS—A total of 55 samples were analyzed from 14 severely obese adolescents and from 17 severely obese adolescents following bariatric surgery (RYGB, 10; SG, 7). Median BMI was similar between the RYGB and SG groups. The median 24 hour excretion of oxalate was significantly elevated in the RYGB group. Calcium and uric acid excretion as well as the median supersaturation (SS) of calcium oxalate, calcium phosphate, and uric acid were similar among all groups.

CONCLUSIONS—Elevated excretion of oxalate in the urine of severely obese adolescents and in those who have undergone RYGB may portend increased risk for kidney stone formation. Larger

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longitudinal studies are needed to verify these findings and to determine the clinical risk of developing stone disease in these patient populations.

Keywords

urinary metabolic indices; obesity; nephrolithiasis

INTRODUCTION

The prevalence of nephrolithiasis in adults is increasing in parallel with the obesity epidemic, and epidemiologic studies have demonstrated a significant association between obesity and increased nephrolithiasis risk. Kidney stones were previously thought to be uncommon in children and adolescents but in the younger age group the incidence appears to also be increasing[1, 2]. Previous observational studies in obese adults have shown abnormal urinary metabolic indices that predispose to crystal aggregation and calculus formation[3, 4]. In addition, gastric bypass procedures have been implicated in the development of enteric hyperoxaluria[5]. Few studies have been performed in severely obese children and adolescents. The purpose of this study was to assess urinary chemistry in severely obese adolescents and determine whether alterations in lithogenic salt excretion might be expected following weight loss surgery.

MATERIALS AND METHODS

After obtaining Institutional Review Board approval, a prospective cohort study was performed to assess urinary metabolic profiles in severely obese adolescents presenting to the Surgical Weight Loss Program for Teens at the Cincinnati Children's Hospital Medical Center. The project was conducted as an ancillary study to the Teen-Longitudinal Assessment of Bariatric Surgery (Teen-LABS, U01DK072493), an NIDDK-funded multicenter consortium studying the health benefits and risks in adolescents undergoing weight loss surgery.

Adolescents and young adults (up to age 21) who were being evaluated either prior to or following bariatric surgery were eligible for this study, unless they met any of the following exclusion criteria: history of urologic (urethral, bladder, ureteral, or renal) surgery, renal insufficiency, or a previous known personal history of nephrolithiasis. After enrollment, a general medical history and physical was performed in the clinic. As nephrolithiasis can be familial, a family history of kidney stone disease was elicited and recorded. A basic metabolic panel performed for clinical indications was reviewed to assess for renal insufficiency. All subjects were studied using a standard protocol (two 24-hour urine collections performed at home and sent directly for evaluation at a central laboratory (Litholink Corporation, Chicago, Illinois). Internal quality assurance controls were performed in the laboratory to assess for under-collection and to validate the volume measurement. Subjects were offered a \$25 incentive for participation.

The 24 hour urinary metabolic evaluation was a standard urinary panel which included pH, 24 hour urine volume as well as the excretion of creatinine, calcium, oxalate, citrate, uric acid, magnesium, phosphorus, sodium, potassium, chloride, sulfate, ammonium and urea

nitrogen. Data from two consecutive urine samples were averaged if available and included as one data point in the final analysis. Urinary supersaturation or the proximate free energy to crystallization was defined as the ratio of the concentration of a dissolved salt to its solubility in water. The urinary supersaturation ratios of calcium oxalate, calcium phosphate, and uric acid were calculated using the iterative computer program EQUIL II. Established reference ranges for adults were used in the analysis of specimens from these older adolescents. No samples were excluded for under-collection.

Severely obese adolescents who were enrolled in a 6 month preparatory program prior to bariatric surgery were recruited as non-operative controls. They had not previously undergone any gastrointestinal operation. The post-operative subjects had previously undergone either a RYGB or SG procedure. The RYGB procedure was performed using a standard 100–150 cm Roux limb length[6]. The SG was performed by resection of the majority of the gastric body and fundus along a 34 French intraluminal bougie, starting 6 cm proximal to the distal end of the pylorus. All post-operative subjects were maintained on a standard protocol of vitamin supplements.

Standard descriptive statistics were calculated to summarize subject characteristics. Frequencies and percentages were reported for categorical measures. Medians and interquartile ranges were calculated for continuous variables. Fisher's exact and Kruskal-Wallis tests were used to compare characteristics across study groups. Linear regression modeling analyses were performed adjusting for age, sex, and BMI to evaluate the relationship between surgical (RYGB, SG)/non-surgical groups and urinary metabolic indices. Statistical analysis was performed using SAS version 9.3 (generalized linear model procedure). All reported p-values were two-sided and considered statistically significant at p 0.05.

RESULTS

A total of 31 subjects were enrolled and completed the urinary collection (Table 1). Overall, 55 samples were submitted for analysis. Seven subjects were only able to complete one specimen collection. There were 6 males and 8 females in the non-operative group, and their median age was 17.9 years (range 15 to 20 years). Their average weight was 133 kg (range 126 to 186kg), and their average body mass index (BMI) was 50 kg/m² (range 42 to 68 kg/m²) at the time of urine collection. Five subjects in the non-operative group had a positive family history for nephrolithiasis.

The two post-operative groups consisted of 30 samples from 17 subjects (1 male and 16 female). Ten subjects underwent RYGB, while 7 underwent SG. The collections were obtained at a median age of 18.6 years in the RYGB group and 17.6 years in the SG group. The specimen collection was at a median postoperative time of 12.7 months and 10.0 months for the RYGB and SG groups, respectively. More than 30% BMI reduction was seen on average in the postoperative groups, typical of these procedures (Table 1). The RYGB and SG groups had 3 and 2 subjects with a positive family history for nephrolithiasis, respectively.

The medians and interquartile ranges for the urinary metabolic indices are presented in Table 2. The 24-hour excretion of oxalate was statistically higher in the RYGB group compared to SG ($p=0.04$) and non-operative ($p<0.01$) subjects, while the SG group actually trended lower than the non-operative group, although this did not reach the level of statistical significance ($p=0.17$) (Figure 1). The calcium indices (24-hour excretion of calcium as well as the supersaturation of calcium oxalate) and 24-hour excretion of citrate were similar between the three groups. Uric acid and calcium phosphate supersaturation were also similar between the groups.

Figure 2 shows the percentage of subjects in each study group that had abnormal values for calcium, oxalate, and citrate. Thirty percent of those in the non-operative group and 50% of those in the RYGB group demonstrated oxalate excretion values above the normal range of 40 mg/day. We did not detect any association between the lengths of the roux limbs nor the biliopancreatic limbs and urine oxalate excretion (data not shown). However, the risk of beta error (not detecting a difference when a real difference exists) is considerable given our small sample size. Conversely, none of the SG group had abnormal 24 hour excretion of calcium and oxalate. Overall, 12 of the non-operative subjects (86%) and 11 of the post-operative subjects (65%) had at least one abnormal urinary risk factor for nephrolithiasis. Six non-operative and 6 post-operative subjects had at least two or more abnormal values. Three RYGB subjects had values above the normal reference range for the 24-hour excretion of urinary calcium and/or the supersaturation of calcium oxalate. Two RYGB subjects had low urinary citrate levels. Six subjects had a combination of urinary metabolic abnormalities in addition to a positive family history of nephrolithiasis. No subject has presented with a clinical episode of nephrolithiasis during the study period.

DISCUSSION

This study represents the first controlled assessment of urinary metabolic indices in severely obese adolescents following two distinct weight loss surgical procedures. We also describe for the first time the urine metabolic abnormalities associated with adolescent obesity in a unique but small cohort of severely obese adolescents who have not undergone a gastrointestinal surgical procedure. The most important findings were the increased proportion of severely obese non-operative and post-RYGB subjects with abnormal oxalate excretion, and the low oxalate excretion in subjects who had undergone SG.

Pediatric nephrolithiasis has been increasing in prevalence over the past few decades and is thought to be implicated in up to 1 in 1000 hospital admissions per year in the United States[2]. In addition, obesity in children is now recognized as a major public health concern. It has been estimated by analysis of the National Health and Nutrition Examination Survey (NHANES) that 16% of children aged 6 through 19 are considered overweight and up to 31% are considered at risk of for being overweight[7].

The relationship of increasing BMI and an increased risk of stone formation in adults has been well described and is thought to be related to multiple factors[8]. Excess nutritional intake can cause an increase in the ingestion of lithogenic substances such as calcium, oxalate, and purines. In addition, the metabolic syndrome can alter the renal acid-base

metabolism, with a resultant lower urine pH increasing the risk of uric acid stone formation[4]. Moreover, both medical and surgical weight loss interventions have been associated with the increased risk of kidney stones [9–12].

Several urinary metabolic studies have been performed in obese adults to assess lithogenic risk factors. Duffey et al studied 45 subjects with a mean BMI of 50 kg/m² and found that 98% had at least one risk factor, mainly low urinary volume[3]. Taylor and Curhan reported that subjects with greater BMI values excreted more urinary oxalate, uric acid, sodium, and phosphate than those with lower BMI. A positive association between BMI and urinary calcium excretion in men and stone-forming younger women did not persist, however, after adjustment for urinary sodium and phosphate excretion[8].

Few investigators have studied urinary metabolic indices in obese children. A retrospective review by Eisner et al analyzed the relationship of BMI to quantitative 24-hour urine chemistry studies and found an inverse relationship with BMI and urinary oxalate but an increased level of calcium phosphate supersaturation. In their study, 14 children had a BMI above the 75th percentile but no information was provided on the number of subjects with severe obesity[13]. Sarica and colleagues reported results of timed urinary studies in children in a prospective study of 97 children, most of whom did not have a history of stone disease. Compared to controls, overweight children (greater than BMI of 25) demonstrated higher levels of oxalate and calcium as well as lower levels of citrate, a known stone inhibitor[14].

With the increasing use of weight loss surgery, metabolic derangements have been noted in adults, particularly after intestinal bypass procedures. An early report from Nelson et al presented a series of RYGB patients who developed enteric hyperoxaluria[15]. Two progressed to renal failure requiring chronic renal replacement therapy. Subsequent reports have investigated urinary metabolic risk factors in RYGB patients and found significantly higher urinary oxalate and lower urinary citrate levels post-operatively[10, 16]. Others have found an increase in chronic kidney disease as well as kidney stones in RYGB patients[17]. A putative mechanism for the hyperoxaluria is the enhanced saponification of intestinal calcium with unabsorbed fatty acids due to fat malabsorption[12], leaving less calcium to bind oxalate in the gut. The increased free oxalate is then primarily cleared by the kidney but can form insoluble mineral complexes with urinary calcium. Other mechanisms are currently being evaluated to further the understanding of this process[18].

To our knowledge, studies of vertical sleeve gastrectomy and other restrictive bariatric procedures appear to show a limited effect on overall kidney stone risk[19]. While our preliminary data in this small group of sleeve gastrectomy patients must be confirmed, our results suggest the possibility that sleeve gastrectomy may be associated with a protective effect against stone formation, due to the association with lower urine oxalate levels than seen in both obese controls and RYGB subjects.

In the present study, the RYGB subjects did show a significantly higher oxalate secretion, which is consistent with the previously mentioned adult studies. In contrast, we did not find differences in urinary calcium or citrate indices among the three study groups, which has

been reported in multiple adult bariatric series. However, it is concerning that a majority of patients did have at least one abnormal urinary risk factor. None of these were isolated low urine volume as reported by Duffey[3].

The primary limitation of this study is the relatively low sample size. The results must therefore be considered preliminary, but the point estimates and variability in the measures recorded can inform the design of a more definitive study. Future research with a larger sample size may therefore more definitively address the hypotheses that emerged from this study: severe obesity in pediatric age groups is associated with lithogenic urinary indices and that RYGB but not SG may accentuate some of these risks for stone formation. Finally, from this experience we can surmise that the collection of a 24 hour urine on two consecutive days represents a significant burden for adolescents volunteering for research. Future studies may more effectively offset this burden with increased incentives that are more appropriate for the time burden associated with the tasks.

CONCLUSION

In a group of severely obese adolescents severe obesity and RYGB were associated with elevated excretion of oxalate in the urine. This may predispose them to forming urinary calculi, especially when associated with a positive family history of nephrolithiasis. Further studies are needed with larger sample sizes to verify these findings and to assess the long term clinical risk of forming kidney stones.

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List of Abbreviations

RYGB	Roux-en-Y gastric bypass
SG	Sleeve gastrectomy
BMI	body mass index
SS	supersaturation
NHANES	National Health and Nutrition Examination Survey

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Figure 1.
Abnormal 24 hour urinary excretion rates (%)

Key to the Box Plot

Figure 2.
24 hour excretion rates of oxalate in the study groups

Table 1

Patient Demographics

<i>Demographic</i>	<i>Non-operative (n=14)</i>	<i>RYGB (n=10)</i>	<i>SG (n=7)</i>	<i>p-value</i>
Sex, n				0.02
Male	6	0	1	
Female	8	10	6	
Age (years), Median	17.9	18.6	17.6	0.07
Current Weight (kg), Median	133	105	94	< 0.01
Current BMI (kg/m ²), Median	50	36	32	< 0.01
Pre-op BMI (kg/m ²), Median	N/A	52	51	0.37
Time since surgery (months), Median	N/A	12.7	10.0	0.38
Family history of nephrolithiasis, n	5	3	2	0.99

Table 2

Comparison of urinary metabolic indices (median and interquartile range)

	Normal Range	Non-operative	RYGB group	SG group	P-value ¹
Volume (liters)	>1.5	1.31 (0.85,1.73)	1.49 (1.04,1.88)	0.95 (0.44,1.73)	0.74
pH	5.6 – 6.5	6.2 (5.7,6.6)	6.2 (6.0,6.5)	6.1 (5.9,6.6)	0.87
Calcium (mg/day)	<300 M <250 F	124 (65.9,172.0)	83.5 (66.6,126.1)	120 (53.2,150.4)	0.32
Uric acid (g/day)	<0.80 M <0.75 F	0.61 (0.44,0.87)	0.57 (0.50,0.64)	0.40 (0.29,0.70)	0.24
Citrate (mg/day)	>325	590 (412.7,822.9)	646 (526.5,675.4)	687 (268.5,769.0)	0.94
Oxalate (mg/day)	<40	34.1 (22.9,42.9)	41.8 (35.9,60.9)	26.4 (37.8,34.6)	0.01
Sodium (mmol/day)	50 – 150	183 (121,253)	190 (164, 244)	142 (76, 195)	0.10
Urea nitrogen (g/day)	6 – 14	10.4 (7.4, 11.3)	8.9 (7.6, 11.0)	7.6 (3.9, 13.0)	0.13
SS Calcium oxalate	6 – 10	7.21 (4.49,9.13)	5.02 (3.52,8.16)	5.23 (3.43,12.27)	0.88
SS Calcium phosphate	0.5 – 2	0.82 (0.53,2.15)	0.64 (0.49,1.10)	1.07 (0.52,1.56)	0.61
SS Uric acid	0 – 1	0.75 (0.41,1.46)	0.49 (0.20,1.22)	0.83 (0.35,1.10)	0.76

¹Results of a linear regression analysis between study groups

M=male

F=female

SS=supersaturation