Urinary Stone Disease in Adults With Celiac Disease: Prevalence, Incidence and Urinary Determinants

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Purpose: Intestinal diseases may cause urinary stone disease via hyperoxaluria or diarrhea induced hyperconcentrated acidic urine. Data are missing on urinary stone disease in celiac disease, a common malabsorptive disorder. In this study we analyzed urinary stone disease and urine composition in adults with celiac disease.

Materials and Methods: Study patients were 18 years or older, untreated, and newly diagnosed with celiac disease by serum markers and jejunal biopsy. Clinical presentation of celiac disease was assessed focusing on 5 disorders of diarrhea, and deficiency of calorie (low body mass index or weight loss), lipid (low prothrombin time or low serum lipids), iron (low hemoglobin or low serum ferritin) and calcium (low serum calcium or low bone densitometry). Urinary stone disease history was assessed by questionnaire (imaging, stone excretion, stone disruption/removal). Urinary variables were measured in a 24-hour collection in a subgroup of patients.

Results: Under untreated conditions (baseline) urinary stone disease was independent of celiac disease presentation and more prevalent in patients with celiac disease than in a population sample used as a control (608 and 3,540, 7.9% and 5.0%, sex and age adjusted odds ratio 4.0, 95% CI 2.7–5.9). Excluding from analysis individuals with baseline urinary stone disease, the incidence of urinary stone disease history was not significantly different between the treated celiac disease (gluten-free diet) and control population (458 and 3,003, 2.4% vs 3.9%). The urine of untreated patients with celiac disease differed from that of healthy volunteers with 120% higher oxalate and 43% lower calcium (in 45 and 45, $p < 0.001$). A gluten-free diet corrected urinary abnormalities ($p < 0.01$).

Conclusions: Urinary stone disease risk is high in untreated patients with celiac disease independent of overt malabsorption. Hyperoxaluria is likely the underlying disorder. A gluten-free diet reduces urinary stone disease risk and oxaluria.

Key Words: urinary calculi, celiac disease, prevalence, incidence

Urinary stone disease depends on the alteration of a complex equilibrium between promoters and inhibitors of stone formation in the urine.[1] Intestinal diseases may cause USD through various mechanisms that eventually lead to hyperoxaluria and/or concentrated acidic urine.[1–3] Hyperoxaluria is a heterogeneous disorder that reflects oxalate hyperabsorption secondary to lipid malabsorption, or high permeability of colonic mucosa or loss of oxalate degrading bacteria.[2,3] Concentrated acidic urine usually reflects dehydration and acidosis secondary to diarrhea.

Celiac disease is the most common form of intestinal malabsorption in adults in the Western world.[4] In patients with CD the ingestion of gluten containing cereals induces a variable malabsorptive syndrome ranging from a subclinical disorder (common) to overt malabsorption (rare).[5] Data on the possible association between CD and USD are limited to anecdotal case reports.[6,7] CD causes opposite changes in 2 promoters of lithogenesis because it increases urinary oxalate secondary to oxalate hyperabsorption[7,8] and decreases urinary calcium secondary to calcium malabsorption.[9] Thus, for USD CD might act as a risk factor or as a protecting factor. In this study we investigated USD and urinary lithogenic factors in adults with CD under untreated conditions and after treatment with a gluten-free diet.

METHODS

The study cohort consisted of patients 18 years or older diagnosed with untreated CD from 1996 to 2006. CD was diagnosed using serum autoantibodies (anti-endomysium and anti-tissue-transglutaminase subtype 2) and jejunal biopsy.[4] CD was defined with onset at a pediatric age in cases of dental enamel defects[10] and/or the report of low growth rate. The clinical presentation of CD at diagnosis (baseline) was assessed focusing on 5 disorders of diarrhea, and defi-

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ciency of calorie, iron, calcium and lipid. Diarrhea (chronic or recurrent) was defined as the report of 3 or more liquid voids per day. Calorie deficiency was defined as low BMI (less than 18.5 kg/m^2) and/or the report of weight reduction greater than 5% in the last year. Iron deficiency was defined as low hemoglobin (less than 13 gm/dl in men, less than 12 gm/dl in women) and/or low serum ferritin (less than 10 ng/ml) and/or as the report of treatment with iron in the last year. Calcium deficiency was defined as low serum calcium (serum total calcium less than 2.125 mmol/l after normalization for serum protein)[11] and/or as a Z-score below −1 at bone densitometry (average of 4 measurements by dual photon absorptiometry, 1 at lumbar vertebra and 3 at femoral sites).[12] Lipid deficiency was defined as serum total cholesterol less than 120 mg/dl and/or serum triglycerides less than 50 mg/dl and/or prothrombin time less than 70%.[13] A score calculated as the number of disorders per patient was used for evaluation of CD severity. After diagnosis patients with CD were prescribed a gluten-free diet and a yearly visit as required by the Italian National Health System for evaluation of dietary compliance (anti-transglutaminase antibodies) and nutritional status (weight, blood hemoglobin and serum cholesterol).

USD and Lithogenic Factors

History of USD was assessed by a trained physician using a questionnaire, and 3 criteria of evidence of stone(s) at imaging examinations (x-ray or echo), excretion of stone(s) and procedures for stone disruption/removal (lithotripsy or endoscopy or surgery).[14–16] USD diagnosis was defined as incidental when done in patients with CD by imaging examinations requested for reasons other than USD. The questionnaires for definition of USD in large cohorts were previously validated.[14–16] In a subgroup of patients with CD laboratory evaluation included the measurement of 24-hour urinary excretion of modulators of lithogenesis (oxalate, calcium, phosphate, uric acid and citrate) and of creatinine (index of collection completeness).[17]

Study Design and Statistics

The first set of analyses investigated if, under untreated conditions, the prevalence of USD history differed among patients with different clinical presentations of CD. The second set of analyses investigated if the prevalence of USD history was high in untreated patients with CD compared to a sample of the general Italian population that periodically took the same questionnaire on USD.[15,16] A population based group was preferred to other control groups (healthy volunteers or patients with other disorders) to reduce the bias of low numbers. The confounding of CD within the population sample was considered negligible because the prevalence of CD is less than 1% in the general population.[18]

The third set of analyses investigated if the incidence of USD history is high in patients with CD regularly treated with a gluten-free diet. Patients were included in these analyses if they were without USD history at baseline and were diagnosed with CD before May 2003. These criteria were used to select patients who could complete treatment with a gluten-free diet lasting 4 years or more by May 2007. A long-term treatment was designed to increase the number of cases with incident USD and, thus, the statistical power of the analyses. The USD questionnaire was administered to these patients with CD at the last yearly visit (defined as followup). Duration of treatment was calculated as followup date minus baseline date. The incidence of USD history in individuals originally without USD was compared between treated patients with CD and the control population. Untreated patients with CD could not be used as a comparator because it is unethical to delay the treatment of CD for long-term studies.

The fourth set of analyses investigated urinary modulators of lithogenesis in patients with CD under untreated conditions and after treatment with a gluten-free diet. These analyses were limited to patients with CD diagnosed in 2005 (baseline). Urinary measurements were done at baseline (untreated condition) and after completion of 1-year treatment with a gluten-free diet (followup). Data of patients with CD were compared to data of healthy volunteers.

Statistical procedures included ANOVA, chi-square analysis, calculation of 95% CI, logistic analysis for calculation of OR without and with control for other variables, correlation analysis, and the paired t test. The construction of receiver operating characteristic curves with calculation of the area under the curve was used to assess the discriminant power for USD or urinary abnormalities. Comparisons of USD history between patients with CD and the control population were done by gender and age stratum or with adjustment for gender and age because gender and age are correlates of USD history.[1,16] Analyses were repeated excluding cases

TABLE 1. *Descriptive statistics in untreated patients with CD at diagnosis*

No. women/men (%)	491/117	(80.8/19.2)
Mean pt age ± SD	32.5 ± 10.7	
No. pt age (%):		
18–24	222	(36.5)
25–34	205	(33.7)
35–44	116	(19.1)
45–54	62	(10.2)
55–63	23	(3.8)
Mean kg wt ± SD	58.1 ± 12.0	
Mean m height ± SD	1.65 ± 0.08	
Mean kg/m^2 BMI ± SD	21.3 ± 3.6	
No. reporting wt reduction (%)	259	(42.6)
Mean gm/dl hemoglobin ± SD	12.0 ± 2.3	
Mean μg/l ferritin ± SD	24.2 ± 43.9	
No. reporting iron therapy (%)	312	(51.3)
Mean % prothrombin time ± SD	87.9 ± 18.0	
Mean mg/dl serum cholesterol ± SD	154.2 ± 35.4	
Mean mg/dl serum triglycerides ± SD	89.9 ± 53.8	
Mean mg/dl serum total calcium ± SD	8.98 ± 1.13*	
Mean gm/dl serum total protein ± SD	7.20 ± 4.28	
Mean mg/dl serum normalized calcium ± SD	8.92 ± 1.21*	
Av Z-score bone mineral density ± SD	−0.91 ± 1.03	
No. with onset at pediatric age (%)†	203	(33.4)
No. disorders (%):		
Diarrhea‡	298	(49.0)
Calorie deficiency	302	(49.7)
Iron deficiency§	391	(64.3)
Lipid deficiency	120	(19.7)
Calcium deficiency	87	(14.3)
No. score (%):		
With no disorder	62	(10.2)
With 1 disorder	158	(26.0)
With 2 disorders	196	(32.2)
With 3 disorders	133	(21.9)
With 4 disorders	52	(8.6)
With 5 disorders	8	(1.3)
No. with USD (%)	48	(7.9)
No. with incidental USD diagnosis (%)	8	(1.3)

* Multiplier for conversion to mmol/l 0.25.
† With enamel defects and/or reporting low growth.
‡ Reporting chronic or recurrent diarrhea.
§ Low hemoglobin and/or low ferritin and/or reporting iron therapy.

TABLE 2. *Characteristics of untreated patients with CD with or without USD history*

	With USD	Without USD
No. pts with CD	48	560
% Male	20.8	18.7
Mean pt age	35.0	32.3
% CD onset in pediatric age*	43.8	32.2
% Disorders:		
Diarrhea†	52.1	48.5
Calorie deficiency‡	54.2	49.0
Iron deficiency§	64.3	60.4
Lipid deficiency‖	20.8	19.5
Calcium deficiency¶	18.8	13.9
% Score:		
With 0 or 1 disorder	33.3	36.5
With 2 disorders	31.3	32.2
With 3–5 disorders	35.4	31.3

p Not significant (>0.05) in comparison by ANOVA or chi-square analysis between patients with USD and those without USD.
* With enamel defects and/or reporting low growth.
† Reporting chronic or recurrent diarrhea.
‡ Low BMI and/or reporting weight loss.
§ Low hemoglobin and/or low ferritin and/or reporting iron therapy.
‖ Low prothrombin time and/or low serum cholesterol and/or low serum triglycerides.
¶ Low serum calcium and/or low bone mineral density.

with incidental USD diagnosis to exclude the bias secondary to possible differences in the frequency of imaging examinations between cases of CD and the control population. Calculations of the study power could not be done in the absence of information about USD frequency in patients with CD.

RESULTS

Descriptive Statistics

A total of 608 untreated patients with CD were included in the study (age range 18 to 63 years). The majority were women, younger than 45 years, without CD onset at a pediatric age, with iron deficiency and with a presentation characterized by none or few disorders (table 1). The population used as comparator is described in several reports.[15,16,19,20] Briefly it consisted of 3,540 individuals (1,635 men and 1,905 women) 18 to 63 years old to match the age of patients with CD. The 45 healthy volunteers used as a comparator for analyses of urinary variables were selected to accurately match gender, age and weight of the 45 patients with CD with urinary data. These volunteers were without USD history, with no sign of malabsorption and with no serum marker of CD.

Clinical Presentation of Untreated CD and USD

Patients with CD with USD did not differ compared to those with CD without USD for gender distribution, baseline age and CD presentation (table 2). The trend toward frequent CD onset at a pediatric age in patients with USD was not significant ($p = 0.102$). None of the 5 single disorders, nor the score of CD severity nor CD onset at a pediatric age had significant power to discriminate USD history (AUC under ROC $p > 0.18$). Prevalence of USD history was not associated with CD severity (8.2% in patients with 0 to 1 disorder, 7.7% in patients with 2 disorders and 8.8% in patients with 3 disorders, analysis of linear trend $p = 0.830$). Findings were similar with sex and age adjustment or excluding patients with incidental USD diagnosis (not shown).

USD Prevalence in Untreated CD vs Control Population

Table 3 shows data on USD history prevalence by gender and age stratum. USD history was more prevalent in untreated CD than in the control population, a finding that was consistent in women of all ages with CD and in men with CD younger than 45 years. The association between untreated CD and USD history was also significant after exclusion from analyses of patients with CD with an incidental USD diagnosis (sex and age adjusted OR 3.22, 95% CI 2.1–4.8). The OR of USD history in untreated CD was similar in analyses by gender (age adjusted OR for men and women 2.90 and 4.53, 95% CI 1.4–6.1 and 2.8–7.3, respectively) and tended to decrease with age in analyses by age stratum (OR by age in table 3). The sex and age adjusted OR for those younger than 35 years was higher than that of those 35 years or older (OR 15.30 and 1.91, 95% CI 6.7–34.3 and 1.1–3.3).

USD Incidence in Treated CD vs Control Population

Of the original 608 untreated patients with CD 458 were without baseline USD and completed the treatment of a gluten-free diet lasting 4 or more years with good compliance. The majority of these 458 patients with CD were women (364) younger than 45 years (408), without CD onset in pediatric age (356), with iron deficiency (312) and with a clinical presentation characterized by none or 1 disorder (278). The gluten-free diet increased weight, hemoglobin and serum cholesterol over baseline values in these 458 patients with CD (mean ± SE of individual changes +4.7 ± 0.4 kg for

TABLE 3. *Prevalence of USD history in the control population and in untreated patients with CD by gender and age*

	18–24 Yrs		25–34 Yrs		35–44 Yrs		45–54 Yrs		55–63 Yrs		Overall	
Female control population:												
Total	226		334		373		467		505		1,905	
No. with USD history (%)	0	(0)	3	(0.9)	7	(1.9)	25	(5.4)	43	(9.3)	78	(4.1)
Female pts with CD:												
Total	156		174		102		41		18		491	
No. with USD history (%)	4	(2.6)	21	(12.1)	6	(5.9)	3	(7.3)	4	(22.2)	38	(7.7)
Male control population:												
Total	210		338		329		385		373		1,635	
No. with USD history (%)	0	(0)	6	(1.8)	15	(4.6)	37	(9.6)	42	(11.3)	100	(6.1)
Male pts with CD:												
Total	56		31		14		11		5		117	
No. with USD history (%)	6	(10.7)	2	(6.5)	1	(7.1)	1	(9.1)	0	(0.0)	10	(8.5)
OR (95% CI)*	31.7 (3.9–255.6)		9.3 (4.0–21.7)		2.7 (1.1–7.0)		1.2 (0.4–3.6)		2.1 (0.7–6.2)		4.0 (2.7–5.9)†	

* Sex adjusted by logistic regression.
† Sex and age adjusted by logistic regression.

TABLE 4. *Urinary variables*

	Untreated Pts With CD	Healthy Volunteers
No. men/women	9/36	9/36
Mean age	36.9	35.8
Mean mg/24 hrs/kg wt urinary creatinine	17.72	18.11
Mean ml/24 hrs urine vol	1,078	1,246
Mean mg/24 hrs urinary calcium	99.2*	175.0
Mean mg/24 hrs urinary phosphorus	729.7	733
Mean mg/24 hrs urinary oxalate	56.0*	25.5
Mean mg/24 hrs urinary urate	318.6	342.4
Mean mg/24 hrs urinary citrate	511.8	569.3

* ANOVA $p < 0.001$ vs healthy volunteers.

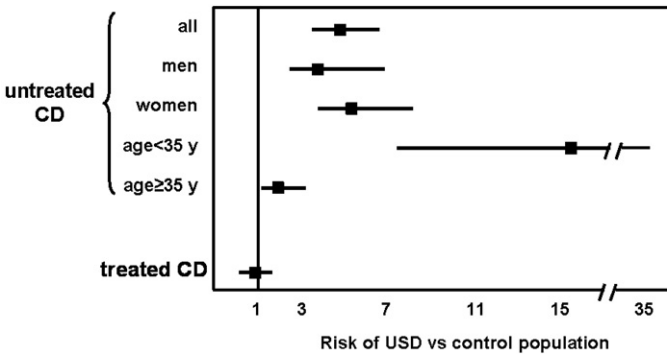

FIG. 2. Results of analyses of association of CD with USD history under untreated conditions and while on treatment with gluten-free diet. Sex and age adjusted odds ratio of USD history (95% CI) in patients with CD compared to sample of general population (USD risk = 1).

weight, +1.5 ± 0.1 gm/dl for hemoglobin, +20.7 ± 1.6 mg/dl for serum cholesterol, paired t test $p < 0.01$).

Of the original 3,540 members of the control population 3,003 were without baseline USD with repeated administration of the USD questionnaire. After a followup of similar duration in patients with CD and the control population (7.4 and 7.7 years, ANOVA $p = 0.462$) the incidence of USD history in the treated CD population was not significantly different compared to the control population (11 and 117, percent data 2.4% and 3.9%, 95% CI 1.0–3.8 and 3.2–4.6). In sex and age adjusted analysis the risk of incident USD in treated CD was almost the same as that in the control population (OR 0.95, 95% CI 0.49–1.83, $p = 0.880$). The findings were similar in analyses including individuals with USD history at baseline (not shown).

Urinary Modulators of Lithogenesis in CD

A total of 45 patients with CD were included in analysis. The majority of these patients were women (36), younger than 45 years (35), without CD onset at pediatric age (27), with iron deficiency (32) and with a clinical presentation characterized by none or 1 disorder (32). In comparison to gender, age and weight matched healthy volunteers, untreated patients with CD had significantly lower urinary calcium (−43%) and significantly higher urinary oxalate (+120%) in urine collections with similar completeness (table 4). Oxaluria more than 50 mg/24 hours was present in 25% of patients but in none of the healthy volunteers. CD severity under untreated conditions correlated with urinary calcium but not with urinary oxalate (fig. 1). Indices of CD presentation (CD onset at a pediatric age, the 5 single disorders, cumulative score) did not have a discriminant power for hyperoxaluria (analysis of AUC under ROC $p > 0.34$). Findings were similar in sex and age adjusted analysis (not shown).

After 1 year of treatment there were significant increases over baseline in weight, hemoglobin and serum cholesterol (mean changes +6.6 kg, +0.9 gm/dl and +18.2 mg/dl, respectively, $p < 0.05$). For urinary variables the treatment induced significant changes only in calcium (mean change over baseline +66.7 mg/24 hours, $p < 0.01$) and oxalate (mean change over baseline −21.4 mg/24 hours, $p < 0.01$).

DISCUSSION

The analysis of USD in adults with CD is summarized in figure 2. Cross-sectional data indicated that in comparison to a sex and age matched population sample, untreated adults with CD had an excess of USD history in both sexes and all age strata. The excess of USD in patients with untreated CD was not associated with a single clinical sign of present CD or with a cumulative index of CD severity. Adult patients with CD on regular treatment with a gluten-free diet had a USD history incidence similar to that of the control population. Finally, hyperoxaluria and hypocalciuria

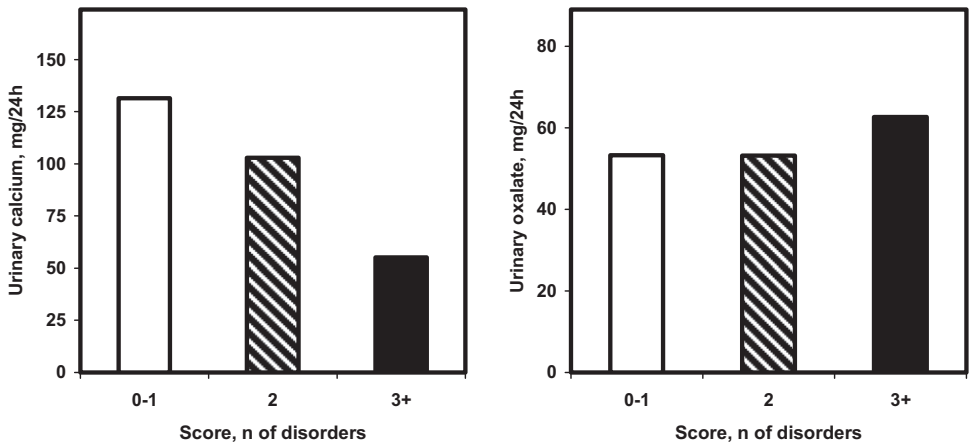

FIG. 1. Mean urinary excretion of calcium and oxalate by severity of CD presentation (score) in untreated patients. Number of patients per stratum 16, 16 and 13. Linear trend along groups $p = 0.006$ for urinary calcium, $p = 0.568$ for urinary oxalate.

were the 2 urinary abnormalities in untreated CD and were both correctible with a gluten-free diet.

A limitation of this study could be the different number of individuals in the CD cohort and in the control population, resulting in differing power of analyses. A post hoc calculation suggests that this possibility is unlikely. An overall OR of 4.0 in the cross-sectional association between untreated CD and USD together with the datum of a 3.9% incidence of USD in the control population suggests that, in case of no effect of gluten-free diet on USD in CD, the rate of USD incidence in treated patients with CD should have been much higher than the rate actually found (incidence expected in a noneffective treatment $4.0 \times 3.9\% \times 458$ patients = 71; actual incidence was 11).

High oxaluria was the only lithogenic abnormality found in the urine of untreated patients with CD. The definition of the mechanism(s) underlying hyperoxaluria was beyond the scope of this study. Data suggest that high oxaluria in adults with CD reflected a dysfunction not directly dependent on lipid malabsorption as in steatorrhea associated hyperoxaluria.[2,3] High oxaluria was not associated with lipid deficiency, nor with other single signs of malapsorption or with CD severity in contrast to the linear association between CD severity and urinary calcium. Thus, oxaluria could be high in adults with untreated CD also because of other mechanisms (high permeability of colonic mucosa and/or loss of intestinal oxalate degrading bacteria) as in other intestinal diseases.[2,3] Treatment with a gluten-free diet normalized oxaluria in patients with CD in agreement with the concept that the exclusion of gluten from the diet is per se sufficient to normalize intestinal function in most patients with CD.[21] The pattern of findings on USD paralleled the pattern of findings on oxaluria. USD frequency was high under untreated conditions but not while on long-term treatment with a gluten-free diet. As for high oxaluria the excess of USD in untreated patients was not associated with isolated signs of malabsorption or with CD severity. Thus, the results support the idea that USD in untreated CD is secondary to intestinal hyperoxaluria amenable to control with a gluten-free diet.

The results of the study have also practical implications. The USD excess in adult patients with CD with none or few symptoms of malabsorption implies that USD may be at times one of the first appearing disorders of subclinical CD. The observation of a 7.9% prevalence of USD in untreated patients with CD together with previous data reporting an approximate prevalence in the general population of 1% for CD[18] and 6% for USD[1–16] suggests that CD could account for approximately 1% to 1.5% of all cases of USD. It is reasonable to assume that in patients with USD secondary to CD the delay of the correct diagnosis and the correct treatment exposes patients to the progression of the malabsorptive disorder and, thus, to the development of other complications including the formation of new urinary stones and/or the growth of preexisting stones. In this regard the availability of noninvasive methods for CD diagnosis would be of great usefulness.[22]

CONCLUSIONS

The study reports the existence in adults of an association between untreated CD and USD in the absence of overt malabsorption. The underlying disorder appears to be hyperoxaluria not necessarily associated with other signs of overt malabsorption. A gluten-free diet reduces USD risk and oxaluria.

Abbreviations and Acronyms

BMI = body mass index
CD = celiac disease
USD = urinary stone disease

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