Urinary excretion of oxalate, calcium, magnesium, and uric acid in inflammatory bowel disease

Relationship to urolithiasis

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Recently, the importance of hyperoxaluria in Crohn's disease and its relationship to urolithiasis has been emphasized. It has been known for many years that urolithiasis may be a complication of inflammatory disease and that the predominant stone is calcium oxalate; but interest in the antecedent state of hyperoxaluria in these patients has resulted from recent work.[1-7] It is recognized that hyperoxaluria may be a significant factor in the urolithiasis which occasionally occurs in patients with inflammatory bowel disease.

Conflicting views on the mechanism of hyperoxaluria in inflammatory bowel disease have been expressed. Smith et al[3] felt that bile salt glycine, spilling into the colon because of ileal malabsorption, was converted to glyoxylate by bacteria, was absorbed from the portal vein, and then oxidized to oxalate in the liver. This group subsequently changed their views and postulated that an excessive amount of hepatic glycine was required for bile salt conjugation with an increased production of glycine precursors in the liver, and that this included glyoxylate.[4] The glyoxylate would then be converted to oxylate. Admirand et

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al[2] suggested an acquired defect in hepatic glyoxylate metabolism. Recently, Chadwick et al[6] and Stauffer et al[7] suggested that increased absorption of dietary oxalate is the mechanism for hyperoxaluria in inflammatory bowel disease. All of the recent work has focused primarily on ileal disease and has been associated mainly with Crohn's disease rather than with ulcerative colitis. The association of uric acid urinary calculi following ileostomy for treatment of ulcerative colitis was studied earlier by Maratka and Nedbal[8] and by Breuer et al.[9]

Because the relationship of hyperoxaluria, urolithiasis, ileal disease, and inflammatory bowel disease is presumed, recent work has been in this area, but no comprehensive studies have been undertaken with prospective determination of urinary excretion of oxalate, calcium, magnesium, and uric acid. The aim of our study was to measure prospectively, in a large series of unselected patients with inflammatory bowel disease, urinary excretion of oxalate, calcium, magnesium, and uric acid, and to relate the findings to the clinical features encountered. Comparison would be made with control subjects and between patients with Crohn's disease and ulcerative colitis. Although there was primary interest in oxalate excretion in the urine, assessment was to be made which might detect any other metabolic abnormalities or differences. Finally, an attempt was to be made to determine clinically applicable predictive features arising from these observations which might identify patients most likely to develop renal calculi and to initiate any appropriate therapy.

Materials and methods

Patients were chosen for the study because they were admitted to the Cleveland Clinic Hospital from November 1971 to March 1973. The main criteria for selection was the patient's ability to have the appropriate studies performed; critically ill patients were not included in this study. Patients with abnormal serum creatinine values were also excluded. The control group were not hospitalized patients and constituted mainly healthy volunteers who were willing to undergo the required laboratory and roentgenographic studies. Patients with other types of gastrointestinal illness were not included. The character of the inflammatory bowel disease was well defined by previously established criteria[10] in all patients studied. No patients with inflammatory bowel disease of an unspecified nature, in which a diagnosis of ulcerative colitis or Crohn's disease could not be established, were included in this study.

Laboratory studies were performed on all patients. Serum calcium, magnesium, creatinine, uric acid, carbon dioxide, potassium, chloride, and sodium determinations were made. In addition, intravenous urograms were performed and specimens for urine cultures were obtained. The other studies included collection of 24-hour urine specimens for determination of pH, creatinine, calcium, magnesium, uric acid, and oxalate values. Oxalate was determined by the method of Archer et al.[11]

Clinical data

Eighty patients with Crohn's disease were included in the study. There were 42 men and 38 women in this

group. The mean age of the patients was 36.5 years and the mean duration of disease was 9.7 years. Among these 80 patients were 51 with disease involving the terminal ileum and right colon, 15 patients with involvement of the ileum and jejunum, and 14 patients with involvement initially confined to the colon. Of the 80 patients with Crohn's disease, 41 had undergone previous operations for the disease. These included 22 with resection of the terminal ileum, five with bypass of the terminal ileum, six with ileostomy without resection or bypass, and eight with ileorectal anastomosis and subtotal colectomy. Ten patients had undergone two operations.

There were 18 patients with ulcerative colitis, 10 men and eight women, with a mean age of 41.5 years. The average duration of disease was 8.2 years. Ten of the patients with ulcerative colitis had undergone some type of operation, including seven with ileostomy, two with ileorectal anastomosis and one with partial colectomy. Thus, 51 of the 98 patients with inflammatory bowel disease had undergone some type of operation and 10 patients had undergone two operations.

As indicated, there were 27 people in the control group, making a total of 125 patients studied from November 1971 to March 1973.

Collection of adequate urine specimens was the major difficulty with this unselected study. In addition to the 125 patients studied, 52 others had to be excluded because of inadequate urine collection for the 24-hour studies. The data adequacy was assessed by urinary creatinine and urine volume over the 24-hour period which was chosen for study. All patients were excluded who had 24-hour urinary creatinine values of less than 1,000 mg. The mean urinary volume for the 80 patients with Crohn's disease was 1,586 cc in 24 hours; for the 18 patients with ulcerative colitis, the mean volume was 1,489 cc in 24 hours; for the 27 controls, the mean urinary volume in 24 hours was 1,420 cc. The mean 24-hour creatinine excretion for the 80 patients with Crohn's disease was 1,321 mg; for the 18 patients with ulcerative colitis, the mean 24-hour urinary creatinine was 1,332 mg; for the 27 controls, the mean 24-hour urinary creatinine was 1,356 mg. Thus, these values allowed us to be reasonably certain of adequate collection of urine.

All patients and controls were on either a general hospital diet or a low residue diet during this study. Because there is a wide range of dietary oxalate[6, 7, 11, 12] no attempt was made to limit the dietary oxalate. However, whether or not this is clinically significant is very much in question.[6, 7] The usual American diet contains between 50 and 150 mg of oxalate.[13] A few foods, spinach, rhubarb, tea, cocoa, and parsley, contain large amounts of oxalate. Our laboratory used the method described by Archer et al[11] for determination of urinary oxalate. Work recently reviewed by Hodgkinson[12] continued to emphasize that "an appreciable part of the urinary oxalate is of endogenous origin" and thus only partly related to dietary oxalate. The recent studies by Chadwick et al[6] and Stauffer et al[7] indicated that there was an increased absorption of dietary oxalate rather than a great variation or significant increase in dietary oxalate which resulted in hyperoxaluria. Thus, despite this theoretical limitation, we felt that the study was clinically valid, primar-

Table 1. Urinary excretion in inflammatory bowel disease; average values

Substance (mg/24 hr)	Crohn's disease 80 patients	Ulcerative colitis 18 patients	Controls 27 patients
Calcium	159	197[2]	152
Uric acid	864	734	772
Magnesium	47[4]	48[3]	86
Oxalate	25[1]	21	18

[1] Statistically significant $p < .06$.
[2] Statistically significant $p < .05$.
[3] Statistically significant $p < .0005$.
[4] Statistically significant $p < .0001$.

ily since the goal was to evaluate unselected patients with inflammatory bowel disease and controls who were following their usual diets.

Results

The serum data were found to be within normal limits and the values for serum calcium, magnesium, uric acid, and creatinine, as well as sodium, potassium, chloride, and carbon dioxide, showed no differences among the three groups. No patient had an abnormal urogram (e.g., inflammatory bowel disease with resultant narrowing of the ureter) or a positive urine culture; patients who did were excluded from the study, since it could be presumed that renal calculi would be increased in patients with urinary stasis or infection or both.

Therefore, the study and analysis of data centered on the urinary excretion of calcium, uric acid, magnesium, and oxalate in 24 hours in patients with inflammatory bowel disease and in controls. The excretion of these substances was compared among the total group of patients (*Table 1*). All data were subjected to statistical analysis using a *t* test, and p values were given for significant data. All data were analyzed independently without knowledge of the clinical situation. Patients with Crohn's disease and ulcerative colitis had less magnesium excretion in the 24-hour period than the controls ($p < .0001$ and $p < .0005$, respectively). Likewise, the patients with Crohn's disease had higher amounts of oxalate in the urine in 24 hours than the controls ($p < .06$). It should be noted that the mean excretion of urinary oxalate among the control patients in this series was 18 mg in 24 hours. It has been shown that there is a considerable range in urinary excretion, generally considered to be between 10 and 40 mg per 24 hours. The mean excretion in the study by Archer et al[11] was 22 mg in 24 hours, and this range of excretion was also emphasized by Hodgkinson.[12]

The data were then analyzed according to the anatomic location of disease for the 80 patients with Crohn's disease (*Table 2*). There were 51 patients with ileocolic disease, 15 with Crohn's disease of the small intestine, and 14 with Crohn's disease involving the colon. The patients with ileocolic Crohn's disease had significantly lower urinary calcium ($p < .04$), magnesium ($p < .0006$), and oxalate ($p < .03$). Those with Crohn's disease of the small intestine had lower urinary magnesium ($p < .03$) and higher oxalate excretion ($p < .05$) when compared with patients with colonic Crohn's disease and ulcerative colitis and control patients.

Next, data on the influence of operation are listed in *Table 3*. Of the 98 patients with inflammatory bowel disease, 51 had 61 operations. The patients with ileal resection had less urinary magnesium ($p < .0001$) and more urinary oxalate ($p < .01$), highly

Table 2. Urinary excretion in inflammatory bowel disease; average values; influence of anatomic location of disease; Crohn's disease, 80 patients

Substance (mg/24 hr)	Ileocolic 51 patients	Small intestine 15 patients	Colon 14 patients	Ulcerative colitis 18 patients	Controls 27 patients
Calcium	113[2]	187	248	197	152
Uric acid	945	782	582	734	772
Magnesium	42[4]	48[3]	40	48	86
Oxalate	27[3]	29[1]	14	21	18

[1] Statistically significant $p < .05$.
[2] Statistically significant $p < .04$.
[3] Statistically significant $p < .03$.
[4] Statistically significant $p < .0006$.

Table 3. Urinary excretion in inflammatory bowel disease; average values; influence of operation

Substance (mg/24 hr)	Ileal resection 23 patients	Ileal bypass 6 patients	Ileostomy 19 patients	Ileorectal anastomosis 13 patients	Controls 27 patients
Calcium	130	102[1]	143	129	152
Uric acid	759	586[1]	746	698	772
Magnesium	31[5]	26[3]	38[4]	44[2]	86
Oxalate	33[3]	27	18	17	18

[1] Statistically significant $p < .07$.
[2] Statistically significant $p < .05$.
[3] Statistically significant $p < .01$.
[4] Statistically significant $p < .001$.
[5] Statistically significant $p < .0001$.

significant when compared with the controls. The patients with ileal bypass had significantly less urinary calcium ($p < .07$), uric acid ($p < .07$), and magnesium ($p < .01$) values, and those with ileostomy and ileorectal anastomosis had less urinary magnesium excretion ($p < .001$ and $p < .05$, respectively).

Therefore, a statistically significant pattern emerged from the results of the study based on the comparison listed above. There was significantly less urinary magnesium and significantly more urinary oxalate among patients with Crohn's disease, Crohn's disease involving the ileum, and Crohn's disease involving the ileum for whom an ileal resection had been performed.

Patients with renal calculi

Analysis of the data revealed that nine of the 98 patients with inflammatory disease had renal calculi. All nine patients had Crohn's disease with the diagnosis established prior to development of the renal calculus and thus represented 11% of the 80 patients with Crohn's disease in this study. There were six women and three men in this group; the mean age of these

Table 4. Urinary excretion in inflammatory bowel disease; average values; patients with renal calculi

Substance (mg/24 hr)	Renal calculi 9 patients	Total Crohn's group 80 patients	Ulcerative colitis 18 patients	Controls 27 patients
Calcium	53[3]	159	197	152
Uric acid	605	864	734	772
Magnesium	34[2]	47	48	86
Oxalate	33[1]	25	21	18

[1] Statistically significant $p < .01$.
[2] Statistically significant $p < .001$.
[3] Statistically significant $p < .0005$.

patients was 41 years. All had Crohn's disease of long duration with a mean duration of disease of 18 years. Eight of the nine patients had ileal disease and eight of the patients had undergone operation. One patient had colonic Crohn's disease, underwent an ileostomy, and later had a uric acid stone. All of the other patients were found to have calcium stones, by analysis, clinically, or roentgenographically. Six of these eight patients had undergone resection of the terminal ileum of at least 50 cm or more, and one had undergone an ileal bypass of approximately the same magnitude. One patient had ileal Crohn's disease and had not undergone an operation. Thus, eight of the nine patients had ileal disease and eight of the nine patients underwent operation (one with ileostomy had uric acid stones).

The urinary data for these nine patients were then analyzed and compared with the total group of patients with Crohn's disease, those with ulcerative colitis, and the controls (*Table 4*). It can be noted that there was a statistically significant decrease in urinary calcium ($p < .0005$) and magnesium ($p < .001$) excretion and statistically significant increase in urinary oxalate ($p < .01$) excretion in these nine patients. The mean urinary oxalate excretion was 33 mg in 24 hours, compared to 18 mg in 24 hours for the patients in the control group. Excluding three patients with low urinary oxalate excretion, including the one with uric acid stones, the six others had mean urinary oxalate values of 43 mg in 24 hours. Thus, a statistically significant difference emerged among the patients with renal calculi. Also, there was a statistical significance, both in a decrease in urinary calcium and magnesium excretion, and an increase in urinary oxalate excretion among such patients.

Statistical analysis

As indicated, all data were subjected to statistical analysis (*Tables 1 through 4*). As shown in *Table 1,* the patients with Crohn's disease had a moderately statistically significant increase in urinary oxalate and a highly significant decrease in urinary magnesium as compared with controls. When the anatomic location of Crohn's disease was identified (*Table 2*), it was shown that the highest significance was related to disease of the ileum. For the patients with small intestine disease and disease of the ileum, there was a moderately statistically significant increase

in urinary oxalate and decrease in urinary magnesium as compared with the patients with Crohn's disease involving the colon, ulcerative colitis, and the controls. When the influence of operation was evaluated (*Table 3*), it was further defined that the patients with ileal resection had more statistically significant increase in urinary magnesium than had been noted in any of the previous groups or subgroups. This decrease in urinary magnesium was also documented for all of the other patients with inflammatory bowel disease who underwent operation. The patients with renal calculi demonstrated the most highly statistical significance in the entire study, namely, the mean increase in urinary oxalate and mean decrease in urinary calcium and magnesium values.

Discussion

Previous studies concerned with inflammatory bowel disease, urolithiasis, and hyperoxaluria have been done on patients with renal stones or on those highly suspected of having stones. Therefore, it seemed useful to obtain data on an unselected group of patients with inflammatory bowel disease on a prospective basis to determine if the relationship with hyperoxaluria held true, and if quantitative values or other features could be obtained which might enable anticipation of renal stone development in inflammatory bowel disease. This study confirmed what might have been anticipated based on previous studies,[1-3, 6, 7] but is important, in our opinion, because it was carried out prospectively in a group of unselected but homogeneous patients with inflammatory bowel disease.

Of the patients with inflammatory bowel disease, the type of patient who might be anticipated to develop renal calculi is one with Crohn's disease of long duration involving the ileum. In our study, all patients with renal calculi had Crohn's disease of long duration with a mean of 18 years. All had ileal disease and six of the nine with renal calculi had undergone ileal resection of 50 cm or more. Six of the nine patients with renal calculi had urinary oxalate excretion higher than the mean of the control patients, although not as high as has been reported in previous studies.[1, 3] Mean hyperoxaluria was thus observed among patients with the following disorders: long standing Crohn's disease, with ileal disease or resection, and with renal calculi. This could very likely result from increased absorption of oxalate suggested by Stauffer et al.[7]

In addition, and less understood, were the highly statistically significant mean decreases in urinary excretion of calcium and magnesium found in these same patients. Decrease in urinary calcium was also suggested by data from Smith et al;[3] the basis of this finding may be increase in fecal loss. The presence of one uric acid stone in the series is not unexpected, since the patient had undergone a previous ileostomy, which is known to be predisposed to uric acid calculi because of aciduria and decreased urinary volume.[8, 9]

The decrease in urinary magnesium may influence the development of renal stones in inflammatory bowel disease by altering solubility of other crystalloids in the urine.

Even though this study does not relate directly to the two recent reports which emphasize the role of dietary oxalate,[6, 7] the value of a study of

unselected patients with inflammatory bowel disease is to determine the clinical setting in which renal calculi are likely to occur and thus be able to anticipate their development. Whether or not one would attempt to alter the dietary intake of oxalate by regulating the quantity of tea, spinach, rhubarb, cocoa, or parsley in the diet of patients with Crohn's disease can only be a conjecture, and especially so since the exogenous oxalate intake does not appear to be as significant as the enhanced absorption of dietary oxalate indicated by these two studies. Therefore, probably the exogenous oxalate would not be as significant as one might believe because of the relatively low percentage of oxalate absorbed under normal circumstances.[6, 7, 11, 12]

The purpose of this study was not to evaluate therapy in any form, and thus the effectiveness of the use of cholestyramine[3] or taurine[2] could not be evaluated. Nevertheless, the consistent findings on a prospective study of this sort, in our opinion, respresents a valuable addition to the understanding of the phenomenon of development of renal calculi among patients with inflammatory bowel disease.

Summary

Recently, emphasis has been placed on hyperoxaluria in Crohn's disease and its relationship to urolithiasis. An unselected prospective study of 125 patients was undertaken from November 1971 to March 1973. There were 80 patients with Crohn's disease, 18 with ulcerative colitis, and 27 controls. Data were analyzed statistically and comparison was made among groups, anatomic location of the disease, and operation performed. Investigative studies included serum electrolytes, urine cultures, serum and 24-hour urinary creatinine, calcium, magnesium, oxalate, uric acid, and urography. No statistical differences were found in data on serum, urine cultures, urinary creatinine values, and urography.

Patients with ulcerative colitis had less urinary magnesium excretion ($p < .005$) and more calciuria ($p < .05$) than the controls. Those with Crohn's disease had less urinary magnesium ($p < .0001$) and more oxaluria ($p < .06$) than the controls. Of the patients with Crohn's disease, urinary oxalate levels were higher with ileal disease than with colon involvement, and maximum after ileal resection ($p < .01$).

Nine patients (11%) had urolithiasis. All had longstanding ileal Crohn's disease (mean 18 years), eight had operations, five had ileal resections. All but one had calcium stones. Urinary oxalate was increased ($p < .01$) and magnesium and calcium values were decreased.

In this series of patients with inflammatory bowel disease, urolithiasis was observed in those with ileal Crohn's disease of long duration, often after ileal resection, and with hyperoxaluria and decreased urinary calcium and magnesium excretion.

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References

1. Dowling RH, Rose GA, Sutor DJ: Hyperoxaluria and renal calculi in ileal-disease. Lancet 1: 1103–1106, 1971.
2. Admirand WH, Earnest DL, Williams HE: Hyperoxaluria and bowel disease. Trans Assoc Am Physicians 84: 307–312, 1971.

3. Smith LH, Fromm H, Hofmann AF: Acquired hyperoxaluria, nephrolithiasis, and intestinal disease. Description of a syndrome. N Engl J Med **286:** 1371–1375, 1972.
4. Hofmann AF, Tacker MM, Fromm H, et al: Acquired hyperoxaluria and intestinal disease. Evidence that bile acid glycine is not a precursor of oxalate. Mayo Clin Proc **48:** 35–42, 1973.
5. Admirand WH: Hyperoxaluria and bowel disease. N Engl J Med **286:** 1412–1413, 1972.
6. Chadwick VS, Modha K, Dowling RH: Mechanism of hyperoxaluria in patients with ileal dysfunction. N Engl J Med **289:** 172–176, 1973.
7. Stauffer JQ, Humphreys MH, Weir GJ: Acquired hyperoxaluria with regional enteritis after ileal resection. Role of dietary oxalate. Ann Intern Med **79:** 383–391, 1973.
8. Maratka Z, Nedbal J: Urolithiasis as a complication of the surgical treatment of ulcerative colitis. Gut **5:** 214–217, 1964.
9. Breuer RI, Gelzayd EA, Kirsner JB: Urinary crystalloid excretion in patients with inflammatory bowel disease. Gut **11:** 314–318, 1970.
10. Farmer RG, Hawk WA, Turnbull RB Jr: Regional enteritis of the colon: a clinical and pathologic comparison with ulcerative colitis. Am J Dig Dis **13:** 501–514, 1968.
11. Archer HE, Dormer AE, Scowen EF, et al: Studies on the urinary excretion of oxalate by normal subjects. Clin Sci **16:** 405–411, 1957.
12. Hodgkinson A: Determination of oxalic acid in biological material. Clin Chem **16:** 547–557, 1970.
13. Zarembski PM, Hodgkinson A: The oxalic acid content of English diets. Br J Nutr **16:** 627–634, 1962.