Scanning Microscopy

Volume 7 | Number 1 Article 40

10-31-1992

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Scanning Microscopy, Vol. 7, No. 1, 1993 (Pages 371-380)
Scanning Microscopy International, Chicago (AMF O'Hare), IL 60666 USA

0891-7035/93$5.00+.00

RENAL STONE FORMATION IN PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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(Received for publication May 11, 1992, and in revised form October 31, 1992)

Abstract

Kidney stones are more common in patients with inflammatory bowel disease (IBD) than in the general population. The main lithogenetic risk factors were evaluated in patients affected by Crohn's disease and ulcerative colitis. Our results show the presence of several factors, besides hyperoxaluria, in patients with IBD although their behaviour appears different in Crohn's disease and ulcerative colitis at pre- and post-operative stages. Before surgery in patients with Crohn's disease we found a decreased citrate ($p < 0.001$) and magnesium ($p < 0.005$) excretion together with a low urinary volume ($p < 0.001$) and pH ($p < 0.005$). After surgery patients with Crohn's disease showed a further reduction of magnesium and citrate. Patients with ulcerative colitis before surgery showed a reduced citrate excretion ($p < 0.05$) and a more acidic pH ($p < 0.05$) than healthy subjects. Surgical treatment of proctocolectomy with ileal pouch-anal anastomosis seems to increase the risk of stone formation; in fact, after surgery we observed a relevant decrease of urinary volume ($p < 0.001$), pH ($p < 0.0001$) and urinary excretion of citrate ($p < 0.0001$) as well as magnesium ($p < 0.005$). Patients with IBD seem to be at greater risk of stone formation than patients with idiopathic calcium lithiasis; in fact, they show a lower excretion of citrate ($p < 0.001$) and magnesium ($p < 0.001$) together with a low urinary pH ($p < 0.001$) and volume ($p < 0.001$). Urinary volume reduction is probably one of the major risk factors together with the decrease of small molecular weight inhibitors that is a constant finding in all patients with IBD.

Key Words: Renal stones, inflammatory bowel disease, Crohn's disease, ulcerative colitis, risk factors.

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Introduction

Renal stone formation is a well-recognized complication of inflammatory bowel disease [4, 10, 13, 20, 23, 24]. In 1968, Gelzayd *et al.* [13] examined 885 patients with chronic inflammatory bowel disease (IBD) and found a renal stone incidence of 7.2%; 72% of these stones were composed of calcium oxalate. According to the results of Smith [23], and Dobbins and Binder [10], the nephrolithiasis incidence in patients with IBD is about twice that of the general population. Stones are composed mostly of calcium oxalate although uric acid stones form far more frequently in these patients. Therefore, the ratio between these two types of renal stones appears to be 3:1, a ratio significantly lower than that observed in idiopathic calcium stone formers (12:1) [9]. According to some authors [20], this complication might be linked to surgical treatment more than intestinal disease and/or medical treatment. Renal stone formation incidence in patients submitted to surgical treatment ranges from 5% to 15% [14, 16, 20, 22].

Examination of urine in patients with IBD reveals several abnormalities that, except for oxalate [11], are due to malabsorption of water, alkali and protein. These urinary alterations include urinary volume decrease [20, 23], acidic urinary pH [23, 24], hypomagnesiuria [4, 23, 24], pyrophosphate reduced excretion [24], hypocitraturia [23] and enteric hyperoxaluria [25]. Enteric hyperoxaluria is primarily due to increased intestinal absorption of dietary oxalate at colon level [7, 8]; other studies have suggested that enteric hyperoxaluria might depend on high dietary intake of protein or on reduced bacterial degradation of oxalate [1]. Enteric hyperoxaluria was considered to be one of the major risk factors promoting renal stone formation in patients with IBD submitted to ileal resection and/or ileostomy [13, 20].

The aim of this work was to establish in 66 patients affected by Crohn's disease or ulcerative colitis the following points:

a) urinary changes in the main risk-factors before surgical treatment;

b) urine chemistry changes caused by surgical procedures;

c) different behaviour of urinary abnormalities in

Table 1. Ulcerative colitis: Risk factors urinary excretion.
Values are expressed as mean ± standard deviation (SD); p values are given for healthy subjects versus patients with ulcerative colitis before (UC) and after surgery (IPAA), and for UC versus IPAA group.

		HS	UC	IPAA
Uric Acid	mg/24h	514.0 ± 147	403.0 ± 223	468.4 ± 157
Ca	mg/24h	205.0 ± 112$^{\#}$	287.0 ± 182$^{\#\wedge}$	156.7 ± 97.4$^{\wedge}$
Mg	mg/24h	87.1 ± 35.1$^{\$}$	82.6 ± 48$^{£}$	46.5 ± 17$^{\$£}$
PO_4	mg/24h	693.0 ± 337	528.0 ± 361	780.5 ± 291
Oxalate	mg/24h	27.1 ± 10.4$^{\wedge\wedge}$	17.7 ± 6.9$^{\wedge}$	16.6 ± 6.7$^{\wedge}$
Citrate	mg/24h	654.0 ± 297$^{\wedge\&}$	386.0 ± 207$^{\wedge}$	231.2 ± 161$^{\&}$
GAGs	μM/24h	35.5 ± 14.9	38.1 ± 20.3	34.3 ± 13.3
Volume	ml/min	1.01 ± 0.4$^{\$}$	0.96 ± 0.53$^{"}$	0.57 ± 0.23$^{\$"}$
pH		5.84 ± 0.32$^{*\&}$	5.56 ± 0.57*	5.19 ± 0.35$^{\&}$

$^{\#}0.05 < p < 0.10$; $^{*}p < 0.05$; $^{"}p < 0.02$; $^{\wedge}p < 0.01$; $^{£}p < 0.005$; $^{\$}p < 0.001$; $^{\&}p < 0.0001$.

Table 2. Ulcerative colitis: Urinary factors concentration.
The values are expressed as mean ± SD; p values are given for healthy subjects (HS) versus patients with ulcerative colitis before (UC) and after surgery (IPAA), and for UC versus IPAA group.

		HS	UC	IPAA
Uric Acid	mg/dl	45.3 ± 19.8$^{"\wedge}$	35.5 ± 24.2$^{"\wedge}$	62.5 ± 24.4$^{\wedge\wedge}$
Ca	mg/dl	16.4 ± 8.9$^{\|"}$	22.5 ± 10.8$^{\|}$	20.1 ± 12.5$^{"}$
Mg	mg/dl	7.1 ± 2.5*	6.0 ± 1.5	5.9 ± 2.8*
PO_4	mg/dl	71.4 ± 25.4$^{\wedge\&}$	42.9 ± 23.2$^{\wedge\&}$	106.5 ± 55$^{\&\&}$
Oxalate	mg/l	14.9 ± 8.6$^{\wedge}$	15.4 ± 6.8$^{"}$	22.2 ± 10.3$^{\wedge"}$
Citrate	mg/l	616.0 ± 316$^{\$\#}$	360.0 ± 295$^{\$}$	297.0 ± 283$^{\#}$
GAGs	μM/l	31.3 ± 18$^{\wedge}$	30.5 ± 12.5$^{"}$	46.0 ± 25$^{\wedge"}$

$^{"}0.05 < p < 0.10$; $^{*}p < 0.02$; $^{\|}p < 0.01$; $^{\$}p < 0.05$; $^{\wedge}p < 0.005$; $^{\&}p < 0.001$; $^{\#}p < 0.0001$.

patients with IBD and in patients with idiopathic calcium lithiasis.

Material and Methods

The study included 66 patients affected by ulcerative colitis (N = 38) or Crohn's disease (N = 28). The disease activity of Crohn's disease was assessed by Crohn's disease activity index (CDAI), described by Best *et al.* [3]; the disease was considered to be quiescent at CDAI < 150, and active at CDAI > 150. The activity of ulcerative colitis was assessed by the criteria suggested by Truelove and Witts [26]: according to these authors the disease was classified into 3 categories: mild, moderate and severe. Disease activity of Crohn's disease was quiescent in 24 cases (12 unresected and 12 resected) and active in 4 cases. Six patients with ulcerative colitis had a mild disease, 4 patients had a moderate disease. Steatorrhea was not present in any of the cases. The indication for surgery in patients with Crohn's disease were: recurrent small bowel obstruction (N = 6), intestinal fistulas (N = 5) and laparotomy for suspected appendicitis (N = 3). All but 5 patients with ulcerative colitis had pancolitis and underwent surgical treatment either for continuous active disease unresponsive to medical treatment (N = 18) or acute severe colitis (N = 10).

The patients were subdivided into 4 groups according to the period in which metabolic study was performed:

a) Patients with ulcerative colitis (UC) before surgery (8 males and 2 females with mean age of 34.4 ± 11.1 years).

b) Patients with ulcerative colitis submitted to proctocolectomy with ileal pouch-anal anastomosis (IPAA) (20 males and 8 females with mean age of 31.6 ± 10.8 years).

c) Patients with Crohn's disease (CD) at preoperative stage (8 males and 6 females with mean age of 32.0 ± 5.5 years).

d) Patients with Crohn's disease submitted to ileal resection and right hemicolectomy with end-to-end ileotransversostomy (IRRHC) (6 males and 8 females with mean age of 40.3 ± 15 years).

All the subjects were studied in an ambulatory setting on their normal home diet and did not receive any oral or parenteral supplementation, or drugs at time of the urine analysis. A normal renal function evaluated as endogenous creatinine clearance (GFR > 85 ml/min)

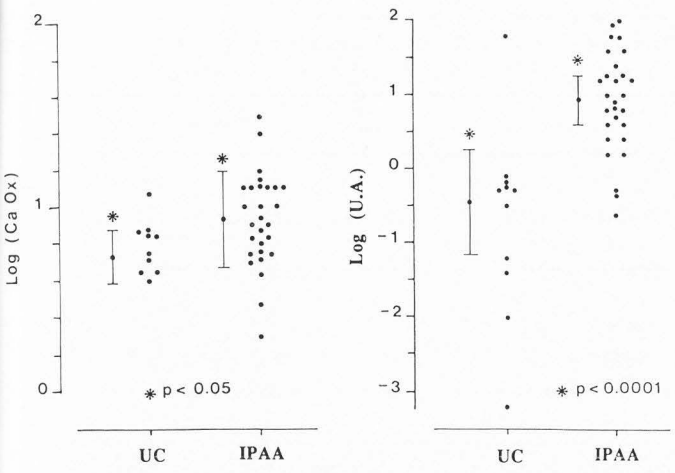

Figure 1. Relative supersaturation indices for calcium oxalate and uric acid in patients with ulcerative colitis before (UC) and after surgery (IPAA). The bars indicate standard deviation (SD).

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was present in all cases; proteinuria, urinary tract infection and renal tubular acidification disorders were absent.

The metabolic evaluation included measurements of serum and urinary creatinine, uric acid, calcium, magnesium. Additional urinary analytes included oxalate, citrate, glycosaminoglycans (GAGs), pH and urinary volume. Each value for urinary analytes excretion was based on two consecutive 24-hours collections; the patients were carefully instructed as to the proper procedure to collect 24-hours urine specimens which were collected in plastic bottles with thymol and concentrated hydrochloric acid as preservatives. The same metabolic study was performed on 100 patients with idiopathic calcium oxalate nephrolithiasis (66 males and 34 females) with a mean age of 40.1 $\pm$ 14.2 years.

Enzymatic methods were employed to determine oxalate and citrate [5, 17]; GAGs assay was performed according to the Samuell method [21]. The other urinary analytes were measured with conventional methods as already described [6]. The normal values of all parameters were obtained in 51 healthy subjects (HS) (25 males and 26 females) with a mean age of 36.1 $\pm$ 14.3 years, previously examined [5].

The statistical study was done with Student's t-test. Relative supersaturation indices for uric acid and calcium oxalate were obtained for each patient from nomograms [18].

Results

In this paper, the data of the urinary stone risk factors in patients with IBD, who showed a renal stone incidence of 8.3% at preoperative stage and of 11.9% after surgery, are reported. The results obtained in our patients are considered separately according to the different types of IBD.

Table 1 summarizes the results obtained in patients with ulcerative colitis before and after surgery. Patients of the UC group showed a higher calcium excretion than HS even though this data did not reach statistical significance ($t = 1.89$; $0.05 < p < 0.10$). After surgery urinary calcium excretion decreased significantly in the group of patients submitted to proctocolectomy with ileal pouch-anal anastomosis (IPAA) when compared with UC group ($t = 2.65$; $p < 0.01$), while it was similar to the HS group. Patients with ulcerative colitis displayed a significantly lower excretion of urinary oxalate both before ($t = 2.74$; $p < 0.01$) and after surgery ($t = 4.42$; $p < 0.001$).

The results of statistical tests of the data in Table 2 were as follows: Citrate urinary excretion in patients with ulcerative colitis was significantly lower both before ($t = 2.72$; $p < 0.01$) and after surgery ($t = 6.02$; $p < 0.0001$) than in HS. Urinary pH too resulted more acid before surgery than in HS ($t = 2.19$; $p < 0.05$) and even more so after surgical treatment ($t = 7.28$; $p < 0.0001$). The magnesium urinary excretion of the UC group showed a relevant lowering both before ($t = 3.52$; $p < 0.005$) and after surgery ($t = 4.31$; $p < 0.001$) in comparison with HS. Patients of the IPAA group showed also a significant decrease of urinary volume in comparison with HS ($t = 4.63$; $p < 0.001$) and UC ($t = 2.60$; $p < 0.02$) subjects. The decrease of urinary volume observed in the IPAA group induced a significant increase of urinary concentration of uric acid ($t = 3.05$; $p < 0.005$), oxalate ($t = 1.94$; $0.05 < p < 0.10$), and GAGs ($t = 1.86$; $0.05 < p < 0.10$) observed in the UC group as summarized in Table 2. Moreover the IPAA concentration of uric acid ($t = 3.4$; $p < 0.005$), calcium ($t = 1.94$; $0.05 < p < 0.10$), and GAGs ($t = 3.01$; $p < 0.005$) was higher than that of HS. Citrate urinary concentration showed a progressive lowering in UC ($t = 2.36$; $p < 0.05$) and IPAA ($t = 4.45$; $p < 0.0001$) when compared with HS. The increase of uric acid, calcium and oxalate concentration associated with a lowering of pH and magnesium and citrate concentration induced a relevant increase of relative supersaturation indices for calcium oxalate ($p < 0.05$) (Fig. 1) and uric acid ($p < 0.001$) (Fig. 1) from pre- to post-operative stage.

These data suggest a high probability of crystal formation; in fact in our study we found crystalluria in patients with ulcerative colitis only after surgical treatment. Crystalluria incidence was 30% and it was composed as follows: 93% calcium oxalate dihydrate (CaOxD) (Fig. 2) and 7% uric acid. In these patients CaOxD aggregates (Fig. 3) were present in 11.1% of the cases. Oxalate concentration was significantly higher in patients with crystals than in those without crystals ($t = 2.88$; $p < 0.01$) and even higher in those with aggregates.

The results obtained in patients with Crohn's disease (and the results of the statistical tests) were as follows (summarized in Table 3): urinary magnesium excretion resulted lower than in HS both before surgery

Table 3. Crohn's disease: Risk factors urinary excretion.
Values are expressed as mean ± SD; p values are given for healthy subjects (HS) versus patients with Crohn's disease before (CD) and after surgery (IRRHC), and for CD versus IRRHC group.

		HS	CD	IRRHC
Uric Acid	mg/24h	514.0 ± 147	440.0 ± 151	374.0 ± 177
Ca	mg/24h	205.0 ± 112	178.0 ± 131	166.0 ± 104
Mg	mg/24h	87.1 ± 35.1$^{\wedge}$	54.4 ± 26$^{\wedge\$}$	35.2 ± 25.4$^{\$}$
PO_4	mg/24h	693.0 ± 337	742.0 ± 179	617.0 ± 268
Oxalate	mg/24h	27.1 ± 10.4	22.3 ± 7.7	27.2 ± 13.5
Citrate	mg/24h	654.0 ± 297**	338.0 ± 233*	215.0 ± 253*
GAGs	μM/24h	35.5 ± 14.9	37.3 ± 14.7	29.6 ± 18.1
Volume	ml/min	1.01 ± 0.4*	0.56 ± 0.15$^{*\#}$	0.86 ± 0.41$^{\#}$
pH		5.84 ± 0.32$^{\wedge *}$	5.48 ± 0.54$^{\wedge}$	5.28 ± 0.31*

$^{\$}$ $0.05 < p < 0.10$; $^{\#}p < 0.02$; $^{\wedge}p < 0.005$; $^{*}p < 0.001$.

Table 4. Crohn's disease. Urinary factors concentration.
Values are expressed as mean ± SD; p values are given for healthy subjects (HS) versus patients with Crohn's disease before (CD) and after (IRRHC) surgery, and for CD versus IRRHC group.

		HS	CD	IRRHC
Uric Acid	mg/dl	45.3 ± 19.8$^{£*}$	57.2 ± 21.6$^{£\wedge}$	31.1 ± 17.2$^{*\wedge}$
Ca	mg/dl	16.4 ± 8.9$^{\$}$	21.4 ± 15.9$^{\$}$	14.4 ± 6.3
Mg	mg/dl	7.1 ± 2.5$^{\#}$	6.8 ± 2.8$^{\#}$	2.7 ± 1.7$^{\#\#}$
PO_4	mg/dl	71.4 ± 25.4$^{*\$}$	92.6 ± 46.2**	55.9 ± 33.1$^{\$*}$
Oxalate	mg/l	14.9 ± 8.6$^{\&*}$	29.9 ± 13.8$^{\&*}$	22.2 ± 11.4**
Citrate	mg/l	616.0 ± 316$^{\$\#}$	422.0 ± 260$^{\$\wedge}$	174.0 ± 294$^{\#\wedge}$
GAGs	μM/l	31.3 ± 18	49.9 ± 23.8$^{"}$	26.6 ± 19.1$^{"}$

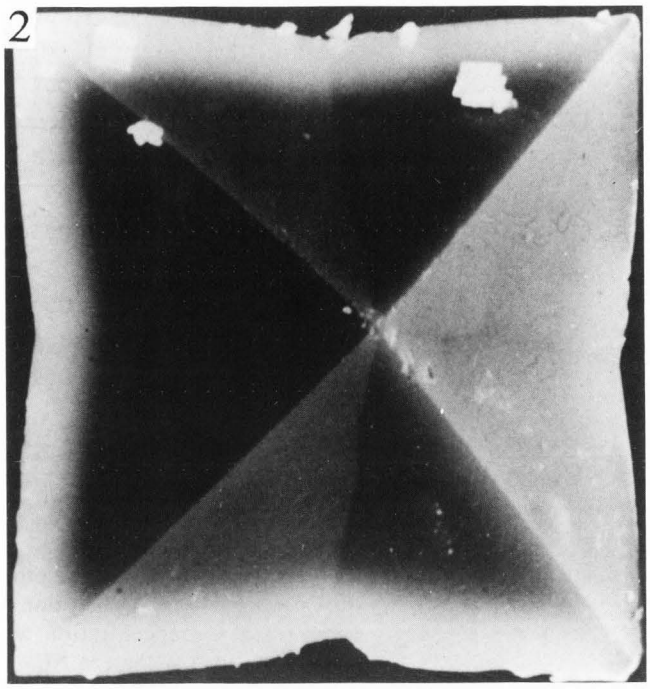
$^{£}$ $0.05 < p < 0.10$; $^{\$}p < 0.05$; $^{*}p < 0.02$; $^{"}p < 0.01$; $^{\wedge}p < 0.005$; $^{\&}p < 0.001$; $^{\#}p < 0.0001$.

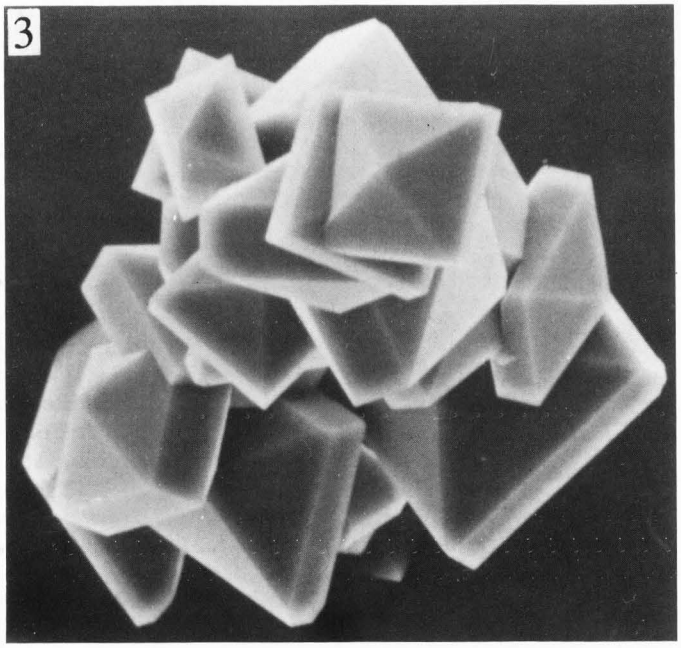
($t = 3.24$; $p < 0.005$) and after surgery ($t = 5.39$; $p < 0.001$). Patients with Crohn's disease also showed before ($t = 3.67$; $p < 0.001$) and after surgery ($t = 5.05$; $p < 0.001$) a significant decrease of citrate excretion in comparison with HS. Urinary pH too resulted more acid than in HS before surgery ($t = 3.17$; $p < 0.005$) and even more so after surgical treatment ($t = 5.84$; $p < 0.001$). Patients of the CD group showed also a relevant decrease in urinary volume in comparison with HS ($t = 2.57$; $p < 0.02$); after surgery patients with Crohn's disease showed an increase of urinary volume ($t = 2.63$; $p < 0.02$).

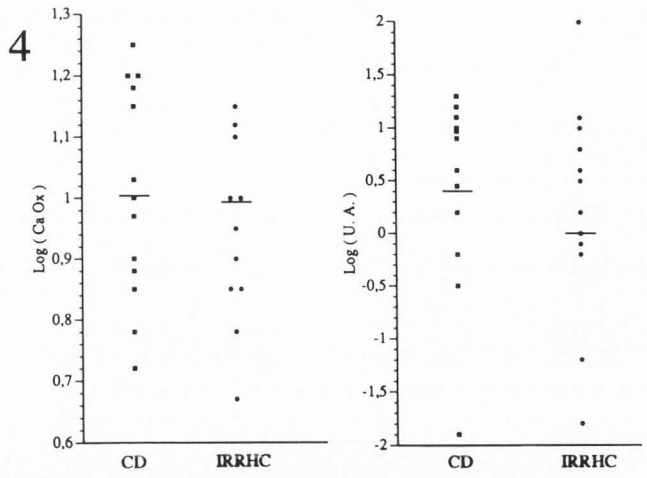
The contrasting behaviour of urinary volume in patients with Crohn's disease before and after surgical treatment caused an opposite modification of urinary analyte concentration, except for that of citrate and magnesium (Table 4) that resulted higher in the CD group in comparison with both HS and IRRHC groups. On the contrary, the CD group citrate concentration ($t = 2.07$; $p < 0.05$) was significantly lower than in HS, with a further relevant lowering after surgery (IRRHC versus HS: $t = 4.94$; $p < 0.0001$; CD versus IRRHC: $t = 2.85$; $p < 0.01$) (Table 4). Magnesium concentration showed a significant decrease only after surgical treatment ($p < 0.0001$) (Table 4). The study of relative supersaturation indices for uric acid and namely for calcium oxalate showed no significant modification before and after surgery (Fig. 4) even though a larger dispersion of the data was present.

In patients with Crohn's disease, crystalluria incidence at preoperative stage was 30.7% and decreased after surgery to 23.5%. Furthermore, before surgery only calcium oxalate dihydrate (CaOxD) crystals (Fig. 2) were present in urine; after surgery CaOxD crystals were present in 50% of the patients while the other 50% showed uric acid crystals (Fig. 5). At the preoperative stage patients with crystals showed a greater calcium concentration ($t = 3.64$; $p < 0.005$) in comparison with patients without crystals. On the contrary no difference was found in oxalate and uric acid concentration between patients with and without crystalluria. After surgery, citrate excretion was reduced in all subjects but principally in patients with crystalluria which showed a severe hypocitraturia (68.2 ± 33.2). Moreover, patients without crystalluria showed a greater urinary volume ($t = 2.54$; $p < 0.02$) and a less acidic urinary pH.

According to some authors [5], renal stone formation in patients with IBD is more frequent after surgical







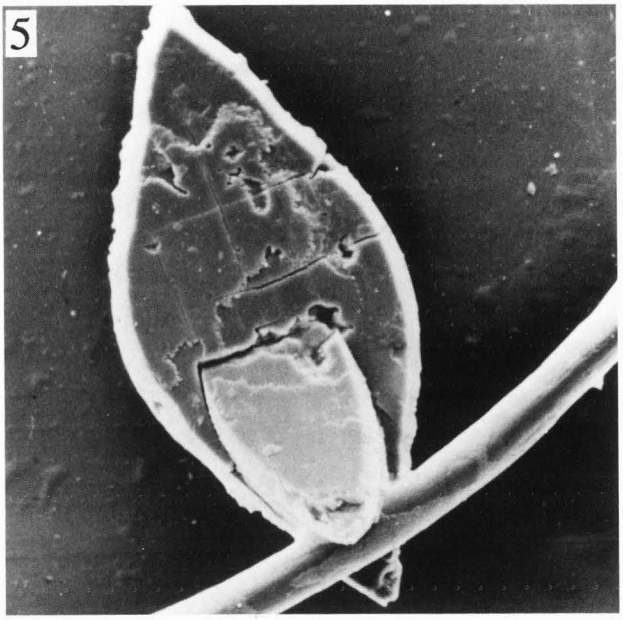


Figure 2. Calcium oxalate dihydrate single crystal.

Figure 3. Calcium oxalate dihydrate aggregate.

Figure 4. Relative supersaturation indices for calcium oxalate and uric acid in patients with Crohn's disease before (CD) and after surgery (IRRHC).

Figure 5. Uric acid aggregate.

treatment; therefore, a comparative analysis was performed on the urinary excretion of the main lithogenetic factors between a group of patients with idiopathic calcium oxalate nephrolithiasis (SF), and IRRHC and IPAA groups (Table 5). Urinary calcium excretion resulted lower both in IRRHC ($t = 2.99$; $p < 0.001$) and in IPAA ($t = 4.46$; $p < 0.001$) than in SF. Urinary magnesium too resulted lower in IRRHC ($t = 6.52$) as well as in IPAA group ($t = 7.11$; $p < 0.0001$) when compared with SF. Patients both of IRRHC ($t = 1.88$; $0.05 < p < 0.10$) and IPAA groups ($t = 7.26$; $p < 0.001$) showed a lower excretion of oxalate in comparison with SF. SF displayed also a higher excretion of uric acid in comparison with IRRHC ($t = 3.47$; $p < 0.005$) and IPAA group ($t = 3.23$; $p < 0.005$). Oxalate urinary excretion appeared reduced in IRRHC ($t = 1.88$; $0.05 < p < 0.10$) and in IPAA ($t = 7.26$; $p < 0.001$) subjects.

Table 5. Urinary excretion of the main risk factors in stone formers (SF) and in patients with IBD after surgery (IPAA, IRRHC).

Values are expressed as mean ± SD; p values are given for stone-formers (SF) versus patients with Crohn's disease (IRRHC) and ulcerative colitis (IPPA) after surgery, or for IRRHC versus IPAA group.

		SF	IPAA	IRRHC
Uric Acid	mg/24h	647.5 ± 298$^{\pounds\pounds}$	468.4 ± 157$^{\pounds}$	374.0 ± 177$^{\pounds}$
Ca	mg/24h	257.0 ± 107$^{\#\pounds}$	156.7 ± 97$^{\#}$	166.0 ± 104$^{\pounds}$
Mg	mg/24h	83.5 ± 26$^{\#\#}$	46.5 ± 17$^{\#}$	35.2 ± 24$^{\#}$
Oxalate	mg/24h	33.7 ± 12$^{\&\#}$	27.2 ± 13$^{\&}$	16.6 ± 6.7$^{\#}$
Citrate	mg/24h	468.0 ± 204$^{\#\#}$	215.0 ± 253$^{\#}$	231.2 ± 161$^{\#}$
GAGs	μM/24h	30.5 ± 7.4$^{\wedge}$	34.3 ± 13	29.6 ± 18
Volume	ml/min	1.52 ± 0.49$^{\$\#}$	0.57 ± 0.23$^{\$}$	0.86 ± 0.41$^{\#}$
pH		5.79 ± 0.69$^{\#*}$	5.19 ± 0.35$^{\#}$	5.28 ± 0.31*

$^{\&}$ 0.05 <p< 0.10; $^{\wedge}$p < 0.025; *p < 0.01; $^{\pounds}$p < 0.005; $^{\#}$p < 0.001; $^{\$}$p < 0.0001

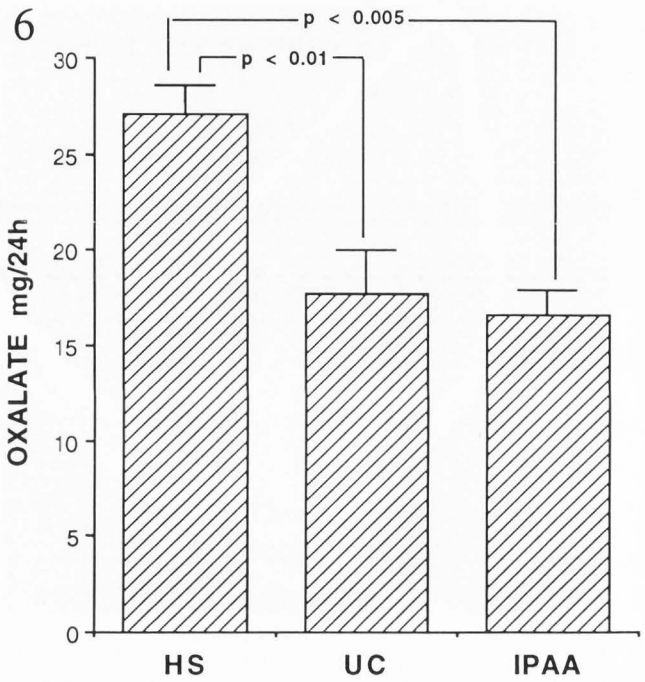


Figure 6. Oxalate urinary excretion in healthy subjects (HS) and in patients with ulcerative colitis before (UC) and after surgery (IPAA). Values are mean ± SE.

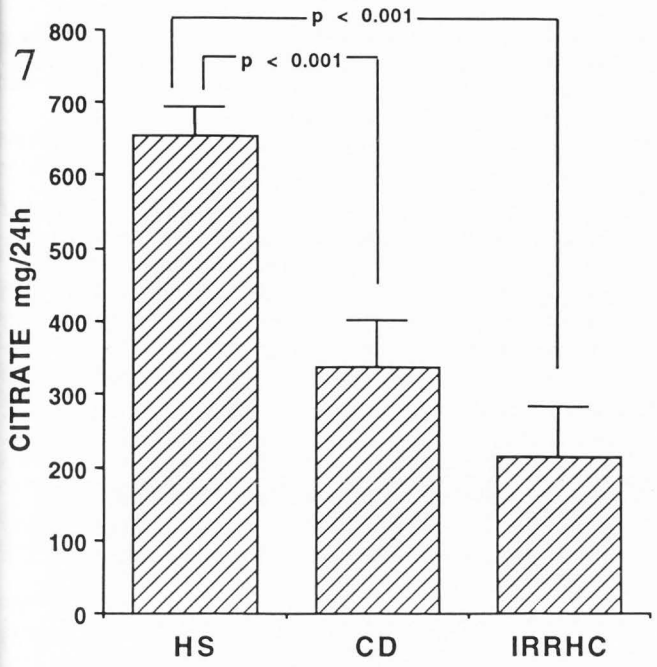
Citrate urinary excretion too was lower in IRRHC ($t = 4.22$; $p < 0.001$) and in IPAA ($t = 5.68$; $p < 0.001$) groups when compared with the SF group. Urinary volume appeared significantly lower in IRRHC ($t = 4.82$; $p < 0.001$) and in IPAA ($t = 9.93$; $p < 0.001$) than in SF. On the contrary, GAGs excretion was similar (IRRHC) or even higher (IPAA: $t = 2.02$; $p < 0.025$) than in SF. Finally, urinary pH too was lower in IRRHC ($t = 2.75$; $p < 0.001$) and in IPAA ($t = 4.45$; $p < 0.001$) than in SF. The decreased urinary excretion of calcium, magnesium, uric acid and oxalate observed in patients with IBD after surgical treatment might be explained by the lower urinary volume that, on the other hand, increases their concentration with the exception of the citrate. In fact, citrate urinary concentration was lower in patients with IBD after surgery than in SF.

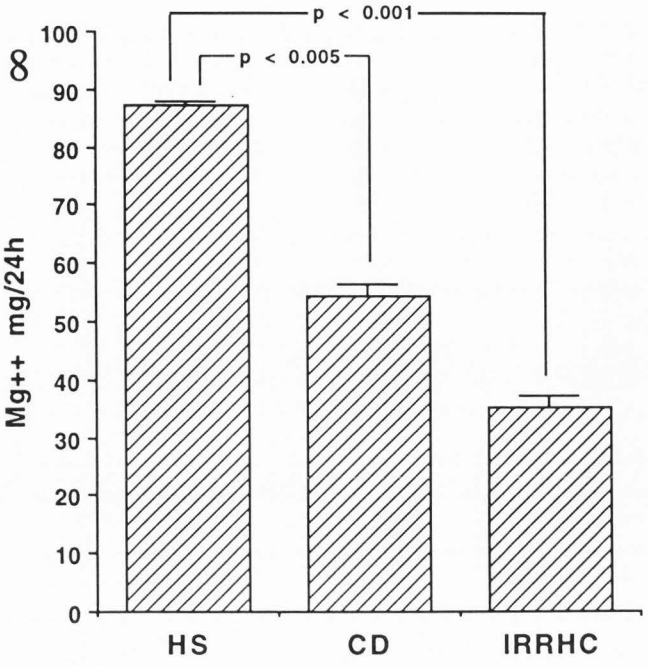
Discussion and Conclusions

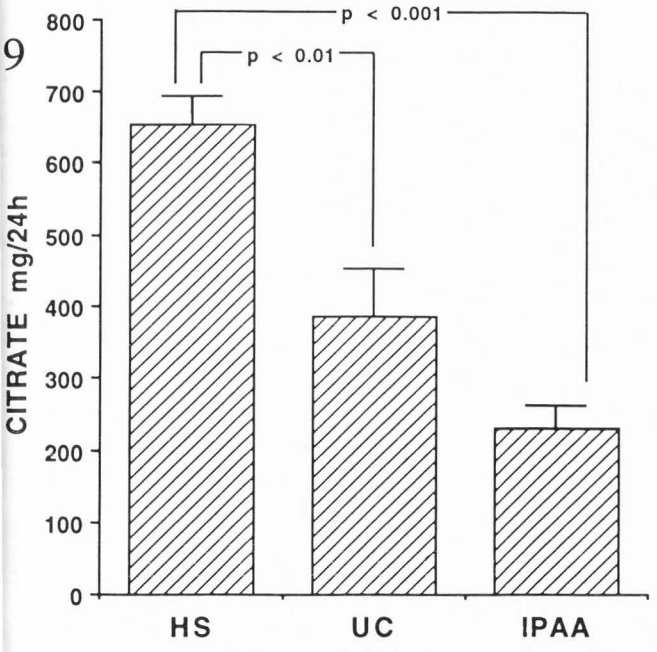
Renal stone formation has been shown to be a common complication in patients with IBD before and after surgery with a higher frequency than in the general population [10]; in fact, we found a renal stone incidence of 8.3% at preoperative stage and of 11.9% after surgery.

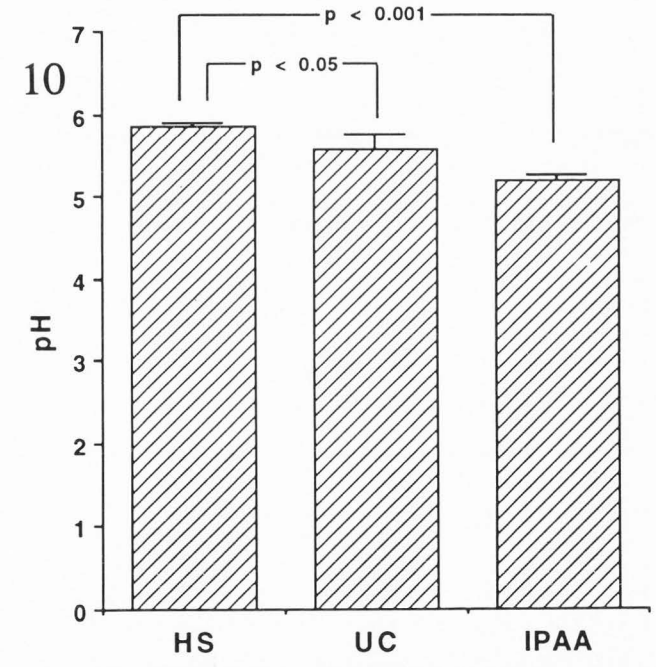
Several pathogenetic mechanisms promoting stone formation have been suggested [2, 5, 6, 21] and among them a pivotal role was attributed to the presence of enteric hyperoxaluria linked to a greater oxalate absorption at colon level. This mechanism was observed especially in patients with Crohn's disease of the distal ileum without contemporary colon impairment, submitted to surgical treatment. Furthermore, urinary oxalate excretion is usually normal, or even lower than in normal subjects, in patients who have undergone total colectomy (Fig. 6). Our results show that several factors besides hyperoxaluria may be present in patients with IBD before and after surgical treatment even though their behaviour appears to be different in Crohn's disease and ulcerative colitis at pre- and postoperative stages.

In patients with Crohn's disease, the main risk factors seem to be a decreased citrate (Fig. 7) and magnesium (Fig. 8) excretion together with a low urinary volume and pH (Table 3). Urinary volume reduction is probably one of the major risk factors inducing in these patients a higher concentration of oxalate, calcium and uric acid in comparison with HS (Table 4). Thus, uric acid and calcium oxalate saturation indices were increased in almost all patients to the level of spontaneous precipitation (Fig. 4). Surgical treatment did not modify their degree of urinary saturation (Fig. 4). At this stage, patients with Crohn's disease displayed a further









Figures 7 and 8. Citrate (**Figure 7**) and magnesium (**Figure 8**) urinary excretion in healthy subjects (HS) and in patients with Crohn's disease before (CD) and after surgery (IRRHC). Values are mean ± SE.

Figures 9 and 10. Citrate urinary excretion (**Figure 9**) and urinary pH (**Figure 10**) in healthy subjects (HS) and in patients with ulcerative colitis before (UC) and after surgery (IPAA). Values are mean ± SE.

lowering of magnesium (Fig. 8) and citrate (Fig. 7) excretion although the urinary volume was increased. Moreover, hypocitraturia incidence increased from 38% before to 60.5% after surgery.

Also, patients with ulcerative colitis before surgery presented some urinary abnormalities such as a reduced citrate excretion (Fig. 9) and a more acidic urinary pH that might promote uric acid and/or calcium oxalate renal stone formation. Surgical treatment of proctocolectomy with ileal pouch-anal anastomosis seems to increase the risk of uric acid and/or calcium oxalate stone formation. In fact, after surgery a relevant decrease of urinary volume (Table 1), pH (Fig. 10) and

urinary excretion of small weight inhibitors (i.e., citrate, magnesium) (Table 1) was observed. Urinary volume reduction ($p < 0.02$) (Table 1) again represents one of the major urinary risk factors inducing, in these patients, a relevant increase of oxalate and uric acid concentration and thus of their relative supersaturation indices (Fig. 1).

The progressive lowering of pH values may also promote renal stone formation of uric acid or calcium oxalate through epitaxial growth mechanism. These alterations suggest that this type of surgical treatment also induces a continuous intestinal loss of water, sodium and alkali as already described [5, 21] in patients submitted to permanent ileostomy. The reduced urinary excretion of small weight inhibitors such as magnesium ($p < 0.005$) (Table 1) and citrate ($p < 0.01$) (Fig. 9) is due to intestinal malabsorption of electrolytes (K, Mg) and bicarbonate [2]. In particular, after surgery a relevant increase was observed of hypocitraturia incidence that changes from 30% to 60.7%. The reduced excretion of small molecular weight inhibitors is a constant result in all patients with IBD, while we found a normal concentration and excretion of high molecular weight inhibitor GAGs before and after surgery in all these patients. Our results showed a progressive increase of hypocitraturia incidence in both groups of patients after surgery; the hypocitraturia incidence of IRRHC and IPAA groups was significantly higher than that found in our idiopathic calcium stone formers (12.6%). Hypocitraturia has been recognized as a common biochemical abnormality in calcium oxalate nephrolithiasis. Citrate is able to form soluble complexes with calcium and thus influences considerably its availability for crystal formation [12, 19]. Moreover, citrate can absorb on the surfaces of calcium oxalate crystals and interfere with their growth and agglomeration [15, 19].

Patients with IBD present several urinary abnormalities that may promote renal stone formation even though enteric hyperoxaluria is absent; moreover, there are some differences according to the type of IBD as well as to the time of patients' metabolic evaluation. In fact, patients with Crohn's disease before surgery displayed a greater number of potential abnormalities which may promote the stone formation within the urinary tract than subjects affected by ulcerative colitis. Surgical treatment seems to modify the risk-factor pattern increasing the probability of stone formation particularly in patients with ulcerative colitis.

In conclusion, our results suggest that patients with IBD show a higher risk of renal stone formation in comparison with patients affected by idiopathic calcium lithiasis. Therefore, a careful metabolic follow-up seems to be very important to maintain the urinary level of lithogenetic factors near the normal range with therapeutic and dietary measures.

Acknowledgments

Thanks are due to Prof. G. Biagini (Institute of Histology, Bologna University) for help in scanning microscopy study of crystalluria. This work was supported by 60% grant.

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Discussion with Reviewers

R.D. Rothstein and P.F. Malet: The authors state that all patients had normal renal function. It is unclear then what larger group these 66 patients with IBD were drawn from. One would assume that there were other IBD patients with impaired renal function.
Authors: To evaluate the risk factors promoting renal stone formation, a normal renal function is a prerequisite; in fact, an impairment of renal function introduces several modifications of the risk factors; so only the patients with normal renal function were sent to our laboratory for risk factors study.

R.D. Rothstein and P.F. Malet: What medications the patients were on should be noted, as many medications could affect the metabolic status of the patients?
Authors: As stated in the text, patients sent for the metabolic study did not receive any oral or parenteral supplementation or drugs at time of the urine analysis.

R.D. Rothstein and P.F. Malet: Did any patients actually form stones?
W.C. Thomas: Did any of the patients with inflammatory bowel disease have calculi?
Authors: From our data, the incidence of renal stones at pre-operative stage as well as after surgery was 8.3 and 11.9%. The number of patients with renal stones was slightly higher in those with Crohn's disease, but the total number of patients is too low and the follow-up too short to obtain exact information about this point. The follow-up is now in progress confirming a higher incidence of stone formation in patients with Crohn's disease without any difference between before and after surgery.

R.D. Rothstein and P.F. Malet: There is a great overlap between UC and IPAA for CaOx; are these two populations truly different?
Authors: As stated in the text, there were modifications before and after surgery of the concentration of both lithogenetic salts and inhibitors; supersaturation indices are modulated by the changes of these factors. In our patients, according to literature, the supersaturation indices are very high and near to 1. These results justify the higher tendency to renal stone formation observed in these subjects and so the overlap between the two groups.

H. Böhles: Please provide more information about the patients with respect to disease activity as defined by an activity index.
Authors: We did not correlate the disease activity with the results of the risk factors as our aim was to evaluate the risk factors modifications in basal conditions and after surgery.

W.C. Thomas: Please state the sex and age range of healthy subjects and those with idiopathic stone disease.
Authors: In addition to data presented in the text, the results were not divided according to sex as there were too few patients in each group for a correct statistical evaluation. Moreover, we had previously studied the different excretion of lithogenetic salts and inhibitors according to sex in healthy subjects and calcium stone-formers where we found some differences in healthy subjects between males and females. However, we

found that these differences disappear in renal stone formers, even though there is not a general agreement in literature. In any case, if we consider, for example, the citrate excretion, a value lower than 250 mg/24h indicates a pathological condition independent of sex. Another example could be the study of calcium excretion; in fact, we can speak of hypercalciuria when the calcium excretion is higher than 4 mg/kg/24h in males as well as in females.

R.D. Rothstein and P.F. Malet: Can you compare, how the type of operation performed would physiologically influence the risk for nephrolithiasis? Are there any fundamental biological differences between Crohn's disease and ulcerative colitis that would differently affect the rate of stone formation?
Authors: We can only give an appropriate answer to these questions when the follow up of our patients will be longer, although from our results patients with ulcerative colitis after surgery show a greater number of potential abnormalities, which may promote stone formation.

R.D. Rothstein and P.F. Malet: How would fat malabsorption, that might be present, influence the risk of stone formation?
Authors: The fat malabsorption might increase at colon level the oxalate absorption but in our patients steatorrhea was always absent.