Upalna bolest crijeva i bubreg – postoji li povezanost?

Mikolašević, Ivana; Milić, Sandra; Mijandrušić-Sinčić, Brankica; Lukenda Žanko, Vesna; Jelić Pranjić, Ita; Mavrinac, Vojko; Krznarić-Zrnić, Irena; Rački, Sanjin; Štimac, Davor; Orlić, Lidija

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INFLAMMATORY BOWEL DISEASE AND KIDNEY – IS THERE A CONNECTION?

IVANA MIKOLAŠEVIĆ[1,2], SANDRA MILIĆ[2], BRANKICA MIJANDRUŠIĆ-SINČIĆ[2], VESNA LUKENDA ŽANKO[3], ITA JELIĆ PRANJIĆ[1], VOJKO MAVRINAC[2], IRENA KRZNARIĆ-ZRNIĆ[2], SANJIN RAČKI[1], DAVOR ŠTIMAC[2] and LIDIJA ORLIĆ[1]

Rijeka University Hospital Center,
[1]Department of Nephrology, Dialysis and Kidney Transplantation,
[2]Department of Gastroenterology and
[3]Dr. Josip Benčević General Hospital, Department of Internal Medicine, Slavonski Brod, Croatia

The aim of the present study was to investigate whether patients with inflammatory bowel disease (IBD) have some degree of renal involvement. Furthermore, we investigated whether this connection is related to active bowel disease. In this cross-sectional study, 50 patients diagnosed with IBD, mean age 47.1±16.5 years, were recruited from September 2012 to September 2013. The diagnosis of IBD was based on clinical history, endoscopic, histological and radiological findings. Disease activity was assessed using the UC activity index (UCAI) for ulcerative colitis (UC) and Crohn's disease activity index (CDAI) for Crohn's disease (CD). There were 38% of UC patients and 62% of CD patients. The prevalence of abnormal albuminuria in UC and CD patients was 21.1% and 29%, respectively. There was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, as well as a high correlation between albumin-creatinine ratio (ACR) and UCAI score in UC patients, but these correlations were not statistically significant, probably due to the small number of UC patients. On the other hand, estimated glomerular filtration rate (eGFR) showed negative correlation with disease activity in CD patients (r=-0.569; p=0.05), while there was no statistically significant correlation between active UC and eGFR (r=0.343; p=NS). In conclusion, abnormal albuminuria is quite frequent in patients with IBD. It seems that patients with IBD have some degree of glomerular damage, mainly those with CD. Collaborative, prospective studies conducted by gastroenterologists and nephrologists are needed to investigate this association.

Key words: inflammatory bowel disease, extraintestinal manifestation, kidney

Address for Correspondence: Ivana Mikolašević, MD, Ph
Clinical Department of Nephrology, Dialysis and Kidney Transplantation,
Clinical Department of Gastroenterology
Rijeka University Hospital Center
HR-51000 Rijeka, Croatia
E-mail: ivana.mikolasevic@gmail.com

INTRODUCTION

Inflammatory bowel diseases (IBD) comprise two types of chronic intestinal disorders: Crohn's disease (CD) and ulcerative colitis (UC). CD involves the ileum and colon, but it can affect any region of the intestine, often discontinuously. UC involves the rectum and may affect part of the colon or the entire colon (pancolitis) in an uninterrupted pattern. In CD, the inflammation is often transmural, whereas in UC the inflammation is typically confined to the mucosa[(1)].

The extraintestinal manifestations of IBD are common and may occur in 25%-40% of patients. Inflammatory manifestations in the skin, eyes, liver and joints are considered primary manifestations. Development of primary extraintestinal manifestation appears to increase the risk of developing a second extraintestinal manifestation. Most IBD patients with extraintestinal manifestations have colonic inflammation, although some patients develop them prior to the onset of colonic symptoms. Extraintestinal manifestations are usually present at the time of active phase of IBD[(2)].

In recent years, there have been reports on renal and urologic complications of IBD. They were mostly found to be related to ureteral obstruction by oxalate stones, cystitis, acute tubular necrosis due to volume depletion and AA amyloidosis. Nephrolithiasis and obstructive uropathy are especially seen with small bowel dysfunction[3-5]. In a great proportion of IBD patients, ureteral obstruction is not caused by stones. This noncalculus obstruction can occur in 50%-73% of CD patients and 50% of UC patients, and is usually caused by retroperitoneal local inflammation or by surgical complication (sutures) or colon cancer[6].

There have also been reports of interstitial nephritis, mainly due to applied anti-inflammatory therapy, such as 5-aminosalicylic acid (5-ASA). Serious renal impairment is reported to occur in 1 of 500 patients treated with 5-ASA derivative. On the other hand, there are some reports that renal tubular damage is an extraintestinal manifestation of IBD and not a toxic side effect of anti-inflammatory therapy using 5-ASA or sulfasalazine[7-10].

Furthermore, renal failure due to glomerulonephritis (GN) caused by the immune complex has been reported in several cases as an extraintestinal manifestation of IBD. The types of immune complex GN that have been described due to IBD are membranoproliferative GN, mesangial proliferative GN, membranous nephropathy, IgA nephropathy, IgM nephropathy, minimal-change disease and antiglomerular basement membrane GN. Renal disease occurred in a setting of active IBD in many of reported cases. However, the question is whether renal disease occurs only related to active IBD[6, 11].

According to these observations, the association between IBD and kidney remains unclear and has to be investigated. The aim of the present study was to investigate whether patients with IBD (CD and UC) have some degree of renal involvement. Furthermore, we investigated whether this connection is related to active bowel disease and occurs due to the duration of bowel disease.

PATIENTS AND METHODS

In this cross-sectional study, 50 patients diagnosed with IBD were recruited from September 2012 to September 2013. The diagnosis of IBD was based on clinical history, endoscopic, histological and radiological findings. There were 31 (62%) patients with CD and 19 (38%) patients with UC. Disease activity was assessed using standardized questionnaires. The activity of UC was quantified using the UC activity index (UCAI) introduced by Rachmilewitz. A score ≥6 was considered to be suggestive of active UC. Furthermore, endoscopic activity of UC was also evaluated according to the reliable endoscopic index established by other researchers. The activity of CD was estimated according to the Best CD activity index (CDAI).

Patients with signs of urinary tract infection, known renal disease, hypertension, diabetes mellitus, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic drugs, patients with a current or recent pregnancy were excluded from this analysis. Furthermore, patients who had morphological changes of kidney (proven by ultrasound) were also excluded from the study. Extraintestinal manifestations were recorded in nine IBD patients. The most common extraintestinal manifestation was arthritis.

Blood samples were analyzed for routine hematological and biochemical indices including burn, serum creatinine, liver tests (AST, ALT, GGT and ALP), serum iron and ferritin, C-reactive protein (CRP), serum complement C3 and C4, as well as immunoglobulin levels by standard clinical chemistry techniques. Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula. Additionally, patients provided 24-h urine collection which was used for estimation of albuminuria, sodium, potassium, burn and creatinine clearance. In all patients, cytological analysis of urine was also performed. Urinary albumin concentrations were expressed in mg/24h. Albumin-creatinine ratio (ACR) was expressed in mg/mmol. Clinical and laboratory data were collected at the time of study initiation.

For this analysis, patients were stratified into two groups according to type of IBD into UC and CB groups.

Statistical analysis of data was performed using descriptive statistics (mean and standard deviation). Categorical variables were tested by χ^2-test or Fisher test. Testing of the importance of difference between two independent groups was performed using t-test or ANOVA. Pearson or Spearman correlation coefficient was used to express correlations between variables. The level of statistical significance was set at $p < 0.05$. Statistical analysis was performed using MedCalc statistical software package, version 10 (MedCalc, Mariakerke, Belgium).

RESULTS

There were 31 patients with CD and 19 patients with UC. Of the patients with CD, five had colonic disease, eight had ileal disease, and 18 had small and large bowel disease. Of the patients with UC, six had pancolitis, five had left-sided colitis and eight had procto-sigmoiditis.

Thirty-one IBD patients had an active bowel disease. The mean age of our patients (34 male and 16 female) was 47.1±16.5 years and the mean duration of disease 141±153.4 months.

First, we were interested to analyze whether there is any difference in demographic, clinical and laboratory data of our patients with respect to the type of IBD. For this analysis, patients were stratified into two groups according to the type of IBD: UC and CB groups. Demographic and clinical characteristics of the 50 patients according to the type of IBD are shown in Table 1A. There was no significant between-group difference according to age, sex or duration of bowel disease.

Table 1A
Patient characterisities according to type od inflammatory bowel disease (UC or CD)

Characteristic	UC (n=19)	CD (n=31)	p
Age (yrs) (X±SD)	45.4±10.6	43.4±16.7	NS
Sex:			
Male, n (%)	11 (57.9)	23 (74.2)	NS
Female, n (%)	8 (42.1)	8 (25.8)	NS
CDAI, n (%)	/	123.8±51.4	
UCAI (Mayo score), n (%)	5.9±3.4	/	
Duration of disease (months), n (%)	144.2±173.9	135.8±121.2	NS
Therapy			
5-ASA, n (%)	8 (42.1)	11 (35.5)	
Corticosteroid, n (%)	7 (36.8)	10 (32.3)	
Azathioprine, n (%)	4 (21.1)	15 (48.4)	
Biological therapy, n (%)	5 (26.3)	11 (35.5)	

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index;
UCAI = UC activity index; 5-ASA = 5-aminosalicylic acid derivative; NS = nonsignificant

Laboratory data of our patients are shown in Table 1B. The prevalence of albuminuria in UC and CD patients was 21.1% and 29%, respectively. Although CD patients had higher 24-h albuminuria and ACR, these differences were not statistically significant (Table 1B).
In the next step, we were interested to investigate correlation among various renal tests and clinical data in IBD patients. There was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, but this correlation was not statistically significant, probably due to the small number of UC patients (Table 2A). Table 2B shows correlation between ACR and clinical data in UC and CD patients. There was a high correlation (r=0.737) between ACR and MCS score in UC patients, although it was not statistically significant (p=0.09), probably due to the small number of patients. On the other hand, eGFR showed a statistically significantly negative correlation with disease activity in CD patients (r=-0.569; p=0.05). Also, statistical significance was almost reached in the correlation between eGFR and duration of bowel disease in CD patients (r=-0.391; p=0.09) (Table 2C).

DISCUSSION

Extraintestinal manifestations of IBD are common and probably reflect systemic inflammation, autoimmune susceptibility, metabolic and nutritional derangement, or drug-related toxicity[12,13]. In our study, there was a high negative correlation between duration of bowel disease and 24-h albuminuria in UC patients, as well as high correlation between ACR and MCS score in UC patients, but these correlations were not statistically significant, probably due to the small number of UC patients. Also, eGFR showed a statistically significant negative correlation with disease activity in CD patients. Statistical significance was almost reached in the correlation between eGFR and duration of bowel disease in CD patients. We suppose that by increasing the number of UC and CD patients, all these correlations would reach statistical significance.

The first two reports of glomerulonephritis in association with IBD appeared in the European literature in 1976[14,15]. Kidney disease as a complication of IBD has been the subject of case reports until recently. In 2014, Ambruzs *et*

al.[12] published a case series examining IBD and kidney disease. This was the largest clinicopathologic series to date on this topic. They evaluated a large series of kidney biopsy specimens from patients with IBD (45 CD cases and 38 UC cases). The most common indication for kidney biopsy in their analysis was acute or chronic kidney failure and nephrotic-range proteinuria. IgA nephropathy was the most common diagnosis, followed by interstitial nephritis, arterionephrosclerosis, acute tubular injury, proliferative GN and minimal-change disease.

Table 1B

Laboratory data according to type od inflammatory bowel disease (UC or CD)

Characteristic	UC (n=19)	CD (n=31)	p
CRP (mg/L)	49.3±67.8	48.6±87.3	NS
Complement C3	1±0.2	1±0.3	NS
Complement C4	0.2±0.1	0.3±0.1	NS
IgA	3.1±1	3.1±1.3	NS
IgM	1.5±0.8	1.2±0.5	NS
IgG	14±3.7	12.6±4.8	NS
Serum creatinine (μmol/L)	77.5±22.2	74.1±16.9	NS
Urea (mmol/L)	3.9±1.4	4.4±1.7	NS
eGFR (ml/min/1.73 m^2)	95.3±30.2	95.2±31.5	NS
Creatinine clearence (mL/min)	93.4±29.6	104.9±46.2	NS
Urinary albumin (mg/24 h)	0.1±0.1	0.171±0.2	NS
ACR (mg/mmol)	7.8±4.7	12.5±16.2	NS

CD = Crohn's disease; UC = ulcerative colitis; CRP = C-reactive protein;
eGFR = estimated glomerular filtration rate; ACR = albumin-creatinine ratio;
NS = nonsignificant; data are presented as X±SD

Table 2A

Correlation between 24-h albuminuria and clinical data in UC and CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.304	NS	/	/
CDAI	/	/	0.171	NS
Duration of bowel disease (months)	-0.509	NS	-0.125	NS

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index;
NS = nonsignificant

Table 2B

Correlation between albumin-creatine ratio and clinical data in UC and CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.737	0.09	/	/
CDAI	/	/	-0.093	NS
Duration of bowel disease (months)	-0.221	NS	-0.051	NS

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index;
NS = nonsignificant

Table 2C

Correlation between estimated glomerular filtration rate and clinical data in UC nad CD patients

	UC (n=19)		CD (n=31)	
	r	p	r	p
UCAI	0.165	NS	/	/
CDAI	/	/	-0.569	0.05
Duration of bowel disease (months)	-0.315	NS	-0.391	0.09

CD = Crohn's disease; UC = ulcerative colitis; CDAI = Best CD activity index; UCAI = UC activity index; NS = nonsignificant

The exact mechanism linking IBD and kidney is still poor understood. Recent investigations have highlighted the close relationship between the kidney and gastrointestinal (GI) tract, a term frequently referred to as the kidney-gut axis in patients with chronic kidney disease. According to data, two important pathophysiological concepts have evolved. The first refers to the production and accumulation of toxic end-products derived from increased bacterial fermentation of protein and other nitrogen-containing substances in the GI tract. The second refers to translocation of endotoxins and live bacteria from gut lumen into the bloodstream due to damage to the intestinal epithelial barrier and quantitative/qualitative alterations of the intestinal microbiota associated with the uremic milieu. In both cases, these gut-centered alterations may have relevant systemic consequences in chronic kidney disease patients, since they are able to trigger chronic inflammation[16]. Some animal and human studies suggest that prebiotics and probiotics may have therapeutic roles in maintaining a metabolically-balanced gut microbiota and reducing progression of chronic kidney disease and uremia-associated complication in these patients[17]. Additionally, an increasing number of reports have associated mucosal inflammation or infection with IgA nephropathy. Thus, IgA nephropathy in IBD probably represents a complex interplay of mucosal inflammation, loss of antigenic exclusion, and tolerance, chronic immune stimulation, and dysregulated IgA production and transport[12, 18]. On the other hand, there is growing evidence related to genetics, intestinal microbiota composition, and the immune system factors such as precursors for the initiation and progression of intestinal conditions. The use of certain probiotic microorganisms has been touted as a possible and promising therapeutic approach in reducing the risk of IBD, specifically UC[19, 20]. According to these observations, immune mechanism and gut microbiota are probably the pathogenic links between IBD and glomerulonephritis, but further studies are warranted on this topic.

Tubulointerstitial injury can also result from an indirect response through the induction of systemic inflammatory or immune reactions. Some animal and human studies support the role of immune-mediated mechanisms in tubulointerstitial nephritis[9]. 5-ASA is currently the treatment of choice for IBD patients. It can be administered as sulfasalazine (5-ASA+sulfapyridine) or mesalazine (5-ASA+gel resins)[6]. Most reported cases of tubulointerstitial nephritis in IBD occurred in patients treated with 5-ASA derivatives, which have known nephrotoxic effects. The exact mechanism is not fully understood, but some authors support the idea that it probably represents an idiosyncratic, delayed-type hypersensitivity that is independent of dose and duration of exposure[17]. However, there are some reports that renal tubular damage is an extraintestinal manifestation of IBD rather than a toxic side effect of anti-inflammatory therapy using 5-ASA or sulfasalazine. This appears to be more common in CD than in UC. According to these studies, it is possible that interstitial nephritis as an extraintestinal manifestation of IBD is maybe secondary to systemic immune dysregulation and cytokine activation[6-10, 17].

Although our study had several limitations such as observational study design, relatively small number of patients, absence of kidney biopsy, and the fact that patient and renal disease outcomes were not examined, it still raised a number of unanswered questions related to kidney function monitoring and outcome in patients with UC and CD. First, what is the exact risk of developing renal complications in IBD patients? Second, what kidney function markers correlate best with IBD activity or what patient clinical data would help us better identify those IBD patients that are at a higher risk of developing kidney complications, including drug-related nephrotoxicity? Third, how often should kidney function be monitored in patients with IBD? Are there some urinary markers which may indicate early renal impairment in IBD patients? Finally, could probiotics become a useful treatment option for kidney complications in IBD patients? Collaborative studies by gastroenterologists and nephrologists should help provide answers to these questions.

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SAŽETAK

UPALNA BOLEST CRIJEVA I BUBREG – POSTOJI LI POVEZANOST?

I. MIKOLAŠEVIĆ[1,2,] S. MILIĆ[2], B. MIJANDRUŠIĆ-SINČIĆ[2], V. LUKENDA ŽANKO[3], I. JELIĆ PRANJIĆ1, V. MAVRINAC[2] , I. KRZNARIĆ-ZRNIĆ[2], S. RAČKI[1], D. ŠTIMAC[2] i L. ORLIĆ[1]

Klinički bolnički centar Rijeka,
[1]Klinika za nefrologiju, dijalizu i transplantaciju bubrega,
[2]Klinika za gastroenterologiju, Rijeka i
[3]Opća bolnica "Dr. Josip Benčević", Odjel za internu medicinu, Slavonski Brod, Hrvatska

Cilj ove studije bio je ispitati imaju li bolesnici s upalnom bolesti crijeva u nekoj mjeri promjene na bubregu. Štoviše, ispitivali smo odnosi li se ta povezanost na aktivnu bolest crijeva. U ovoj presječnoj studiji okupili smo od rujna 2012. do rujna 2013. godine 50 bolesnika srednje dobi od 47,1±16,5 godina s dijagnozom upalne bolesti crijeva postavljenom na osnovi anamneze, endoskopskih, histoloških i radioloških nalaza. Aktivnost bolesti procjenjivali smo indeksom aktivnosti ulceroznog kolitisa (UC activity index, UCAI) i indeksom za Crohnovu bolest (Crohn's disease index, CDAI). Bilo je 38% bolesnika s ulcertivnim kolitisom (UK) i 62% bolesnika s Crohnovom bolešću (CB). Učestalost abnormalne albuminurije bila je 21,1% u bolesnika s UK i 29% u onih s CB. Nađena je visoka negativna korelacija između trajanja bolesti crijeva i 24-h albuminurije u bolesnika s UK, kao i visoka korelacija između odnosa albumin-kreatinin (ACR) i zbira UCAI u bolesnika s UK, ali te korelacije nisu bile statistički značajne, vjerojatno zbog malog broja bolesnika s UK. S druge strane, procijenjena stopa glomerularne filtracije (estimated glomerular filtration rate, eGFR) pokazala negativnu korelaciju s aktivnošću bolesti u bolesnika s CB (r=-0,569; p=0,05), dok nije bilo statistički značajne korelacije između UK i eGFR (r=0,343; p=NS). Zaključujemo da je abnormalna albuminurija dosta česta u bolesnika s upalnom bolesti crijeva. Čini se da bolesnici s tom bolešću imaju do neke mjere oštećenje glomerula, pretežito oni s CB. Da se istraži ta povezanost potrebne su zajedničke prospektivne studije gastroenterologa i nefrologa.

Ključne riječi: upalna bolest crijeva, ekstraintestinalne manifestacije, bubreg