Renal insufficiency in IBD — Prevalence and possible pathogenetic aspects

Christian Primas a,⁎, Gottfried Novacek a, Karin Schweiger a, Andreas Mayer b, Alexander Eser a, Pavol Papay a, Cornelia Gratzer a, Sieglinde Angelberger a, Clemens Dejaco a, Walter Reinisch a, Harald Vogelsang a

a Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Austria
b LKH St. Pölten, Department of Internal Medicine II, St. Pölten, Austria

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KEYWORDS
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Abstract

Background and aims: Extraintestinal manifestations of parenchymatous organs like kidney are rarely noticed in Inflammatory Bowel Disease (IBD). The aim of this study was to investigate the prevalence of renal insufficiency (RI) in IBD and look for potential causative factors and pathogenetic aspects.

Methods: The study consists of two parts; the first determined the prevalence of RI in IBD and the second possible causative factors. For the first part all patients with IBD who had been investigated at our institution in the period from March 2006 to December 2007 were included. For the second part 25 IBD patients with RI were matched with 50 IBD patients without RI. To determine causative factors several gastroenterologic and renal parameters were compared between these two groups.

Results: Eleven out of 775 patients with IBD had RI, all of them suffering from Crohn’s disease (CD). This led to a prevalence of 1.99% for patients with CD and of 0% for patients with ulcerative colitis (UC).

Concerning IBD risk factors only duration of disease (p = 0.002) and length of resected small bowel (p = 0.004) had a significant impact. Two nephrologic parameters, recurrent urolithiasis and the number of interventions due to kidney stones, were risk factors for the development of RI (p = 0.03).

Conclusions: RI is a rare (2%) but relevant complication in CD, not found in UC. Extensive small bowel resection and recurrent urolithiasis seem to be the major causative factors.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gut consisting mainly of two distinct entities, namely Crohn’s disease (CD) and ulcerative colitis (UC). Apart from the intestinal manifestation, there is also a wide range of extraintestinal manifestations including renal insufficiency which may sometimes gain greater importance than the underlying disease due to their severity and possible life-threatening consequences.\(^2\) They can be divided into reactive manifestations (often associated with inflammatory disease activity) and genuine extraintestinal complications (due to metabolic or anatomical abnormalities caused directly by IBD).\(^2\)

Although some extraintestinal manifestations are more common in CD, they can be found in both entities and add significantly to the burden of the disease.\(^3\) The prevalence of extraintestinal manifestations in IBD varies from 6%–46%.\(^4\)–\(^6\) Often joints (arthropathies), skin (erythema nodosum and pyoderma gangraenosum) or eyes are involved, however parenchymatous organs may be affected as well. These manifestations are not frequently encountered and therefore rarely reported; the best known is primary sclerosing cholangitis (mostly linked to UC), a chronic inflammatory condition of the intra- and extrahepatic bile ducts leading to fibrosis and death.\(^1\)–\(^3\) Other involvement of parenchymatous organs as kidney or lung is hardly mentioned in the literature. Searching the literature specifically for renal involvement only few data can be found; so far there are no data available focusing solely on the prevalence of renal insufficiency in IBD.

Therefore the aim of this study was to analyze a possible relationship between renal insufficiency (RI) and IBD. The first task was to determine the prevalence of RI in IBD and to look for a possible difference between CD and UC. The second one was to investigate if renal impairment might be a complication of the underlying disease or just a side effect of drugs – at least some of them, mainly cyclosporine, are known to have a nephrotoxic potential – used to treat the disease. In order to fulfill these tasks this study was conducted which was the first so far focusing specifically on renal – and not on urological – involvement in IBD and investigating causative factors and pathogenic aspects of renal insufficiency in IBD.

2. Material and methods

This study consists of two parts: The first part was to determine the prevalence of renal insufficiency in IBD and the second part to enlighten the possible causes and pathogenic aspects. To determine the prevalence of RI in IBD all patients who had been investigated in the period from March 2006 to December 2007 at the Department of Gastroenterology in the General Hospital of Vienna suffering from IBD were retrospectively analyzed. 775 IBD patients were included, 552 suffering from CD (246 male, 306 female), and 201 suffering from UC (108 male and 93 female). 20 patients were diagnosed with colonic IBDU and in two patients no diagnosis could be found (which were therefore excluded). No patients with IPAA were included in this study.

For the second part of the study, the IBD databases from the General Hospital of Vienna and from the department of gastroenterology at the LKH St. Pölten were used. 30 patients with renal insufficiency could be detected, 28 suffering from CD (15 male, 13 female) and 2 with ulcerative colitis (1 male, 1 female). Only 25 patients (13 male, 12 female) could be included. One patient (with CD) was excluded due to lack of data, and two patients were excluded because no matched controls could be found. Both patients with ulcerative colitis were excluded from further statistical analysis due to too low number colitis patients identified with RI. Inclusion criteria were defined as follows: elevated level of serum creatinine above 1.5 mg/dl measured at least two times over a period of at least one month under stable circumstances and not during acute exacerbations with high fluid losses. For the control group 50 patients (26 male, 24 female) were found, matched by gender, age at time of investigation, and duration of disease (±5 years).

Concerning the pathogenesis of renal insufficiency, several parameters were investigated, both gastroenterological and nephrological and compared between the two groups. The gastroenterologic parameters were location of CD (according to the Montreal Classification with L1 as involvement of the terminal ileum, L2 as colonic involvement, L3 as ileocolonic involvement and L4 as involvement of the upper GI-tract alone – or as modifier to L1 – L3, if concurrent), length of resected small bowel, remaining length of small bowel, number of resected colon segments (colon segments defined as colon ascendens, colon transversum, colon descendens, colon sigmoideum and rectum), duration of IBD at time of investigation and concurrent intake of drugs (especially 5-ASA).

The nephrologic parameters were the number of interventions due to kidney stones, of episodes with urolithiasis, urine Na\(^+\) and Ca\(^{++}\), BUN (blood urea nitrogen), BUN-to-creatinine-ratio, findings in urine samples (e.g. hematuria, proteinuria, leukocyturia) and the presence of amyloidosis in renal biopsy, if done.

To exclude a bias due to known causes for renal insufficiency the presence of hypertension and diabetes was recorded.

The study was approved by the local ethical committee.

For data analysis MS EXCEL 2007 and for statistical analysis IBM SPSS 19.0 were used. Data are presented as frequencies and percentages. Continuous variables are expressed as median and range. For the analysis of continuous data the Mann–Whitney-U-test and for categorical data Fisher’s exact test were used. Differences were considered significant if p value was <0.05. Kendall’s tau was used for correlation analysis.

3. Results

3.1. Prevalence of RI in IBD

11 patients with IBD and RI could be found, all of them suffering from CD. The prevalence for RI in patients suffering from CD in the investigated period was 1.99%, in patients suffering from UC it was 0. This led to an obvious significant difference between patients suffering from CD and patients suffering from UC for developing RI (p = 0.04).

At the time of this investigation the median age of patients with IBD and RI was 64 years (range 45 to 81 years), whereas for patients with IBD without RI it was 43 years (range 19 to 88 years). The median duration of IBD in patients with RI was 29 years (range 2 to 57 years) and for patients without RI 13 years (range 2 to 57 years). As expected patients with RI...
were statistically older (p = 0.001) and had a longer duration of IBD (p = 0.002) compared to patients without RI (see Table 1).

In our database two patients with RI needed regular hemodialysis. When extrapolating this data it would suggest an annual prevalence of 1.63/100.000 (per year).

### 3.2. Potential causative factors of RI in IBD

For the second part (causes of RI, case controlled study) 25 patients were included (13 male, 12 female), all suffering from CD and RI. The matched control group consisted of 50 CD patients (26 male, 24 female) without RI (see Table 2). The median age at time of investigation (patients with RI) was 62 years (range 42–85), the median age at diagnosis of CD was 32 years (range 18–75) with a median duration of CD at time of investigation of 27 years (range 1–53). In the control-group the median age at time of investigation was 61.5 years (range 42–85), the median age at diagnosis of CD was 32.5 years (range 18–65) with a median duration of CD at time of diagnosis of 26 years (range 5–48). The median age at diagnosis of RI was 57.5 years (range 39–81) with a median duration of CD at time of onset of RI of 20 years (range 0–48).

Concerning the location of inflammation there were no significant differences between the two groups with L3 (ileocolonic) being the most common location. Concerning all other gastroenterologic parameters, only the length of resected small bowel showed a significant difference. Sixty of the 75 patients (80%) had undergone surgery, the median length of resected small bowel in the group of patients with RI was 80 cm (range 0–340) compared to 40 cm (range 0–310) in the control group (p = 0.004). 29 of the 75 patients were treated with 5-ASA, 9 with RI and 20 without RI. The median duration of this therapy in patients with RI was 75 months (range 0–264) compared to 33 months (range 0–252) in the control group (p = 0.56).

Concerning the nephrologic parameters four of them (recurrent urolithiasis, number of interventions due to kidney stones, BUN and BUN-to-creatinine ratio) showed a significant difference. 36% of patients with RI suffered from recurrent urolithiasis compared to 12% in the control group (p = 0.029). The median number of interventions due to kidney stones in the group with RI was 0 (range 0 to 20), in the control group it was 0 (range 0 to 3) as well, still resulting in a significant difference (p = 0.025). The median BUN level (reference range 6–25 mg/dl) in patients with RI was 30.1 mg/dl (range 11.3 to 76.5) whereas in the control group it was 12.9 mg/dl (range 4–38) (p < 0.001). The median BUN-to-creatinine ratio in patients with RI was 10 (range 2.3 to 36) whereas in the control group it was 15.2 (range 5.9 to 31) (p = 0.001).

The length of resected small bowel correlated with the number of interventions due to kidney stones (r = 0.27/ p = 0.007).

Data on some nephrologic parameters were not present for all patients (due to ethical considerations not every patient with elevated creatine underwent a renal biopsy) and can therefore only be listed: Amyloidosis was found in 3 cases (12%), and glomerulonephritis was found in 1 case (4%).

### 4. Discussion

In our study 2% of the patients with CD developed renal insufficiency, but none of the patients with UC. There are several studies analyzing renal and/or urinary involvement (occurring in 4 to 23% in IBD-patients), but no study so far has focused solely on renal insufficiency. Many authors evaluating renal involvement also report urogenitary involvement as well which in part explains the big differences on the prevalence of “renal” involvement in IBD. Even the most recent review on renal involvement by Oikonomou describes data on prevalence from studies combining renal and urogenitary (either/or) involvement.

Our study was conducted at a tertiary referral center for IBD, therefore there might be a bias due to the larger number of more severe cases of IBD who are more likely to develop complications. On the other hand patients apparently suffering from renal insufficiency are more likely to be found on a nephrologic ward, therefore we might also have missed some cases with RI and IBD.

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**Table 1** Demographics.

<table>
<thead>
<tr>
<th></th>
<th>IBD without RI</th>
<th>IBD and RI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 (19–88)</td>
<td>64 (45–81)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration of IBD</td>
<td>13 (2–57)</td>
<td>29(2–57)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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**Table 2** Causative factors for RI in IBD.

<table>
<thead>
<tr>
<th></th>
<th>RI</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>25</td>
<td>50</td>
<td>n.s</td>
</tr>
<tr>
<td>Male/female</td>
<td>13/12</td>
<td>26/24</td>
<td>n.s</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (42–85)</td>
<td>61.5 (42–85)</td>
<td>n.s</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>32 (18–75)</td>
<td>32.5 (18–65)</td>
<td>n.s</td>
</tr>
<tr>
<td>Duration of CD</td>
<td>27 (1–53)</td>
<td>26 (5–48)</td>
<td>n.s</td>
</tr>
<tr>
<td>Length of resected small bowel</td>
<td>80 (0–340)</td>
<td>40 (0–310)</td>
<td>0.004</td>
</tr>
<tr>
<td>5-ASA treatment</td>
<td>9 (36%)</td>
<td>20 (40%)</td>
<td>n.s</td>
</tr>
<tr>
<td>Interventions</td>
<td>9 (36%)</td>
<td>6 (12%)</td>
<td>0.029</td>
</tr>
<tr>
<td>BUN (mg/dl)</td>
<td>30.1 (11.3–76.5)</td>
<td>12.9 (4–38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BUN-to-creatinine</td>
<td>10 (2.3–36)</td>
<td>15.2 (5.9–31)</td>
<td>0.001</td>
</tr>
</tbody>
</table>
In our database there were 2 patients with RI in need of regular hemodialysis. When extrapolating this data it would suggest an annual prevalence of 1.63/100,000 (per year), which is approximately 3.4 times higher than the annual prevalence in Austria (in 2007). Although these numbers do not exactly allow a statistically sound analysis, they show the need for an even larger study to answer this question. To determine the exact prevalence of RI in IBD a population based study is warranted. However, to date our study was by far the largest with 775 included patients.

Of course, the question what the causative factors are arises. We found an increased risk in patients with extensive small bowel resections and recurrent urolithiasis. A relevant feature among IBD patients (12%–28%) is nephrolithiasis which has a high prevalence of developing urolithiasis in IBD is 10 to 100 times greater than the risk for general hospital patients. Reasons for that may be volume depletion (leading primarily to uric acid stones) and hyperoxaluria in CD. Small bowel resection leads to both volume depletion and hyperoxaluria – therefore promoting stone formation and the development of RI. Supporting that, there was a correlation between the length of resected small bowel and the number of interventions due to urolithiasis. Although it would have been interesting, there is only limited data on the nature of the stones found in our patients, as the stones are not routinely analyzed.

So far most papers focused on the effect of 5-ASA on renal function, thus discussing a drug induced side effect rather than an extraintestinal manifestation. The data on that topic remains ambiguously – a first study from Zehnter et al. (after some case reports) seemed to favor renal dysfunction caused by 5-ASA but this is only available as an abstract. Schreiber et al. confirmed that this results in a larger point prevalence study. A review on this topic showed a 1% risk of a reversible rise in serum creatinine levels, but no clinically significant deterioration in renal function could be observed. Later Herrlinger showed that minimal renal dysfunction was related to disease activity rather than the use of 5-ASA. In 2004 the results of a large British epidemiologic study were published showing that the overall incidence of renal disease appears to be low and not dose related to 5-ASA. The 5-ASA study group confirmed this in a prospective study, showing that renal impairment in IBD is “not frequently” (35 out of 1529 patients) observed and only rarely associated with 5-ASA treatment. Poulou reported that subclinical renal damage was caused by IBD itself and not by 5-ASA. A more recent review in 2007 concluded that 5-ASA nephrotoxicity seems to be idiosyncratic in nature rather than dose related to 5-ASA and exceptional. In our study there was no difference concerning the intake of 5-ASA between the patients with RI and the control group.

Other causes for renal impairment – found in the literature – include amyloidosis, glomerulonephritis, tubulointerstitial nephritis, and nephrolithiasis. There are many case reports on amyloidosis, but reviewing the literature the overall prevalence in IBD seems to be below 1%. Glomerulonephritis has recently emerged as an extraintestinal manifestation and seems to be very rare with about 40 reports in the literature; it appears to be linked to disease activity as renal function improves after remission of IBD.

Tubulointerstitial nephritis seems to be a common clinical feature among IBD patients, manifesting with proteinuria. As with glomerulonephritis there seems to be a correlation with disease activity.

The emergence of new drugs and the use of more potent drugs earlier in the course of IBD might prevent irreversible damage to the small bowel, therefore reducing the need for surgery. Thus long-term the prevalence of RI in IBD will hopefully be reduced. In the meantime it would be important to pay attention to older patients with resections in the small bowel and/or urolithiasis and to closely monitor them for signs of RI.

Conflict of interest

The authors declare that there is no conflict of interest related to this article.

Acknowledgment

We thank Christoph Mayer for the careful collection of these data in his diploma thesis. CP — collection and analysis of data, and writing of manuscript GN and HV — design of study, collection and analysis of data, and provision of significant advice CD, and WR — collection of data and provision of significant advice PP — provision of significant advice AM — conduct of study and collection of data KS, AE, CG, and SA — collection of data All authors read and approved the final version of the manuscript.

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