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ORIGINAL ARTICLE

Inflammatory bowel disease in patients undergoing renal biopsies

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ABSTRACT

Background. There are no good data in the literature on the prevalence of inflammatory bowel disease (IBD) in patients with kidney disease and we do not know whether IBD affects the course of kidney disease or if the type of IBD is an influential factor. The aim of this study was to evaluate the prevalence of IBD among patients who have undergone renal biopsies due to clinical indications and to elucidate whether the presence of IBD influences renal and patient outcomes.

Methods. We collected retrospective data on concomitant diseases, especially IBD, from adult patients undergoing renal biopsy for any clinical indication between 2000 and 2012 at Tampere University Hospital, Tampere, Finland. Information was systematically collected on the activity of IBD, medication for IBD, surgery performed for IBD and markers of kidney function.

Results. Of the 819 patients biopsied, 35 (4.3%) had IBD. The prevalence of IBD was 13.3 and 4.6% in patients with tubulointerstitial nephritis (TIN) and immunoglobulin A nephropathy (IgAN), respectively. In comparison, the prevalence of IBD in the Finnish population is 0.6%. Ulcerative colitis and Crohn's disease were equally represented. The presence of IBD showed no impact on renal and patient outcomes.

Conclusions. IBD should not be overlooked in patients undergoing renal biopsies, especially those diagnosed with TIN or IgAN. The renal findings did not associate with the activity of intestinal inflammation. Whether a concomitant IBD truly affects the course of chronic kidney disease should be examined in further studies.

Keywords: chronic kidney failure, IgA glomerulonephritis, inflammatory bowel diseases, Interstitial nephritis, renal biopsy

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INTRODUCTION

Many publications have raised our awareness of the relationship between kidney diseases and increased intestinal permeability. Chronic kidney disease (CKD), and especially uraemia, alters the intestinal barrier and microbiome. The loss of the ability to prevent the influx of microbial toxins and other harmful products leads to local and systemic inflammation, which can further promote deterioration in kidney function [1–3]. This phenomenon probably promotes cardiovascular diseases as well, which are one of the leading causes of death in patients with end-stage renal disease (ESRD) [4]. Interestingly, intestinal permeability seems to be already increased in the earlier stages of CKD [5]. The linkage between the most common primary glomerulopathy [6], immunoglobulin A nephropathy (IgAN) and the mucosa is well known [7, 8]. Genome-wide association studies (GWASs) in patients with IgAN have identified risk loci in the genes involved in intestinal mucosa integrity and the immune network [9]. In one recent study, patients with IgAN who had persistent proteinuria were treated with targeted-release enteric budesonide, which resulted in a significant reduction in proteinuria [10].

Inflammatory bowel diseases (IBDs), including ulcerative colitis (UC) and Crohn's disease (CD), are increasingly common chronic inflammatory disorders of the gastrointestinal tract: the prevalence of IBD is currently 0.2–0.7% in Western countries [11–14]. Inflammation affects the large intestine and rectum in UC [15], whereas inflammation and progressive bowel damage can be present in any part of the intestine in CD [16]. A third entity is unclassified IBD (IBDU), in which inflammation of the intestine with chronic colitis is present but no characteristic histological signs of UC or CD are found [11]. IBD requires lifelong management. Renal damage in patients using 5-aminosalicylic acid (5-ASA) medication is a rare but well-documented complication [17–20]. IBD is not restricted to the gastrointestinal tract; 6–47% of sufferers also experience extraintestinal manifestations (EIMs) [21, 22]. The organs most commonly affected include the skin, eyes, joints and biliary tract [21]. The prevalence of renal or urinary manifestations can be as high as 20%, and they are largely explained by urological complications such as nephrolithiasis [23, 24]. Renal diseases in conjunction with IBD have been the subjects of primarily case reports [25, 26], and only a few register-based case series have been published [27, 28].

The aims of this study were to evaluate the prevalence of IBD among patients who have undergone renal biopsies due to clinical indications and to elucidate whether the presence of IBD has an influence on renal and patient outcomes.

MATERIALS AND METHODS

Patients and study design

The study cohort comprised 824 consecutive patients >16 years of age who had undergone a renal biopsy due to clinical indications at the Division of Nephrology at Tampere University Hospital (TAUH), Tampere, Finland, between January 2000 and December 2012. The data were missing in five patients, giving the study population of 819 patients. All patients included in the study provided written informed consent. If the same patient was biopsied twice during the study period, then the first diagnostic biopsy was included in the study. Renal biopsy specimens were taken and processed using standard methods as described earlier [29]. All specimens were studied with light and immunofluorescence microscopy by two renal pathologists. The indications for renal biopsies were classified into three groups: (i) abnormal urinary finding, including focal nephritic syndrome (haematuria and daily urinary protein excretion <1.5 g), diffuse nephritic syndrome (haematuria and daily urinary protein excretion >1.5 g), nephrotic syndrome (daily urinary protein excretion >3.5 g without haematuria), proteinuria (daily urinary protein excretion 0.3–3.5 g without haematuria) and haematuria (daily urinary protein excretion <0.3 g); (ii) renal insufficiency (elevated creatinine level) and (iii) any other indication. Based on the histopathological findings of the renal biopsy specimens, five groups were categorized: glomerular diseases, tubulointerstitial diseases, vascular diseases, other findings (e.g. cystic and congenital diseases) and no glomeruli (inadequate sample) [30]. Patients were divided into two groups based on whether they were diagnosed with IBD or not.

Clinical data on kidney disease

The histories of all 819 patients were retrospectively collected from the medical records of TAUH between 2014 and 2016 [8]. Plasma creatinine concentration, quantitative 24-h urinary protein excretion and haematuria data were gathered from medical records at the time of the renal biopsy and the most recent follow-up. The urine dipstick test for haematuria was dichotomized as negative (values 0 or +) or positive (++ or +++). Estimated glomerular filtration rate (eGFR) was defined using the Chronic Kidney Disease Epidemiology Collaboration equation [30]. The annual change in eGFR was calculated by dividing the difference between the final and baseline values of eGFR by the number of years of follow-up. Only patients followed up for >1 year after the renal biopsy with preserved kidney function (no transplantation or chronic dialysis started during follow-up) were included in the calculations of kidney function at the most recent follow-up. Furthermore, data on chronic dialysis treatment or renal transplantation during follow-up were recorded and collectively called ESRD. The follow-up for individual patients was concluded at the last office visit or the last reliable set of laboratory results, whichever was closer to the time of data collection.

Clinical data on IBD

Information regarding other diagnosed diseases, including IBD, was collected systematically. The EIMs comprised diseases of organs commonly accepted to be involved in IBD—diseases of the joints, eyes, skin, liver, biliary tract and urinary tract—as well as thrombotic events. Detailed data on IBD activity, medication, location, surgery and EIMs were collected. The immunomodulatory medications for IBD included azathioprine, methotrexate, glucocorticoids or tumour necrosis factor (TNF) inhibitors. IBD flare-up was defined as the need for systemic glucocorticoid medication equivalent to ≥30 mg of prednisolone. The site of IBD was determined by means of endoscopy or gastrointestinal imaging (e.g. enteric magnetic resonance imaging) reports and grouped into five different categories as follows: proctitis, left-sided colitis (including proctosigmoiditis), pancolitis/ileocolonic, small intestinal (no colonic affliction) and unknown. Abdominal surgery denoted any surgical procedure to the intestine (including appendectomy); operations on abdominal fistulas, strictures, hernias or abscesses and cholecystectomy.

Statistical methods

The data are presented as medians and ranges for continuous variables and numbers and percentages for categorical

Table 1. Basic characteristics of patients undergoing renal biopsy, indications for renal biopsies and renal biopsy findings

	Patients with IBD ($n = 35$)		Patients without IBD ($n = 784$)		P-value
	n	%	*n*	%	
Male	20	57.1	491 62.6	0.593	
Age, median (range), years	49 (18–76)		59 (16–85)		0.026
Weight, median (range), kg[a]	71 (46–112)		81 (23–150)		0.022
Height, median (range), cm[b]	172 (160–187)		173 (120–198)		
Indications for renal biopsies					0.285
Abnormal urinary finding[c]	22	62.9	586	74.7	
Renal insufficiency	12	34.3	185	23.6	
Other causes	1	2.9	13	1.7	
Renal biopsy findings					0.026
Glomerular diseases	17	48.6	556	70.9	
Tubulointerstitial diseases	10	28.6	98	12.5	
Vascular diseases	1	2.9	18	2.3	
Other findings	7	20.0	98	12.5	
Inadequate sample	0	0	14	1.8	
Previous kidney transplantation	2	5.7	56	7.1	0.747

Number of subjects available: [a]453, [b]639. [c]Focal nephritic syndrome, diffuse nephritic syndrome, nephrotic syndrome, proteinuria, haematuria.

variables. Groups were compared using the chi-square test, Fisher's exact test, independent *t*-test or Mann–Whitney U-test, as appropriate. Survival (ESRD as event) was determined using Kaplan–Meier curves and differences between IBD (yes/no) were compared by log-rank test. Univariate and multivariable analyses (adjusted for age, gender and presence of IBD) were performed using Cox proportional hazards regression. Hazard ratios and their 95% confidence intervals are given. All tests were two-sided and $P < 0.05$ was considered statistically significant. All statistical testing was performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Ethical consideration

The study protocol was approved by the Ethics Committee of Tampere University Hospital. All subjects gave written informed consent at the time of the renal biopsy.

RESULTS

Patient characteristics, renal biopsy findings and the prevalence of IBD

Twenty-eight (3.4%) of 819 patients had IBD at the time of renal biopsy and an additional 7 patients were diagnosed with IBD during the follow-up. Therefore a total of 35 (4.3%) patients had IBD (Table 1). The patients with IBD were younger than the patients without IBD. There were no differences in indications for renal biopsy between the patients with and without IBD (Table 1).

The most common renal biopsy finding in the patients with IBD was acute (four patients) or chronic (four patients) tubulointerstitial nephritis (TIN). Altogether, 22.9% of the patients with IBD presented with TIN, while 7 patients (20.0%) had IgAN. Ten patients had glomerular diseases other than IgAN, two patients had tubulointerstitial diseases other than TIN and eight patients had findings categorized as vascular diseases or other renal findings (Table 2). Tubulointerstitial diseases were more often found in the patients with IBD when compared with patients without IBD (28.6 versus 12.5%; $P = 0.017$) and glomerular diseases dominated in the patients without IBD when compared with patients with IBD (70.9 versus 48.6%; $P = 0.007$). Among the patients without IBD, TIN was diagnosed in 6.7% and IgAN in 18.4% of patients. Overall, the prevalence of IBD in the patients with TIN was 13.3%. Seven of 151 patients (4.6%) with IgAN had IBD compared with 8 of 308 patients (2.6%) with a glomerular disease other than IgAN ($P = 0.164$).

Patients with IBD and TIN were almost exclusively women (seven of eight patients), while no sex difference was found in patients with TIN and with no IBD (female 50.0%). Patients with a glomerular disease (including IgAN) and IBD were predominantly male [14/17 patients (82.4%)]. A preponderance of males was also found in patients with glomerular disease and no IBD [344/556 patients (61.9%)].

Table 2. Renal biopsy findings in 35 patients with IBD

Diagnosis	*n*
Glomerular diseases	
IgA GN	7
Membranous GN	2
IgM GN	2
Extracapillary GN	1
Mesangial, proliferative GN	1
Mesangial, sclerosing GN	1
Focal segmental glomerulosclerosis	1
Glomerulosclerosis, NOS	1
Amyloid nephropathy	1
Tubulointerstitial diseases	
Acute TIN	4
Chronic TIN	4
Myeloma cast nephropathy	1
Acute tubular necrosis	1
Vascular diseases	
Arteriosclerosis (hyalinic)	1
Other findings	
Normal finding	3
Morphologic description only	2
Chronic cellular graft rejection	2

NOS, not otherwise specified.

Table 3. Renal function at the time of renal biopsy and at the latest follow-up

	Patients with IBD ($n = 35$), median (range)	Patients without IBD ($n = 784$), median (range)	P-value
At renal biopsy			
Plasma creatinine (μmol/L)	133 (56–671)	123 (17–1776)	0.921
eGFR[a] (mL/min/1.73 m^2)	44 (6–130)	51 (2–172)	0.711
24-h urinary protein excretion (g/day)[b]	0.8 (0.1–6.4)	1.5 (0.1–24.2)	0.040
Haematuria, *n* (%)[c]	12 (37.5)	346 (46.9)	0.366
At the latest follow-up			
Duration of follow-up (months)	59 (0–178)	66 (0–183)	0.619
Plasma creatinine (μmol/L)[d,e]	90 (49–276)	104 (11–1013)	0.137
eGFR (mL/min/1.73 m^2)[d,e]	78 (19–117)	57 (4–197)	0.118
Annual change of eGFR (mL/min/1.73 m^2/year)[d,f]	0 (−11–35)	−1 (−84–70)	0.086

[a]eGFR was calculated by the Chronic Kidney Disease Epidemiology Collaboration equation. Number of subjects available:
[b]621;
[c]769;
[d]excluded if treated with dialysis, had received renal transplantation during the follow-up or the follow-up had lasted <12 months;
[e]567;
[f]552.

Renal outcomes

The median follow-up time was 59 months in patients with IBD and 66 months in patients without IBD. There was no difference between the groups in eGFR at the time of renal biopsy or at the most recent follow-up. Patients with IBD had significantly lesser amounts of proteinuria at the time of renal biopsy (Table 3). The 24-h urinary protein excretion was quantitated in 26 of 35 patients with IBD. Of these, nine (34.6%) were using immunomodulatory medication at the time of renal biopsy. Yet the amount of proteinuria did not differ between those who were on immunomodulatory medication and those who were not (median of the 24-h excretion 0.8 and 0.9 g, respectively; P = 0.833). Two patients with IBD (5.7%) and 142 patients without IBD (18.1%) progressed to ESRD (P = 0.068). In Figure 1, a Kaplan–Meier curve shows the difference between patients with and without IBD and the occurrence of ESRD. We also performed Cox logistic regression analysis to determine the risk factors for ESRD (Table 4). Male gender was found to be a strong and independent predictor of ESRD, but the presence of IBD did not associate with the risk for ESRD.

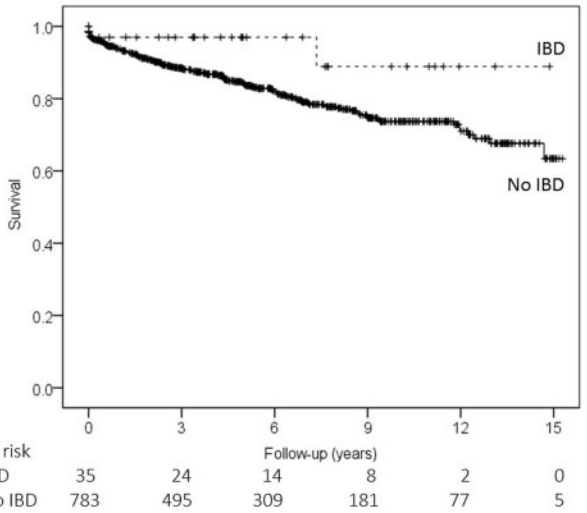

FIGURE 1: Kaplan–Meier survival curves for 35 patients with IBD and 783 patients with no IBD for progression to ESRD (log-rank P = 0.086).

Phenotypes of IBD

Altogether, there were 14 cases of CD, 14 cases of UC and 7 cases of IBDU. Neither CD nor UC seemed to dominate in the different renal findings for TIN (three CD, four UC and one IBDU), IgAN (four CD and three UC) or other GD (four CD, four UC and two IBDU). All patients with TIN had a previous diagnosis of IBD and all of them used or had prior use of 5-ASA medication at the time of renal biopsy. Similarly, patients with glomerular diseases who had a diagnosis of IBD at the time of renal biopsy (13 patients) all had a history of 5-ASA medication. Altogether, 37.1% of the patients with IBD were taking either steroid or other immunomodulatory medication (azathioprine, methotrexate or TNF inhibitor) at the time of the renal biopsy. In terms of inflammatory activity, one-quarter (7/28) of the patients with previous IBD had a flare-up of IBD during the year preceding the renal biopsy.

Diffuse intestinal inflammation (pancolitis or ileocolonic) was the most common (54.2%) location of IBD, irrespective of the renal finding. Nine of 35 (25.7%) patients had undergone abdominal surgery. Most of the patients with IgAN and IBD had an EIM (71.4%), while just 12.5% of the patients with TIN and 20.0% of the patients with other glomerular diseases had an EIM.

DISCUSSION

This study showed the prevalence of IBD among people undergoing renal biopsy to be as high as 3.4%; during the follow-up, the prevalence of diagnosed IBD was further elevated to 4.3%. As the pathogenesis of diseases can presumably take a variable number of years before clinical symptoms arise and the spectrum of symptoms of both renal diseases and IBD is wide, a clear determination cannot be made as to whether renal disease or IBD preceded the other in individual patients.

The prevalence of IBD in our study was large compared with that found (0.2%) in a previous study by Ambruzs *et al.* [27]. The major difference in the prevalence of IBD in these two studies is most likely explained by differences in study designs. Between 1986 and 2008, the prevalence of IBD has increased from 0.2 to 0.6% in Finland [11, 12]. There are few published prevalence

Table 4. Univariate and multivariable Cox regression analysis of risk factors for ESRD among 819 patients who underwent renal biopsy due to clinical indication

	Univariate		Multivariable	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age	1.01 (1.00–1.02)	0.010	1.01 (1.00–1.02)	0.024
Male gender	1.71 (1.19–2.47)	0.004	1.66 (1.15–2.40)	0.007
IBD	0.31 (0.08–1.27)	0.104	0.34 (0.08–1.36)	0.126

rates of IBD globally, but they seem to vary from 0.2 to 0.7% [11, 13, 14]. Thus the prevalence of IBD in the present cohort of patients who had a clinical indication for the renal biopsy was approximately 7-fold compared with that in the general population.

The prevalences of IBD in patients with TIN and IgAN were as high as 13.3 and 4.6%, respectively. This is about 20- and 8-fold the IBD prevalence in the general population, respectively. In previous studies, the prevalence of IBD in IgAN patients has varied from 0.7 to 1.6% [27, 31, 32]. To our knowledge, the prevalence of IBD in patients with TIN has not been published before. There is no way to differentiate patients in this cohort for whom TIN was related to 5-ASA medication, as all the patients with TIN had an ongoing or previous history of 5-ASA use. Thus the high prevalence of IBD in patients with TIN might have been related to 5-ASA medication even though the correlation of 5-ASA to TIN has remained controversial in the literature [18, 20, 33]. In general, patients without IBD had greater amounts of proteinuria at the time of renal biopsy, a finding that most likely is explained by the dominance of glomerular diseases in patients without IBD. The preponderance of the female gender in patients with IBD and TIN was noteworthy, but the small number of patients with both IBD and TIN might have influenced the results. The finding of a male majority in patients with glomerulonephritis (GN) in general has been noted in earlier publications [34, 35] and recently in patients with IBD and GN as well [28]. Patient cases of TIN and IBD have not shown female dominance [33, 36, 37].

The connection between IgAN and intestinal inflammation is clearly recognized [7]. The HLA-DR1 allele for IgAN and the HLA-DR1/DQw5 allele for CD have led to a theory of a common genetic basis for both diseases [24]. GWASs in patients with IgAN have identified risk loci in genes involved in intestinal mucosal integrity and the immune network. Some of the risk alleles for IgAN are also associated with the risk for IBD [9]. The number of inflammatory cells in the intestinal mucosa increased in patients with GN [38–40]. However, no previous publication has shown such a high prevalence of IBD in patients with IgAN.

Previously, more than half of the patients with IgAN have presented with various other parallel diseases [31, 32]. No published data exist on the incidence of IBD and IgAN in association with a third disease entity, but patient cases of such triads have been published [41–43], as has one recent case series [28]. In our cohort, 71% of patients with IBD and IgAN had another EIM.

Male gender presented as a risk factor for ESRD. This finding is in line with previous publications [44, 45]. IBD was not related to an elevated risk for ESRD. The impression that the activity of IBD affects renal disease can arise when reading published patient cases [46–48]. Defining the activity of the disease in a retrospective manner is rather inaccurate. We can assume, based on the data shown, that the patients in the present study did not represent particularly difficult cases of colitis. Fewer than half of the patients with a previous diagnosis of IBD either had a flare-up during the preceding year before the kidney biopsy or were on an immunomodulatory medication at the time of the renal biopsy. Nevertheless, more than half had no clinical sign of active intestinal inflammation, and when the total population of 35 patients with IBD was evaluated, about one-third of the patients with IBD had intestinal inflammatory activity at the time of the renal biopsy. A quarter of the patients with IBD had undergone abdominal surgery at any given time point, either before or after the kidney biopsy. No clear difference was noticed in the concomitance of renal disease and IBD, as CD and UC were equally represented. In a recent letter published by Hungarian researchers, the few cases of GN found in patients with IBD were more often in conjunction with CD [28].

The renal biopsies in this study were taken at one centre and analysed by two renal pathologists. The unifying indications for renal biopsies as well as the interpretation of the renal samples are the strengths in the present study. Patients with renal diseases in our university hospital district are mostly followed up and treated in the nephrology unit of the university hospital. In a similar way, most of the patients with active IBD are followed-up by the university hospital. Thus we have been able to collect real-life data with long follow-up times. Due to the retrospective nature of the study, some of the information collected may be inaccurate or insufficient. Another obvious limitation is that some of the patients with no diagnosed IBD might have had clinically silent IBD, but the number of such patients presumably would be low and would not affect the results of the study.

To conclude, our study showed a remarkable prevalence of IBD in patients undergoing renal biopsy for any clinical indication. IBD should be kept in mind when the renal biopsy finding is either TIN or IgAN. A lack of obvious gastrointestinal symptoms does not necessarily indicate the absence of IBD, as more than half of the patients biopsied were asymptomatic at the time of biopsy. We do not yet know whether the coexistence of IBD and CKD results in one influencing the other. This cohort was too small to show either the benefit or disadvantage of IBD for CKD even though patients with IBD did well when compared with patients without IBD. Thus further studies are needed to examine the significance of concomitant IBD in patients with CKD.

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AUTHORS' CONTRIBUTIONS

All authors participated in the design of the study. J.P., R.N. and M.M. collected the data. J.P. and H.H. analysed and

interpreted the data. J.P. drafted the article. All authors read, revised and approved the final manuscript.

CONFLICT OF INTEREST STATEMENT

The authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The manuscript contents have not been copyrighted or previously published, except in abstract form for the Annual Medical Congress arranged by the Finnish Medical Society Duodecim and the Medical Society of Tampere, Finland. We have no conflicts of interest to declare.

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