The Egyptian Journal of Hospital Medicine (October 2022) Vol. 89, Page 4312- 4316

Renal Status of Inflammatory Bowel Disease Patients in Assiut University Hospital: Single Center Study

Faiza Kamal Abl El-khalek Khalifa*, Hala Mostafa Kamel, Samir Kamal Abdul-Hamid
Department of Internal Medicine, Faculty of Medicine, Assiut University, Assiut, Egypt
***Corresponding author:** Faiza Kamal Abd El-khalek Khalifa, **Mobile:** (+20) 01060564991, **E-mail:** faizakamal002@gmail.com

ABSTRACT

Background: Idiopathic inflammatory bowel disease (IBD) is characterised by significant gastrointestinal tract inflammation. IBD is strongly correlated with extraintestinal symptoms (EIMs). Renal complication is considered as one of the EIMs.

Objective: The current study was done to assess whether patients with inflammatory bowel disease have some degree of renal involvement and also to determine if associated with disease activity or not.

Patients and methods: A cross sectional study included a total of 121 patients who were confirmed to have inflammatory bowel disease were enrolled in the study. Thorough history taking and clinical evaluation of enrolled patients were done. Different data of the patients were gathered based on development of kidney disease

Results: A total of 20 (16.5%) patients were found to have kidney disease. Patients with kidney disease had significantly younger age at time of diagnosis (36.40 ± 9.66 vs. 29.65 ± 8.19) and longer disease duration (2.63 ± 1.28 vs. 4.11 ± 2.47) in comparison to those without kidney disease. Based on the current study, predictors of kidney disease in patients with inflammatory bowel disease were younger age of diagnosis, duration of the disease and family history of chronic disease.

Conclusion: Early detection of these kidney manifestations is of major importance, and regular monitoring of renal function in IBD patients could help guide therapy and eventually reduce the overall morbidity.

Keywords: Renal impairment, Kidney disease, Inflammatory bowel disease.

INTRODUCTION

The hallmark of inflammatory bowel disease (IBD) is recurrent bouts of gastrointestinal tract inflammation brought on by an inappropriate immune response to gut bacteria. Ulcerative colitis and Crohn's disease, two idiopathic intestinal diseases that differ in their location and degree of gut wall involvement, are included in the category of "inflammatory bowel disease" [(1)].

IBDs, or inflammatory bowel illnesses, can affect many other bodily systems in addition to the digestive system. Extraintestinal symptoms of IBD, which include organs outside the gastrointestinal system, are more commonly known [(1-3)].

EIMs might happen more or less frequently depending on the organ involved. EIMs can happen both before and after an IBD diagnosis. They can have a significant negative effect on individuals with IBD's quality of life, often even more so than the intestinal condition itself. According to reports, 4% to 23% of IBD patients have renal and urine involvement, which often manifests as urinary calculi, fistulas, and ureteral blockage [(4, 5)].

This study was conducted to detect whether patients with inflammatory bowel disease (IBD) have some degree of renal involvement and also to determine if associated with disease activity or not.

PATIENTS AND METHODS

Study design and setting

A cross sectional hospital based study was conducted at Department of Internal Medicine of Assiut University Hospitals. It was done in period between January 2020 and December 2020.

Ethical consideration:

This work was conducted in accordance with Code of Good Practice and the guidelines of Declaration of Helsinki, 7th revision, 2013. Also, approval by Institutional Review Board, Faculty of Medicine, Assiut University was obtained. The study was registered on clinicaltrials. gove with NCT04301297. Patients signed informed consent.

Inclusion criteria: Any patient with clinical, laboratory, radiological and/or histopathological evidence of IBD was enrolled in the study.

Exclusion criteria:

Any patient with one or more of the following criteria was excluded;

- Signs of urinary tract infection
- Known renal disease
- Hypertension
- Diabetes mellitus
- Use of nonsteroidal anti-inflammatory drugs (NSAIDs) or other nephrotoxic drugs known rather than those used in the protocol of therapy of IBD
- Recent pregnancy
- Morphological changes of kidney (proven by ultrasound)
- Patient's refusal

Sample size calculation:

Total coverage sample where any patient fulfilled the inclusion criteria during the study period was recruited in the study. A total of 121 patients who were proven to have IBD were enrolled in the study.

Received: 3/5/2022
Accepted: 4/7/2022

Methodology:

Patients were questioned about their symptoms (diarrhoea (blood, mucus), abdominal pain, vomiting, weight loss, extraintestinal manifestations, fistulas, perianal disease (in Crohn's disease (CD)), and fever, family history (IBD, celiac disease, colorectal cancer), and pain in the lower left quadrant of the abdomen in cases of moderate to severe UC or in the right lower quadrant of the abdomen, which is common in CD or around the umbilicus.

Routine laboratory investigations were done that included: urea and serum creatinine, liver tests (transaminases, albumin and bilirubin), C-reactive protein (CRP). Estimated glomerular filtration rate (eGFR) was calculated according to the Modification of Diet in Renal Disease (MDRD) formula to assess degree of renal affection and its stage in those patients and 24-h urine collection was used for estimation of albuminuria.

Outcome:

Primary outcome was to assess frequency of renal insufficiency in patients with IBD while secondary outcome was to determine different stages of renal impairment and different independent factors that could be predictors for renal affection in such patients.

Statistical analysis

Recorded data were analyzed using the statistical package for the social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD) and compared with Student t test. Qualitative data were expressed as frequency and percentage and compared with Chi^2 test. Multivariate regression analysis was used to determine the independent risk factors for renal affection in patients with IBD. Level of confidence was kept at 95% hence, P value was significant if was < 0.05.

RESULTS

Frequency of kidney disease among studied patients (Figure 1):

A total of 20 patients were found to have kidney disease while the other 101 patients didn't have kidney disease (KD).

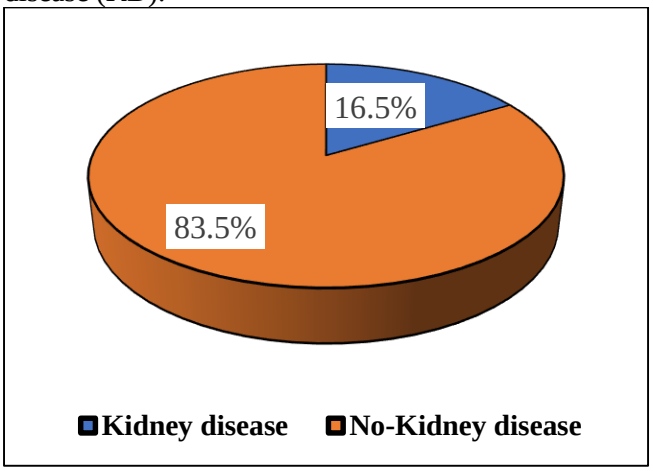

Figure (1): Frequency of kidney disease in the current study

Baseline data of studied patients based on presence of KD (Table 1):

Patients with KD had significantly younger age at time of diagnosis in comparison to those without KD. Patients with KD had significantly longer duration of IBD's disease. Eighteen (17.8%) and 3 (15%) patients of those with KD and those without KD were smokers, respectively.

Table (1): Baseline data of studied patients based on presence of KD

	Kidney disease		P value
	No (n= 101)	Yes (n= 20)	
Age of diagnosis (year)	36.40 ± 9.66	29.65 ± 8.19	< **0.001**
Sex Male Female	 50 (49.5%) 51 (50.5%)	 9 (45%) 11 (55%)	0.45
Body mass index (kg/m^2)	25.67 ± 2.20	26.06 ± 1.34	0.42
Duration of the disease (year)	2.63 ± 1.28	4.11 ± 2.47	**0.01**
Smoking	18 (17.8%)	3 (15%)	0.52
Type of IBD Ulcerative colitis Crohn's disease	 71 (70.3%) 30 (29.7%)	 11 (55%) 9 (45%)	0.14
Family history of CKD	3 (3%)	9 (45%)	< **0.001**
Family history of IBD	14 (13.9%)	1 (5%)	0.27

Data expressed as frequency (percentage) or mean± standard deviation; KD: kidney disease; IBD: inflammatory bowel disease; CKD: chronic kidney disease

Type of management among studied patients based on kidney disease (Table 2):

Both groups had insignificant difference as regard different types of therapy with exception of significantly higher frequency of 5-amino salicylic acid in patients with KD.

Table (2): Type of management among studied patients based on kidney disease

	Kidney disease		P value
	No (n= 101)	Yes (n= 20)	
Steroid therapy	92 (91.1%)	17 (85%)	0.31
Thiopurine	30 (29.7%)	7 (35%)	0.41
5-amino salicylic acid	48 (47.5%)	15 (75%)	**0.02**
Biological therapy	43 (42.6%)	7 (35%)	0.35

Data expressed as frequency (percentage).

Baseline laboratory data of studied patients based on presence of KD (Table 3):

It was found that both groups had insignificant differences as regard baseline laboratory data with exception of significantly lower serum albumin and glomerular filtration rate and significantly higher CRP, blood urea, serum creatinine and proteinuria among patients with KD in comparison to those without KD.

Table (3): Baseline laboratory data of studied patients based on presence of KD

	Kidney disease		P value
	No (n= 101)	Yes (n= 20)	
Hemoglobin (mg/dl)	11.30 ± 1.52	10.88 ± 1.67	0.29
Platelets (10^3/ul)	319.19 ± 77.92	334.70 ± 68.74	0.49
Leucocytes (10^3/ul)	7.19 ± 1.66	5.96 ± 1.92	0.05
Sodium (mmol/l)	139.88 ± 3.78	138 ± 2.53	0.30
Potassium (mg/dl)	4.06 ± 0.53	4.18 ± 0.40	0.36
Calcium (mg/dl)	9.05 ± 0.43	9.07 ± 0.27	0.84
Albumin (mg/dl)	4.57 ± 0.55	3.34 ± 0.84	**< 0.001**
Alanine transaminase (u/l)	23.07 ± 5.84	22.30 ± 5.64	0.63
Random blood sugar (mg/dl)	135.68 ± 27.58	138.70 ± 28.95	0.65
ESR (ml/h) 1st hour 2nd hour	 33.03 ± 7.60 74.90 ± 14.45	 34.76 ± 7.98 76.53 ± 17.02	 0.08 0.66
C-reactive protein (mg/dl)	4.15 ± 0.86	11.71 ± 2.61	**< 0.001**
Creatinine (mg/dl)	55.67 ± 12.45	154.67 ± 34.56	**< 0.001**
Urea (mg/dl)	24.78 ± 5.34	34.56 ± 8.04	**0.03**
Proteinuria (mg/day)	87.77 ± 19.85	708.95 ± 79.04	**< 0.001**
eGFR (ml/min/1.73 m^2)	93.13 ± 16.38	45.41 ± 11.73	**< 0.001**
Complement 3 (mg/dl)	91.05 ± 22.72	94.70 ± 22.45	0.38
Complement 4 (mg/dl)	27.38 ± 6.40	26.65 ± 5.54	0.07
Ferritin (mcg/l)	204.02 ± 34.62	155.89 ± 27.07	0.50
Iron (mcg/dl)	40.60 ± 9.45	28.80 ± 6.67	0.23

Data expressed as mean± standard deviation. KD: kidney disease; ESR: erythrocyte sedimentation rate; eGFR: estimated glomerular filtration rate

Predictors of Kidney disease in patients with inflammatory bowel disease (Table 4):

Based on the following study, predictors of kidney disease in patients with inflammatory bowel disease were; younger age of diagnosis, duration of the disease, and family history of CKD.

Table (4): Predictors of kidney disease in patients with inflammatory bowel disease

Variables	OR	95% CI	P value
Age of diagnosis	5.67	2.34-12.34	< 0.001
Duration of disease	3.45	1.55-5.91	< 0.001
Family history of CKD	2.10	1.50-4.22	< 0.001
5-amino salicylic acid	0.45	0.24-1.58	0.23
Serum albumin	1.12	1.11-2.20	0.56

CKD: chronic kidney disease; OR: odds ratio; CI: confidence interval.

DISCUSSION

There are few data in the literature focused on the incidence of kidney disease (KD) in patients with IBD. The current study was conducted over one-year duration to assess frequency and risk factors for kidney disease in patients with inflammatory bowel disease. To date, also only a few epidemiological studies had investigated the risk of renal insufficiency in patients with IBD.

The study enrolled 121 patients with IBD based on clinical, radiological and histological evaluation. Out of those patients, 20 (16.5%) patients had KD. This result was consistent with previous reports that estimated renal affection was between 6% to 46% of all patients with IBD **(6).** Also, in line with the current study **Lewis *et al.*** **(7)** evaluated the incidence of renal failure (diagnosed using an arbitrary cut-off for GFR of <60ml/min/1.73 m^2) in a population of 251 patients with IBD (66.1% with CD). The results of this study showed a prevalence of KD of 15.9% (10.34% chronic RD, 5.56% acute RD)**.** In a large population-based retrospective cohort study demonstrates that IBD is associated with development of CKD stages 3 – 5 after adjustment for common CKD risk factors. The age-standardized incidence rate of CKD among patients with IBD is 130.3 per 100,000 person-years (95% CI 121.9 – 139.0) compared to 91.3 per 100,000 person-years (95% CI 87.6 – 95.2) in age-, sex-, and practice-matched individuals without IBD **(8).**

Several mechanisms might explain why patients with IBD have a high risk of KD. First, KD may result from a systemic inflammatory response via an immunologic mechanism that determines the disease activity of the intestines. Low-grade systemic inflammation was found to contribute to renal dysfunction, and consequently, it has emerged as a novel risk factor for KD **(9).**

Indeed, previous reports have demonstrated that elevated inflammatory and pro-inflammatory cytokines functioned as early predictors of kidney

disease. Moreover, serum C-reactive protein (CRP) levels were elevated in patients with end-stage renal disease (ESRD) that was initiated. A clear increase in the serum CRP level was also observed in those patients [(10)].

Last, several epidemiologic studies have shown that patients with IBD have an increased risk of developing nonalcoholic fatty liver disease (NAFLD), and up to 33.6% of patients with IBD have NAFLD. NAFLD is also associated with proteinuria and may present poor renal outcome. Therefore, NAFLD may be regarded as a differential diagnosis of asymptomatic urinary abnormalities in IBD and careful consideration should be given to the occurrence of kidney disease [(11-14)].

In the current study, we found both groups had insignificant differences regarding baseline data with exception of age of diagnosis, duration of the disease and family history of CKD. This was consistent with study of **Lewis *et al.*[(7)]** who found that patients with KD had longer duration of the disease and higher frequency of positive family history of CKD.

Also, in the current study it was found that both groups had insignificant difference as regard different types of therapy with exception of significantly higher frequency of 5-amino salicylic acid (5-ASA) in patients with KD (15 (75%) vs. 48 (47.5%)). In line with these findings, there have been several studies examining kidney disease associated with IBD medications such as 5-ASA [(15-17)]. Most of the kidney disease typically occurred within the first year of using a 5-ASA, although there were exceptions and the kidney disease does not seem to be dose dependent [(18)]. Other studies have argued against the notion that 5-ASA usage can cause kidney disease [(19)]. So currently, there is no clear agreement in the literature.

Based on the current study, predictors of kidney disease in patients with inflammatory bowel disease were younger age of diagnosis (OR= 5.67), longer duration of the disease and family history of CKD (OR= 2.10). We found that use of 5-ASA wasn't a predictor for KD in patients with IBD.

The association between IBD and CKD declines with increasing age is supported by **Park and colleagues'[(20)]** recent study of the association between IBD and end stage kidney disease (ESKD) among South Koreans. In subgroup analyses in that study, age younger than 40 conferred a higher hazard of ESKD compared to age 40 or older. The mechanism of declining strength of association of IBD and CKD with increasing age demonstrated in our study and Park's study is uncertain.

In agreement with the current study, which stated that persons with IBD, common IBD medications such as 5-ASA's, azathioprine, and methotrexate are not associated with lower eGFR compared to not using those medications. These findings have important implications for clinical practice, as gastroenterologists often monitor the renal function of patients receiving 5-ASAs to avoid nephrotoxicity [(8)].

Because this study indicates that all patients with IBD are at increased risk for CKD and that the risk is not conferred by 5-ASA use, it may be reasonable to periodically monitor renal function in all patients with IBD, not just those taking 5-ASAs.

Similarly, **Lewis *et al.*[(7)]** stated that with multivariable analysis demonstrated that older age was associated with a 30% increase in the likelihood of developing kidney disease and that patients with a history of renal problems post-IBD diagnosis were more likely to have KD.

One of the main limitations of the current study were relatively small sample size and being conducted in single tertiary center where the patients with IBD used in our study might not be representative of the IBD population as a whole as these patients might represent patients with a more severe course, requiring hospitalization than those whose disease is managed adequately from only an outpatient setting. Multicenter future studies on large sample size are warranted to confirm such results.

CONCLUSION

Early detection of these kidney manifestations is of major importance, and regular monitoring of renal function in IBD patients by measuring serum creatinine and glomerular filtration rate could help guide therapy and eventually reduce the overall morbidity. It's recommended to perform such study on larger number of patients with long term follow up in multi centers to firm the findings of this study.

Conflict of interest: The authors declare no conflict of interest.
Sources of funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Author contribution: Authors contributed equally in the study.

REFERENCES

1. **Su C, Judge T, Lichtenstein G (2002):** Extraintestinal manifestations of inflammatory bowel disease. Gastroenterology clinics of North America, 31(1):307-27.
2. **Vavricka S, Schoepfer A, Scharl M *et al.* (2015):** Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis., 21(8):1982-92.
3. **Garber A, Regueiro M (2019):** Extraintestinal manifestations of inflammatory bowel disease: Epidemiology, etiopathogenesis, and management. Current Gastroenterology Reports, 21(7): 31-35.
4. **Shield D, Lytton B, Weiss R *et al.* (1976):** Urologic complications of inflammatory bowel disease. The Journal of Urology, 115(6):701-6.
5. **Pardi D, Tremaine W, Sandborn W *et al.* (1998):** Renal and urologic complications of inflammatory

bowel disease. The American Journal of Gastroenterology, 93(4):504-14.

6. **Danese S, Semeraro S, Papa A *et al.* (2005):** Extraintestinal manifestations in inflammatory bowel disease. World Journal of Gastroenterology, 11(46):7227.
7. **Lewis B, Mukewar S, Lopez R *et al.* (2013):** Frequency and risk factors of renal insufficiency in inflammatory bowel disease inpatients. Inflammatory Bowel Diseases, 19(9):1846-51.
8. **Vajravelu R, Copelovitch L, Osterman M *et al.* (2020):** Inflammatory bowel diseases are associated with an increased risk for chronic kidney disease, which decreases with age. American Gastroenterological Association, 18(10):2262-8.
9. **Vlassara H, Torreggiani M, Post J *et al.* (2009):** Role of oxidants/inflammation in declining renal function in chronic kidney disease and normal aging. Kidney International, 114: 3-11.
10. **Martínez J, Saus C, Morey A *et al.* (2002):** Crohn's disease and renal amyloidosis. Acute renal failure. Nefrologia: Publicacion Oficial de la Sociedad Espanola Nefrologia, 22(4):397-402.
11. **Bessissow T, Le N, Rollet K *et al.* (2016):** Incidence and predictors of nonalcoholic fatty liver disease by serum biomarkers in patients with inflammatory bowel disease. Inflammatory Bowel Diseases, 22(8):1937-44.
12. **Lapumnuaypol K, Kanjanahattakij N, Pisarcik D *et al.* (2018):** Effects of inflammatory bowel disease treatment on the risk of nonalcoholic fatty liver disease: a meta-analysis. Eur J Gastroenterol Hepatol., 30(8):854-60.
13. **Velciov S, Gluhovschi G, Sporea I *et al.* (2011):** Asymptomatic urinary anomalies, hematuria and proteinuria, in patients with inflammatory bowel disease. Preliminary study. Rom J Intern Med., 49(2):113-20.
14. **Wijarnpreecha K, Thongprayoon C, Boonpheng B *et al.* (2018):** Nonalcoholic fatty liver disease and albuminuria: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol., 30(9):986-94.
15. **Corrigan G, Stevens P (2000):** Interstitial nephritis associated with the use of mesalazine in inflammatory bowel disease. Alimentary Pharmacology & Therapeutics, 14(1):1-6.
16. **Mahmud N, O'Toole D, O'Hare N *et al.* (2002):** Evaluation of renal function following treatment with 5-aminosalicylic acid derivatives in patients with ulcerative colitis. Aliment Pharmacol Ther., 16(2):207-15.
17. **Ransford R, Langman M (2002):** Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut, 51(4):536-9.
18. **Gisbert J, González-Lama Y, Maté J (2007):** 5-Aminosalicylates and renal function in inflammatory bowel disease: a systematic review. Inflammatory Bowel Diseases, 13(5):629-38.
19. **Elseviers M, D'Haens G, Lerebours E *et al.* (2004):** Renal impairment in patients with inflammatory bowel disease: association with aminosalicylate therapy? Clinical Nephrology, 61(2):83-9.
20. **Park S, Chun J, Han K *et al.* (2018):** Increased end-stage renal disease risk in patients with inflammatory bowel disease: A nationwide population-based study. World J Gastroenterol., 24(42):4798-808.