Editorial

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Journal of Clinical & Experimental Nephrology
ISSN 2472-5056

2016
Vol.1 No.1:01

DOI: 10.21767/2472-5056.100001

Inflammatory Bowel Diseases Accompanied by Renal Impairment

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Received date: Nov 2, 2015; **Accepted date:** Nov 9, 2015; **Published date:** Nov 16, 2015

Citation: Skamnelos A, Giagkou E, Malakos Z, Katsanos KH, Christodoulou DK (2015) Inflammatory Bowel Diseases Accompanied by Renal Impairment. J Clin Exp Nephrol 1: 1. DOI: 10.21767/2472-5056.100001

A Note on Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is a chronic systemic disorder, which mainly affects the bowel. However, both ulcerative colitis (UC) and Crohn's disease (CD) are often associated with extra intestinal manifestations, complications, and other autoimmune disorders. These manifestations can involve almost any organ system, including the musculoskeletal, dermatologic, hepatopancreatobiliary, ocular, renal, and pulmonary systems, and can provoke an interesting challenge to physicians managing IBD patients [1]. In our days, an increasing number of kidney manifestations and complications in patients suffering IBD are mentioned, profoundly due to therapists' vigilance. Many pathophysiological pathways have been accused for renal involvement. Kidney damage can be provoked by the disease itself, from secondary extra intestinal complications of the disease (malnutrition), or side effects of therapy. Aim of this paper is to review the renal involvement in IBD so that it can be easily recognized and rapidly treated. Severe long-standing disease consists a predisposing factor for renal complications that answer in 4-23% of patients [2]. Uric acid and oxalate stones are met in a number 10-100 times greater than for the general population. Glomerulonephritis is mentioned in several reports on patients with IBD at least 27 patients; of these 7 had CD, 17 had UC and 3 were indeterminate. Tubular abnormalities were seen in 31% of CD and in 23% of UC patients who were not on ASA. Furthermore, IBD is an uncommon cause of secondary amyloidosis. Lastly, there are drugs used to treat IBD (amino salicylates, cyclosporine) with significant possibility of renal toxicity [3,4]. The hazard of nephrolithiasis is 10-100 times greater than the general population it patients with IBD, specifically those with ileocolic CD who undergo surgery. Kidney stones consist mostly of calcium oxalate or uric acid and occur more often in the right urinary tract. Urate stones are caused by increased acidic urine due to intestinal fluid and bicarbonate losses. Furthermore, the loss of electrolytes (potassium, magnesium) with diarrhea impedes crystallization. Thus, treatment of urate stones includes treatment of diarrhea, alkalinizing the urine and increasing fluid intake. Increased intestinal absorption of oxalate (enteric hyperoxaluria) leads to the production of calcium oxalate stones. Bile salt mal absorption in a dysfunctional terminal ileum (diseased or resected) results in fat mal absorption, that bind intraluminal calcium, decreasing the amount of calcium bound to oxalate (this last complex is poorly absorbed) resulting in increased oxalate absorption. Enteric hyperoxaluria is infrequent in patients with colectomy, ileostomy or jejunostomy, since the majority of oxalate is absorbed in the colon but can be met in parenteral nutrition, minimal oral intake, even in patients with colectomies [5,6]. A good strategy for preventing the recurrence of calcium oxalate stones includes hydration, oral urinary alkalization, low fat and oxalate diet, increasing the dietary intake of calcium and restricting the intake of salt. The gold standard imaging technique for the detection kidney stones in asymptomatic population is ultrasound [7]. Different histological patterns of glomerulonephritis, as a form of renal involvement in patients with IBD, have been reported: immunoglobulin *IgA* nephropathy, *IgM* nephropathy and membranous, mesangiocapillary, focal segmental and anti-glomerular basement membrane glomerulonephritis. There is no association with duration of disease and IBD can present with or after the GN. There is a male predominance and association with the active inflammation in the bowel or biliary system. Glomerulonephritis is directly associated with intestinal or biliary disease activity, and it has been indicated that remission of bowel inflammation improves renal function. There is no connection with duration of disease and there is a male predominance. Histological lesions may vary from minimal change nephropathy and *IgA* nephropathy to rapidly progressive crescentic GN with or without tubulointerstitial nephritis. The genetic connection of IBD and *IgA* nephropathy could be the base of the explanation in their correlation. Hematuria, nephritic syndrome oliguria, proteinuria, elevated serum creatinine and edema are the usual symptoms, signs and laboratory findings in patient's clinical presentations. Treatment includes steroid administration and bowel resection if there is no response [2,8]. Although tubulointerstitial nephritis has been reported in patients with IBD and ASA therapy, it is also considered an extra intestinal manifestation. This admission was supported by counting the urinary enzymes beta-N-acetylglucosaminidase *(b-NAG),* dipeptidylpeptidase 4 (DPP4) and alanine amino peptidase (AAP) before initiating therapy in patients with active UC and after an effective treatment. In particular, enzymuria (elevated B-NAG levels) changed to normal values, pointing out

that this could be an extra intestinal manifestation [10,11]. An infrequent but very significant extra intestinal renal manifestation of IBD that may change disease prognosis even more the intestinal disease is secondary amyloidosis. The incidence of Amyloidosis ranges from 0.3% to 10.9% in CD patients and from 0% to 0.7% in UC patients. Amyloidosis is more common in ileocolitis, than in ileitis or colitis and has a male preponderance [2,12]. Early diagnosis of renal amyloidosis in patients with IBD meliorates patients' prognosis. There is a range of expression. Usually renal involvement occurs with asymptomatic proteinuria or manifestations of nephritic syndrome. Levels of serum amyloid are elevated in proportion to disease activity as an acute phase protein. This happens more frequently in CD than in UC [12]. The response of IBD related secondary amyloidosis to treatment has been varied. Several reports demonstrated that medical or surgical treatment has stabilized or improved 65 renal diseases while others suggested no benefit with. Medical treatment includes immunosuppressive drugs (such as azathioprine, methotrexate and cyclosporine), corticosteroids, colchicine and dimethylsulfoxide. Recent case reports proved the efficacy of anti-TNFα therapy (infliximab) [13]. Drug-induced nephrotoxicity is not infrequent in IBD. The 5-aminosalicylic (5-ASA) in its different forms (sulfasalazine, mesalazine, olsalazine) is the first line drug in patients with IBD. Data from studies describing renal impairment by 5-ASA show contradictory conclusions. Some claim an incidence of interstitial nephritis of >1% while others reported that 5-ASA treatment has no effect on renal function. Recent studies have confirmed the presence of alterations of sensitive markers of renal dysfunction in patients with IBD, although no relation between amino salicylate dose or extent or duration of disease was seen. Some cases of acute renal failure associated with amino salicylate therapy may describe a dose independent allergic condition, which may represent a clinical entity different from the findings reported. At present no clinical data have been presented suggesting that chronic treatment with amino salicylates is unsafe unless a hypersensitive reaction occurs [14]. Cyclosporine is a potentially toxic drug that is effective only in fulminant UC and severely active CD. The exact mechanism of chronic Cyclosporine nephrotoxicity remains unclear, although intra renal activation of the renin-angiotensin system has been suggested to play a significant role and is characterized by arteriolopathy, striped interstitial fibrosis and tubular atrophy. Patients undergoing Cyclosporine treatment for autoimmune diseases, including IBD, will have a 20% reduction in the glomerular filtration rate. Nephrotoxicity is related to the dose of cyclosporine. However the risk of irreversible renal damage seems limited if Cyclosporine is given in a relatively low starting dose and reduction or discontinuation of Cyclosporine usually improves renal function after 5-7 days [14,15]. Concomitant use of other nephrotoxic agents should be avoided and patients with preexisting renal dysfunction should not be treated with cyclosporine. Although previous studies reported that *TNF-α* inhibitors may have some beneficial effects in the treatment of glomerulonephritis, data from recent studies and greater observation of *TNF-α* inhibitors clinical usage conclude controversially that *TNF-α* inhibitors may be involved with a causative role in the emergence of renal complications such as glomerulonephritis. IBD are systemic disorders and not restricted to the intestine, almost every site of the body can be affected by the inflammatory process. The possibility of contributing disease complications, especially through the side effects of treatment, should always be born in mind. The distinction between disease and treatment side effects can be extremely difficult. However, careful patient follow up, clinical laboratory evaluation critically contributes to patients favorable outcomes.

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