Review Article

Renal Involvement in Inflammatory Bowel Diseases

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Abstract

The prevalence of extraintestinal manifestations in inflammatory bowel diseases varies from 6% to 46%. The aetiology of extraintestinal manifestations remains unclear. There are theories based on an immunological response influenced by genetic factors. Extraintestinal manifestations can involve almost every organ system. They may originate from the same pathophysiological mechanism of intestinal disease, or as secondary complications of inflammatory bowel diseases, or autoimmune diseases susceptibility. The most frequently involved organs are the joints, skin, eyes, liver and biliary tract. Renal involvement has been considered as an extraintestinal manifestation and has been described in both Crohn’s disease and ulcerative colitis. The most frequent renal involvements in patients with inflammatory bowel disease are nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis and amyloidosis. The aim of this review is to evaluate and report the most important data in the literature on renal involvement in patients with inflammatory bowel disease. Bibliographical searches were performed of the MEDLINE electronic database from January 1998 to January 2015 with the following key words (all fields): (inflammatory bowel disease OR Crohn’s disease OR ulcerative colitis) AND (kidney OR renal OR nephrotoxicity OR renal function OR kidney disease OR renal disease OR glomerulonephritis OR interstitial nephritis OR amyloidosis OR kidney failure OR renal failure) AND (5-aminosalicylic acid OR aminosalicylate OR mesalazine OR TNF-α inhibitors OR cyclosporine OR azathioprine OR drugs OR pediatric).

Keywords: Inflammatory bowel diseases; renal disease; extraintestinal manifestation

1. Introduction

The prevalence of extraintestinal manifestations (EIMs) in inflammatory bowel diseases (IBDs) varies from 6%–46%.1 Although understanding of the pathogenesis of IBDs has improved considerably during the last decade, the aetiology of EIMs remains unclear. The mechanisms that have been suggested include contributions of genetic factors, infectious agents, circulating bacterial endotoxins and immune-complex deposition. EIMs can involve almost every organ system. It is not always possible to identify the pathophysiological mechanism underlying an organ’s involvement in IBD; it may originate from the same pathophysiological mechanism as intestinal disease, or as a secondary complication of IBDs, or autoimmune diseases (e.g. thyroid autoimmune diseases). The most frequently involved organs are the joints (peripheral arthritis, sacroiliitis, ankylosing spondylitis), the skin (erythema nodosum, pyoderma gangrenosum), the eyes (episcleritis, uveitis), the liver and the biliary tract (primary sclerosing cholangitis, gallstones).2 Renal involvement has been considered as an EIM and has been described both in Crohn’s disease (CD) and in ulcerative colitis (UC).3–5 The most frequent renal diseases in patients with IBD are: nephrolithiasis, tubulointerstitial nephritis, glomerulonephritis and amyloidosis (Table 1). As in other EIMs, renal manifestations can be considered as dependent on the same immunological mechanism that determines intestinal inflammatory diseases, directly related to intestinal activity. Another hypothesis to be considered is that renal involvement is an independent of bowel disease, due to its autoimmune mechanism of action; otherwise, it could be related to...
metabolic disorders that develop in IBD. Finally, kidney pathologies in IBD have been associated with side effects of drugs.6–8

The aim of this review is to evaluate and report the most important data in the literature on renal involvement in IBD patients, trying to outline the most suitable methods and timing to monitor kidney functionality. Bibliographical searches were performed of the MEDLINE electronic database from January 1998 to January 2015 with the following key words (all fields): (inflammatory bowel disease OR Crohn’s disease OR ulcerative colitis) AND (kidney OR renal OR nephrotoxicity OR renal function OR kidney disease OR renal disease OR glomerulonephritis OR interstitial nephritis OR amyloidosis OR kidney failure OR renal failure) AND (5-aminosalicylic acid OR aminosalicylate OR mesalazine OR TNF-α inhibitors OR cyclosporine OR azathioprine OR drugs OR pediatric).

2. Nephrolithiasis

The prevalence of nephrolithiasis among patients with IBD is higher than in the general population, ranging from 12% to 28%,6–12 especially in patients with IBD who have undergone surgical bowel procedures, such as total colectomy with ileostomy, small bowel resection or intestinal bypass. Diarrhoea and malabsorption, often described in IBD patients, are risk factors for renal stone formation. Nevertheless, Parks et al.10 demonstrated that, in the absence of surgery, bowel disease patients with stones cannot be distinguished from common stone formers. Cury et al.11 demonstrated that not only previous surgery but also the extent of disease contributes to nephrolithiasis; in particular, they observed that ileocolonic disease, and not ileal disease, was a significant risk factor for nephrolithiasis. Furthermore, the risk is higher in CD compared with UC,7 probably because in CD there is often ileocolic involvement. Renal stones in patients with IBD are usually composed of uric acid and calcium oxalate. The formation of uric acid stones, linked with urine uric acid supersaturation, is promoted by low urine pH (resulting from alkali lost in the stool) and low urine volume (especially in patients who have undergone colon surgery) (Figure 1). Urine alkalinization, increased water intake and administration of citrate can prevent recurrent formation of uric acid stones. Hyperoxaluria is frequently found in patients with IBD and is defined as excess urinary excretion of oxalate (>45 mg/d). In particular, in these patients enteric hyperoxaluria can be observed that is dependent on increased intestinal absorption of oxalate, due to ileal disease and, in consequence, increased urinary oxalate excretion, causing calcium oxalate stones. Enteric hyperoxaluria depends on different mechanisms (Figure 1). One of these is represented by bile salt malabsorption in the diseased or resected distal ileum. The consequence of this condition is fat malabsorption, which leads to a decrease in the amount of calcium bound to oxalate and an increase in oxalate absorption.5 A further two mechanisms can be considered: the first is related to increased colonic epithelium permeability to oxalate and the second is related to gastrointestinal decolonization of Oxalobacter formigenes and subsequent reduction of intestinal oxalate catabolism (Figure 2). Oral administration of Oxalobacter has been shown to decrease urinary oxalate concentration in humans.14

Parks et al.10 have demonstrated that low urine volume and low urine pH are the main stone-forming abnormalities in patients with colon resection. Moreover, hyperoxaluria is extremely elevated after an intestinal bypass procedure, and slightly elevated after small bowel surgery.19 McConnell et al.7 showed that lower urinary concentrations of magnesium and citrate (stone inhibitors), relative to calcium (stone promoter), may be more important in lithogenesis in IBD than hyperoxaluria.

Jonassen et al.15 demonstrated that exposure to oxalate generates toxic responses in renal epithelial cells, including altered membrane surface and cellular lipids, changes in gene expression, disruption of mitochondrial function, formation of reactive oxygen species and

Table 1. Renal involvement in inflammatory bowel disease.

<table>
<thead>
<tr>
<th>Nephrolithiasis</th>
<th>Glomerulonephritis</th>
<th>IgA nephropathy</th>
<th>IgM nephropathy</th>
<th>Membranous glomerulonephritis</th>
<th>Mesangiocapillar glomerulonephritis</th>
<th>Focal segmental glomerulonephritis</th>
<th>Anti-glomerular basement membrane glomerulonephritis</th>
<th>Tubulointerstitial nephritis</th>
<th>Drug-related</th>
<th>Not drug-related</th>
<th>Renal amyloidosis</th>
</tr>
</thead>
</table>

Figure 1. Pathogenesis of nephrolithiasis in inflammatory bowel disease.
decreased cell viability. Chronic exposure of renal epithelial cells to oxalate can produce renal cell desensitization to oxalate stimulation; this condition may have profound effects on the outcome of renal stone disease by impairing protective responses. Recurrent nephrolithiasis may be related to the development of chronic kidney disease and end-stage kidney disease, necessitating preventive identification of this complication. Ultrasound is highly effective in showing large stones (>5 mm) and is the preferred screening method for renal stones in asymptomatic populations.

3. Glomerulonephritis

Glomerulonephritis is a form of renal involvement in patients with IBD (both CD and UC). Different histological patterns of glomerulonephritis in IBD have been described: immunoglobulin (Ig) A nephropathy, IgM nephropathy, and membranous, mesangiocapillary, focal segmental and anti-glomerular basement membrane glomerulonephritis. Glomerulonephritis would appear to be directly connected to intestinal disease activity, and improvement of renal function after remission of bowel inflammation has been demonstrated. Ambruzs et al. have demonstrated a major incidence of IgA nephropathy among IBD patients with acute or chronic kidney failure after kidney biopsies. Furthermore, they highlighted that the prevalence of IgA nephropathy was significantly higher in patients with IBD than in patients without IBD. Immunoglobulin A nephropathy in IBD is likely to represent an unclear complex of interaction of mucosal inflammation, loss of antigenic exclusion and tolerance, chronic immune stimulation, and dysregulated IgA production and transport. The correlation between IgA nephropathy and IBD could be explained by a genetic connection between IgA nephropathy and IBD; in particular, most loci involved in the pathophysiology of IgA nephropathy are either directly associated with the risk of IBD or maintenance of the intestinal epithelial barrier with its response to mucosal pathogens. Moreover, genetic linkage between IgA nephropathy and IBD has been suggested because of the presence of HLA-DR1 in IgA nephropathy and HLA-DR1/DQw5 in CD. Finally, there is no conclusive information regarding the pathophysiology of the other histological pattern (IgM nephropathy and membranous, mesangiocapillary, focal segmental and anti-glomerular basement membrane glomerulonephritis).

4. Tubulointerstitial nephritis

Tubulointerstitial nephritis (TIN) has also been reported in patients with IBD. Although most cases have been associated with 5-aminosalicylate (5-ASA), cyclosporin A and tumour necrosis factor α (TNFα) inhibitor exposure, it is often difficult to establish whether renal dysfunction can be considered an EIM or whether it is due to medical treatment. However, some recent papers have highlighted the link between tubulointestinal damage and IBD activity. Alpha-1-microglobulin (α1-MG), N-acetyl-β-D-glycosaminidase (β-NAG), β2-microglobulin (β2-MG) and cystatin C are proteins that are characterized by low molecular weight, normally filtered by the glomerulus, and, in healthy kidneys, almost entirely reabsorbed in the proximal tubule. Increased quantities of these proteins in the urine can be considered a marker of tubular damage. Kidney tubule damage has frequently been observed in IBD and is more strongly related to disease activity than drugs. Herrlinger et al. demonstrated in their cohort of patients with IBD that increased tubule marker proteins occurred in the majority of their patients and were related to disease activity rather than to ASA treatment. Poulu et al. also described a positive correlation between tubule proteinuria and intestinal disease activity in IBD patients. Furthermore, Fraser et al. concluded that tubule proteinuria is an EIM of IBD, unrelated to 5-ASA treatment. Tokuyama et al. described a case of acute interstitial nephritis unrelated to drugs that lead to kidney failure, and Izedine et al. described primary chronic interstitial nephritis in CD, diagnosed before or simultaneously with CD diagnosis, that led to end-stage renal failure in 3 out of their 4 patients. Cases of TIN unrelated to treatment have also been described in paediatric populations. In particular, Marcus et al. reported two paediatric cases of TIN diagnosed simultaneously with the onset of intestinal symptoms of CD; in these patients, renal pathology evolved independently of intestinal disease. The same clinical evolution was observed by Waters et al. in two paediatric CD patients treated with steroids, who showed no renal function improvement despite intestinal disease improvement (Table 2). These results are in contrast with other papers that demonstrated clinical improvement of EIM (renal, liver, lung and skin manifestations) during steroid or TNFα-inhibitor therapy used for intestinal disease. A granuloma without eosinophilic infiltrate was observed in several untreated CD patients who underwent kidney biopsy. The presence of a predominantly lymphocytic infiltrate with non-necrotizing granuloma in renal biopsy further supported a diagnosis of TIN secondary to CD, rather than a drug-induced manifestation. Among the cohort described by Izedine et al., one patient with TIN secondary to CD underwent renal transplantation; deterioration in renal function during a post-transplantation relapse of CD suggested that the kidneys might be an extraintestinal target in CD.

5. Renal amyloidosis

Secondary amyloidosis (AA) is a rare but significant complication of IBD that may influence prognosis even more than the underlying
Table 2. Published reports of renal involvement in paediatric inflammatory bowel disease (IBD) patients.

<table>
<thead>
<tr>
<th>First author</th>
<th>Age (y)</th>
<th>Gender</th>
<th>IBD</th>
<th>Renal pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shahrani Muhammad</td>
<td>11/F</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Larcher</td>
<td>15/M</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Behrens</td>
<td>15/M</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Skalova</td>
<td>15/M</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Uslu</td>
<td>15/F</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Waters</td>
<td>12/M</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Marcus</td>
<td>11/F</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Frandsen</td>
<td>17/M</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Van Biervliet</td>
<td>11/F</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Benador</td>
<td>16/M</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Arend</td>
<td>18/M</td>
<td>CD</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Co</td>
<td>14/M</td>
<td>UC</td>
<td>TIN</td>
<td></td>
</tr>
<tr>
<td>Takemura</td>
<td>10/M</td>
<td>CD</td>
<td>IgA nephropathy</td>
<td></td>
</tr>
<tr>
<td>McCallum</td>
<td>11/M</td>
<td>CD</td>
<td>IgA nephropathy</td>
<td></td>
</tr>
<tr>
<td>Ridder</td>
<td>12.6/F</td>
<td>UC</td>
<td>Glomerulonephritis, membranous</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>Ishiwada</td>
<td>14/F</td>
<td>UC</td>
<td>IgM nephropathy</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>Torio</td>
<td>9/M</td>
<td>UC</td>
<td>TIN</td>
<td>Nephrolithiasis</td>
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<tr>
<td>Hueppelshaeuser</td>
<td>6–18 (27 cases; 19 M, 8 F)</td>
<td>CD</td>
<td>Nephrolithiasis</td>
<td></td>
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<tr>
<td>Yamamoto</td>
<td>13/M</td>
<td>UC</td>
<td>Nephrolithiasis</td>
<td></td>
</tr>
<tr>
<td>Kirschner</td>
<td>11/M</td>
<td>CD</td>
<td>AA</td>
<td></td>
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</table>

AA, secondary amyloidosis; CD, Crohn’s disease; F, female; M, male; TIN, tubulointerstitial nephritis; UC, ulcerative colitis.

disease. The incidence of AA ranges from 0.3% to 10.9% in CD patients and from 0% to 0.7% in UC patients.45–49 The time lapse between onset of IBD and diagnosis of AA is different: AA is usually diagnosed 10–15 years after IBD diagnosis,47 is sometimes discovered simultaneously with IBD,47,51 and is rarely described before IBD onset.52 The most common clinical presentation of AA is renal amyloidosis, with a frequency of up to 90% in some series.53–56 Renal AA usually manifests as proteinuria and nephrotic syndrome and may progress to renal failure; sometimes renal failure can be present in the absence of significant proteinuria.2 Some patients may even reach severe renal failure requiring dialysis and renal transplantation. Early diagnosis of the association between IBD and renal AA improves patients’ prognosis. The objective of treatment in these patients is to treat the underlying disease, to prevent the formation of amyloid precursor protein, and to treat the AA already established in the affected organs. Immunosuppressive drugs (such as azathioprine, methotrexate and cyclosporin), corticosteroids, colchicine, dimethylsulfoxide and an elemental diet have been proposed as treatment for AA. However, the effectiveness of this regimen has not been established.45,49,51 Eprodisate has also been utilized in the treatment of amyloidosis. It inhibits amyloid protein polymerization and deposition in tissues and slows the decline in glomerular filtration rate (GFR) in AA amyloidosis patients; but actually has little effect on proteinuria and survival.55 Several recent case reports have demonstrated the efficacy of anti-TNFα therapy (infliximab) in patients with amyloid nephropathy associated with IBD, in particular in CD patients.55–59 In these reports, therapy induced rapid responses in proteinuria accompanied by the suppression of disease activity, although the serum creatinine level was not always reversible, even after the administration of infliximab. Even though the efficacy of infliximab has been demonstrated, this treatment cannot completely restore renal function, but it seems that the progression of damage can be halted. Cabezuelo et al.60 reported two possible mechanisms of how anti-TNFα agents can improve amyloid nephropathy in inflammatory diseases: (1) reducing glomerular inflammation and increasing glomerular permeability to albumin, induced by TNFα cytokines and interleukin-6; and (2) reducing the synthesis of acute-phase proteins mediated by the same cytokines. There are reports suggesting that amyloidosis improves after surgical treatment, while on the other hand there are reports that show significant morbidity and even mortality after surgery.5,49

4. Drug-induced nephrotoxicity

Aminosalicylates, azathioprine, cyclosporin and TNFα inhibitors may be involved in renal impairment. However, it is not always possible to clarify the mechanism of these drugs in kidney damage. In many cases it remains unclear whether renal impairment is an EIM or a drug adverse effect.

4.1. 5-Aminosalicylates and sulphasalazine

The use of 5-ASA is the first therapeutic approach in IBD patients. The incidence of nephrotoxicity in IBD patients receiving 5-ASA has not been clearly determined, but it has been suggested that renal impairment may occur in up to 1 in 100 patients treated with 5-ASA, although clinically important damage occurs in only 1 in 500 patients.6 Several studies reported an incidence of interstitial nephritis of >1% but others suggested that 5-ASA treatment has no effect on renal function. Gisbert et al.7 after a review of the literature, evaluated the incidence of nephrotoxicity in IBD patients treated with 5-ASA at approximately less than 0.5%. However, these data are based on relatively low numbers of patients, mainly case reports, with limited follow-up. The main clinical manifestation attributed to 5-ASA toxicity is TIN.6 Symptoms are usually unspecific, such as malaise, fever and skin rash, and sometimes eosinophilia can be detected on blood analysis. The exact mechanisms of induction of TIN are unknown. Some case reports8–10 reported renal impairment, in particular TIN, as dose-dependent ‘analgesic nephropathy’, resulting from inhibition of cyclooxygenases or the hypersensitivity reaction. Furthermore, the nephrotoxic effect of 5-ASA treatment is supported by alteration of creatinine and azotemia levels, which partially resolved after discontinuation of the drug.5 Several clinical trials have demonstrated that TIN in IBD patients, during mesalazine treatment, is related to an idiosyncratic reaction unrelated to dosage or time of exposure, suggesting that cumulative exposure is not a significant factor for TIN development.11–15 The onset time of potential 5-ASA-induced renal damage is reported most often within the first 12 months of treatment, but it has also been observed after several years of therapy.5,47 It has also been reported that partial improvement or even complete recovery of renal function after discontinuation of 5-ASA is helped by starting steroid therapy (intravenously and/or per os).12–15 Discontinuation of 5-ASA, associated with steroid therapy, would appear to lead to restoration of renal function in 40–85% of cases, diagnosed within 10 months from the start of treatment.5,12 When
diagnosis is delayed beyond 18 months from the beginning of treatment, only one-third of cases show recovery of renal function, and this is usually only partial. Although most case reports indicate reversibility after drug discontinuation, in some cases permanent clinical kidney dysfunction has been observed. It has been calculated that about 10% of patients with 5-ASA nephrotoxicity will develop end-stage renal disease. Renal function should be monitored at the beginning of treatment with 5-ASA. Furthermore, 5-ASA therapy should be suspended when renal impairment is discovered. Literature evidence demonstrates that 5-ASA discontinuation alone is usually not sufficient to lead to restoration of renal function, so steroid treatment may be recommended. Utilization of sulfasalazine was also related to nephrotoxicity. In an analysis of spontaneous reports of adverse events in the UK, Ransford and Langman reported that 5-ASA-related nephrotoxicity appeared to be more frequent in patients treated with mesalazine than in patients treated with sulfasalazine. Logan and van Staa, in a large epidemiological study including almost 40,000 patients, showed that the risk of renal toxicity in patients taking mesalazine and sulfasalazine was similar (1.2 and 1.7 per 1000 people/y, respectively). This result is in agreement with previous retrospective and case–control studies. Van Staa et al. reported comparable risks of nephrotoxicity in a large population of adult IBD patients treated with mesalazine and sulfasalazine (0.17 and 0.29 cases per 100 people/y, respectively). Based on the available literature data, the risk of nephrotoxicity in IBD patients thus seems to be similar for mesalazine and sulfasalazine treatment, and the difference is not statistically significant.

4.2. TNFα inhibitors

TNFα inhibitors are normally used in the treatment of CD and, most recently, UC, with good results in terms of tolerability, low-grade side effects and control of intestinal and extraintestinal manifestations. Infliximab (a chimeric anti-TNF IgG1 monoclonal antibody) and adalimumab (a recombinant anti-TNF IgG1 monoclonal antibody) are the most commonly used TNFα inhibitors. A positive effect of TNFα inhibitors on renal amyloidosis in IBD patients has been described. However, TNFα inhibitors can be involved in renal damage. In particular, a possible causative effect for infliximab, adalimumab and etanercept in glomerulonephritis or lupus nephritis has been reported. These case reports involved patients affected by other autoimmune diseases (psoriatic arthritis, rheumatoid arthritis, psoriasis) and there are no data regarding renal involvement in IBD patients treated with TNFα inhibitors. Some authors have described TEN in IBD patients during infliximab therapy associated with mesalazine, but no true correlation has been confirmed. Ramos-Calas et al. demonstrated TNFα inhibitor involvement in renal impairment through the effect of anti-TNFα antibodies (produced during therapy) on glomerular visceral epithelial cells, inducing apoptosis. Charles et al. proposed that the binding of infliximab to TNFα on the cell surface could probably result in apoptosis. Induction of anti-nuclear antibodies (ANA), anti-dsDNA and anti-neutrophil cytoplasmic antibodies (ANCA) formation during therapy with TNFα inhibitors may induce one to consider a possible link between these drugs and lupus-like immune complex glomerulonephritis, ANCA-related necrotizing glomerulonephritis and crescentic glomerulonephritis. Additional data on renal involvement in IBD patients during treatment with TNFα inhibitors are necessary.

4.3. Azathioprine

Azathioprine is a thiopurine widely used for maintenance therapy in IBD patients. Thiopurines are safe to use and well tolerated, nevertheless dose adjustment or withdrawal of therapy should be considered in non-responder patients, or in the case of adverse effects (including nephrotoxicity). Renal involvement was reported in two papers in patients treated with azathioprine, affected by Wegener’s granulomatosis and rheumatoid arthritis respectively. In both cases, renal involvement manifested as interstitial nephritis. Case reports of renal impairment related to azathioprine in IBD patients have not been found.

4.4. Cyclosporin A

Cyclosporin A (CsA) is a calcineurin inhibitor with immunosuppressive effects and is indicated as a second-line therapy in the case of severe UC or in severely active CD. Treatment with CsA is often limited by severe adverse effects, particularly nephrotoxicity, which manifests clinically as acute or chronic renal damage. Nephrotoxicity during CsA treatment depends on duration of the treatment and dosage. The mechanism of acute renal damage is characterized by intense afferent arteriolar vasoconstriction, resulting in decreased renal blood flow and GFR, with a consequent increase in serum creatinine. Vasoconstriction is mediated by endothelin, thromboxane A2, nitric oxide synthase inhibition and activation of the sympathetic nervous system. Chronic renal damage is characterized especially by irreversible interstitial fibrosis and also by arteriolar alterations. Shang et al. have proposed intrarenal activation of the renin–angiotensin system as a mechanism of chronic CsA nephrotoxicity.

4.5. Tacrolimus

Tacrolimus is usually used as initial induction therapy in steroid-refractory acute IBD. Nephrotoxicity is described among the side effects, and renal histological lesions are similar in patients treated with CsA.

Ogata et al. reported an increase in serum creatinine levels up to 30% above baseline in 14.8% of their IBD patients treated with tacrolimus for 10 weeks (blood tacrolimus level of 5–15 ng/mL). A similar observation was made by Sandborn et al., who highlighted an increase in serum creatinine level of up to 30% in 38% of their patients treated with tacrolimus; they suggested that the potential nephrotoxic effect of tacrolimus will likely limit administration of the drug in high doses, but information regarding the long-term effects of tacrolimus therapy on renal function is lacking. Bousvaros et al. described a population of 14 paediatric IBD patients with severe UC or CD treated with oral tacrolimus (blood tacrolimus level of 10–15 ng/mL) associated with intravenous corticosteroid. Nephrotoxicity has not been described in patients with prolonged use of tacrolimus (average 3 months).

Baumgart et al. reported that in IBD patients treated with tacrolimus and without pre-existing renal pathology, the median serum creatinine level was never higher than 1 mg/dL. Watson et al. reported nephrotoxicity (defined as creatinine >1.5× baseline level) in 11% of patients in a population of paediatric and young adult patients with steroid-refractory colitis treated with tacrolimus for 4 months at the median dose of 0.2 mg/kg/d (blood tacrolimus medium level 11 ng/mL). The creatinine levels returned to normal after the tacrolimus dose was reduced or after transition to maintenance therapy.

5. Renal involvement in paediatric IBD patients

Extraintestinal manifestations of IBD occur in 20–35% of children with CD and in 15% of those with UC. There are few papers
that describe renal involvement in paediatric IBD patients. These papers report cases of nephrolithiasis, glomerulonephritis, TIN and AA (Table 2). Our literature review documented 50 cases of renal involvement in paediatric IBD patients. Of these patients, 72% were male and 80% had CD. Out of 50 patients, 58% suffered from nephrolithiasis, 30% developed TIN, 10% glomerulonephritis and 2% AA. These data highlighted that in paediatric IBD patients, as in adult IBD patients, the most frequent renal pathology is nephrolithiasis. Furthermore, the most evident renal involvement among paediatric UC patients was TIN, which occurred in 66% of all UC paediatric patients with renal pathology. Moreover, we underline that only 7 patients out of the 50 considered (14%) presented an onset of renal disease (TIN or glomerulonephritis) before or at the same time as the diagnosis of IBD. Azathioprine

5. Renal insufficiency
There are few data in the literature focused on the incidence of renal insufficiency (RI) in patients with IBD. Primas et al. found that the prevalence of RI in a population of IBD patients (72% with CD) was 1.99% in CD patients and 0% in UC patients. In the same study, they also investigated factors that can influence the incidence of RI in IBD patients (25 patients with CD). The length of resected small bowel, urolithiasis, number of interventions due to urolithiasis, blood urea nitrogen (BUN) values and BUN-to-creatinine ratio were considered statistically significant factors. There was no statistically significant evidence of a relationship with the duration of the intestinal disease. Lewis et al. evaluated the incidence of renal failure (diagnosed using an arbitrary cut-off for GFR of <60 ml/min/1.73 m²) in a population of 251 patients with IBD (66.1% with CD). The results of this study showed a prevalence of RI of 15.9% (10.34% chronic RI, 5.56% acute RI). In the group of IBD patients with RI, the main related factors were the duration of intestinal disease, the presence of EIMs (in particular joint involvement and primary sclerosing cholangitis) and a history of urolithiasis or renal diseases (documented after the diagnosis of IBD). Treatment with 5-ASA could not be considered a risk factor.

6. Conclusions
Extraintestinal manifestations of IBD are varied and concentrated mainly on the joints, skin and eyes. Urinary tract or renal involvement is extremely rare, and includes nephrolithiasis, tubulointerstitial nephritis and amyloidosis. Nephrolithiasis, caused by calcium oxalate or urate, has been reported in approximately 4–23% of patients with CD and can be considered the most frequent renal manifestation in IBD; moreover, it can be considered a rare but noticeable extraintestinal presentation of paediatric IBD.
Drug-induced nephrotoxicity seems more frequent and has been described in adult populations. Based on the existing literature, and considering that no precise guidelines are available, it is useful to periodically monitor renal function in IBD patients through observation of azotaemia and creatinine levels and, above all, monitoring GFR using the MDRD (modification of diet in renal disease) method and creatinine clearance (CrCl) using 24-hour urine collection. Monitoring of blood and urine electrolytes, urinalysis (to check the presence of leucocyturia and low-density urine) and 24-hour urinary protein can be useful but not specific. Tubular enzymuria (ß2-MG, ß-NAG, ß1-MG, cystatin C) may be a more sensitive and specific marker of renal damage, but it is not yet available as a screening method. The GFR seems to be the most reliable sensitive and specific marker of renal damage, but it is not yet available as a screening method. The GFR should be monitored before and after starting therapy with 5-ASA, CsA and TNF inhibitors, and should be checked after 1, 3 and 6 months. If no alterations are observed, checks can be made once a year (Figure 3). However, so far there is no evidence that such monitoring of renal function and clinical management improves patient outcomes.

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**Conflict of Interest**

None of the authors have conflicts of interest relevant to this article to disclose.

**Author Contributions**

Claudio Romano and Domenico Corica conceptualized this study along with contributing to data acquisition and interpretation, drafted the article, approved the final manuscript as submitted and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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**References**


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80. Ransford RA, Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut 2002;51:536–9.
81. Logan RF, van Staa TP. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. Gut 2003;52:1530; author reply 1530–1.


