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Bidirectional Interaction Between the Gastrointestinal System and the Kidney: Pathophysiological and Clinical Perspective

In depth review

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ABSTRACT

The gastrointestinal (GI) system and the kidneys, though anatomically separate, are functionally interconnected through shared responsibilities in maintaining fluid-electrolyte balance, acid-base homeostasis, immune regulation, and hormonal signaling. Disruptions in one system often lead to secondary complications in the other, highlighting the need for a comprehensive understanding of their bidirectional interactions. Kidney involvement in GI diseases commonly results from mechanisms such as fluid loss, malabsorption, systemic inflammation, and exposure to toxins, as seen in conditions like inflammatory bowel disease (IBD), celiac disease, liver failure, and enteric infections. Conversely, GI complications frequently arise in the context of chronic kidney disease (CKD), dialysis, and immunosuppressive therapies post-transplantation, manifesting as symptoms including uremic gastropathy, anorexia, and enteropathy. This review explores these interactions under two main categories: renal complications of GI diseases and GI manifestations of kidney disorders. It also discusses the underlying pathophysiological mechanisms and clinical implications, emphasizing the importance of an integrated, multidisciplinary approach. By highlighting current knowledge gaps, the review aims to foster future research in this complex and clinically significant area. Understanding these bidirectional interactions can inform individualized patient care and improve outcomes in both GI and renal disease contexts.

KEYWORDS: Gastrointestinal system, Kidney diseases, Gut-kidney axis

Overview of Gastrointestinal System and Kidney Interactions

The gastrointestinal (GI) system and kidneys are two distinct systems that play critical roles in maintaining intracorporeal homeostasis. Although there is no direct anatomical connection between these systems, there is a close cooperation through many physiological processes such as fluid-electrolyte balance, acid-base regulation, immune responses and hormonal signaling. Therefore, pathological conditions affecting one system can also influence the other [1]. This interaction is seen clinically in the form of kidney dysfunction that develops during GI diseases and GI complications that occur in kidney diseases [2].

Kidney involvement in GI diseases is often mediated by fluid and electrolyte loss, malabsorption, toxin exposure, or systemic inflammation. In particular, kidney function may be directly or indirectly affected in inflammatory bowel diseases (IBD), celiac disease, liver failure and enteric infections [3–6]. Similarly, the GI system can be significantly affected by kidney diseases. Complications such as uremic gastropathy, enteropathy and anorexia are common in patients with chronic kidney disease (CKD), and treatments such as hemodialysis and peritoneal dialysis may further exacerbate GI symptoms [7, 8]. In addition, post-transplant infections due to immunosuppression and drug side effects may also lead to GI complications [9, 10]. The main interactions between the GI system and the kidneys are shown in Figure 1.

In this review, kidney involvement in GI system diseases and GI complications arising in kidney diseases will be examined under two separate headings; the pathophysiological basis and clinical reflections of this interrelationship will be discussed (Table 1). The aim is to better understand these complex interactions in pediatric and adult patients and to draw attention to the importance of a multidisciplinary approach. It is also aimed to lay the groundwork for future research by revealing the knowledge gaps in these areas.

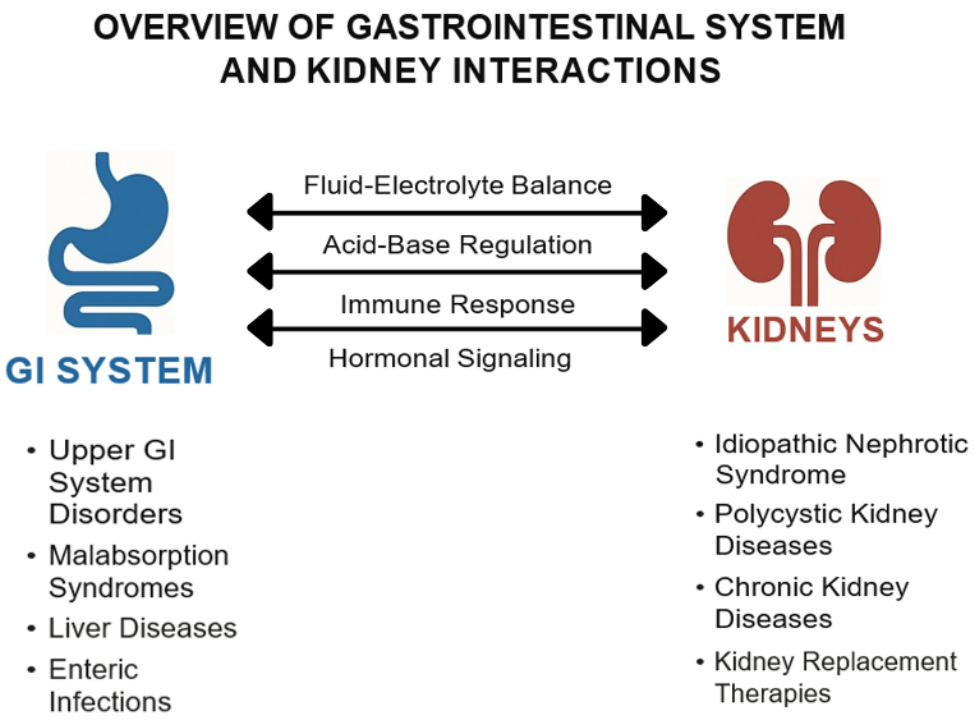

Figure 1. Bidirectional interactions between gastrointestinal system and the kidney.

Mechanisms of Kidney Involvement in GI Diseases	
Upper GI System Disorders	
GERD	Use of PPI and associated ATIN
	Use of PPI and PPI-related nephropathy
***H. pylori* Infection**	Systemic inflammation induced by persistent infection
	Immune complex-mediated kidney injury due to mucosal IgA secretion
	Metabolic disturbances such as insulin resistance and dyslipidemia due to *H. pylori*
Malabsorption Syndromes	
Inflammatory Bowel Diseases	Nephrolithiasis and nephrocalcinosis due to enteric hyperoxaluria
	Glomerulonephritis due to antigen-specific immune responses
	AKI and CKD due to systemic inflammation, medication toxicity, and malnutrition
Celiac Disease	IgAN due to galactose-deficient IgA1
	CKD due to increased intestinal permeability and immune activation
	Diabetic nephropathy due to high prevalence of T1DM
	Nephrolithiasis due to intestinal malabsorption or altered renal handling
	UTI due to impaired urinary tract motility, dysfunction of the bladder, changes in gut microbiota
Liver Diseases	
Primary Hyperoxaluria	Nephrolithiasis/nephrocalcinosis and associated CKD due to hepatic enzyme deficiencies in glyoxylate metabolism
Wilson's Disease	Tubular dysfunctions due to copper deposition
	Glomerular involvement due to immune complex-mediated mechanisms
	Drug-induced nephrotoxicity caused by chelation therapy
Chronic Liver Disease	Decreased kidney perfusion and reduced GFR due to splanchnic vasodilation, activation of RAAS system and sympathetic nervous system
	Systemic inflammation due to impaired hepatic detoxification
	Hepatorenal syndrome due to advanced liver disease
Enteric Infections	
STEC-HUS	Endothelial damage and subsequent thrombotic microangiopathy due to systemic dissemination of Shiga toxins
	GI System Involvement in Kidney Diseases
Idiopathic Nephrotic Syndrome	Edema of the bowel wall due to hypoalbuminemia
	Mesenteric arterial thrombosis due to hypercoagulable state
	Spontaneous bacterial peritonitis due to immunosuppression
	Peptic ulcer disease and drug-related mucosal injury due to steroid therapy
Polycystic Kidney Disease	Polycystic liver disease due to ADPKD
	Congenital hepatic fibrosis due to ARPKD
Chronic Kidney Disease	Uremic gastropathy or delayed gastric emptying due to uremia
	GI bleeding due to mucosal fragility and platelet dysfunction
	Abdominal discomfort or paralytic ileus due to bowel wall edema
	Systemic inflammation due to translocation of endotoxins
	Alterations in the gut microbiome (dysbiosis) due to uremia
	Constipation due to restricted fluid intake, dietary limitations, and phosphate binders
	Protein-energy wasting and deficiencies in essential nutrients due to decreased appetite
Kidney Replacement Therapies	Hypotension-related gut hypoperfusion, mesenteric ischemia and colonic angiodysplasia-related bleeding due to hemodialysis
	Increased intra-abdominal pressure, leading to early satiety, gastroesophageal reflux, abdominal fullness, or hernias due to peritoneal dialysis
	Bacterial or sclerosing encapsulating peritonitis
	Nausea, diarrhea, oral ulcers, and anorexia due to immunosuppressive therapy
	Opportunistic infections due to immunosuppressive therapy

Table 1. Mechanisms of kidney involvement in GI system diseases and GI involvement arising in kidney diseases. GI: Gastrointestinal, GERD: Gastroesophageal reflux disease, PPI: Proton-pump inhibitor, ATIN: Acute tubulointerstitial nephritis, IgA: Immunoglobulin A, AKI: Acute kidney injury, CKD: Chronic kidney disease, IgAN: Immunoglobulin A nephropathy, T1DM: Type 1 diabetes mellitus, UTI: Urinary tract infection, GFR: Glomerular filtration rate, RAAS: Renin-angiotensin-aldosterone system, STEC-HUS: Shiga toxin-producing *Escherichia coli*-hemolytic uremic syndrome, ADPKD: Autosomal dominant polycystic kidney disease, ARPKD: Autosomal recessive polycystic kidney disease.

Material and Methods

This article is a narrative review that examines the bidirectional interactions between the GI system and the kidneys, focusing on the underlying pathophysiological mechanisms and associated clinical outcomes, comprehensively reviewing of the current literature. Methodological rigor and principles of reproducibility were applied during both the literature selection and manuscript preparation processes. The literature search was conducted using the PubMed, Scopus, and Web of Science databases, covering publications from January 2000 to December 2024. Results were limited to studies published in English. The keywords and their combinations used were: “gastrointestinal system”, “kidney diseases”, “gut-kidney axis”, “renal replacement therapies”, and “microbiota”. The study included case reports and original research examining GI system findings or mechanisms in different stages of kidney disease, as well as review articles directly related to the topic. Publications and abstracts with limited relevance to the topic or that did not directly examine the kidney-GI relationship were excluded from the study.

In this narrative review, experimental studies such as animal models were used to understand potential biological pathways. While observational studies were evaluated to determine the relationships between the GI system and the kidneys in human populations, interventional studies provided the strongest evidence for potential effects. Unless supported by evidence from multiple study types, definitive causal statements were avoided, and neutral terms such as associated or linked were used.

Kidney Involvement in Gastrointestinal Diseases

Upper Gastrointestinal System Disorders

Gastroesophageal Reflux Disease

Gastroesophageal reflux disease (GERD) is a common chronic condition characterized by the retrograde flow of gastric contents into the esophagus, resulting in symptoms such as heartburn, regurgitation, and, in some cases, esophagitis. The pathophysiology of GERD involves a combination of factors including lower esophageal sphincter dysfunction, impaired gastric emptying, and increased intra-abdominal pressure. GERD affects a significant proportion of the global population and often requires long-term pharmacological management, particularly with proton pump inhibitors (PPIs), which are the mainstay of treatment. Although PPIs are effective in controlling acid-related symptoms and healing mucosal damage, their long-term use has raised concerns regarding potential adverse effects, including those on kidney functions [11].

One of the most recognized renal complications associated with PPIs is acute tubulointerstitial nephritis (ATIN). In a pediatric study, 11.1% of patients with ATIN had a history of PPI use [12]. This is an immune-mediated hypersensitivity reaction characterized by interstitial inflammation and tubular injury. Clinically, PPI-induced ATIN may present with non-specific symptoms such as fatigue, nausea, or subtle kidney dysfunction, often leading to underdiagnosis. Histological confirmation through kidney biopsy typically reveals interstitial edema, lymphocytic infiltration, and eosinophils [12].

Recent studies have identified an association between chronic PPI use and an increased risk of CKD and kidney failure in adults. Although a direct causal relationship is still under investigation, repeated or subclinical episodes of ATIN, as well as PPI-induced alterations in magnesium homeostasis and gut microbiota, have been proposed as contributing mechanisms [13]. The risk of PPI-related nephropathy appears to be more pronounced in elderly patients, individuals with pre-existing kidney impairment, and those using PPIs for prolonged periods without appropriate clinical

indication. Importantly, PPI-related kidney injury may be partially reversible if recognized early and the offending agent is discontinued [14].

These findings underscore the need for cautious and evidence-based prescribing of PPIs, emphasizing regular reassessment of their indication and duration. In patients requiring long-term acid suppression, kidney function should be periodically monitored, and alternative therapies may be considered when appropriate.

Helicobacter pylori Infection

Helicobacter pylori (*H. pylori*) is a gram-negative, spiral-shaped bacterium that colonizes the gastric mucosa and is a well-established cause of chronic gastritis, peptic ulcer disease, and gastric malignancies. Beyond its GI manifestations, H. pylori infection has been increasingly studied for its potential systemic effects, including those on kidney function [15].

Several epidemiological and experimental studies have suggested a link between chronic *H. pylori* infection and kidney impairment, although the exact mechanisms remain incompletely understood, and pediatric data are limited. One proposed pathway involves systemic inflammation induced by persistent infection. *H. pylori* stimulates the release of pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein, which may contribute to endothelial dysfunction and glomerular injury, particularly in individuals with pre-existing susceptibility [16]. A second pathway is the activation of the immune complex-mediated mechanism due to mucosal immunoglobulin A (IgA) secreted against *H. pylori.* Chronic *H. pylori* infection has been associated with the development of immune-mediated renal diseases, including IgA nephropathy (IgAN). Molecular mimicry and immune cross-reactivity between bacterial antigens and kidney tissues may play a role in this association [17]. In addition, *H. pylori* may contribute to metabolic disturbances such as insulin resistance and dyslipidemia, which are recognized risk factors for CKD [18]. Although a direct causal relationship has not been definitively established, the cumulative evidence indicates that chronic infection could act as a modifiable risk factor in the progression of kidney dysfunction [18]. Moreover, in kidney transplant recipients, *H. pylori* infection is of particular clinical relevance due to the immunosuppressed state, which may alter the typical presentation and increase the risk of GI complications such as peptic ulcer disease and bleeding. Additionally, chronic *H. pylori* infection may contribute to systemic inflammation, potentially affecting graft function and long-term outcomes. Some studies in adults have suggested that pre-transplant screening and eradication of *H. pylori* may reduce the incidence of post-transplant GI morbidity and support better kidney graft survival [19]. In a study evaluating adult patients with membranous nephropathy and *H. pylori* infection, the mean proteinuria value before eradication therapy was 2.42 ± 3.24 g/day, while three months after eradication therapy, the proteinuria level decreased to 1.26 ± 1.73 g/day ($p = 0.031$) [20].

In another study, a high urine albumin-to-creatinine ratio was detected in adult patients with *H. pylori*-positive peptic ulcers, and a significant 51.5% decrease in the albumin-to-creatinine ratio was observed in these patients after eradication therapy [21]. These results suggest that eradication therapy is beneficial in alleviating kidney damage and reducing the risk of CKD.

Overall, while further research is needed to clarify the causal pathways, current data highlight a possible connection between *H. pylori* infection and renal involvement through systemic inflammation, immune dysregulation, and metabolic derangement. These findings raise important considerations regarding the evaluation and management of *H. pylori* in patients with or at risk of kidney disease.

Malabsorption Syndromes

Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD), which include Crohn's disease and ulcerative colitis, are chronic immune-mediated conditions of the GI tract. While ulcerative colitis is typically limited to the colon with continuous mucosal inflammation, Crohn's disease may affect any segment of the GI tract and is characterized by transmural, patchy inflammation. IBD frequently begins in adolescence or early adulthood and follows a relapsing-remitting clinical course. Although primarily affecting the GI system, IBD is associated with numerous extraintestinal manifestations involving the skin, joints, eyes, liver, and kidneys. Several mechanisms contribute to kidney involvement in IBD, including metabolic disturbances related to malabsorption, drug-induced nephrotoxicity, immune-mediated glomerular disease, and structural complications such as nephrolithiasis and nephrocalcinosis [22].

Kidney involvement is increasingly recognized in children with IBD, yet remains underdiagnosed. One of the most clinically significant kidney complications is enteric hyperoxaluria, particularly in patients with Crohn's disease involving the terminal ileum or those who have undergone ileal resection. Under normal physiological conditions, dietary calcium binds to oxalate in the intestinal lumen, forming insoluble complexes that are excreted in the feces. However, in IBD with fat malabsorption, unabsorbed fatty acids bind calcium, leaving oxalate unbound and more readily absorbed in the colon. This process is exacerbated by increased intestinal permeability and alterations in gut microbiota, particularly the depletion of *Oxalobacter formigenes*, a commensal bacterium that degrades oxalate. The result is enteric hyperoxaluria, which increases the risk of calcium oxalate nephrolithiasis and nephrocalcinosis. In chronic cases, nephrocalcinosis can lead to tubulointerstitial nephritis, interstitial fibrosis, and eventually CKD. Therefore, regular monitoring of kidney functions and urinary parameters is essential, especially in patients with extensive small bowel disease or surgical resections [23].

Emerging evidence suggests that glomerulonephritis (GN) in IBD may result either from antigen-specific immune responses originating in the inflamed gut or from shared genetic and environmental risk factors. GN appears both as an extraintestinal manifestation and as a potentially unrelated co-existing condition, with IgAN being the most frequently reported subtype. Although pediatric data are limited, the observed reduction in proteinuria with enteric budesonide therapy in adult patients with IgAN supports a pathogenic link between intestinal and kidney inflammation [24]. A study utilized bioinformatic and machine learning approaches to identify shared immune-infiltrating features, cross-talk genes, and pathways between IgAN and IBD using datasets from the Gene Expression Omnibus. Immune infiltration analyses revealed no major differences in immune cell profiles between the two diseases. Ten diagnostic cross-talk genes were identified, among which *FDX1* and *NFKB1* were notably elevated in the kidneys of IBD mouse models. Pathway analysis revealed 15 shared signaling pathways, highlighting lipid metabolism as a key contributor. These findings shed light on common immune mechanisms underlying IBD and IgAN, offering potential targets for further research [25].

The risk of acute kidney injury (AKI) and CKD is increased in IBD. The mechanisms underlying this association are not fully understood, but factors such as systemic inflammation, medication toxicity, and malnutrition may contribute. In an adult study assessing the prevalence of AKI and CKD in IBD, the results showed that individuals with IBD had a higher risk for both AKI (HR = 1.96) and CKD (HR = 1.57) compared to those without IBD, even after adjusting for demographic, lifestyle and health factors. Similar risks were found for Crohn's disease and ulcerative colitis. Younger participants had stronger associations between IBD and kidney outcomes [26]. However, in another study, analyses based on genome-wide association data from individuals of European descent revealed that genetic

predisposition to Crohn's disease was significantly associated with an increased risk of CKD, while no such causal association was observed for ulcerative colitis. Furthermore, inverse Mendelian randomization analysis showed that genetic predisposition to CKD did not increase the risk of developing IBD, Crohn's disease or ulcerative colitis. These findings suggest that Crohn's disease has a unidirectional causal effect on CKD and underscore the need for routine renal function monitoring in patients with Crohn's disease [27]. In a cross-sectional study of pediatric patients, one-quarter of 56 IBD patients had evidence of kidney disease, either previously diagnosed or detected by ultrasonography. Kidney length was significantly reduced compared to healthy peers. Use of infliximab was associated with smaller kidneys, while enteral nutrition correlated with preserved kidney size. These findings suggest that children with IBD are at risk for CKD, especially in severe cases, highlighting the need for early renal monitoring in this population [28].

Celiac Disease

Celiac disease is a chronic, immune-mediated enteropathy triggered by the ingestion of gluten – a protein found in wheat, barley, and rye – in genetically susceptible individuals. The pathophysiology involves an inappropriate immune response primarily in individuals carrying HLA-DQ2 or HLA-DQ8 alleles. Upon gluten exposure, tissue transglutaminase (tTG) modifies gluten peptides, increasing their affinity for HLA-DQ2/DQ8 molecules on antigen-presenting cells. This leads to the activation of gluten-specific CD4+ T cells in the lamina propria, resulting in the production of pro-inflammatory cytokines and tissue-damaging immune responses. Concurrently, anti-tTG autoantibodies are produced, which serve as both diagnostic markers and contributors to mucosal injury. The intestinal mucosa displays characteristic histological changes, including villous atrophy, crypt hyperplasia, and increased intraepithelial lymphocytes, ultimately leading to malabsorption [29]. Celiac disease can present with both GI symptoms and a wide range of extraintestinal manifestations, including anemia, growth failure, osteoporosis, and even neurologic or renal involvement.

To investigate the association between celiac disease and kidney disease, genome-wide association from non-overlapping European cohorts was used and a Mendelian randomization study examining ten kidney traits was conducted. The analysis showed that genetic liability to celiac disease was causally associated with an increased risk of IgAN, chronic GN and a modest decrease in estimated glomerular filtration rate [30]. Although pediatric data are limited, findings from a meta-analysis have also shown that adult population with celiac disease have a significantly increased risk of developing kidney diseases, including IgAN and CKD. These findings highlight the need for greater clinical awareness and routine renal monitoring in patients with celiac disease to support early detection and prevention of kidney-related complications [4].

The IgAN is the most common primary GN worldwide, characterized by the deposition of IgA – particularly galactose-deficient IgA1 (Gd-IgA1) – in the glomerular mesangium. This triggers mesangial proliferation, inflammation, and eventually leads to varying degrees of proteinuria, hematuria, and progressive kidney dysfunction. Although the precise pathogenesis remains incompletely understood, IgAN is believed to result from a multi-hit process involving abnormal IgA1 glycosylation, the formation of autoantibodies against Gd-IgA1, and immune complex deposition in the kidney [31]. A potential link between IgAN and celiac disease has been increasingly recognized, given their shared immunological features and genetic predispositions – particularly involving HLA-DQ2/DQ8 alleles. In celiac disease, chronic mucosal inflammation and increased intestinal permeability may facilitate enhanced systemic exposure to dietary antigens and microbial components, leading to overproduction of aberrantly glycosylated IgA1. Moreover, mucosal immune activation in the gut-associated lymphoid tissue may promote the generation of nephritogenic IgA immune complexes that subsequently deposit in the glomeruli. Some studies have also suggested that a gluten-free diet may reduce proteinuria in patients with both IgAN and celiac

disease, supporting the idea of gut-kidney axis involvement [4]. In a case series, kidney biopsies from nine IgAN patients, four of whom had celiac disease, were analyzed for the presence of IgA-tTG co-deposits. Circulating tTG antibodies were measured and frozen tissue sections were examined for colocalization of IgA and tTG. Among the celiac patients, three showed IgA-tTG deposits in the kidney, including two people who had not yet been diagnosed with celiac disease at the time of biopsy. Interestingly, no such deposits were observed in the patient on a gluten-free diet with known celiac disease [32].

In celiac disease, CKD may not only arise as a consequence of IgAN, but also through gut-kidney axis dysregulation, where increased intestinal permeability and immune activation contribute to systemic inflammation and kidney injury. Compromise of the intestinal barrier integrity may allow bacterial lipopolysaccharides to translocate into the systemic circulation. This translocation promotes systemic inflammation and uremic toxicity, both of which are recognized drivers in the onset and progression of CKD [7].

Diabetic kidney disease is increasingly observed in children as the prevalence of type 1 diabetes mellitus (T1DM) rises. Celiac disease, which shares genetic susceptibility with T1DM – especially via HLA-DR3-DQ2 and DR4-DQ8 – coexists in 3-12% of pediatric cases [7]. Celiac disease may also be an independent risk factor for both microvascular and macrovascular complications, potentially through mechanisms like intestinal malabsorption, micronutrient deficiencies such as folate, B vitamins, and hyperhomocysteinemia [33]. These findings support routine screening for celiac disease in T1DM patients and highlight the need for further research into the gut-kidney and gut-vascular axes in this context.

The association between celiac disease and urolithiasis was first reported in the 1970s, with studies identifying hyperoxaluria in over half of affected children [34]. More recent data confirm an elevated risk of recurrent kidney stones – particularly oxalate stones – in individuals with celiac disease. Stone formation requires urinary supersaturation with certain solutes, but in celiac disease, this may be exacerbated by intestinal malabsorption or altered renal handling of compounds like oxalate, calcium, and citrate. These imbalances promote crystallization and stone development [35]. Additionally, gut microbiota dysbiosis plays a role; reduced levels of butyrate-producing bacteria like *Roseburia* lead to increased intestinal oxalate absorption and inflammation, further promoting lithogenesis [36]. This complex interplay between gut permeability, immune activity, and microbial metabolism may explain the higher prevalence of kidney stones in celiac disease.

Individuals with celiac disease have a higher frequency of urinary tract infections (UTIs). This is due to a variety of factors, including impaired urinary tract motility, dysfunction of the bladder, changes in gut microbiota that can promote urinary contamination, reduced immune defense mechanisms, and dysregulated immune responses. In a study evaluating the association between celiac disease and UTIs in the absence of anatomical abnormalities, 22.7% of 97 patients with celiac disease reported at least one episode of UTI, with a female predominance. In the majority of cases, the UTI occurred before the diagnosis of celiac disease. Notably, the cumulative probability of being UTI-free by the age of 18 years was significantly lower in women with celiac disease compared to the general population [37]. These findings point to a possible increased risk of UTIs in female celiac disease patients and potentially warrant closer clinical attention.

Liver Diseases

Primary Hyperoxaluria

Primary hyperoxaluria (PH) is a group of rare, autosomal recessive metabolic disorders characterized by hepatic enzyme deficiencies involved in glyoxylate metabolism. These defects lead to the overproduction of oxalate in the liver, which subsequently binds with calcium to form calcium

oxalate crystals. While oxalate is normally a minor end-product excreted by the kidneys, in PH, its excessive hepatic production surpasses kidney excretion capacity, resulting in crystal deposition in any organ. PH is classified into three types based on the specific hepatic enzyme affected. PH type 1 (PH1), the most severe and common form, results from mutations in the *AGXT* gene encoding the liver-specific enzyme alanine: glyoxylate aminotransferase. PH type 2 (PH2) is due to defects in *GRHPR*, and PH type 3 (PH3) involves mutations in *HOGA1*; both are also expressed in the liver but tend to present with milder clinical manifestations [38].

In PH, calcium oxalate crystals deposit primarily in the kidney tubules and interstitium, resulting in nephrocalcinosis and nephrolithiasis. The mechanical damage caused by the crystals, combined with inflammation and fibrosis, contributes to the development of tubulointerstitial nephritis. Progressive accumulation and stone formation ultimately lead to a decline in glomerular filtration rate and CKD. In many patients with PH1, this progression leads to kidney failure at an early age [38]. To date, distinct clinical forms of PH1 have been identified. Infantile oxalosis typically manifests within the first six months of life, presenting with nephrocalcinosis and early-onset kidney failure. In contrast, childhood-onset cases more commonly begin with symptoms related to kidney stone formation, such as renal colic, hematuria, or urinary tract infections. Additional presentations include disease recurrence following kidney transplantation and, in rare instances, recurrent kidney stones appearing later in adulthood [39]. A nationwide study evaluating the overall clinical characteristics of patients with PH1 found that 92.4% of patients had nephrolithiasis/nephrocalcinosis even at the time of diagnosis. Although individuals with infantile oxalosis were diagnosed at a younger age compared to individuals with childhood-onset PH1, they exhibited more advanced CKD or kidney failure requiring dialysis at the time of diagnosis [40]. Therefore, given the risk of early and progressive kidney involvement in PH, even in asymptomatic stages, timely evaluation of kidney function is essential; close collaboration between nephrology and gastroenterology is crucial to ensure comprehensive and coordinated patient care.

Wilson's Disease

Wilson's disease is a rare autosomal recessive disorder caused by mutations in the *ATP7B* gene, which encodes a copper-transporting ATPase responsible for incorporating copper into ceruloplasmin and excreting excess copper into the bile. Defective *ATP7B* leads to the accumulation of free copper in various tissues, most notably the liver, central nervous system, and cornea. Clinical manifestations are highly variable and age-dependent, ranging from hepatic dysfunction in children and adolescents to neurological and psychiatric symptoms in older individuals [41].

Although kidney involvement is less commonly recognized, it is a relevant extrahepatic manifestation of Wilson's disease, particularly in untreated or advanced cases. Copper deposition in the kidneys may lead to tubular dysfunction, which can be present as aminoaciduria, low-molecular-weight proteinuria, hypercalciuria, or renal tubular acidosis, particularly the distal type. In some patients, nephrolithiasis and hypophosphatemia have also been reported [42]. Moreover, glomerular involvement, although rare, may manifest as proteinuria or even nephrotic syndrome, and IgAN potentially due to immune complex-mediated mechanisms [43]. Chelation therapy with agents such as D-penicillamine may also influence kidney function, either by improving copper overload or, conversely, causing drug-induced nephrotoxicity in some cases [44]. Thus, regular monitoring of kidney parameters should be performed in the management of Wilson's disease, especially in patients receiving long-term chelation therapy.

Chronic Liver Diseases

Chronic liver disease encompasses a wide range of progressive liver disorders that lead to sustained liver inflammation, fibrosis, and ultimately cirrhosis. It can result from various etiologies including

viral hepatitis (especially hepatitis B and C), autoimmune hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease (NAFLD), metabolic and genetic disorders (such as Wilson's disease or alpha-1 antitrypsin deficiency), and biliary tract diseases like primary sclerosing cholangitis. Over time, continuous liver damage impairs hepatic synthetic, metabolic, and detoxifying functions, potentially leading to complications such as portal hypertension, hepatic encephalopathy, ascites, coagulopathy, and increased susceptibility to infections [7].

Chronic liver disease and kidney involvement are closely interconnected through complex systemic and local mechanisms. As chronic liver disease progresses, portal hypertension develops, leading to splanchnic vasodilation. This vasodilation reduces the effective circulating blood volume, resulting in decreased kidney perfusion. In response, the body activates compensatory systems such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and antidiuretic hormone, which together cause renal vasoconstriction and subsequently a significant drop in glomerular filtration rate [5]. Furthermore, impaired hepatic detoxification allows bacterial endotoxins and inflammatory cytokines to enter the circulation, enhancing systemic inflammation and exacerbating kidney dysfunction. Additional contributing factors include acidosis, hyponatremia, hypoalbuminemia, and sepsis, all of which can further impair kidney function [45].

Hepatorenal syndrome (HRS) is a form of functional kidney failure that occurs in individuals with advanced liver disease, most commonly cirrhosis, in the absence of other identifiable structural kidney abnormalities. Based on the duration and progression of kidney dysfunction, HRS is currently classified into two main types: HRS-AKI and HRS-CKD [46].

HRS-AKI is characterized by:

- A rapid decline in kidney function, typically identified by an acute rise in serum creatinine (≥0.3 mg/dL within 48 hours or ≥50% from baseline within seven days) in patients with cirrhosis and ascites.
- It usually occurs following precipitating events such as infections, GI bleeding, or excessive diuretic use.

HRS-CKD refers to:

- A gradual and sustained impairment in kidney function lasting three months or longer,
- Long-standing portal hypertension and diuretic-resistant ascites.

Management of HRS includes prompt identification and treatment of precipitating factors such as infections, GI bleeding, or excessive diuretic use, administration of albumin together with vasoconstrictors such as terlipressin, and early evaluation for liver transplantation when indicated [46]. Given the intricate interplay between the liver and kidneys, early recognition and collaborative management of renal dysfunction in patients with chronic liver disease is essential to improve outcomes and guide appropriate therapeutic strategies.

Enteric Infections

Shiga toxin-producing *Escherichia coli*

Shiga toxin-producing *Escherichia coli* (STEC) infection is primarily a GI illness characterized by abdominal cramping, watery diarrhea that often progresses to bloody diarrhea (hemorrhagic colitis), and, in some cases, fever and vomiting. The GI manifestations are largely attributed to the direct mucosal damage caused by Shiga toxins, which are released by the bacteria in the colon. These toxins disrupt the intestinal epithelial barrier, leading to inflammation, epithelial cell apoptosis, and capillary hemorrhage. Colonoscopy or histological examination in severe cases may reveal mucosal

edema, ulcerations, and hemorrhagic lesions predominantly in the distal colon. Importantly, while the GI symptoms are self-limiting in most patients, a subset – particularly young children and the elderly – are at risk for extraintestinal complications such as STEC-hemolytic uremic syndrome (HUS) (STEC-HUS) [47].

The pathogenic mechanism of kidney involvement in STEC-HUS is primarily driven by the systemic dissemination of Shiga toxins, particularly Stx2, following disruption of the intestinal epithelial barrier. Once in circulation, Shiga toxins exhibit high affinity for globotriaosylceramide (Gb3) receptors, which are abundantly expressed on endothelial cells within the kidney glomeruli. Upon binding to Gb3, the toxins are internalized and inhibit protein synthesis by inactivating the 60S ribosomal subunit, leading to endothelial cell apoptosis and dysfunction. This endothelial injury initiates a prothrombotic state characterized by platelet activation, increased release of von Willebrand factor, and reduced production of antithrombotic mediators such as prostacyclin and nitric oxide. The result is widespread microvascular thrombosis, particularly in glomerular capillaries, which manifests clinically as thrombotic microangiopathy. The ensuing microthrombi cause mechanical damage to erythrocytes, leading to microangiopathic hemolytic anemia, while the consumption of platelets contributes to thrombocytopenia. Concurrently, the glomerular filtration barrier becomes compromised, resulting in AKI, typically presenting with oliguria or anuria, elevated serum creatinine, and signs of fluid and electrolyte imbalance. Proteinuria and hematuria are frequently observed in urinalysis [47]. There is no specific therapy for STEC-HUS, and treatment is primarily supportive, focusing on fluid and electrolyte management, blood pressure control, and, in severe cases, renal replacement therapy. While most pediatric patients recover fully with appropriate supportive care, a subset may develop long-term complications such as CKD, hypertension, or proteinuria [48].

As can be seen, the kidney pathology in STEC-HUS illustrates the critical role of the gut-kidney axis, wherein enteric infections can precipitate severe extraintestinal consequences. STEC-HUS remains one of the leading causes of AKI in children and poses significant clinical challenges due to its rapid onset and potential for long-term renal sequelae.

Gastrointestinal System Involvement in Kidney Diseases

Idiopathic Nephrotic Syndrome

Idiopathic nephrotic syndrome (INS) is the most common glomerular disease in children and also affects adults, though with differing histopathological profiles. It is defined by the classic triad of massive proteinuria (>3.5 g/day), hypoalbuminemia, and generalized edema. In pediatric populations, minimal change disease is the most frequent histological subtype, while in adults, focal segmental glomerulosclerosis and membranous nephropathy are more common. Although the precise pathogenesis of INS remains incompletely understood, immune dysregulation – particularly involving T and B-cell dysfunction and circulating permeability factors – has been implicated in podocyte injury and proteinuria [49]. While the kidney manifestations are central to the diagnosis, INS is increasingly recognized as a multisystem disorder, including those affecting the GI system. GI involvement is often secondary to the systemic consequences of hypoalbuminemia, edema, thrombotic tendency, and immunosuppressive therapy [50].

One of the most common GI manifestations in INS is edema of the bowel wall, which may lead to abdominal discomfort, nausea, vomiting, and even paralytic ileus. In severe cases, bowel wall thickening can mimic conditions such as IBD or ischemia on imaging studies [51]. Additionally, the hypercoagulable state associated with INS increases the risk of mesenteric arterial thrombosis, a rare but life-threatening complication that can present with acute abdominal pain [52]. Moreover,

patients with INS are at increased risk for infections, including spontaneous bacterial peritonitis, especially in those with ascites. The use of corticosteroids and other immunosuppressants further compromises GI immunity and mucosal defense, predisposing to opportunistic infections, peptic ulcer disease, and drug-related mucosal injury [53]. Malabsorption of fat-soluble vitamins (particularly vitamin D) may also occur due to protein loss and intestinal edema, contributing to metabolic bone disease in the long term [54]. Therefore, GI assessment and monitoring are essential components of comprehensive care in patients with INS, particularly in those with persistent hypoalbuminemia or GI symptoms.

Polycystic Kidney Diseases

Polycystic kidney disease (PKD) comprises a group of inherited disorders characterized by the progressive development of fluid-filled cysts in the kidneys, ultimately leading to kidney failure. The two main genetic forms are autosomal dominant PKD (ADPKD) and autosomal recessive PKD (ARPKD), each with distinct clinical and genetic profiles. ADPKD is the most common hereditary kidney disorder, typically caused by mutations in the *PKD1* or *PKD2* genes. It usually manifests in adulthood with bilateral kidney enlargement, hypertension, and gradual loss of kidney function. ARPKD, in contrast, is a rarer and more severe form, caused by mutations in the *PKHD1* gene and often present in infancy or early childhood with enlarged echogenic kidneys. While kidney manifestations are the hallmark of both forms, GI involvement is an important aspect of the disease, particularly in relation to hepatic and biliary complications [55].

In ADPKD, one of the most frequent extrarenal manifestations is polycystic liver disease (PLD), which occurs in up to 80% of patients over the age of 30 [56]. Although often asymptomatic, extensive liver cysts may cause abdominal distension, early satiety, gastroesophageal reflux, and even mechanical bowel compression. Cyst infection or hemorrhage can also cause acute abdominal pain and mimic intra-abdominal sepsis [57]. In ARPKD, the most prominent GI-related manifestation is due to congenital hepatic fibrosis, which can lead to portal hypertension. This may result in splenomegaly, esophageal varices, hematemesis, and ascites, posing serious risks, especially in pediatric patients. The combination of hepatobiliary and kidney dysfunction in ARPKD is sometimes referred to as a hepatorenal fibrocystic disease [58]. In both forms of PKD, GI symptoms may also arise from complications of CKD, such as uremic gastropathy, anorexia, and nausea, or from treatment-related factors, including immunosuppressive therapy following transplantation [57]. Thus, careful GI assessment is essential in the multidisciplinary management of PKD patients, particularly those with advanced disease or hepatic involvement.

Chronic Kidney Diseases

Chronic kidney disease is a progressive condition characterized by a sustained reduction in glomerular filtration rate and the accumulation of uremic toxins. While the kidney and cardiovascular consequences of CKD are well known, GI involvement is also frequent and significantly affects morbidity, nutritional status, and quality of life. Many of the GI manifestations in CKD stem from uremia-related metabolic disturbances, chronic inflammation, altered intestinal permeability, and the effects of therapeutic interventions [59].

Common uremic symptoms such as anorexia, nausea, vomiting, metallic taste, and weight loss are frequently reported and may reflect uremic gastropathy or delayed gastric emptying. In advanced stages, mucosal fragility and platelet dysfunction can predispose patients to GI bleeding, while bowel wall edema may cause abdominal discomfort or paralytic ileus [2]. Uremia also contributes to impaired gut barrier function, leading to increased intestinal permeability – often referred to as "leaky gut" – which facilitates the translocation of endotoxins and contributes to systemic inflammation through the gut-kidney axis [7].

Oral and esophageal manifestations, including dry mouth, oral ulcers, gingivitis, and uremic fetor, are commonly observed [60]. In parallel, CKD is associated with significant alterations in the gut microbiome (dysbiosis), including the proliferation of urease-producing and proteolytic bacteria. This dysbiosis increases the generation of gut-derived uremic toxins such as indoxyl sulfate and p-cresyl sulfate, which have been implicated in endothelial dysfunction, cardiovascular disease, and further progression of kidney injury [61].

Gastrointestinal motility disturbances are also common; constipation often results from fluid restriction, a low-fiber diet, oral iron supplementation, or use of phosphate binders. Conversely, diarrhea may occur due to certain medications such as magnesium-based antacids, antibiotics or infectious etiologies, especially in immunosuppressed patients [62]. Nutritional impairment is another major consequence of GI involvement in CKD. Reduced oral intake due to GI symptoms, combined with malabsorption and inflammation, can lead to protein-energy wasting and deficiencies in essential nutrients, including fat-soluble vitamins, vitamin B12, and folate. This contributes to muscle wasting, frailty, and increased vulnerability in elderly CKD patients [63].

In summary, the GI system plays a central and multifaceted role in the clinical course of CKD. A comprehensive understanding and management of GI involvement is essential to improve outcomes, reduce complications, and enhance the overall well-being of CKD patients.

Kidney Replacement Therapies

Kidney replacement therapies (KRT), including hemodialysis (HD), peritoneal dialysis (PD), and kidney transplantation, are life-sustaining treatments for patients with kidney failure. Each modality has distinct physiological impacts and potential GI complications, which should be considered in patient management and nutritional planning. GI symptoms may arise due to the dialysis process itself, associated fluid shifts, metabolic changes, or immunosuppressive therapy [8].

Hemodialysis is the most commonly used modality for KRT. GI complications during or after dialysis sessions are frequent and may include nausea, vomiting, abdominal cramps, and hypotension-related gut hypoperfusion. HD is also associated with increased gut permeability, which can facilitate endotoxemia and systemic inflammation [64]. Constipation is common due to restricted fluid intake, dietary limitations, and phosphate binders [65]. Rare but serious GI complications include mesenteric ischemia and colonic angiodysplasia-related bleeding, particularly in long-term HD patients [66].

Peritoneal dialysis involves the instillation of dialysate into the peritoneal cavity, and its GI manifestations are often related to increased intra-abdominal pressure, leading to early satiety, gastroesophageal reflux, abdominal fullness, or hernias [67]. Peritonitis is a significant complication and may present with abdominal pain, fever, and diarrhea or paralytic ileus [68]. Chronic exposure of the peritoneum to dialysate can lead to sclerosing encapsulating peritonitis, a rare but severe condition causing intestinal obstruction [69]. Additionally, glucose absorption from dialysate may exacerbate dyslipidemia, insulin resistance, and obesity, contributing indirectly to metabolic complications that affect gut function [70].

While kidney transplantation restores kidney function and offers superior quality of life, it introduces unique GI risks, primarily due to immunosuppressive therapy. Common GI side effects of calcineurin inhibitors and mTOR inhibitors include nausea, diarrhea, oral ulcers, and anorexia [71]. Mycophenolate mofetil is particularly associated with diarrhea, colitis, and GI bleeding, sometimes mimicking IBD [72]. Strategies to mitigate drug-related GI adverse effects include dose splitting, using enteric-coated formulations, or switching to an alternative immunosuppressive class when feasible [72–74]. Opportunistic infections, such as cytomegalovirus colitis or *Clostridioides difficile* infections, are more frequent in the post-transplant setting. They should be considered in

patients with new or worsening GI symptoms; cytomegalovirus infection can be initially screened with polymerase chain reaction (PCR) or antigen testing, while *Clostridioides difficile* should be evaluated with stool toxin assays or PCR [75, 76]. Moreover, long-term immunosuppression also increases the risk of GI malignancies, including colorectal and gastric cancers [77].

Conclusion

The complex and dynamic interplay between the GI system and the kidneys reflects a bidirectional relationship in which dysfunction in one organ system can significantly impact the other. GI symptoms are common across all stages of kidney disease and may arise from uremia, dialysis modalities, immunosuppressive therapies, or alterations in gut microbiota. Conversely, GI disorders such as infections, inflammatory conditions, and medication-induced mucosal injury can contribute to kidney injury through immune activation, systemic inflammation, or volume and electrolyte disturbances. Recognizing these interactions is crucial for early diagnosis, targeted management, and prevention of complications. A multidisciplinary approach that incorporates nephrologic and gastroenterologic expertise will be essential to optimize outcomes in patients affected by these intertwined organ systems.

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