Upper Gastrointestinal Disorders Among Dialysis Patients

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ABSTRACT

The prevalence of co-morbid gastrointestinal symptoms is high in dialysis patients, and dyspeptic symptoms, such as nausea, vomiting, and epigastric burning are the most common symptoms. Upper gastrointestinal disorders (e.g., peptic ulcer disease and gastroparesis) underlie most of these symptoms, while less common but severe complications are also likely that include gastrointestinal bleeding from gastric antral vascular ectasia, erosions or ulcers. Incidence of gastrointestinal disorders is considered to increase with the duration of renal failure, independent of dialysis modality. While uremia and dialysis have been linked to an increased risk of gastrointestinal tract lesions, pathogenesis of gastrointestinal dysfunction in end-stage renal disease is considered to be multifactorial and has not yet been clarified. In addition, conflicting data exist on the association of renal dysfunction with gastrointestinal disorders, and there are no explicit guidelines for the management of co-morbid gastrointestinal problems in patients with concomitant renal failure. Herein, we review the common upper gastrointestinal disorders that occur among dialysis patients, with an emphasis on prevalence, pathogenesis and diagnostic strategies.

Keywords: End-stage renal disease, peritoneal dialysis, hemodialysis, upper gastrointestinal tract, pathogenesis

DIYALIZ HASTALARINDA ÜST GASTROINTESTİNAL SİSTEM HASTALIKLARI

ÖZET


Anahtar sözcükler: Son dönemde renal hastalı, peritoneal diyaliz, hemodializ, üst gastrointestinal sistem, patogenez

Gastrointestinal diseases represent the most common, non-renal, chronic disorders that accompany end-stage renal disease (ESRD) (1,2). ESRD has been associated with a high prevalence, from 70% to 79%, of co-morbid gastrointestinal symptoms, which appear to be independent of dialysis modality, while the incidence of these GI disorders increases with the duration of renal failure (2-4). The
most common gastrointestinal symptoms in dialysis patients include dyspeptic symptoms, such as nausea, vomiting, and epigastric burning (2,4-8). Less common but severe complications include gastrointestinal bleeding from gastric antral vascular ectasia, erosions or ulcers (8).

Underlying these symptoms is a wide spectrum of gastrointestinal diseases that include the upper gastrointestinal (UGI) tract [e.g., peptic ulcer disease (PUD) and gastroparesis], the lower gastrointestinal (LGI) tract (e.g., diverticular disease, angiodysplasia, mesenteric ischemia, ischemic colitis, colonic perforation, fecal impaction and stercoral ulcer, dialysis-related amyloidosis, encapsulating peritoneal sclerosis, and idiopathic dialysis ascites), and the accessory digestive glands (e.g., cholecystitis, cholecystolithiasis, hepatitis, and pancreatitis) (7,9).

A great number of gastrointestinal complications have been reported to accompany renal failure based on the interrelationship of gastrointestinal and renal diseases (8) (Table 1).

While uremia and dialysis have been linked to an increased risk of gastrointestinal tract lesions, pathogenesis of gastrointestinal dysfunction in ESRD is considered (as a) or (to be) multifactorial with the contribution of several factors (2,5,8,10), including gastric hypomotility with delayed gastric emptying (8), capillary fragility and disordered hemostasis of uremia (8), effects of unfiltered humoral factors or toxins (6), hypergastrinemia (11), reduced visceral sensitivity (12), comorbidities (8), and medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) (8,13). In addition, conflicting data exist on the association between renal dysfunction and gastrointestinal disorders with no explicit guidelines for the management of co-morbid gastrointestinal problems in renal failure (2,10).

This review focused on UGI disorders among dialysis patients, the LGI disorders and diseases of accessory digestive glands were not within the scope of the present review. We, therefore, examined the common UGI disorders that occur among dialysis patients with an emphasis on prevalence, pathogenesis and diagnostic strategies.

**Upper gastrointestinal disorders**

Dyspepsia is a set of symptoms suggestive of a reflux, ulcer or motility disorder, while associated with increased likelihood of gastrointestinal complications such as UGI hemorrhage, disturbed quality of life and poor outcome of kidney disease (2,7,14).

### Table 1. Interrelationship of gastrointestinal and renal diseases

<table>
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<th>Gastrointestinal Manifestations of Renal Disease</th>
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| **Acute renal failure** | Gastric and duodenal erosions  
Gastric perforation  
**Chronic renal failure** | Erosive esophagitis  
Erosive and hemorrhagic gastritis  
(Nodular) duodenitis  
Peptic ulcer disease  
Angiodysplasia  
Intussusception secondary to mucosal hemorrhage  
Diverticula in adult polycystic kidney disease (APCKD)  
Salmonella enteritis  
Calcific uremic arteriolopathy  
**Complications of therapy** | Kayexalate sorbitol associated GI mucosal injury  
Anticoagulant and antiplatelet therapy associated GI bleeding  
Mycophenylate mofetil associated GI mucosal injury(transplants)  
**Complications of dialysis** | Acute fluid loss resulting in nonocclusive intestinal ischemia  
Peritonitis (bacterial or chemical) in peritoneal dialysis  
Hernia (+/− obstruction or incarceration) in peritoneal dialysis  
Sclerosing peritonitis in long-term peritoneal dialysis  
**Renal transplantation** | Gastric and duodenal erosions and ulcers  
Esophagitis (often candida)  
Mycophenylate mofetil associated GI mucosal injury  
Perforation of colonic diverticula (especially APCKD)  
Cecal ulceration  
Pseudomembranous colitis (50% of patients receiving antibiotics)  
Nonocclusive vascular insufficiency  
Infections due to chronic immunosupression, especially cytomegalovirus infection and intestinal strongylidiasis  
Posttransplant GI lymphoproliferative disorders  
**Diseases Affecting Both Gastrointestinal and Renal Systems** | Collagen vascular diseases (scleroderma, vasculitides)  
Diabetes mellitus  
Hyperparathyroidism  
Amyloidosis  
Myeloma  
Henoch–Schönlein purpura  
Hemolytic uremic syndrome  
**Renal Manifestations of Gastrointestinal Disease** | Crohn’s disease  
Calcium oxalate stones  
Ureteral obstruction  
Entero or colovesical fistula  
Perinephric abscess  
The prevalence of dyspepsia among ESRD patients on hemodialysis ranges from 48% to 70% that exceeds the rates (40%) in the general population (5,15). High prevalence of dyspeptic symptoms such as nausea, vomiting, epigastric burning and postprandial fullness in patients with renal failure formed the basis of investigations addressing the prevalence of underlying UGI lesions in these patients (7,14).

However, while studies prior to the common use of esophagogastroduodenoscopy (EGD) indicated a higher prevalence of gastric and duodenal ulcers in patients with renal failure compared to the general population (2), later EGD-based studies confirmed a higher prevalence of UGI erosions and inflammation in renal failure but revealed conflicting data on the prevalence of ulcerations (4,16-18). In an endoscopic study, the peptic ulceration was reported to be evident only in 2% of renal failure patients, which was similar to the rates observed in the general population (17).

Studies in uremic patients on maintenance hemodialysis also revealed conflicting data with increased prevalence of gastroduodenal lesions (e.g., gastritis, duodenitis, and peptic ulcers) reported in some studies, whereas the prevalence was found to be similar to the general population in others (6,8). Notably, neither the severity of renal dysfunction nor the duration of hemodialysis was shown to be correlated with the prevalence of gastrointestinal lesions in patients with chronic renal failure (8,19).

In another endoscopic study among dyspeptic patients, the prevalence of peptic lesions and Helicobacter pylori (H. pylori) infection was reported to be 74% and 52%, respectively, in patients with renal failure, while 18% and 36%, respectively, in patients with normal renal function (18). Authors also noted low symptoms scores in uremic patients despite the presence of H. pylori infection (18).

Differences between studies in terms of patient populations, comorbid disorders, sample sizes, investigative techniques, the prevalence of H. pylori infection and the use of NSAID agents have been considered likely to be associated with the occurrence of conflicting results (8). Nonetheless, it should also be noted that dyspepsia is a set of symptoms associated with various conditions ranging from normal functional dyspepsia to organic dyspepsia secondary to gastrointestinal diseases, such as peptic ulcers and cancer (18). Common causes of organic dyspepsia are listed in Table 2 (7).

### Table 2. Differential diagnosis of organic dyspepsia

- Peptic ulcer disease
- Gastroesophageal reflux disease (GERD)
- Biliary pain
- Chronic abdominal wall pain
- Gastric or esophageal cancer
- Gastroparesis
- Pancreatitis
- Carbohydrate malabsorption
- Medications (including potassium supplements, digitalis, iron, theophylline, oral antibiotics [especially ampicillin and erythromycin], NSAIDs, corticosteroids, niacin, gemfibrozil, narcotics, colchicine, quinidine, estrogens, levodopa)
- Infiltrative diseases of the stomach (eg, Crohn’s disease sarcoidosis)
- Metabolic disturbances (hypercalcemia, hyperkalemia)
- Hepatoma
- Ischemic bowel disease
- Systemic disorders (diabetes mellitus, thyroid and parathyroid disorders, connective tissue disease)
- Intestinal parasites (Giardia, Strongyloides)
- Abdominal cancer, especially pancreatic cancer


### Peptic ulcer disease

Although previous studies have suggested a higher incidence of ESRD in patients on dialysis and that of PUD in patients with or without CKD (7,9,20), later on, endoscopic studies showed that PUD was no more frequent in dialysis than in non-dialysis patients (7,9). However, in an EGD study of 299 patients on dialysis and 400 healthy controls, the dialysis population had higher rates of gastritis (77.8% vs. 46.8%), gastric ulcers (11.4% vs. 4.1%) and duodenal ulcers (6.4% vs. 3.3%) (21).

Hence, while incidence of bleeding from PUD was shown to be high in CKD patients, an ongoing debate exists whether the incidence of PUD itself is high in uremic patients when compared to the general population (7,9).

### PUD diagnosis in dialysis patients

The first steps in the management of PUD are to assess H. pylori infection status and to administer NSAIDs therapy (7). Given the association of a high prevalence of UGI symptoms, UGI lesions, and H. pylori infection with renal failure, it has been suggested that all patients with renal failure and dyspepsia should be assessed for H. pylori infection and treated if positive (2,16). However, no correlation of dyspeptic symptoms seems to exist with either H. pylori infection or gastrointestinal lesions in renal failure patients (2,18,22). Moreover, noninvasive tests, such as
serology tests and the urea breath test, are considered less sensitive and specific in cases of renal failure when compared to patients with normal renal function (23,24).

According to the American Gastroenterological Association position statement, the use of EGD is recommended in the evaluation of H. pylori infections in renal failure patients if there is a new-onset dyspepsia without evidence of gastroesophageal reflux disease (GERD) or NSAID use, and in cases of alarming symptoms, such as weight loss, progressive dysphagia or recurrent vomiting, evidence of gastrointestinal bleeding, or a family history of cancer (25).

**PUD risk factors in dialysis patients (NSAIDs vs. H. pylori)**

H. pylori infection and the use of NSAIDs are the two major risk factors associated with PUD with similar significance in dialysis and non-dialysis patients (7,9,26).

A similar incidence of H. pylori infection in patients on regular dialysis when compared to other populations was reported in several studies (4,23,24). However, some studies have reported a higher prevalence of H. pylori infection in renal failure patients than in the general population (16,18), and still others have reported even lower rates of H. pylori infection in uremic patients (21,27), particularly those on hemodialysis (7,28). In another study, lower dyspeptic symptom scores but a higher prevalence of peptic lesions was shown in uremic patients when compared to patients with normal renal function, irrespective of H. pylori infection (18).

The reported prevalence of H. pylori infection in patients with uremia varies from 21% to 73% (16,17,19,23,29) but does not exceed that of the general population (6,8,27). According to a recent consensus, the prevalence of H. pylori infection in chronic renal failure patients receiving peritoneal or hemodialysis is considered to be equal or lower when compared with the subjects with normal renal function in various different geographic populations, regardless of the presence of gastric symptoms (10,21,30).

Suppression of H. pylori growth via elevated urea levels and increased gastric pH due to elevated inflammatory cytokines and the likelihood of partial treatment of H. pylori via commonly used antibiotics in the dialysis population are suggested to contribute to the lower prevalence of H. pylori observed in dialysis patients (9,21).

However, the prevalence of PUD was reported to be higher in dialysis patients with H. pylori infection when compared with dialysis patients without H. pylori infection (21,23) and to individuals with normal renal function (16).

Some studies revealed no association between H. pylori positivity and the prevalence or intensity of dyspeptic symptoms (18,31) or delayed gastric emptying (31) in uremic patients, irrespective of dialysis therapy (18,31). However, this association was closely related to gastroduodenal peptic lesions in dyspeptic patients with normal renal function (18).

**Upper gastrointestinal bleeding**

UGI bleeding from gastritis, duodenitis, peptic ulcers, and telangiectasia is more common in ESRD patients, particularly those on hemodialysis, when compared to the general population. In ESRD patients, the estimated frequency is 21 bleeds per 1,000 patient years with a very high risk of mortality accounting for 3–7% of all deaths (7,8,32,33). Disordered hemostasis of uremia resulting from platelet and endothelial dysfunction, associated anemia, secondary hyperparathyroidism and the use of medications that likely affect the clotting cascade (e.g., clopidogrel, aspirin, and other NSAIDs) are considered risk factors for UGI bleeding (2,9,32,34).

The prognosis of UGI bleeding in ESRD patients is generally worse than in the normal population, and renal insufficiency is considered one of the predictors of mortality in validated UGI bleeding scores alongside age, the presence of shock and other comorbidities (9,35).

**Causes of UGI bleeding**

Among ESRD patients, the duodenum is considered to be the most common site of UGI bleeding (36), while angiodyplasia and gastrointestinal tract erosions refer to the most common causes underlying UGI bleeding (2,7,37,38). Higher rate of angiodyplasia was shown in patients on hemodialysis than in those on peritoneal dialysis (7). Gastric antral vascular ectasia was documented as the most common cause of UGI bleeding as well as recurrent bleeding in patients who received dialysis therapy during emergencies, followed by gastroduodenal ulcer disease (34,39).

However, angiodyplasia has also been indicated to occur at a much lower incidence when considered as a cause of UGI bleeding in patients with ESRD, with incidence similar to the general population (7). No difference was noted in the causes and outcomes of UGI bleeding in patients with (n=40) and without (n=30) chronic renal failure in a retrospective study (39). Therefore, it remains unclear whether angiodyplasia or vascular ectasia has a higher prevalence in uremic patients than in the general population (6–8).
In a larger study of 727 patients with UGI bleeding who underwent diagnostic endoscopy, angiodysplasia was shown to be a more frequent cause of UGI bleeding (13% vs. 1.3%) in patients with renal dysfunction, while gastric ulcer (37%) and duodenal ulcer (23%) were more common causes of bleeding when compared to angiodysplasia in cases of renal failure (37). PUD appears to be the most common cause of UGI bleeding in patients with renal failure (7). Although angiodysplasia may currently be a less frequent cause of UGI bleeding than previously reported (7), it seems to be a more common source of bleeding in patients with more severe and prolonged renal disease (37).

Other than PUD and angiodysplasia, causes of UGI bleeding among uremic patients include esophageal varices, Mallory–Weiss tears, tumors, esophagitis, and Dieulafoy’s lesions (9,40).

**Diagnosis of UGI bleeding**

A higher incidence of gastrointestinal bleeding in the CKD population emphasizes the importance of prompt recognition (9). The value of anemia as well as iron deficiency as a diagnostic sign of gastrointestinal bleeding is limited in patients who are receiving dialysis, while patients with overt gastrointestinal blood loss, rapidly changing hemoglobin levels and a failure to restore iron stores in spite of adequate replacement should undergo further evaluation, including endoscopy (9).

**Risk of recurrent bleeding**

Conflicting data exist concerning the risk of recurrent bleeding in patients with ESRD. Although several studies have reported a higher rate of recurrence of gastrointestinal bleeding in patients with ESRD when compared to those without renal disease as well as when compared to patients with CKD (41), other studies reported a lack of such an increased risk (7,9,40).

**Gastroparesis**

Motility disorders, such as delayed emptying or gastroparesis, may be associated with uremia, thereby leading to anorexia, nausea, and vomiting. Gastroparesis is a frequent indication to initiate dialysis and usually resolves after the onset of renal replacement therapy (7). Data from small-scale studies among renal failure patients revealed inconclusive data on gastric emptying in CKD patients; some noted no difference in gastric emptying in CKD patients when compared to healthy controls (42), while some others indicated a prolonged gastric emptying in CKD patients (43) but not in hemodialysis patients (43,44) when compared to controls (43).

Gastroparesis that is unresponsive to dialysis is sometimes caused by an autonomic neuropathy, particularly if the gastroparesis results from co-morbid diabetes (43,45,46). An overall higher prevalence of gastrointestinal symptoms was reported when renal failure was associated with diabetes rather than other etiologies (3,47). Diabetes mellitus itself has also been considered likely to perpetuate gastroparesis and its resulting symptoms (45). However, gastroparesis is suggested to commonly occur in the absence of diabetes (2,46,47).

Delayed gastric emptying has been reported to occur in as many as 36% of patients with renal failure (48) and has been associated with a high prevalence of dysmotility (46) as well as malnutrition in some patients with ESRD (7).

Delayed gastric emptying was reported in peritoneal dialysis patients (49,50), independent of diabetic status and without associated gastrointestinal symptoms such as nausea and vomiting with gastroparesis (50). In a prospective assessment of gastric emptying in 53 nondiabetic patients (26 on hemodialysis and 27 controls), gastric emptying was shown to be significantly longer in dyspeptic patients on hemodialysis than in healthy controls and in dyspeptic patients on hemodialysis when compared to non-dyspeptic patients on hemodialysis (46).

Nonetheless, the exact pathogenesis of gastroparesis remains unclear in renal failure patients (2).

**Conclusion**

In conclusion, this review has summarized common UGI disorders among dialysis patients with an emphasis upon prevalence, pathogenesis and diagnostic strategies.

Although recent EGD-based studies have confirmed a higher prevalence of UGI erosions and inflammation in patients with renal failure when compared to the general population (4,16,18), *conflicting data on gastric and duodenal ulcers with no evidence on a definite increase in the prevalence of ulcerations in renal failure* (4,16-18).(**I think this sentence needs a verb?!)

Recent consensus showed that the prevalence of H. pylori infection in dialysis patients was equal or lower when compared to subjects with normal renal function in various different geographic populations, regardless of the presence of gastric symptoms (10,21,30). However, the prevalence of PUD was reported to be higher in dialysis patients with H. pylori infection when compared to...
dialysis patients without H. pylori infection (21) and when compared to individuals with normal renal function (16). Nonetheless, PUD appears to be the most common cause of UGI bleeding (7), while gastroparesis commonly occurs among uremic patients in the absence of diabetes, regardless of dialysis modality (2,46,47).

This review emphasizes the differentiation and careful consideration of gastrointestinal symptoms and associated gastrointestinal diseases in dialysis patients, given these patients’ high prevalence and association with poor clinical outcomes if not recognized and managed properly. Given the lack of specific guidelines that formulate appropriate screening and treatment plans, as well as inconclusive data on the prevalence and management of gastrointestinal diseases among dialysis patients, further investigation seems necessary to address the diagnostic models, practice patterns and prognostic characteristics with respect to dialysis modality in large-scale ESRD populations.

References


