Lower Gastrointestinal Disorders Among Dialysis Patients

Diyaliz Hastalarında Alt Gastrointestinal Sistem Hastalıkları

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ABSTRACT

The prevalence of co-morbid gastrointestinal symptoms is high in dialysis patients, while abdominal pain, constipation, diarrhea, anorexia and abdominal bloating are the second-most common group of symptoms following dyspeptic symptoms. Underlying these symptoms is a wide spectrum of lower gastrointestinal disorders such as diverticular disease, angiodysplasia, mesenteric ischemia, ischemic colitis, colonic perforation, fecal impaction and stercoral ulcer, dialysis-related amyloidosis, encapsulating peritoneal sclerosis, and idiopathic dialysis ascites. Also, infarcts due to non-occlusive intestinal ischemia are less common but severe complications. 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 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 lower gastrointestinal disorders that occur among dialysis patients, with an emphasis on prevalence, pathogenesis and diagnostic strategies.

KEY WORDS: End-stage renal disease, Peritoneal dialysis, Hemodialysis, Lower gastrointestinal tract, Pathogenesis

ÖZ

Diyaliz hastalarında komorbid gastrointestinal semptomlar yüksek prevalansa sahiptir. Karın ağrısı, konstipasyon, diyare, anoreksi ve şişkinlik hissi dispeptik semptomlardan sonra en sık gözlenen semptomlardır. Bu semptomlara yol açan alt gastrointestinal sistem hastalıkları geniş bir spektruma sahip olup, divertiküler bağırsak hastalığı, anjiodisplazi, mesenterik iskemi, iskemik kolit, kolon perforasyonu, fekal impaksiyon ve sterkoral ülser, diyaliz amiloidozu, enkapsüle peritoneal skleroz ve idiopatik diyaliz asit bu hastalıklar arasında sayılabilir. Ayrıca, non-okluziv intestinal iskemiye bağlı infarkt gelişimi gibi nadir ancak şiddetli komplikasyonlar da gözlenebilmektedir. Gastrointestinal hastalık insidansının, diyaliz türünden bağımsız ve renal yetmezlik süresi ile orantılı olarak artış gösterdiği kabul edilmektedir. Üremi ve diyaliz gastrointestinal sistem lezyon gelişimi için bir risk faktörü olmakla birlikte, son dönem renal hastalığa bağlı gastrointestinal fonksiyon bozukluğunun çok faktörlü ve henüz tam olarak netlik kazanmamış bir patogeneze sahip olduğu kabul edilmektedir. Ek olarak, renal fonksiyon bozukluğu ve gastrointestinal bozukluklar arasındaki ilişkiye dair çelişkili veriler mevcut olup, renal yetmezlik zemininde gelişen gastrointestinal hastalıkların yönetimine dair özgül kılavuzlar bulunmamaktadır. Bu derleme makalede, diyaliz hastalarında sık gözlenen alt gastrointestinal sistem hastalıkları prevalans, patogenez ve tanısal yaklaşımlar bazında sunulmaktadır.

ANAHTAR SÖZCÜKLER: Son dönem renal hastalık, Periton diyalizi, Hemodiyaliz, Alt gastrointestinal sistem, Patogenez

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INTRODUCTION

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). While the most common gastrointestinal symptoms in dialysis patients include dyspeptic symptoms; abdominal pain, constipation, diarrhea, anorexia and abdominal bloating are also prevalent (2,4-8) along with likelihood of less common but a severe complication of infarcts due to non-occlusive intestinal ischemia (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 I).

The risk of LGI disorders was shown to increase in dialysis patients with a higher prevalence intestinal obstruction or adhesions and abdominal hernia in peritoneal dialysis patients; increased risk of LGI diverticula and bleeding in hemodialysis patients; and a similarly high risk of mesenteric ischemia in dialysis patients regardless of modality (10).

While uremia and dialysis have been linked to an increased risk of gastrointestinal tract lesions, pathogenesis of gastrointestinal dysfunction in ESRD is considered multifactorial with the contribution of several factors (2,5,8,11), 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 (12), reduced visceral sensitivity (13), comorbidities (8), and medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) (8,10). 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 (2,11).

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

LOWER GASTROINTESTINAL DISORDERS

While limited data are available on the incidence and prevalence of LGI tract lesions and bleeding in renal failure, adenomas, carcinomas, and angiodysplasia are more common among CKD patients than in the general population (2,14). A higher prevalence of diverticulosis and diverticulitis than in the general population was noted in patients with polycystic kidney disease with no increase in disease prevalence in renal failure patients relative to the general population (2,15), despite the reported association of ischemic colitis with hemodialysis (2).

LGI disorders of importance to dialysis patients include uremic colitis, ischemic bowel disease, spontaneous colonic perforation, fecal impaction, diverticular disease and angiodysplasia (7).

Although similar predisposing factors underlie an increased risk of UGI and LGI bleeding in CKD patients, limited data are available on the etiology of LGI bleeding in patients with CKD, and most episodes do ameliorate spontaneously. Since re-bleeding remains an important problem, the underlying etiology should be investigated even if the bleeding has stopped (9,16).

Notably, bowel preparation for LGI endoscopy should not employ osmotic cathartics such as phosphate or magnesium given the likelihood of subsequent dangerous increases in serum phosphate or magnesium levels and the risk of further losses of residual renal function in dialysis patients (7).

Uremic Colitis

Uremic colitis is a condition of historical significance that was reported in an autopsy series of patients dying of untreated uremia as extensive colonic and pseudomembranous ulcerations prior to the availability of maintenance dialysis (7). This entity is no longer encountered with the routine use of dialysis, and there are no findings of an enhanced incidence of mucosal lesions on routine colonoscopy among current asymptomatic hemodialysis patients (7,9).

Acute Mesenteric Ischemia and Ischemic Colitis

Mesenteric ischemia is a significant cause of severe acute abdominal pain in renal failure patients and its incidence is higher than in the general population (0.09–0.2% per patient year), especially in hemodialysis patients (0.3–1.9% per patient year) with a lower incidence in peritoneal dialysis patients (1.35% per patient year) (2,17,18). Factors such as older age and co-morbid extensive peripheral vascular disease in ESRD patients are associated with a higher prevalence of ischemic or infarcted bowel in dialysis populations, while episodes of hemodynamic instability and intradialytic hypotension are considered to be associated with a higher incidence of acute mesenteric ischemia in hemodialysis patients (2,7,19).

Diagnosis and Pathogenesis

Intestinal ischemia or infarction among dialysis patients may be asymptomatic or associated with abdominal pain,

Table I: Interrelationship of Gastrointestinal and Renal Diseases (8).

GASTROINTESTINAL MANIFESTATIONS OF RENAL DISEASE
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 autosomal dominant polycystic kidney disease (ADPKD)
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 ADPKD)
Cecal ulceration
Pseudomembranous colitis (50% of patients receiving antibiotics)
Nonocclusive vascular insufficiency
Infections due to chronic immunosuppression, especially
cytomegalovirus infection and intestinal strongyloidiasis
Posttransplant GI lymphoproliferative disorders
DISEASES AFFECTING BOTH GASTROINTESTINAL AND RENAL SYSTEMS
Collagen vascular diseases (scleroderma, vasculitides)
Diabetes mellitus
Hyperparathyroidism
Amyloidosis
Myeloma
Henoch–Schonlein purpura
Hemolytic uremic syndrome
RENAL MANIFESTATIONS OF GASTROINTESTINAL DISEASE
Crohn's disease
Calcium oxalate stones
Ureteral obstruction
Entero or colovesical fistula
Perinephric abscess

Adapted from "Riddell R, Jain D. Gastrointestinal Manifestations of Extraintestinal Disorders and Systemic Disease. Chapter 8. In: Lewin, Weinstein, and Riddell's Gastrointestinal Pathology and Its Clinical Implications. Wloters Kluwer, UK, 2014, pp. 390-393. Available at: http://www.lww.co.uk/media/Riddell-Ch8-Gastrointestinal-Manifestations-of-Extraintestinal-Disorders-and-Systematic-Disease.pdf

gastrointestinal bleeding, or circulatory collapse (7,19,20). Severe pain is considered to be a more likely presentation in case of mesenteric ischemia, whereas overt GI bleeding and mild pain are usually present in ischemic colitis (9). In a retrospective analysis of 15 patients with ESRD who had mesenteric ischemia during an 11-year period, the most prevalent combination of symptoms were reported to be abdominal pain, fever, guarding, and leukocytosis, while the diagnosis was confirmed by colonoscopy (n=4) or surgery (n=11), and CT scanning with an opaque enema (n=8) had a sensitivity of 75% (20).

The symptoms of mesenteric ischemia may also mimic those of peritonitis in peritoneal dialysis patients, which increases the likelihood of an extremely long delay in the initiation of appropriate therapies and thus has a very high mortality rate (21,22). Consequently, the clinical overlap of acute mesenteric ischemia with peritonitis necessitates a high index of suspicion to accurately diagnose the disorder in the setting of peritoneal dialysis. An increase in serum or effluent amylase levels and non-resolving gram-negative fungal or polymicrobial peritonitis despite the appropriate antimicrobial treatment would be highly suggestive of acute mesenteric ischemia (2,7,22).

Data from case series revealed that episodes of intradialytic hypotension, the use of weekly erythropoietin and vasoconstrictive medications, episodes of constipation, vascular calcification on imaging, severe colitis and right-sided lesions were more common in patients with acute mesenteric ischemia or ischemic colitis (2,19,20,23).

Hemodialysis patients with cardiovascular pathology and atherosclerosis are considered to be at increased risk of acute mesenteric ischemia (2,19). Vascular calcification rates among hemodialysis patients with versus without co-morbid mesenteric ischemia were reported to be 100% vs. 49%, respectively (2,19). Given the contribution of atherosclerosis combined with intradialytic hypotension, non-occlusive mesenteric ischemia was reported in most cases of renal failure, while only reported in 25%–60% of cases in the general population (2,24).

Mortality rates associated with acute mesenteric ischemia in uremic patients are very high, ranging from 33% to 73%

(17,19,24,25). Right-sided ischemic colitis lesions and a presentation of both pain and bleeding (when compared to pain alone) have been associated with a more severe outcome and are more common in hemodialysis patients (23,26).

Spontaneous Colonic Perforation

While associated with diverticular disease or obstruction in most patients with normal renal function, colonic perforations occur in association with aluminum-containing antacids, barium studies, fecal impaction, or dehydration among patients with ESRD, and the etiology is unknown in a considerable portion of ESRD patients (7). Colonic perforation has a higher mortality in the uremic population when compared to patients with normal renal function (27,28), and the diagnosis must be considered in patients who present with acute abdominal pain (7).

Fecal Impaction and Stercoral Ulcer

Fecal impaction may occur as a complication of the use of phosphate binders, analgesics, and iron in association with underlying motility disorders, mucosal ulceration, bleeding, perforation, chronic diarrhea and sedentary lifestyle (7).

A stercoral ulcer may develop due to pressure exerted on the colonic mucosa, which is caused by large fecal masses and a subsequent development of tissue necrosis in the form of isolated or diffuse ulcerative lesions throughout the colon, most frequently in the recto-sigmoid region (29). Reduced gut motility, fluid restrictions, and the use of phosphate binders increase the risk of stercoral ulcer development by increasing the risk of constipation in patients with CKD (16). Although they occur rarely, transmural ulcerations are associated with an increased risk of perforation, while mucosal biopsies should also be obtained to rule out malignancy (9).

Angiodysplasia

Angiodysplasia is the most frequent cause of recurrent LGI bleeding in dialysis patients, referring to 19–32% of LGI bleeds in the dialysis population compared to 5–6% of LGI bleeds in the general population (30). Angiodysplasia accounts for approximately 30% of LGI hemorrhage among elderly patients undergoing hemodialysis (31). The most common sites

Table II: Causes of lower gastrointestinal bleeding in chronic kidney disease patients (16).

Occult GI bleeding	Overt GI bleeding	Occult or overt GI bleeding
• Angiodysplasia	• Diverticulosis	• Angiodysplasia
• Diverticulosis	• Ischemic colitis	• Diverticulosis
• Colon cancer	• Hemorrhoids	• Polyps, post polypectomy
• Inflammatory bowel disease	• Anal fissure	• Colon cancer
• Dialysis related amyloidosis	• Stercoral ulceration	• Inflammatory bowel disease

Adapted from "Saeed F, Agrawal N, Greenberg E, Holley JL. Lower gastrointestinal bleeding in chronic hemodialysis patients. Int J Nephrol 2011; 2011: 272535."

of angiodysplasia in the LGI tract are the cecum and ascending colon (32). Bleeding is usually occult and intermittent, while an occasional massive hemorrhage can also develop (9) (Table II).

As in the UGI tract, endoscopy is the most commonly used diagnostic method for angiodysplasia (9). Colonoscopy provides careful inspection of the colonic mucosa for arteriovenous malformations, while small bowel lesions may require wireless capsule endoscopy, push enteroscopy, or the more advanced and invasive device-assisted enteroscopy, such as double-balloon enteroscopy or spiral enteroscopy (9). The diagnosis may be established by arteriography in some patients (7).

Diverticular Disease and Peritonitis (Unique to Peritoneal Dialysis)

Advances in peritoneal dialysis methods have been associated with more frequent diagnosis of fungal, polymicrobial and culture-negative peritonitis, alongside a marked decline in the rates of gram-positive peritonitis (2,33). Differential diagnosis of acute mesenteric ischemia, cholecystitis, appendicitis or diverticulitis is considered necessary in case of gram-negative and polymicrobial peritonitis due to likelihood of underlying bowel micro-perforation or a gross perforation (2,34).

The incidence of diverticular disease is not increased in dialysis patients, except for those with polycystic kidney disease (17,35), and the presentation, diagnosis and treatment characteristics of diverticular disease do not differ with respect to the presence of renal failure (7).

However, diverticular disease in patients with ESRD is associated with unique characteristics compared to patients without renal failure, such as a younger age of onset (<40 years) and a more severe course, a higher incidence of fecal peritonitis in peritoneal dialysis patients and a higher rate of hemorrhage that results from platelet dysfunction or iatrogenic anticoagulation in dialysis patients that requires surgery (7,16,36,37).

Diverticulosis is the most prevalent cause of gastrointestinal leakage in patients on continuous ambulatory peritoneal dialysis (2,16,38,39). Despite lack of evidence on the higher prevalence of diverticulosis in peritoneal dialysis patients compared to the general population, increased risk of peritonitis has been associated with the presence of >10 diverticula, diverticular size of >10 mm, and the presence of diverticula in the ascending, transverse, or descending colon (2,38,39).

The pre-transplant detection of diverticulitis and other disorders, which may result in postsurgical colonic perforation, is extremely important given that perforation is associated with a high mortality rate (60%). In part, this is due to the masking of the signs and symptoms of peritonitis in steroid-treated patients (7,16). In fact, a history of frequent episodes of diverticulitis was considered a relative contraindication to the initiation of peritoneal dialysis as a possible renal replacement therapy (2,7,40).

The incidence of LGI bleeding related to diverticulosis in the CKD population is similar to that in the general population, apart from patients with autosomal dominant polycystic kidney disease on maintenance dialysis who have an increased incidence of diverticula and diverticular bleeding (16).

Encapsulating Peritoneal Sclerosis (Unique to Peritoneal Dialysis)

Being characterized by peritoneal thickening, encapsulation of the bowel and the obstructive ileus symptoms, encapsulating peritoneal sclerosis is a scarce (0.0-4.4%) but lethal complication of peritoneal dialysis (2,41-43). The risk factors associated with encapsulating peritoneal sclerosis are considered to be the peritoneal dialysis duration, prolonged exposure to high glucose containing dialysate, recurrent peritonitis, transition from peritoneal- to hemo-dialysis, and the lack of residual renal function (2,41).

Encapsulating peritoneal sclerosis is diagnosed based on clinical manifestations (e.g., early satiety, abdominal fullness, anorexia, nausea, vomiting, constipation, diarrhea, weight loss, and a loss of ultrafiltration capacity) and radiological findings on abdominal ultrasonography and CT, whereas none of these modalities is considered sensitive or specific for the diagnosis (2,41).

Dialysis-Related Amyloidosis

Although musculoskeletal system manifestations are predominant in dialysis-related amyloidosis, the disease may also affect the GI system (16), which leads to extensive amyloid deposits in the gastrointestinal tract as detected on endoscopic biopsy and is associated with severe gastrointestinal complications, such as gastric and colonic dilatation, paralytic ileus, decreased motility, sporadic bleeding, cecum or sigmoid colon perforation and intestinal necrosis (7,9,16,44,45).

Idiopathic Dialysis Ascites (Unique to Hemodialysis)

Idiopathic dialysis ascites refers to the occurrence of ascites in patients on maintenance hemodialysis in the absence of a clear underlying cause, making it a diagnosis of exclusion (7). Cachexia, volume overload, hypoalbuminemia and malnutrition may present as associated findings (7). There has been a decline in the incidence of idiopathic dialysis ascites due to improved hemodialysis techniques, better control of volume overload, enhanced dialysis doses, and better nutritional status (7).

Pathogenesis

The pathogenesis of idiopathic dialysis ascites is considered to be multifactorial and includes chronic volume overload with hepatic congestion and increased hepatic vein hydrostatic pressure, changes in the permeability of the peritoneal membrane, impaired lymphatic peritoneal resorption and the presence of contributing factors, such as hypoalbuminemia, congestive heart failure and hyperparathyroidism (46-48).

Diagnosis

Along with the proper clinical setting, diagnostic criteria for idiopathic dialysis ascites includes ascitic fluid with the characteristic straw-colored appearance, a high protein content (3 to 6 gm/dL) and a leukocyte count ranging from 25 to 1600 cells/mm^3 (7).

As part of the evaluation, intensive investigations are usually needed to exclude other causes, and a laparoscopic examination is usually required to eliminate various possibilities and to perform appropriate biopsies for histologic examinations and cultures (7).

Prognosis

Idiopathic dialysis ascites is associated with a poor prognosis with mortality in approximately 45% of patients within 15 months of the diagnosis (49,50).

CONCLUSION

In conclusion, this review has summarized common LGI disorders among dialysis patients with an emphasis upon prevalence, pathogenesis and diagnostic strategies. Underlying highly prevalent co-morbid gastrointestinal symptoms in dialysis patients is a wide spectrum of LGI disorders such as diverticular disease, angiodysplasia, mesenteric ischemia, ischemic colitis, colonic perforation, fecal impaction and stercoral ulcer, dialysis related amyloidosis, encapsulating peritoneal sclerosis, and idiopathic dialysis ascites (2,4,7-9). Less common but severe complications include infarcts due to non-occlusive intestinal ischemia (8).

Angiodysplasia is the most common cause of recurrent LGI bleeding in patients on dialysis (30).

Ischemic colitis and mesenteric ischemia seem to be more prevalent in ESRD patients, and hemodialysis patients in particular, relative to the general population (2,16,17) while also being associated with higher mortality rates (17,19,24,25). This is especially true in cases of right-sided ischemic colitis lesions and presentations with both pain and bleeding (compared to pain alone) in hemodialysis patients (23,26). The clinical overlap of acute mesenteric ischemia with peritonitis necessitates a high index of suspicion to accurately diagnose the disorder and to prevent the delay in the initiation of appropriate therapies, which reduces the risk of high mortality in the setting of peritoneal dialysis (2,7,22).

The incidence of diverticular disease was not shown to be increased in dialysis patients, except in those with polycystic kidney disease (15,35), while the presentation, diagnosis and treatment characteristics of diverticular disease did not differ with respect to the presence of renal failure (7). In fact, underlying diverticulosis is the most common cause of gastrointestinal leakage in patients on continuous ambulatory peritoneal dialysis (16,38,39), while a history of frequent episodes of diverticulitis is considered to be a relative contraindication to the initiation of peritoneal dialysis as a possible renal replacement therapy (2,7,40). Encapsulating peritoneal sclerosis is a rare but lethal complication of peritoneal dialysis, while idiopathic dialysis ascites refers to the occurrence of ascites in patients on maintenance hemodialysis and is associated with a poor prognosis and a high mortality (7,16,49,50).

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.

Conflict of Interest: No conflict of interest was declared by the authors.

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