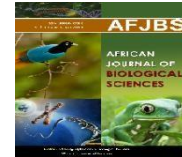


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Gastrointestinal changes in chronic kidney disease patients

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Abstract: Estimating the prevalence of gastrointestinal symptoms among patients with renal failure faces the same obstacles. Studies have been limited by non-standardized definitions of gastrointestinal symptoms and varying patient populations. The prevalence of gastrointestinal symptoms in patients with renal failure is thought to range from 70% to 79%. The prevalence of these disorders is generally similar in predialysis patients, patients on hemodialysis, and patients on peritoneal dialysis. but a trend towards increasing symptoms with increasing duration of renal failure exists. The prevalence of constipation is as high as 63% in patients on hemodialysis and 29% in patients on peritoneal dialysis, compared with a prevalence of 10–20% in the general population. Uremic retention molecules are a large group of molecules that accumulate in the gastrointestinal tract of patients with renal failure and are believed to contribute to the uremic syndrome. Uremic retention molecules produced by microbial metabolism may have a role in the morbidity and mortality associated with renal failure. A considerable proportion of cases of renal failure can be attributed to diabetes mellitus, and as anorexia, nausea, and vomiting are common symptoms in patients with renal failure, the high incidence of gastrointestinal symptoms in patients with renal failure may be induced by gastroparesis. Esophagogastroduodenoscopy has been used to investigate the etiology and prevalence of such lesions. Although results from studies that have used this technique are conflicting, it seems that the frequency of upper gastrointestinal lesions in patients with renal failure is greater than in the general population. The prevalence of positive fecal occult blood test results in patients with CKD is estimated to be 19%. The most common site of upper gastrointestinal tract involvement is the duodenum, as duodenal lesions are found in 61% of ESRD patients with positive fecal occult blood tests

Keywords: *Gastrointestinal changes, chronic kidney disease*

Introduction:

Estimating the prevalence of gastrointestinal symptoms among patients with renal failure faces the same obstacles. Studies have been limited by non-standardized definitions of gastrointestinal symptoms and varying patient populations. The prevalence of

gastrointestinal symptoms in patients with renal failure is thought to range from 70% to 79% .

The prevalence of chronic kidney disease (CKD) and endstage renal disease (ESRD) has increased steadily over the past decade in the US. **(1)**

Studies indicate that between 4 million and 20 million people in the US are affected by CKD, and approximately 560,000 of these patients require dialysis This fact places a burden on primary care physicians to understand and treat common conditions associated with renal failure. Of note, a 1992 study showed that as many as 80% of patients with ESRD rely on their nephrologists for primary medical care. **(2)**

Study	Number of participants	Prevalence of git symptoms	Types of symptoms
Luzza et al.(48)	Hd patients 103 General outpatients 103	Hd patients 70% Outpatient 70%	Hd: burning 50% , bloating 44%,epigastric pain 39%,post prandial swelling 36%
Farsakh et al . (5)	Hd patients 92 Outpatients referred for egd 100	Hd 77 % Outpatient not recorded	Hd :nausea 74 %,vomiting 68 %,anorexia 64 %,constipation 59%,heart burn 52 %
Hammer et al .(39)	Hd patients 105 No control group	Hd 79%	Hd: dyspepsia 46 %,constipation 40%,diarrhea 24 %
Strid et al . (10)	Hd patients 127 Pd patients 55 Predialysis 50 Healthy control 2162	Gsrs: Hd 1.93 Pd 2.07 Predialysis 1.84 Control not given	Hd: abdominal pain 1.67,constipation 1.67, indigestion 1.67 Pd : abdominal pain 2 ,constipation 2.00, indigestion 2.00, diarrhea 1.67
Cano et al .(40)	Hd patients 100 Pd patients 48 Hospital outpatient 145 Control group 145	-Overall prevalence not recorded -constipation and diarrhea were more common in dialysis	Hd : abdominal pain 72 %,constipation 33 %,ibs 21%,heart burn 20 %,vomiting 18 %,diarrhea 17 % Pd :abdominal pain 65%,ibs 33%,constipation 27%,heart burn 21 %vomiting 13 %

The prevalence of chronic kidney disease (CKD) and endstage renal disease (ESRD) has increased steadily over the past decade in the US. **(2)**

Studies indicate that between 4 million and 20 million people in the US are affected by CKD, and approximately 560,000 of these patients require dialysis. This fact places a burden on primary care physicians to understand and treat common conditions associated with renal failure. Of note, a 1992 study showed that as many as 80% of patients with ESRD rely on their nephrologists for primary medical care. **(2)** Although patients with CKD often suffer from comorbidities such as diabetes and coronary artery disease, the most common, non-renal, chronic disorders in patients with ESRD are gastrointestinal disorders. **(2)**

To appropriately evaluate the prevalence of gastrointestinal symptoms in patients with renal failure, the difficulties in estimating their frequency in the general population must first be examined. Gastrointestinal symptoms can either be 'organic' or 'functional', based on the presence or absence of underlying pathology **(1)**

Organic symptoms are associated with a causal gastrointestinal lesion and are influenced by psychological factors, visceral hypersensitivity, and altered gastrointestinal motility **(3)**

The prevalence of functional gastrointestinal disorders is far greater than that of organic disorders. The estimated prevalence of functional gastrointestinal disorders is as high as 80% in the general adult population. **(4)**

Gastrointestinal symptoms

The prevalence of gastrointestinal symptoms in patients with renal failure is thought to range from 70% to 79%. The prevalence of these disorders is generally similar in predialysis patients, patients on hemodialysis, and patients on peritoneal dialysis but a trend towards increasing symptoms with increasing duration of renal failure exists. **(5)**

Constipation

The prevalence of constipation is as high as 63% in patients on hemodialysis and 29% in patients on peritoneal dialysis, compared with a prevalence of 10–20% in the general population. **(6)**

Both segmental and total colonic transit times, as measured by radio-opaque markers, were significantly longer in patients on hemodialysis or peritoneal dialysis than in the general population. The association of constipation with renal failure is attributed to lifestyle changes that relate to renal dysfunction, including reduced levels of activity, reduced fiber intake (owing to potassium restricted diets), use of phosphate binders, and the presence of multiple comorbidities such as diabetes and cerebrovascular disease. **(7)**

Uremic retention molecules

Uremic retention molecules are a large group of molecules that accumulate in the gastrointestinal tract of patients with renal failure and are believed to contribute to the uremic syndrome. Uremic retention molecules produced by microbial metabolism may have a role in the morbidity and mortality associated with renal failure. **(8)**

These molecules are thought to be produced by proteolytic bacteria in the colon and include phenols such as *p*-cresol, as well as indoles and amine. They are probably present at higher concentrations in patients with renal failure than in the general population because of the

altered colonic flora associated with advancing CKD. The alterations in colonic flora may be caused by prolonged colonic transit time, decreased protein digestion in the small bowel, and low dietary fiber. (7)

Current treatment strategies to reduce levels of uremic retention molecules include prebiotic and probiotic therapy to decrease the amount of proteolytic bacterial species in the colon, increasing carbohydrate ingestion to decrease protein fermentation, and increasing the absorption of toxic end products in the colon. (7)

Anxiety and depression

Controversy exists as to whether the gastrointestinal symptoms present in patients with renal failure occur independent of comorbidities. In particular, the estimated prevalence of anxiety and depression in patients with renal failure is as high as 20–30%, with the prevalence of self-reported depression being as high as 68%—much higher than in the general population. (9)

Depression, in turn, is associated with somatic disorders, including gastrointestinal disorders, which suggests that physiological disturbances such as anxiety and depression may contribute to the gastrointestinal symptoms present in patients with renal failure. In both the general population and in patients with renal failure, gastrointestinal symptoms can markedly affect quality of life and psychological well-being. (10)

Gastrointestinal symptoms have also been linked to increased rates of malnutrition, and malnutrition has been independently associated with increased morbidity and mortality in patients with ESRD. (11)

Gastroparesis

Pathogenesis

A considerable proportion of cases of renal failure can be attributed to diabetes mellitus, and as anorexia, nausea, and vomiting are common symptoms in patients with renal failure, the high incidence of gastrointestinal symptoms in patients with renal failure may be induced by gastroparesis. (12)

Of note, studies that have investigated the prevalence of gastroparesis in patients with renal failure have often excluded patients with diabetes, suggesting that gastroparesis commonly occurs in the absence of diabetes. (13)

In 2000, van vlem *et al.* prospectively assessed gastric emptying in 53 nondiabetic patients (26 on hemodialysis and 27 healthy controls). Gastric emptying was significantly longer in dyspeptic patients on hemodialysis than in healthy controls and in dyspeptic patients on hemodialysis than in non-dyspeptic patients on hemodialysis. (14)

Upper gastrointestinal lesions

Prevalence

Esophagogastroduodenoscopy has been used to investigate the etiology and prevalence of such lesions. Although results from studies that have used this technique are conflicting, it seems that the frequency of upper gastrointestinal lesions in patients with renal failure is greater than in the general population. (15)

Studies that have compared the prevalence of upper gastrointestinal lesions in patients with CKD and/or ERSO with dyspeptic individuals who were referred for esophagogastroduodenoscopy are shown in Table 1.

study	Number of participants	Prevalence of lesions	Prevalence of <i>H. pylori</i>
Farsakh et al., (5)	Hd patients:92	Hd :duodenal erosions 12 (13%) Gastric erosions:12(13%) Duodenal ulcer :3 Gastric ulcer :0 Angiodysplasia:1 Biopsy samples: chronic sup-gastritis 60% Atrophic gastritis 10%	49%
Kang et al., (41)	Hd:114	Gastritis, duodenitis:36% Erosions:24% Both:9% Duodenal pseudomelanosis :4% Peptic ulcer 4%	<i>H. pylori</i> not checked
Nardon et al.,(42)	*Hd :11 *Predialysis:39 *Control with dyspepsia:93	Hd/control Esophageal erosions:18%/ 11% Gastric erosions : 56% /16% Duodenal erosions: 36%/2% Duodenal ulcer: 6% / 2 %	CKD 52% Control 36 %
Khadmat et al.,(43)	Dyspeptic predialysis:71 Dyspeptic hd :73 Dyspeptic renal transplant:75 Control :73	Pre hd /hd/rtr /control Erosive oesphagitis: 42%/38%/36%/13% Erosive gastritis: 24%/30%/16%/8% Erosive duodenitis: 26%/29%/24%/20% Hiatus hernia: 9%/12%/16%/11% Duodenal ulcer: 16%/14%/8%/7% Gastric ulcer:6%/0%/0%/3%	Pre hd :66.2% Hd:63% Rtr :40% Control:34.8%

Helicobacter pylori

✓ **Prevalence**

The reported prevalence of *H. pylori* infection varies greatly ranging from 49% to 66% in patients with renal failure and from 35% to 75% in control groups. **(16)**

✓ **Diagnosis**

Given the high prevalence of upper gastrointestinal symptoms, upper gastrointestinal lesions, and potentially high rates of *H. pylori* infection associated with renal failure, some clinicians argue that all patients with renal failure and dyspepsia should be evaluated for *H. pylori* infection and treated if positive. **(15)**

Moreover, other than the *H. pylori* stool antigen test, noninvasive tests, such as serology tests and the urea breath test seem to be less sensitive and specific in patients with renal failure than in patients with normal renal function. **(17)**

Compared with pathological diagnosis by esophagogastroduodenoscopy, the stool antigen test is approximately 97% sensitive and specific for diagnosing *H. pylori* infection in patients with renal failure, the urea breath test is 93.8% sensitive and 85.3% specific, and the serum *H. pylori* antibody test is 87.5% sensitive and 80% specific. **(18)**

Treatment

Once infection is established in patients with renal failure, management of *H. pylori* should follow the same guidelines as for the general population, as proposed by the American Gastroenterological Association. 'Triple therapy', which involves the administration of a proton pump inhibitor, clarithromycin and either amoxicillin or metronidazole should be initiated. no specific regimens for *H. pylori* treatment in renal failure have been recommended by the American Gastroenterological Association **(19)**

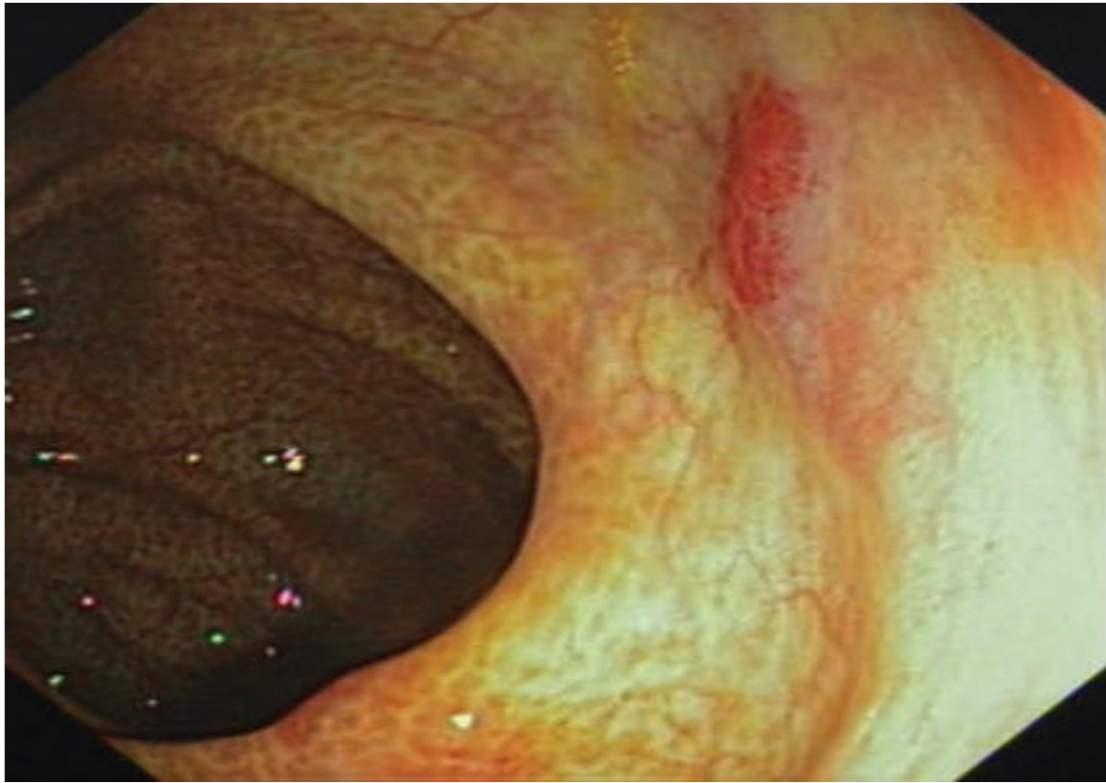
Gastrointestinal bleeding

Gastrointestinal bleeding is a known complication of renal failure; however, its pathogenesis remains uncertain. Some have attributed gastrointestinal bleeding to the effects of uremia on the gastrointestinal mucosa; others have suggested that uremia may affect platelet adhesiveness, which may explain the prolonged gastrointestinal bleeding seen in patients with renal failure. In addition, the role of heparinization and the widespread use of antiplatelet agents in patients on dialysis have been implicated in the etiology of gastrointestinal bleeding. **(20)**

Chronic gastrointestinal bleeding

The prevalence of positive fecal occult blood test results in patients with CKD is estimated to be 19%. The most common site of upper gastrointestinal tract involvement is the duodenum, as duodenal lesions are found in 61% of ESRD patients with positive fecal occult blood tests. **(21)**

The most common site of lower gastrointestinal tract bleeding is the proximal colon. Angiodysplasia and gastrointestinal tract erosions seem to be the most common causes of



upper tract bleeding by contrast, colonic neoplasms are common causes of lower tract bleeding. (22)

Figure 1. Angiodysplasia in the ascending colon, slightly elevated above the mucosa. Permission obtained from Nature Publishing Group Ltd © Barnert, J. & Messmann, H. *Nat. Rev. Gastroenterol. Hepatol.* 6, 637–646 (2009).

Angiodysplasia

Although findings from studies are conflicting, angiodysplasia of both the upper and lower gastrointestinal tract seems to be more common in patients with renal failure than in the general population, causing gastrointestinal hemorrhage in 19–32% of patients. (23)

Zuckerman *et al.* showed that angiodysplasia was the cause of upper gastrointestinal bleeding in 24% of patients with renal failure compared with just 5% of the general population (24)

Furthermore, angiodysplasia may be the most common cause of occult gastrointestinal bleeding of the small bowel when esophagogastroduodenoscopy and colonoscopy are nondiagnostic (25)

Initial treatment of angiodysplasia in the general population can include local ablation with argon plasma coagulation, laser coagulation, or heat coagulation. If these methods fail,

surgical resection is often considered. However, other than case reports of their successful use (26).

Acute upper gastrointestinal bleeding

Acute upper gastrointestinal bleeding occurs more commonly in patients with renal failure than in the general population with an estimated frequency of 21 bleeds per 1,000 patient years. Unfortunately, acute upper gastrointestinal bleeding also carries a very high risk of mortality, and accounts for 3–7% of all deaths in patients with ESRD. (27)

Some risk factors that are traditionally associated with an increased risk of gastrointestinal bleeding, such as use of NSAIDs, aspirin, or anticoagulants, are not associated with an increased risk of bleeding in patients with renal failure. However, other traditional risk factors, such as smoking, disability, and a history of cardiovascular disease are risk factors for upper gastrointestinal bleeding in patients with renal failure. (27)

Lower gastrointestinal bleeding and diverticulosis

A paucity of data exists on the incidence and prevalence of both acute and chronic lower gastrointestinal tract lesions and bleeding in patients with renal failure; however, it seems that adenomas, carcinomas, and angiodysplasia occur with greater frequency in patients with CKD than in the general population (22)

The prevalence of other colonic lesions is increased only in specific populations. For example, the prevalence of diverticulosis is not increased in patients with renal failure compared with the general population it occurs in 32% of patients with renal failure without polycystic kidney disease and in 38% of age-matched controls. However, the prevalence of diverticulosis and diverticulitis is higher in patients with polycystic kidney disease than in the general population, although whether this association is associated with an increased risk of gastrointestinal bleeding is unclear (28).

Acute pancreatitis

The first associations between renal failure and pancreatic lesions were described in autopsy studies from the pre-dialysis era (29)

In 1987, in a postmortem analysis of 78 patients with ESRD who had received hemodialysis, vaziri *et al.* found pancreatic ‘abnormalities’, defined as inflammation, hemorrhage, fibrosis, fatty infiltrations, cysts, hemosiderosis, or amyloid deposits in 47 patients and pancreatitis in 22 patients (30)

Bruno *et al.* reported an incidence of acute pancreatitis of 1 in 614 person years in patients on hemodialysis and 7 in 241 person years for patients on peritoneal dialysis (31)

In 2008, lankisch *et al.* performed a retrospective survey of ESRD patients in dialysis units throughout Germany (68,715 patients on hemodialysis and 3,386 patients on peritoneal dialysis). when patients with a known risk factor for acute pancreatitis were excluded from the analysis, the incidence of acute pancreatitis was 32 cases per 100,000 patient years for those on hemodialysis and 148 cases per 100,000 patient years for those on peritoneal

dialysis, compared with an incidence of 19.7 cases per 100,000 patient years in the general population (32)

Diagnosis

✓ History and physical examination

The most common symptom for ESRD patients presenting with pancreatitis is severe abdominal pain, which occurs in nearly 100% of patients. Other common symptoms include nausea and vomiting, which occurs in 73% and 67% of patients, respectively, and abdominal tenderness, which occurs in 79% of patients. no significant differences exist between patients on hemodialysis and peritoneal dialysis with regard to the presenting signs and symptoms (32)

Treatment and mortality

Most cases of pancreatitis in patients with renal failure can be managed conservatively, that is, with bowel rest or nasogastric suction. As in the general population, drainage and debridement should be reserved for patients with pseudocysts or necrosis. Use of heparin with peritoneal dialysis and hemodialysis should also be minimized to reduce the risk of pancreatic hemorrhage (32)

The overall mortality rates associated with acute pancreatitis in patients on hemodialysis and peritoneal dialysis range from 0% to 58%. As a comparison, the mortality rate associated with acute pancreatitis in the general population is 10% (33)

Acute mesenteric ischemia

In patients on hemodialysis, occurring at a frequency of 0.3–1.9% per patient year.83,84 Histological evidence of mesenteric ischemia has been found in 14% of hemodialysis patients on autopsy. (34)

The high incidence of acute mesenteric ischemia in patients on hemodialysis is thought to be caused by episodes of hemodynamic instability and intradialytic hypotension. (34)

Atherosclerosis combined with intradialytic hypotension may explain why most cases of acute mesenteric ischemia associated with renal failure are found to be non-occlusive mesenteric ischemia. By contrast, 25–60% of cases of acute mesenteric ischemia in the general population are nonocclusive mesenteric ischemia. (35)

Nonischemic colitis

Etiologies

Many different etiologies of colitis exist in patients with CKD. Ischemic, infectious, malignant, and autoimmune etiologies are common in patients with CKD, but uremic colitis, sodium polystyrene sulfonate (SPS)–sorbitol induced intestinal necrosis, and idiopathic colitis have also been reported. All etiologies probably contribute to the increased incidence of 'spontaneous' colonic perforation observed in patients with advanced kidney disease (36)

SPS–sorbitol induced colonic necrosis.

SPS is a cation-exchange resin that is commonly used to treat hyperkalemia in patients with CKD and ESRD. Although SPS is generally well tolerated, it can cause gastrointestinal necrosis when given in combination with sorbitol to prevent constipation. The first description of this adverse effect was published in 1987 following the administration of SPS-sorbitol enemas to uremic postoperative patients. **(37)**

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