Original Research

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Gastrointestinal manifestations of chronic kidney disease

Manifestaciones gastrointestinales de la enfermedad renal crónica

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Abstract

Introduction: There is a wide variety of gastrointestinal clinical manifestations that may increase the deterioration of the quality of life in patients with chronic kidney disease (CKD), which are manageable if properly detected.

Objective: The objective of this work is to perform an updated and analytical re-view of the literature on the manifestations in the digestive tract of patients with chronic deterioration of renal function.

Results: The results indicate that some of the signs and symptoms on the gastrointestinal tract of patients with CKD are individual, and non-specific symptoms such as anorexia, nausea and vomiting predominate, which can be controlled with adequate renal replacement therapy; while others, rarer, such as ascites associated with dialysis, impoverish the prognosis and illustrate the need for transplantation.

Key words: Gastrointestinal diseases, gastrointestinal tract, chronic renal failure, digestive signs and symptoms, symptom assessment, uremia.

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Resumen

Introducción: existe una amplia variedad de manifestaciones clínicas gastrointestinales que pueden aumentar el deterioro de la calidad de vida en los pacientes con enfermedad renal crónica (ERC), que son manejables si se detectan adecuadamente.

Objetivo: el objetivo de este trabajo es realizar una actualización y revisión analíti-ca de la literatura sobre las manifestaciones en el tracto digestivo de pacientes con deterioro crónico de la función renal.

Resultados: los resultados indican que algunos de los signos y síntomas sobre el tracto gastrointestinal de los pacientes con ERC son individuales, y predominan los síntomas inespecíficos como la anorexia, las náuseas y el vómito, los cuales pueden controlarse con una adecuada terapia de reemplazo renal; mientras que otros, más raros, como la ascitis asociada a la diálisis, empobrece el pronóstico e ilustra la necesidad de trasplante.

Palabras clave: enfermedades gastrointestinales, tracto gastrointestinal, insuficiencia renal crónica, signos y síntomas digestivos, evaluación de síntomas, uremia.

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Introduction

The digestive pathologies are frequent in patients with chronic kidney disease (CKD), there is a clear underreporting of the disease, resulting in the lack of knowledge of the mechanisms that lead to a wide range of symptoms, from nausea to Anorexia, and disturbances in the balance of sodium and potassium, contributing to a final state of malnutrition. However, it is estimated that about 80% of patients present some type of symptom in the gastrointestinal tract (GIT) during the course of their disease[1]. However, some of them, such as dyspepsia, may have prevalence not different from that of the general population[2].

In the symptoms of GIT in patients with chronic kidney disease, there is a multifactorial origin. Among them is the retention of toxic and toxic products (endogenous and exogenous), with alteration of the homeostasis of the extracellular environment, iatrogenic origin, the influence of the underlying disease that led to CKD, the higher prevalence of anxiety disorders, Depression and irritable bowel syndrome, therapy and type of renal replacement therapy, alteration in the microbiota and persistent trans mural inflammation of the intestinal mucosa. All of them cause deleterious effects, not only on the function of the digestive tract but also on many organs and systems, which can present not only a series of symptoms but also suffer complications, which in some cases may be asymptomatic, but which manage to constitute A risk for possible complications[1-3].

The management of CKD is aimed at preventing or attenuating the appearance of systemic clinical manifestations resulting from diminished renal function, and to allow the symptomatic management of patients when dialysis and transplantation are necessary to improve the quality of life of these patients sick. The clinical manifestations found in this subgroup can be distributed as follows (Table 1).

Nonspecific symptoms:

Usually present in patients with stage VREC: anorexia, dyspepsia, nausea, vomiting and uremic fetor. They have a prevalence of around 60%[4,5]. In most studies it does not differ from the general population.

Nausea and vomiting: these are the result of uremic syndrome, changes in fluids and electrolytes during dialysis. They disappear with renal replacement therapy[1, 2]. Of these, the origin of anorexia has been studied extensively, finding within the contributing causes: stomatitis, anemia, acidosis, drastic changes in the diet, forced feeding or the use of supplements, alterations in taste of food, uremia, diuretics, dehydration, gastroenteritis, hypokalemia, hyperazoemia and hyperparathyroidism[4,6].

Ureic Fetus: ammoniacal odor produced by nitrogenous metabolites in saliva. It is characteristic the metallic taste that they present[7].

Hypo: posterior to diaphragmatic irritation that disappears with the substitution therapy. If it is not corrected, it finds adequate response to chlorpromazine and metoclopramide[4].

Diarrhea: in these patients there are profound changes in the composition of the intestinal microbiota and alteration of the structure and function of the intestinal epithelial barrier. These alterations lead to the generation and absorption of harmful and toxic byproducts that contribute to systemic inflammation, uremic toxicity, malnutrition and other morbidities.

Table 1.
Distribution in the gastrointestinal tract

Oropharynx	Stomatitis, gingivitis, mumps
Upper digestive tract	Esophagitis, gastro-esophageal reflux, biliary reflux, gastritis, duodenitis, peptic ulcer, angiodysplasias and digestive bleeding.
Lower digestive tract	Constipation, diverticular disease, ischemic colitis, uremic colitis, perforation of the colon, angiodysplasias and digestive bleeding.
Pancreas and bile duct	Pancreatitis, cholelithiasis.
Peritoneum	Ascites associated with dialysis, peritonitis.
Nonspecific	Anorexia, nausea, vomiting, uremic fetor.
Inespecíficos	Anorexia, nauseas, vómito, fetor urémico.

Source: own elaboration

It can present either acutely or chronically: the acute form is distinguished by infectious processes or intestinal irritation, by peritoneal sparings or changes in diet; the chronic form requires complementary studies (co-procultive antibiogram), in order to detect the toxin for Clostridium difficile - if there is suspicion - and endoscopic study. Once the infectious origin is ruled out, loperamide is an effective measure. The treatment consists in the evaluation of the hydroelectrolytic balance (ORS: controlling the amount of potassium and phosphorus individually). For its part, its infectious form (also known as "traveler's diarrhea") causes fever and lasts for more than a week. Immunosuppression: antimicrobial therapy (ciprofloxacin). Once the infectious origin has been ruled out, the use of loperamide is recommended[8,9].

Changes in the patient on peritoneal dialysis: one of the main findings at this level is the increase in leptin levels. This hormone, secreted by the adipocytes, modulates the sensation of satiety and controls the ingestion and the energy expenditure. For this reason, the hormone is associated with the occurrence of cases of anorexia and malnutrition.

The management of patients with anorexia and malnutrition is carried out in a conservative way: low protein diet and dialysis, since the uremic toxicity derived from protein metabolism contributes to the pathophysiology. These measures can alleviate the symptoms of the disease[4, 10-12]

Once these symptoms are present, they are considered a good clinical marker of the need to start with -or increase- dialysis therapy before they contribute significantly to malnutrition, since it is a poor prognostic factor in morbidity and mortality among patients[12,13]. If symptoms do not subside after initiation of substitution therapy, it is necessary to consider other possible causes, such as side effects of medications (more frequent) or anxiety disorders, depression or inter-current processes.

If the technique is peritoneal dialysis, anorexia and inappetence may be due to sensation of abdominal fullness, caused by dialysis fluid or by absorption of glucose through the peritoneum[1,12].

Diseases of the oropharynx: in some cases may exceed 90%, being more common hyperpigmentation of the lips. Stomatitis, gingivitis and mumps may accompany the uremic syndrome, but their frequency has decreased due to better renal replacement therapy. These lesions may be accompanied by fungal super infection, mainly in immune compromised patients[14,15]. Oral hygiene is an essential pillar of the treatment if present[16].

Diseases of the digestive tract

Esophagitis: is present in more than a third of the cases of uremic patients. The prevalence of dialysis patients is similar to that of patients who do not receive it. For the first, it is favored by the increase of intra-abdominal pressure, favoring reflux. The treatment of these patients is not different from that given to the general population with proton pump inhibitors, once the endoscopic study has been done[4,17].

Gastroparesis: usually associated with uremia, if symptoms persist. It usually manifests due to the appearance of autonomic neuropathy, especially in diabetic patients. It is a frequent cause of malnutrition. Symptoms improve when better control of the underlying disease is practiced, as well as with the use of a certain group of drugs such as prokinetics: metoclopramide and domperidone[1,7].

Gallbladder: Bile reflux is found in 19% of patients on hemodialysis and contributes to erosion of the gastric mucosa. There appears to be a similar incidence of cholelithiasis and cholecystitis in patients on hemodialysis than in the general population. After surgical management, the outcomes are similar, if the recommendations indicated for this population are followed[18, 19].

Gastritis: Helicobacter pylori are associated with significant urease activity, with no significant statistical difference, compared to non-dialyzed patients. In addition to the conventional treatment of infection, strict diet control is also required, especially low in phosphorus. In patients with CKD, serum levels of gastrin are increased by increased secretion (which correlates directly with the degree of renal failure), as it is eliminated by the kidney; additionally, cholecystokinin and secretin may be elevated[20-22]. Noninvasive tests (H. pylori) have lower sensitivity in CKD[23].

Peptic ulcer: is prevalent similar to that of the general population, with two associated factors: helicobacteriosis and consumption of NSAIDs. The deterioration in renal function has not been shown to be sufficient to increase the risk of peptic ulcer[24].

Angiodysplasia: affects the microcirculation of the mucosa and sub mucosa of the entire gastrointestinal tract. It is a frequent cause of bleeding in elderly patients, and its incidence is increased in patients on dialysis. For the diagnosis it is necessary the endoscopic study, as well as for the treatment with hemostasis techniques. The other option is angiography and then selective embolization, or estrogen therapy[25, 26].

Constipation: it is more common in patients with dialysis therapy; the condition is favored by a diet low in liquids and fibers, sedentary lifestyle and, in some cases, by the use of phosphorus binders. For treatment, initially dietary measures should be tried, a rational use of chelators, and if it does not resolve constipation, will require the use of laxatives. In this case, osmotic laxatives such as lactulose are of choice. The use of enemas containing phosphorus or magnesium salts should be avoided because of the risk of hyperphosphatemia and hypermagnesemia[27].

Diverticular disease: may develop at an early age, with more severe clinical manifestations than in the general population, or as a complication of constipation. It is a relative contraindication for peritoneal dialysis, given the risk of fecaloid peritonitis. Patients are often complicated with inflammation or perforation, and those who are on transplant waiting lists are especially careful. Its incidence is similar to that of the general population, except in patients with polycystic kidney disease, in whom the incidence is higher[28, 29]. On the other hand, Chang et al.[30], suggest that patients with chronic kidney disease are at higher risk for acute diverticulitis.

Uremic colitis: in the uremic patient, edema of the mucosa, of the sub mucosa, and ulcerations and areas of hemorrhage are generated, with formation of pseudo membranes. However, with

the improvement in renal replacement therapy techniques, its incidence is very low[31, 32].

Perforation of the colon: has a higher incidence in patients on hemodialysis, with an approximate mortality of 70%. Its frequency depends on the underlying cause: adynamic ileus pseudo-obstruction, fecal impaction, dehydration, barium enemas, diverticulitis, amyloidosis, and perforation of colonic ulcer or antacids containing aluminum. In some cases the peritoneal catheter causes necrosis due to the pressure exerted on the intestinal wall and in patients receiving kayexalate can cause necrosis of the colon, especially when used as an enema, together with sorbitol. Its management is usually surgical and poor prognosis[33, 34].

Intestinal ischemia: presents high mortality, increased risk for atheromatosis, hypotension and low cardiac output; his clinic is non-specific, and includes abdominal pain, fever, diarrhea, leukocytosis, and sometimes bleeding. In this group of patients, it is important to avoid precipitating factors, such as excessive ultrafiltration in hemodialysis, falls in cardiac output, vasoconstrictor medications, digoxin or abrupt increases in hematocrit. If the ischemia lasts less than 6 hours, it could be attenuated by means of an angiographic catheter or through the use of vasodilator drugs (prostaglandin agonists or calcium antagonists), and if prolonged, the management is converted to surgery[35].

Ischemic colitis: is characterized by multiple ischemic ulcers, due to hemorrhage in the sub mucosa with adherent pseudo-membrane appearance. Risk factors include small vessel pathologies such as arteriolar hyalinosis, vascular calcifications, vasculitis, amyloidosis, and hypercoagulability states. Usually patients complain of abdominal pain, intense vomiting and fever, usually accompanied by a systemic inflammatory response. It's difficult and delayed diagnosis, in addition to the morbidity of the underlying disease, makes of this complication pathology of bad prognosis and usually of surgical management[36, 37].

Digestive bleeding: The risk of gastrointestinal bleeding in this group of patients is increased by platelet dysfunction associated with uremia, intermittent use of heparin, and an increase in the incidence of gastric, duodenal, esophageal, and Angiodysplasia[38] ulcers. Jutabha and Jensen[39], in a prospective series of 1000 cases of upper gastrointestinal bleeding, reported the following distribution of causes: peptic ulcer, 55%; Esophagogastric varices 14%; Arteriovenous malformation (angiodysplasia), 6%; Mallory-Weiss tears, 5%; Tumors and erosions, 4%; Dieulafoy's injury, 1%; Others, 11%. The evaluation and treatment of patients with upper gastrointestinal bleeding is similar to those with and without end-stage renal disease. Regardless of the underlying cause of bleeding, efforts should be made in this population to reverse the underlying observed abnormalities. In this case, it is necessary to correct the defect of platelet aggregation with dialysis, transfusions, erythropoietin - in case of anemia - and desmopressin[40].

Diseases of the pancreas and the bile duct:

Pancreatitis: the etiology is similar to that of the general population. These types of patients predispose them to alcohol abuse, hypercalcemia, immunosuppression and hypertriglyceridemia. In patients with peritoneal dialysis, it is necessary to make a differential diagnosis with bacterial peritonitis, a condition that has a similar clinic, in which the appearance of the replacement fluids may be clear or hemorrhagic. For the diagnosis of pancreatitis, a high serum amylase concentration is required three times the upper limit of normal and the measurement of amylase in peritoneal fluid with a value greater than 100 U[41]. The principles of management of dialysis-associated pancreatitis, particularly among patients undergoing hemodialysis, do not differ from those without renal failure. Therefore, the treatment of acute pancreatitis is aimed at correcting any underlying

predisposition factor and pancreatic inflammation itself. Among peritoneal dialysis patients there is no evidence that interruption of dialysis is absolutely necessary in all patients with acute pancreatitis. Thus, the overall prognosis is probably not altered upon discontinuation of peritoneal dialysis[42].

Cholelithiasis: The formation of stones can be due to biliary hyper-secretion, the formation of defective mycelia, the presence of biliary mud or a disorder of calcium metabolism. Its clinic is equal to that of the general population[19].

Ascites associated with dialysis: the diagnosis of cirrhosis should be excluded; is characterized by being resistant, with no evident cause, edema, cachexia and hypotension. Ascitic fluid has exudate characteristics with high protein content (from 3 to 6 gr.), which must be differentiated from a neoplastic or tuberculous ascites. The pathophysiology is poorly understood and 69% of the cases present a history of peritoneal dialysis; 45% of cases die in the first 15 months. Treatment should improve nutritional status, salt restriction, increase ultrafiltration and paracentesis, and even consider the technique of renal replacement. However, their response to treatment remains poor. In these cases the transplant is considered a good therapeutic option to solve the problem in the short term[43, 44].

There are also complications due to the diseases that led to kidney failure. In the case of polycystic kidney disease, diverticulosis, hiatal hernia, dilatation of the biliary tract, hepatic and pancreatic cysts are often seen. Diabetes, with gastro-paresis, diarrhea, atheromatosis, intestinal ischemia and intestinal embolism, vasculitis with digestive bleeding[45, 46], as well as other systemic diseases that can cause renal and gastrointestinal damage, are not related (Table 2). Complications related to the technique of peritoneal dialysis include reflux oesophagitis, hernias, and bowel erosion by catheter pressure, sclerosing peritonitis, and pancreatitis. Complications related to hemodialysis include nausea, vomiting, anxiety, hunger, intestinal ischemia due to hypotension, digestive bleeding from heparin and pancreatitis induced by accidental hemolysis[11, 47, 48].

Gastrointestinal manifestations in renal transplantation

After renal transplantation gastrointestinal manifestations are common (about 20% of the cases), generating morbidity in these patients. Some of the manifestations follow post-immunosuppressive therapy (especially mycophenolate mofetil and steroids), while others are directly related to pre-transplant gastrointestinal morbidity, antibiotic use or infections. The most common clinical manifestations are nonspecific: nausea, vomiting and abdominal pain; however, esophageal infections by candida, herpes or cytomegalovirus, ulcerous peptic disease, diarrhea and perforation in the colon or digestive bleeding have also been described. Prior to the screening for helicobacteriosis, gastritis and peptic ulcer were present in 4% of patients. However, with conventional therapy there is adequate control over pathology. The most frequent cause of diarrhea in these patients is viral gastroenteritis, self-limiting in patients with immunodepression, especially with mycophenolate. Pseudomembranous colitis can occur in up to 50% of patients receiving antibiotics or other bacteria and parasites. In elderly transplanted patients and in those with polycystic kidney disease, the frequency of cecal ulcerations, diverticular disease, and vascular insufficiency is increased. Finally, the gastrointestinal tract is also a site of onset of post-transplant lymph proliferative disorders[49-50].

Table 2.
Diseases with renal and gastrointestinal involvement

Location	Symptom
Diabetes	Stomatitis, gingivitis, mumps
Multiple myeloma	Esophagitis, gastro-esophageal reflux, biliary reflux, gastritis, duodenitis, peptic ulcer, angiodysplasias and digestive bleeding.
Hyperparathyroidism	Constipation, diverticular disease, ischemic colitis, uremic colitis, perforation of the colon, angiodysplasias and digestive bleeding
Purpura Henoch-Schonlein	Hematuria, proteinuria, hypertension -from nausea, vomiting, abdominal pain, paralytic ileus to gastrointestinal hemorrhages-, intestinal ischemia and necrosis, intestinal invagination, intestinal perforation.
Diseases of vascular collagen	Scleroderma-vasculitis.

Source: own elaborationa.

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Ethical Responsibilities

Protection of people and animals

The authors state that no human or animal experiments have been performed for this research.

Confidentiality of data

The authors state that no patient data appears in this article.

Right to privacy and informed consent

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Interest conflict

The authors declare no conflict of interest.

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