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Exceptional Case

EXCEPTIONAL CASE

Gastrointestinal complications induced by sevelamer crystals

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Abstract

Background: Sevelamer is a phosphate binder widely used in chronic kidney disease (CKD) patients. Sevelamer, as well as other resin-based binders, can crystallize leading to the formation of concretions. Sevelamer crystals (SC) have been associated with gastrointestinal (GI) mucosal injury. We describe three new cases of GI lesions associated with SC and review previously reported cases.

Methods: We describe three new cases of GI lesions associated with SC and review previously reported cases.

Results: We found 16 previously reported cases of SC-induced GI lesions. The mean patient age was 61 years (interquartile range 51.5–71.75), 62.5% were females and 10 patients were diabetic. In 13 cases, SC was found inside the GI mucosa. Six patients had history of major abdominal surgery. GI bleeding was the most common clinical symptom ($n = 7$), with three patients presenting with acute abdomen requiring surgical intervention. Although, SC-induced lesions were observed in all GI segments, intestine was involved in 81% of the cases. Endoscopic examination revealed mainly erosions and ulcerations ($n = 7$) and pseudoinflammatory polyps ($n = 5$). No association between sevelamer doses and the severity of GI lesions was found. However, diabetics patients seemed to develop GI lesions with smaller doses of sevelamer as compared with non-diabetic patients, in spite of their fewer GI comorbidities.

Conclusions: SC-induced GI lesions should be considered in CKD patients treated with sevelamer who present GI symptoms, especially lower GI bleeding, once other causes have been ruled out. Diabetics seem more prone to develop SC-associated GI lesions. Sevelamer therapy should be avoided if possible in patients with a history of major abdominal surgery or chronic constipation, because of the high risk of serious GI complications.

Key words: chronic kidney disease, crystals, gastrointestinal lesions, hyperphosphataemia, sevelamer

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Introduction

Treatment of hyperphosphataemia is critical in chronic kidney disease (CKD) patients, given its well-known association with vascular calcification [1], endothelial damage [2] and increased mortality [3]. Phosphate binders, widely used to decrease oral phosphate absorption, are the mainstay of treatment.

Sevelamer is a calcium free phosphate binder that circumvents the positive calcium balance induced by calcium-based binders (CBBs), which is associated with increased mortality in CKD patients [4]. In addition it has been suggested that sevelamer has other beneficial pleiotropic effects [5]. Sevelamer is a non-absorbable resin able to bind the phosphate in the gastrointestinal (GI) tract. It is, however, commonly associated with GI symptoms such as vomiting, nausea, diarrhoea, dyspepsia, abdominal pain and flatulence [6]. In addition, sevelamer may cause or worsen constipation, leading in some cases to faecal impaction [7, 8] and more severe GI complications; therefore, it is contraindicated in patients with bowel obstruction [6].

Sevelamer, as well as other resins, can crystallize in the GI tract, leading to the formation of concretions. Swanson *et al.* [9] described sevelamer crystals (SC) for the first time in 2013, as rusty yellow-brownish crystals with a characteristic "fish scale" pattern, embedded inside an eroded or ulcerated GI tract mucosa in CKD patients. They also reproduced identical crystals *ex vivo* after crushing a sevelamer tablet and histologically processing it [9]. Since Swanson's report, 5 additional cases have been reported [10–13]. Nevertheless, this sevelamer side effect remains unrecognized by many nephrologists, partly due to the fact that only one of these publications appeared in a renal journal [13].

Here we describe 3 cases of Sevelamer crystals-associated GI injury and a present review of the published data about this complication. Our aim is to characterize the GI lesions induced by sevelamer, identify the risk factors for their appearance and provide clinical guidance for their proper diagnosis and treatment.

Results

Case 1

A 51-year-old diabetic woman with end-stage renal disease (ESRD) due to polycystic kidney disease presented to the emergency department with weakness and intermittent painful haematochezia over the previous 2 weeks. She had a long-standing CKD history, including a renal transplant 9 years previously and peritoneal dialysis for the last 5 years. She had severe CKD–mineral and bone disorder (CKD–MBD) that had required a previous parathyroidectomy and was on a high dose of phosphate binders (lanthanum carbonate 3 g/day plus sevelamer carbonate 4.8 g/day and sevelamer hydrochloride 4 g/day). On admission, her rectal examination revealed a big anal fissure secondary to an internal haemorrhoid as well as melena. The laboratory evaluation revealed a haemoglobin of 6.7 g/dL. Endoscopic investigation found multiple erosions along the GI tract (oesophagus, stomach, duodenum, and colon). Biopsies of the lesions were taken for histological examination, which showed non-specific inflammatory changes. Bowel inflammatory disease, in particular Crohn's disease, was ruled out. The anal fissure progressively resolved with conservative management, and a parallel improvement in haemoglobin levels was observed. During the following months, anaemia worsened again, requiring high doses of erythropoietin stimulating agents and weekly intravenous iron supplementation. Blood was found again on stool examination. A colonoscopy revealed a large ulcer in the ileocecal valve. On histology, the ulcer consisted of focal erosion with bacterial material mixed with SC (Figure 1A and B). She was on proton pump inhibitors and denied the use of non-steroidal anti-inflammatory drugs. She was given a 14 days course of metronidazole and her sevelamer binders (both sevelamer carbonate and sevelamer hydrochloride) were switched to calcium carbonate. In the following weeks, an improvement in haemoglobin levels (from 9.1 mg/dL to 11.1 mg/dL) was observed and no blood was found on the next stool examination.

Case 2

A 53-year-old male with ESRD due to crescentic glomerulonephritis presented with intermittent painless rectal bleeding of 3 months duration. His past medical history included a renal transplant 21 years previously and haemodialysis over the past 6 years. A sigmoidectomy had been performed 3 years earlier because of sigmoid perforation. He was being treated for severe calciphylaxis of the legs and arms with sodium thiosulfate, bisphosphonates, dialysis intensification, vitamin K and phosphate binders (sevelamer hydrochloride 8 g/day). A colonoscopy revealed multiple lesions in the colon, suggestive of regenerative pseudopolyps and inflammation. Histological examination showed chronic colitis with low inflammatory activity. No specific treatment was given. During the following year intermittent rectal bleeding persisted and repeated endoscopic examinations showed inflammatory polyps (Figure 2) in the stomach and colon accompanied by colonic diverticulosis. Microscope examination of a lesion in the ileocecal valve revealed a pseudoinflammatory polyp with fibrotic mucosal changes and foreign body reaction, to yellowish-red crystals embedded into submucosal fibro-histiocytic areas [haematoxylin & eosin (H&E) staining] (Figure 1C and D). Intestinal calciphylaxis was ruled out on the basis of the histological findings and the clinical presentation, and a CT scan revealed just mild vascular calcification. At that point, the aetiology of GI bleeding was not pursued because the crystals were uncharacterized, and the patient improved to some extent with conservative treatment, proton pump inhibitors (titrating the dose as needed) and reducing haemodialysis anticoagulation. Eight months later, the crystals seen in the ileocecal biopsy were categorized as SC. In view of his reasonable GI evolution and the diagnosis of calciphylaxis, the sevelamer dose was reduced. This was followed by an improvement in the patient's clinical condition, cessation of rectal bleeding and a significant increase in haemoglobin levels.

Case 3

A 76-year-old woman with ESRD secondary to diabetic nephropathy on haemodialysis for more than 1.5 years was investigated for intermittent low GI bleeding and severe anaemia. Her medical history included other comorbidities such as diabetes mellitus, obesity, refractory hypertension and Chronic obstructive pulmonary disease. She was known to have CKD-MBD treated with sevelamer. Endoscopic examination revealed chronic gastritis, diverticulosis and several gastric and colonic polyps. Superficial erosions were found that were initially attributed to non-steroidal anti-inflammatory drugs. However, her GI bleeding persisted after the discontinuation of these drugs until the patient received a kidney transplant. The GI bleeding

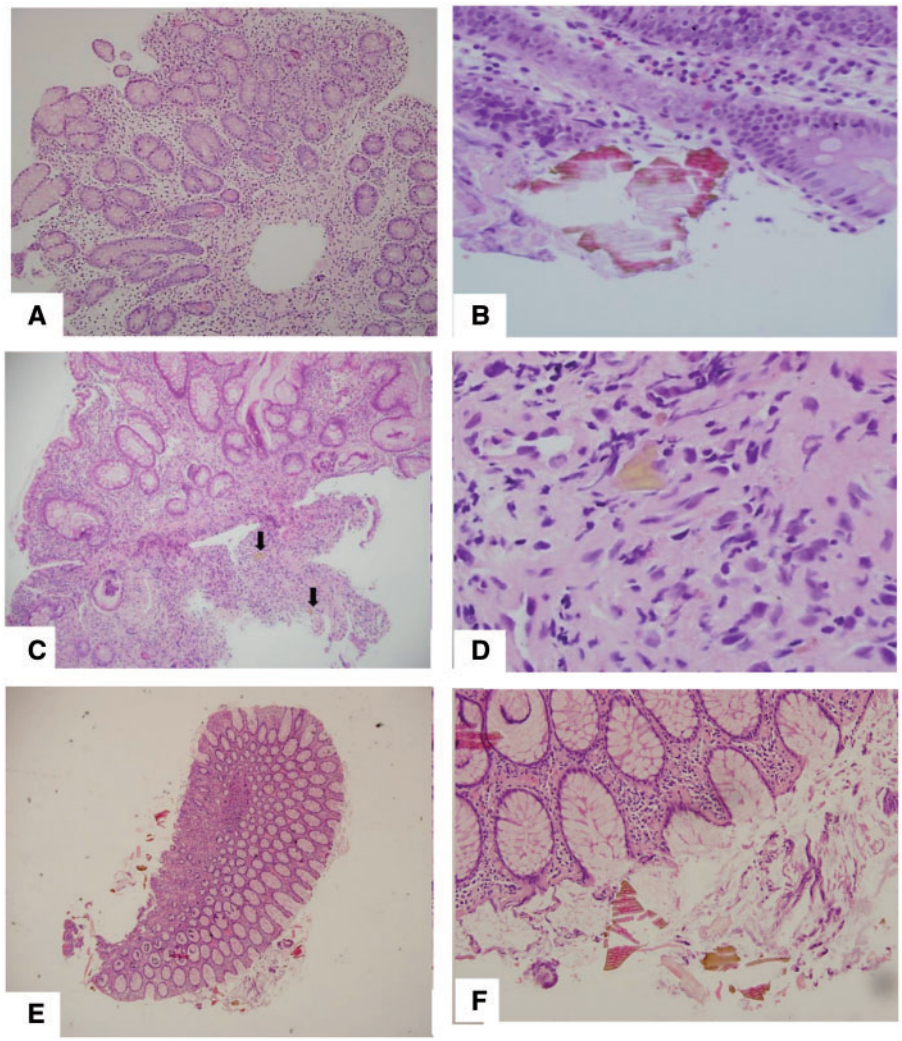

Fig. 1. Characteristic histological features of SC from three distinct cases. (A) and (B) are from colorectal mucosa of Case 1. (**A**) Architectural distortion showing active chronic colitis. H&E magnification 100×. (**B**) Characteristic SC, shaded with two-toned reddish/yellow and linear accentuations close to areas of erosion and bacteria. H&E magnification 400×. (C) and (D) are from Case 2. (**C**) Polipoid colorectal mucosa with features of chronic colitis showing crypts distortion and fibrosis. SC can be found in areas of fibrosis (arrows). H&E magnification 200×. (**D**) SC around fibrosis areas with 'fish scale pattern on a yellow background'. H&E magnification 200×. (E) and (F) are from Case 3. (**E**) Colorectal mucosa without erosions showing superficial SC. H&E magnification 100×. (**F**) High power view of mucosa showing SC surrounded by mucous and detritus without any erosions or inflammation. Distinctive pink-yellow stripes on SC. H&E magnification 100×.

disappearance clearly coincided with sevelamer discontinuation and not with renal function improvement, since she had delayed graft function after transplantation. Histological material was re-examined and superficial SC crystals were found surrounded by mucous and detritus (Figure 1E and F).

Summary of the previously reported Sevelamer-crystals induced GI lesions

We examined the previously reported cases of sevelamer induced GI lesions ($n = 13$) [7, 9–13], in addition to our cases ($n = 3$). Demographic and clinical characteristics are summarized in Table 1. Mean age was 61 years (interquartile range 51.5–71.75) with a female predominance (62.5%) and a high percentage of diabetics ($n = 10$). All the patients had chronic kidney disease, 8 patients were on haemodialysis, 3 on peritoneal dialysis, and 5 non-dialysis CKD. Two patients were on anticoagulant drugs, whereas 2 others were receiving antiplatelet therapy. Ten patients were on sevelamer carbonate, 4 on sevelamer hydrochloride, and 1 on both. The mean sevelamer dose was 4.8 g/day (Table 1).

Three patients had previous GI disease, namely, dyspepsia ($n = 2$) and ulcerative colitis ($n = 1$). Six patients had undergone major abdominal surgery: colostomy ($n = 2$), colon resection ($n = 1$), supraadrenalectomy ($n = 1$), hysterectomy and oophorectomy ($n = 1$) and orthotopic liver transplant ($n = 1$).

The most frequent clinical presentation was GI bleeding (44% of the cases), followed by acute abdomen and GI discomfort (19% each); 3 patients were asymptomatic. SC lesions were observed in all the GI segments. Ascending/descending colon was affected in 8 patients, whereas the small intestine was affected in 37% of cases ($n = 6$), the oesophagus in 25% ($n = 4$), the stomach in 18.8% ($n = 3$), and sigmoid colon and rectum in 12.5% each. In four patients there was more than one GI segment affected.

Endoscopical examination was performed in 13 patients. Ulcerations and erosions were observed in 7 patients, followed by inflammatory polyps ($n = 5$) and peptic changes ($n = 4$). The main histological lesions described were ulcerations in 9 patients,

necrosis in 6 patients and acute inflammation in 5 patients, followed by ischaemic injury ($n = 3$) and inflammatory polyp ($n = 3$).

SC were found in all the cases, except in the case reported by Madan *et al.* [7]. SC were usually found inside GI mucosa ($n = 13$).

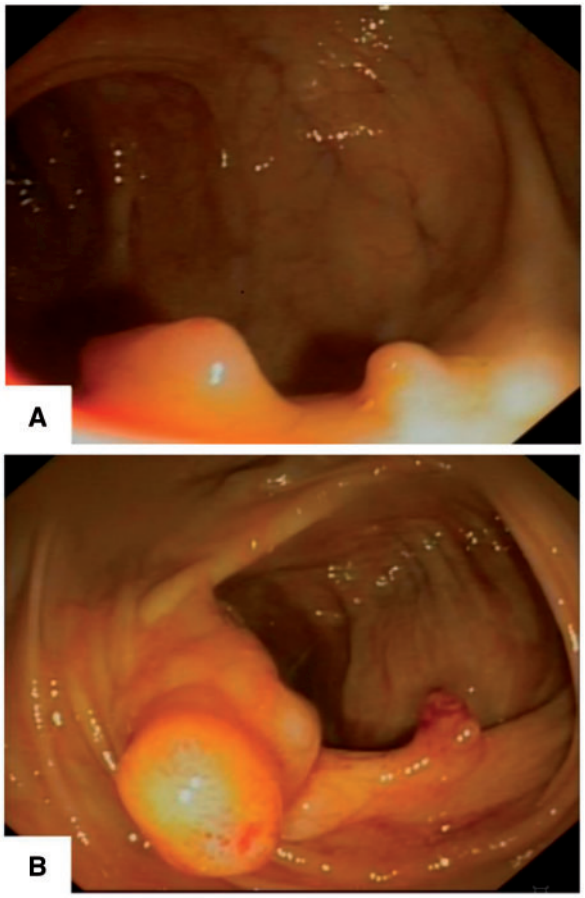

Fig. 2. Endoscopical images showing pseudoinflammatory polyps belonging to Case 2.

In two cases, the detection of SC coincided with a GI infection, one of them caused by *Clostridium difficile*.

Three patients required surgical intervention due to incarcerated hernia ($n = 1$) and colonic perforation ($n = 2$). In all those cases, SC were described around the eroded mucosae on the resected GI tract [9, 12, 13]. Sevelamer faecoliths were observed in two cases [7, 13] and in the case reported by Kim *et al.* it resulted in colonic perforation[13].

We did not find any association between sevelamer dose and the quantity or severity of GI lesions. Similarly, no association was found between sevelamer presentation (powder or chewable) or anion content (carbonate or hydrochloride).

We noted a high prevalence of diabetics (62.5%) in the cohort. Diabetics seem to develop SC-associated GI lesions with a smaller dose compared with non-diabetic (non-DM) patients [4.8 (interquartile range 2.1, 4.8) vs 7.2 (3.4, 8.1) g/day respectively], in spite of their fewer prior abdominal surgeries (two DM vs four non-DM), although the differences were not significant.

Discussion

Sevelamer is a widely used phosphate binder, recently recommended by the KDIGO guidelines [14] in order to reduce the calcium positive imbalance produced by CBBs in CKD patients. In addition, several researchers have suggested that sevelamer could have pleiotropic effects, such as improvement in cholesterol levels [15], reduction of pro-inflammatory mediators [16] and some uraemic toxins like *p*-cresol [17], and even decreasing haemoglobin A1c and advanced glycation end products [18]. Sevelamer is a polymeric anion exchange resin, usually well tolerated, although occasionally it can cause minor GI symptoms, such as vomiting, nausea and flatulence [6]. In common with other resins, it can cause or worsen constipation [8], therefore it is contraindicated in patients with bowel obstruction [6]. Sevelamer is composed of a carbon polymer backbone within a non-absorbable hydrogel containing ammonia that can be formulated as carbonate (Renvela®) or hydrochloride (Renagel®). Sevelamer is dissociated by the acidic milieu in the stomach, releasing the polymer that binds phosphate within the

Table 1. Brief summary of previous reports of GI lesions induced by SC

Author [Reference]	Year of publication		Age (years)	Male gender (Yes)	DM (Yes)	Sevelamer		SC inside mucosa
						Kind (Yes)	Dose (g/day)	
Madan *et al.* [7]	2008	Case 1	61	0	1	NA	NA	0
Swanson *et al.* [9]	2013	Case 1	59	0	1	1	9.6	1
		Case 2	68	1	1	1	4.8	1
		Case 3	38	1	0	1	4.8	1
		Case 4	49	0	0	1	7.2	1
		Case 5	53	1	1	1	2.4	1
		Case 6	66	1	0	1	NA	1
		Case 7	81	1	1	1	4.8	1
Chintamaneni *et al.* [10]	2014	Case 1	61	0	0	0	7.2	1
Ortiz-Ruiz *et al.* [12]	2015	Case 1	62	0	1	1	NA	1
		Case 2	73	0	1	1	NA	1
Kim *et al.* [13]	2016	Case 1	17	0	0	0	2.1	0
Tieu *et al.* [11]	2016	Case 1	74	0	1	1	4.8	1
Yuste *et al.* (present article)	2017	Case 1	51	0	1	0 + 1	3.2	1
		Case 2	53	1	0	0	9	1
		Case 3	76	0	1	0	0.8	0
Median (IQR) or number (%)			61 (51.5, 71.75)	6 (37.5%)	10 (62.5%)	11 (68.8%)	4.8 (2.4, 7.2)	

Data are expressed as the total number or the median and interquartile range (IQR), or as the total number and percentage. NA: not available. Sevelamer kind (yes): sevelamer carbonate.

Table 2. Differences between resins crystals

	Sevelamer	Polystyrene sulfonate	Cholestyramine
Endoscopic findings	GI erosions and ulcerations, pseudoinflammatory polyps, bezoar	GI erosions and ulcerations, polyps, bezoar	Unspecific GI erosions and ulcerations
Lesions location	Preferably in colon, but could affect all the segments	Upper and lower GI tract	Upper GI tract
Histological findings			
Crystals location	Inside mucosa or around epithelium surface	Adhered to the epithelium surface or around inflammatory exudates	
Shape	Irregular	Rhomboidal or triangular	
Mosaic pattern	Yes, broad and curved 'fish scale'	Yes, narrow 'fish scale' due to perpendicular lines of intersection	No, sometimes with irregular 'cracking' lines
Polarized	Non-polarized	Non-polarized	–
H&E stain	Two-toned colour imparted by bright pink linear accentuations with a rusty yellow background	Violet	Bright orange
PAS/D stain	Violet	Magenta	Grey or hot pink

intestine, producing phosphate crystalline concretions that are excreted in the faeces.

Although the first description of sevelamer inducing a GI lesion was reported in 2008 by Madan *et al.* [7], it was Swanson and co-workers that provided the first proper description of SC observed in the largest cohort so far published ($n = 8$) [9]. Moreover, Swanson *et al.* reproduced *ex vivo* SC, confirming their histological findings. SC are non-polarized crystals, with a distinctive fish scale pattern violet with periodic acid-Schiff (PAS)-Alcian special staining and 2-toned colour yellowish/brownish with H&E (Table 2). SC has been reported in patients treated with all sevelamer formulations (carbonate and hydrochloride) and presentations (powder or chewable). We could not find any association between sevelamer dose and the quantity or severity of the GI lesions.

The clinical expression of SC induced GI injury can range from abdominal discomfort to acute abdomen, with lower GI bleeding being the most common presentation. More frequent and aggressive injuries seem to be reported among patients with previous major surgeries or chronic constipation. It seems reasonable that delayed GI emptying could promote bigger and more frequent sevelamer crystalline concretions, causing more severe injuries. Similarly, diabetics seem to be more prone to SC-induced GI damage and with smaller sevelamer doses as compared with non-diabetics. Diabetic GI involvement frequently induces oesophageal dysmotility, gastroparesis and enteropathy [19] that could predispose to SC deposition. This upper GI impairment could explain the more frequent upper GI injuries observed among diabetics.

Importantly, some patients with histologically proven mucosal injury induced by SC remain asymptomatic or with minor manifestations. Swanson *et al.* found SC among 3 asymptomatic patients undergoing routine endoscopical examination. In 2 of their 3 asymptomatic patients, endoscopical lesions were reported [9]. Likewise, we observed slight clinical manifestations among our Cases 1 and 2, where the persistence of GI bleeding was suspected because of resistant anaemia with unsatisfactory response to iron supplementation and high doses of erythropoietin stimulating agents requirement.

GI lesions induced by SC were considered initially as restricted to the lower GI tract, especially the colon. However, later reports showed that SC-related lesions can involve the whole GI tract, and in 25% of the patients more than one GI segment is affected. However, larger studies about sevelamer-induced GI lesions are necessary to determine the GI segment more commonly involved. Endoscopic findings include erosions, ulcerations and pseudoinflammatory polyps. It is thought that to cause these lesions, SC should be deposited on the GI mucosa and then trapped and embedded within it, causing a foreign body reaction that could evolve into pseudoinflammatory polyp or an open wound in the case of ulcerations. Moreover, similar to polystyrene sulfonate (PS) crystals [20], SC could crystallize massively forming a faecolith leading to faecal impaction [7, 13]. Interestingly, it has been reported that injuries induced by other resins, like PS and colesthyramine, are reversible after resin withdrawal. Although no endoscopic confirmation was available, the improvement in serum haemoglobin levels (our Cases 1 and 2) and the absence of blood in stool examination after sevelamer withdrawal (our Case 1) would suggest a similar reversibility of the damage caused by sevelamer.

CKD is associated with upper GI dysmotility and abnormal digestive secretion and absorption [21], abnormalities that may potentially predispose to sevelamer crystallization. Besides, sevelamer is also able to bind bile acids in the intestinal tract [22], further reducing digestive secretions.

SC should be differentiated from other resin crystalline concretions able to induce GI tract injuries [20]. Polystyrene sulfonate crystals (PSC), like SC, are non-polarizable crystals with a "fish scale" pattern [20]. However, PSC can be differentiated from SC with stain [violet colour with H&E, and magenta with PASdiastase (PAS/D)] [9], as well as, its perpendicular intersecting lines in the mosaic pattern (Table 2). Cholestyramine crystals (CC) are easily distinguished due to the absence of CC mosaic pattern [20] (Table 2).

Our study is just a case series, so we are unable to distinguish the causes and consequences of the association between GI lesions and SC. Similarly, we cannot exclude other possible or enhancing causes of GI injuries. Therefore, although a mere coincidental SC deposition on a previously damaged area is a possibility, the foreign body reaction observed around SC strongly suggests causality.

Although the number of reported cases (16, including our 3 cases) is small, the real incidence of SC-induced GI complications could be higher. Future studies analysing the presence of SC in GI lesions of patients with CKD treated with sevelamer, and the influence of sevelamer discontinuation (or lowering doses) in patients with GI complications, could provide relevant

data on this subject and rule out other causes. GI lesions induced by SC should be considered in CKD patients receiving this drug who present with GI symptoms, especially lower GI bleeding, once other causes have been reasonably ruled out. Diabetics treated with sevelamer seem to be more prone to these lesions. Sevelamer therapy among patients with major abdominal surgeries or chronic constipation should be preferably avoided, due to the high risk of serious GI complications such as faecal impaction. SC could be a hidden cause of resistant anaemia among CKD patients through asymptomatic GI blood losses.

Conflict of interest statement

None declared.

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