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The Impact of GLP-1 Receptor Agonists on Ulcerative Colitis Patients – Following Restorative Ileal Pouch Anal Anastomosis

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Abstract: Background: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are increasingly used for obesity and metabolic disease and may exert anti-inflammatory effects in inflammatory bowel disease. However, their effects on gastrointestinal motility may have distinct implications in patients with surgically altered intestinal anatomy. We evaluated the temporal relationship between recent GLP-1RA initiation and pouchitis in patients with a prior restorative ileal pouch–anal anastomosis (IPAA). Methods: We retrospectively reviewed patients with a history of total proctocolectomy and restorative IPAA who were admitted with pouchitis between January 2016 and January 2026 and had initiated GLP-1RA therapy within the preceding 6 weeks. Demographic characteristics, body mass index (BMI), and clinical features were descriptively evaluated. Results: Six patients met inclusion criteria, including three men and three women. The mean age was 37 years (range, 27–49 years), and the mean BMI was 40.2 kg/m^2. All patients had recently initiated GLP-1RA therapy before admission for pouchitis. The temporal association between GLP-1RA exposure and the development of pouch-related symptoms raises the possibility of an association between altered gastrointestinal transit and pouch inflammation. Discussion: Although GLP-1RAs may exert beneficial anti-inflammatory effects, pharmacologically mediated gastrointestinal hypomotility may have opposing consequences in patients with an ileal pouch. Altered transit, luminal stasis, and changes in the pouch microbial environment may contribute to mucosal inflammation. Further investigation is warranted to clarify the relationship between GLP-1RA therapy, intestinal motility, and pouchitis.

CASE PRESENTATION

We present the case of a 48-year-old man admitted with progressive abdominal pain localized primarily to the suprapubic region. His vital signs were notable for sinus tachycardia, with a heart rate ranging from 105 to 112 beats per minute; otherwise, he remained hemodynamically stable. Laboratory evaluation demonstrated mild leukocytosis, with a white blood cell count of 12.54 k/μL. His serum creatinine had increased from a baseline of 1.02 mg/dL to 1.42 mg/dL. On physical examination, the abdomen was mildly distended with localized suprapubic tenderness. There was no guarding, rigidity, or rebound

tenderness. Computed tomography (CT) of the abdomen and pelvis demonstrated postsurgical changes consistent with prior total colectomy and restorative ileal pouch–anal anastomosis (IPAA). The distal small bowel was dilated and contained multiple air-fluid levels, with a possible transition point as the small bowel entered the pelvis immediately proximal to the ileal pouch. These findings raised concern for a possible mechanical small bowel obstruction.

The patient's medical history was significant for ulcerative colitis (UC), for which he had undergone total proctocolectomy with restorative IPAA more than 20 years previously. He had no other significant medical comorbidities. His only medication was semaglutide, which had been initiated approximately 3 weeks before presentation.

A presumptive diagnosis of pouchitis was initially made, and the patient was started on metronidazole. His prior history was notable for only a single episode of pouchitis, which had occurred more than 10 years earlier and had been successfully managed nonoperatively.

Metronidazole 500 mg every 8 hours was initiated promptly. Within 48 hours, the patient's clinical condition improved significantly. His abdominal distension resolved, and he began passing flatus. His diet was subsequently advanced and was well tolerated. The leukocytosis resolved, serum creatinine returned to baseline, and the sinus tachycardia resolved. The patient was discharged home in stable condition.

BACKGROUND

Ulcerative colitis (UC) affects approximately 2 million individuals worldwide and represents one of the major inflammatory bowel disease (IBD) phenotypes. The disease is characterized by chronic mucosal inflammation and ulceration involving the colon and rectum. Clinical manifestations may include increased stool frequency, urgency, tenesmus, fecal incontinence, seepage, rectal bleeding, and abdominal or pelvic pain.[1] In patients with prolonged or recurrent pouchitis, the risk of dysplasia and neoplasia may be increased. Although advances in medical therapy have substantially improved disease control and enabled many patients to achieve prolonged remission, medically refractory disease may ultimately require surgical intervention. Total proctocolectomy is generally considered curative for the colonic manifestations of UC.

Restorative ileal pouch–anal anastomosis (IPAA) permits restoration of intestinal continuity following proctocolectomy. The ileal pouch functions as a neorectal reservoir through which intestinal contents pass before evacuation through the anal canal. However, the pouch is susceptible to inflammatory complications, most notably pouchitis. Pouchitis has been reported in approximately 10%–20% of patients with an ileal pouch. Clinical manifestations may include increased stool frequency, urgency, tenesmus, rectal bleeding, abdominal discomfort, and pelvic pain, often resembling the symptoms of the patient's original UC flare. Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have experienced a substantial increase in clinical use, particularly in the management of obesity and metabolic disease. Although GLP-1 receptor agonists have demonstrated substantial benefits across the broader population, their effects on the ileal pouch reservoir in patients with restorative IPAA remain incompletely understood. We therefore sought to evaluate the potential impact of GLP-1 receptor agonist therapy on the ileal pouch in this patient population.

METHODS

We performed a retrospective review of patients with a history of total proctocolectomy and restorative ileal pouch–anal anastomosis (IPAA) who were admitted with a diagnosis of pouchitis between January 2016 and January 2026. Patients were included if they had initiated glucagon-like peptide-1 receptor agonist (GLP-1RA) therapy within the 6 weeks preceding admission. Demographic characteristics, body mass index (BMI), GLP-1RA exposure, and clinical presentation were reviewed. Given the limited number of identified patients, the analysis was descriptive and no inferential statistical testing was performed.

RESULTS

Six patients met the inclusion criteria. The cohort consisted of three men and three women, with a mean age of 37 years (range, 27–49 years). The individual ages were 27, 28, 34, 37, 48, and 49 years. The mean BMI was 40.2 kg/m^2. All patients had a history of total proctocolectomy with restorative IPAA and had initiated GLP-1RA therapy within 6 weeks of admission for pouchitis. The temporal relationship between GLP-1RA initiation and the development of pouch-related symptoms was consistent across the identified cases, raising the possibility of an association between recent GLP-1RA exposure, altered gastrointestinal transit, and the development of pouchitis.

DISCUSSION

The diagnostic gold standard for pouchitis is pouchoscopy with targeted biopsy and histopathologic evaluation. In addition to confirming the presence and severity of inflammation, pouchoscopy permits direct assessment of the pouch mucosa, evaluation for structural complications, identification of dysplasia or neoplasia, and, in selected cases, therapeutic intervention.[2,3]

The initial treatment of pouchitis generally consists of antimicrobial therapy. Metronidazole, commonly administered at a dose of 500 mg, has historically been used as a first-line antibiotic for the treatment of pouchitis. A 2023 study evaluated 271 patients treated with antibiotic monotherapy or combination therapy, comparing ciprofloxacin, metronidazole, and combination ciprofloxacin-metronidazole therapy. The analysis demonstrated no significant difference in relapse rates or treatment nonresponse among the treatment groups.[4]

Patients with pouchitis refractory to antibiotic therapy may require escalation to corticosteroids and/or advanced immunomodulatory therapy, including interleukin-targeted agents and tumor necrosis factor (TNF) inhibitors. Following pharmacologic induction of remission, maintenance therapy may include probiotics; however, available evidence remains equivocal regarding their ability to prevent relapse or reduce the risk of eventual pouch failure.[5]

Pouch excision or explantation is reserved for highly refractory cases and is performed relatively infrequently. The morbidity associated with pouch excision, combined with the loss of absorptive small-bowel length, can result in substantial long-term consequences for the patient. Pouch failure has been reported in approximately 10%–13% of

patients at 10 years in some studies, with reported mortality rates ranging from 0.58% to 1.4%.[6,7] In another study evaluating robotic pouch excision and revision, pouch failure rates reached 30%, with a mean operative time for pouch explantation of 372 minutes.[8] Chronic perineal wounds were reported more frequently at institutions with lower volumes of ileal pouch–anal anastomosis procedures, underscoring the potential importance of institutional and surgeon experience in the management of complex pouch-related disease.[9,10]

ETIOLOGY AND PATHOPHYSIOLOGY OF POUCHITIS

The pathogenesis of pouchitis is multifactorial and remains incompletely understood. Proposed mechanisms include alterations in the intestinal microbiome, mucosal ischemia, nonsteroidal anti-inflammatory drug (NSAID) exposure, immune-mediated inflammation, and other disturbances in the complex interaction between the host immune system and the intestinal microbial environment.

Crohn's-like disease of the pouch (CLDP), or pouchitis associated with Crohn's disease–like phenotypes, represents a distinct and clinically challenging disease process. Management generally requires treatment of the underlying inflammatory disease in conjunction with antimicrobial therapy when clinically indicated.[11]

The creation of an ileal pouch alters the normal anatomy and physiology of the gastrointestinal tract by directing small-bowel contents into a reservoir that terminates at the anal canal. This anatomical rearrangement results in significant changes in luminal exposure, bacterial composition, epithelial adaptation, and mucosal immune signaling. Prolyl hydroxylase domain-containing enzymes (PHD1 and PHD2) regulate adaptive gene expression through modulation of hypoxia-inducible factor (HIF) signaling. These pathways may influence inflammatory responses within pouch epithelial cells. Experimental pharmacologic approaches, including the use of dimethyloxalylglycine (DMOG), have been investigated for their ability to modulate PHD activity and promote the expression of tight-junction proteins, thereby reducing intestinal epithelial apoptosis and potentially attenuating pouch inflammation.[12]

Although the pathogenesis of pouchitis has historically focused primarily on immune-mediated mechanisms, emerging evidence also implicates stromal cells in the maintenance and propagation of chronic inflammation. Stromal cell–mediated inflammatory signaling may contribute to transmural inflammation and disruption of intestinal barrier function.[13]

In 2024, the American Gastroenterological Association (AGA) published clinical guidance addressing the management of pouchitis following restorative IPAA. Key recommendations included the use of chronic antibiotic therapy in patients with recurrent episodes of pouchitis, particularly those with chronic antibiotic-dependent pouchitis (CADP). For patients with chronic antibiotic-refractory pouchitis (CARP) or those unable to tolerate antibiotic therapy, the AGA recommends consideration of advanced immunosuppressive therapy, with corticosteroids used in selected clinical circumstances.[14] Recent studies evaluating biologic agents, including vedolizumab and ustekinumab, have demonstrated promising efficacy in the treatment of refractory pouch-related inflammatory disease.[15] In patients with cuffitis, the AGA recommends treatment with topical mesalamine or topical corticosteroid therapy.[16]

In patients with UC and an ileal pouch who also have obesity, GLP-1RA therapy has been associated with a reduced risk of recurrent pouchitis and decreased reliance on antidiarrheal medications.[17] Retrospective studies have further suggested that GLP-1RA therapy may attenuate intestinal inflammation, preserve epithelial barrier integrity, and promote favorable alterations in the gut microbiome in patients with colitis.[18] In a separate study, GLP-1RA therapy significantly reduced the production of proinflammatory mediators, suggesting a potential anti-inflammatory effect in UC. Mechanistically, GLP-1 signaling was associated with inhibition of protein kinase B/nuclear factor kappa B (AKT/NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which may contribute to reduced inflammatory signaling.[19]

From a weight-management perspective, GLP-1 agonists have demonstrated a favorable safety and efficacy profile in both UC and Crohn's disease populations.[20] In one study, reductions in total cholesterol and glycated hemoglobin were observed but did not reach statistical significance; nevertheless, the overall adverse-effect profile was considered acceptable.[21] One of the larger retrospective studies included 16,242 patients with IBD treated with GLP-1RAs. Patients receiving GLP-1RA therapy experienced greater weight loss and fewer hospitalizations compared with the comparator population.[22] However, the retrospective design of this study limits the ability to establish causality and introduces the potential for selection bias and residual confounding.

Despite emerging evidence suggesting that GLP-1 receptor agonists may have anti-inflammatory effects in patients with inflammatory bowel disease, their effects on gastrointestinal motility may have distinct implications in patients with surgically altered intestinal anatomy. GLP-1 receptor agonists are known to influence gastrointestinal transit and may promote delayed gastric emptying and gastrointestinal hypomotility. In patients with an ileal pouch, these effects may be clinically relevant because the pouch functions as a surgically created reservoir with altered transit dynamics and a microbiome distinct from that of the native small intestine.

The combination of an ileal reservoir and pharmacologically induced slowing of gastrointestinal transit may theoretically increase luminal dwell time and promote stasis within the pouch or distal small bowel. Prolonged exposure of the pouch mucosa to luminal contents may alter the local microbial environment, promote dysbiosis, and increase exposure to bacterial metabolites or other luminal factors capable of activating mucosal inflammatory pathways. In this context, GLP-1RA therapy could potentially have opposing effects: systemic or direct anti-inflammatory effects may coexist with a local proinflammatory influence mediated through altered gastrointestinal motility and luminal stasis.

CONCLUSION

The present case, and case series, raise the possibility that impaired gastrointestinal transit may represent an underrecognized contributor to pouchitis in selected patients. The patient's initiation of semaglutide approximately 3 weeks before presentation, followed by the development of symptoms suggestive of impaired distal intestinal transit and rapid clinical improvement after antimicrobial therapy and restoration of bowel function, provides a temporal association that warrants further investigation. Although a causal

relationship cannot be established from a single case, the temporal sequence raises the hypothesis that GLP-1RA-associated gastrointestinal hypomotility may contribute to pouch inflammation through mechanisms involving intestinal stasis, altered microbial composition, and disruption of mucosal homeostasis. The close temporal relationship between recent GLP-1RA initiation and the development of pouch-related symptoms in this cohort raises the possibility of an association between GLP-1RA exposure, altered gastrointestinal transit, and pouchitis.

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