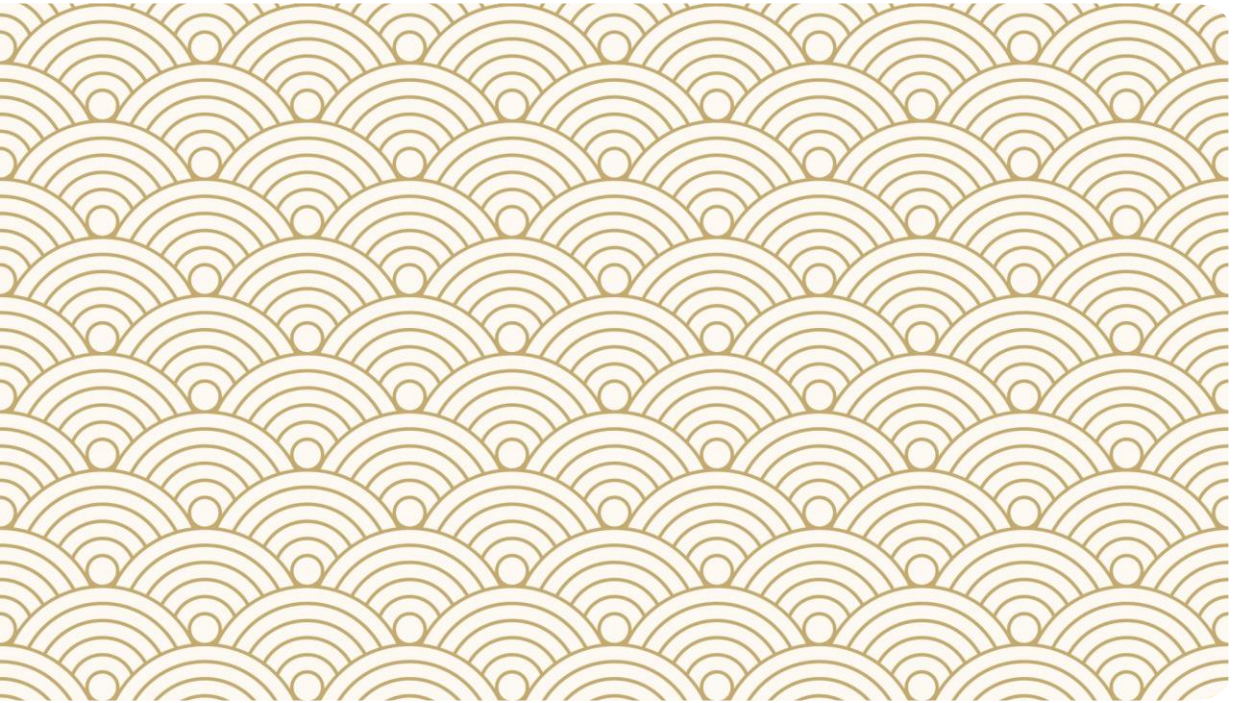


Diabetes and the Gut

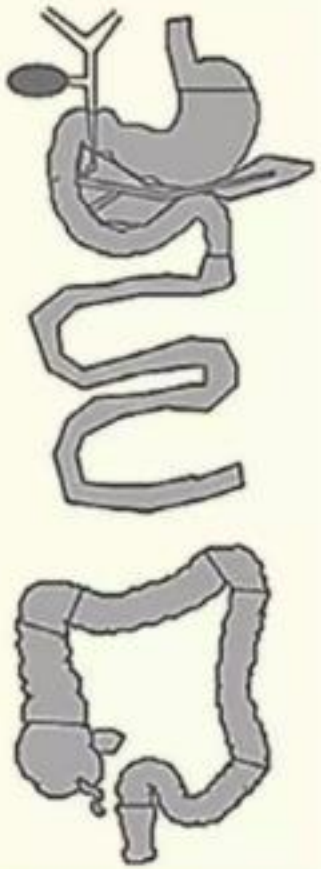
Issam Turk, MD

11/14/2024

MONUMENT HEALTH

Introduction

- 50% suffer from GI symptoms “distressing”
- Figures are underestimated: diabetes is known for its CVD legacy
- Many has been discussed but the most famous is gastroparesis
- GI motor dysfunction may have an impact on glycemic control or at least QoL.



GI manifestations of diabetes	Associated disease	Clinical presentation
↓ Gallbladder motility		Gallstones
Antral hypomotility pylorspasm		Gastric stasis, bezoars
↓ Gastric accommodation		Dyspepsia
↓ α2-adrenergic tone in enterocytes	Exocrine pancreatic insufficiency	Diarrhea, steatorrhea, intestinal pseudoobstruction
Small bowel (SB) dysmotility	Celiac sprue	Gastric or SB stasis or rapid SB transit
	SB bacterial overgrowth Bile acid malabsorption	Diarrhea, malabsorption
Colonic dysmotility		Constipation or diarrhea
Anorectal dysfunction Sensory neuropathy *IAS-sympathetic dysfunction* *EAS-pudendal neuropathy*		Disordered defecation or fecal incontinence

Esophagus

- Less studies than stomach
- Share similar pathogenesis
- Acute hyperglycemia inhibits esophageal motility and reduces the basal lower esophageal sphincter pressure
- Reduction of cholinergic activity and vagal parasympathetic dysfunction.

Fraser RJ, et al. Diabetologia. 1990;33:675–680.
De Boer SY, et al. Gastroenterology. 1992;103:775–780.
Lam WF, et al. Digestion. 1993;54:48–53.

Esophagus (cont.)

- Heart burn “as a part of GERD”
  - ❑Reflux
  - ❑Non erosive GERD
- Dysphagia “potentially indicating esophageal motor dysfunction”
- Disordered esophageal motility leads to pill induced esophagitis due to pill impaction
- Candidiasis sometimes draw our attention to lowered immunity “diabetes impair neutrophil function and opsonization”

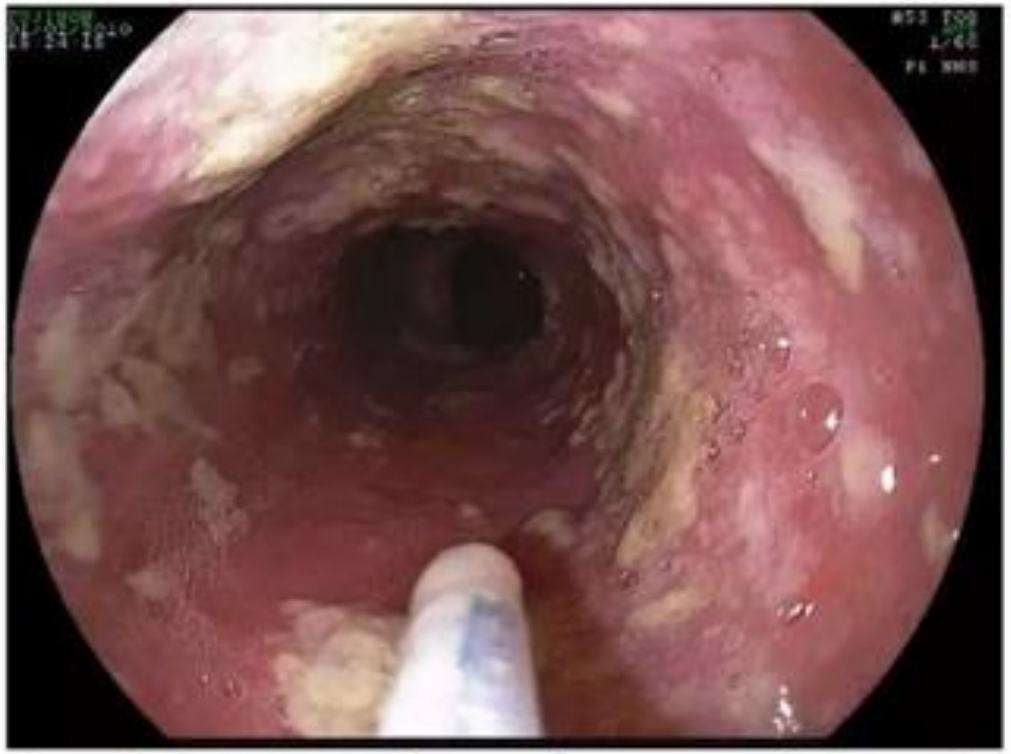


Figure 1: Gastrointestinal upper endoscopy: several white patches

Stomach - Diabetic Gastroparesis

ASYMPTOMATIC GASTRIC RETENTION IN DIABETICS (GASTROPARESIS DIABETICORUM) *

By Paul Kassander, M.D., *Manchester, New Hampshire*

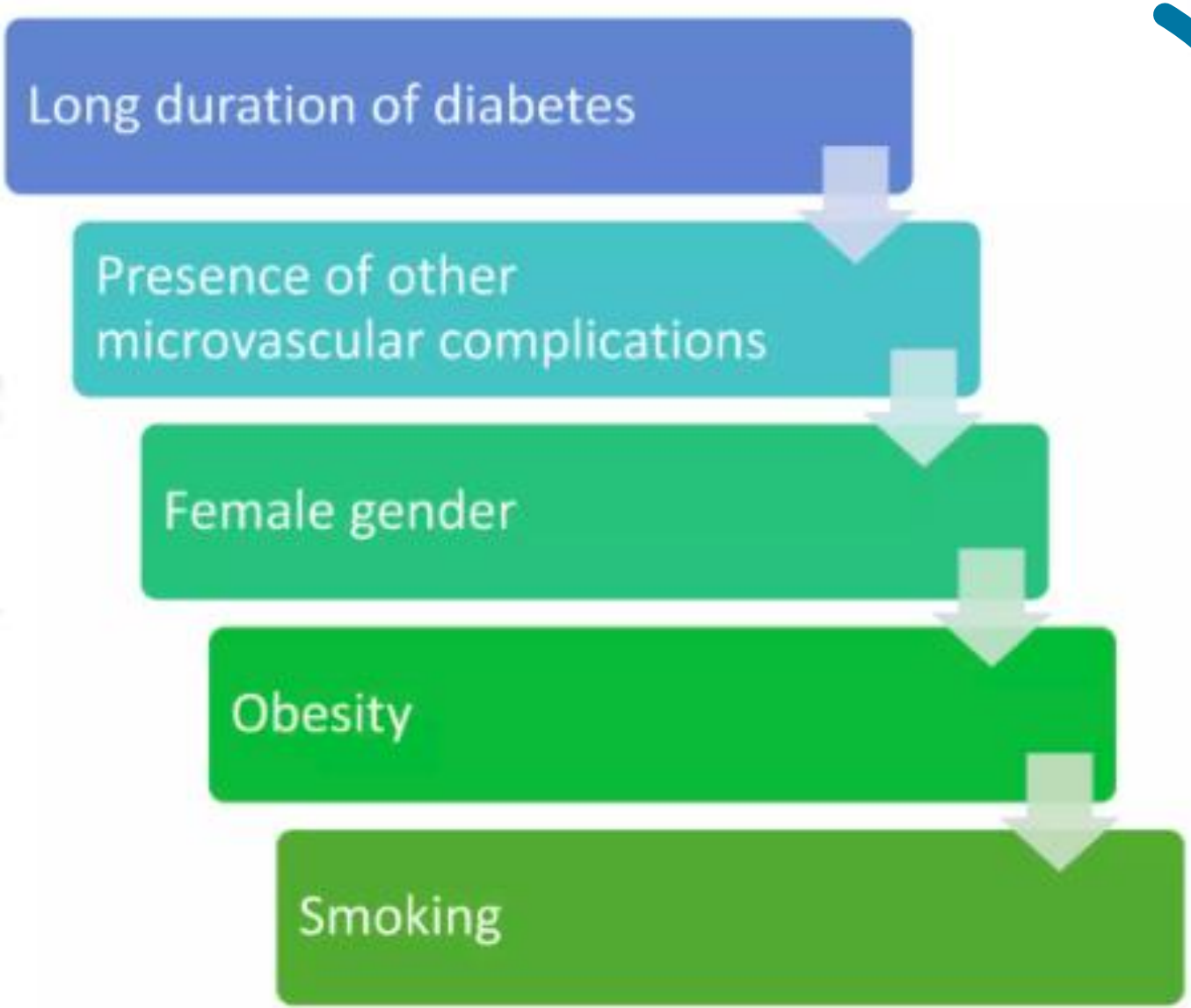
- Described by Paul Kassander: 6 cases in 1958 and coined the term "gastroparesis diabetocorum"
- He suggested that "gastroparesis could impact adversely on glycemic control".
- Modern definition: abnormally delayed gastric emptying of solid food in the absence of mechanical obstruction

It may occur in T1D or T2D not necessary = poor prognosis

Epidemiology

- The ‘true’ incidence and prevalence of diabetic gastroparesis globally remain uncertain
- Diabetes is the leading cause of gastroparesis: 30%
- In T1DM from DCCT-EDIC: delayed gastric emptying of a solid meal occurred in 47%
- It is not exclusive for T1D, it may occur in both types
- Awareness of this condition improves it and decrease its incidence

Risk Factors



Camilleri M, Chedid V, Ford AC, et al. Gastroparesis. Nat Rev Dis Primers. 2018;4:41.

Stomach vs diabetes

The rate of gastric emptying = major determinant of postprandial glycemia in both health and diabetes

Novel anti-diabetic medications e.g., short acting GLP-1 RA, diminish postprandial glycemic excursions by slowing gastric emptying

Gastroparesis is less in well controlled diabetes (even longstanding)

Marathe CS et al. Diabetes Care. 2013;36:1396–1405.
Watson LE et al. Diabetes Res Clin Pract. 2019;154:27–34.
Boronikolos GC et al. Diabetologia. 2015;58:1175–1182.

Gastric Emptying Study

Gastric emptying study (GES) results are reported as the percentage of a meal remaining in the stomach at various time points after eating:

- **30 minutes:** At least 70% of the meal remains in the stomach
- **1 hour**: 30–90% of the meal remains in the stomach
- **2 hours**: Less than or equal to 60% of the meal remains in the stomach
- **4 hours**: Less than or equal to 10% of the meal remains in the stomach

Gastroparesis management

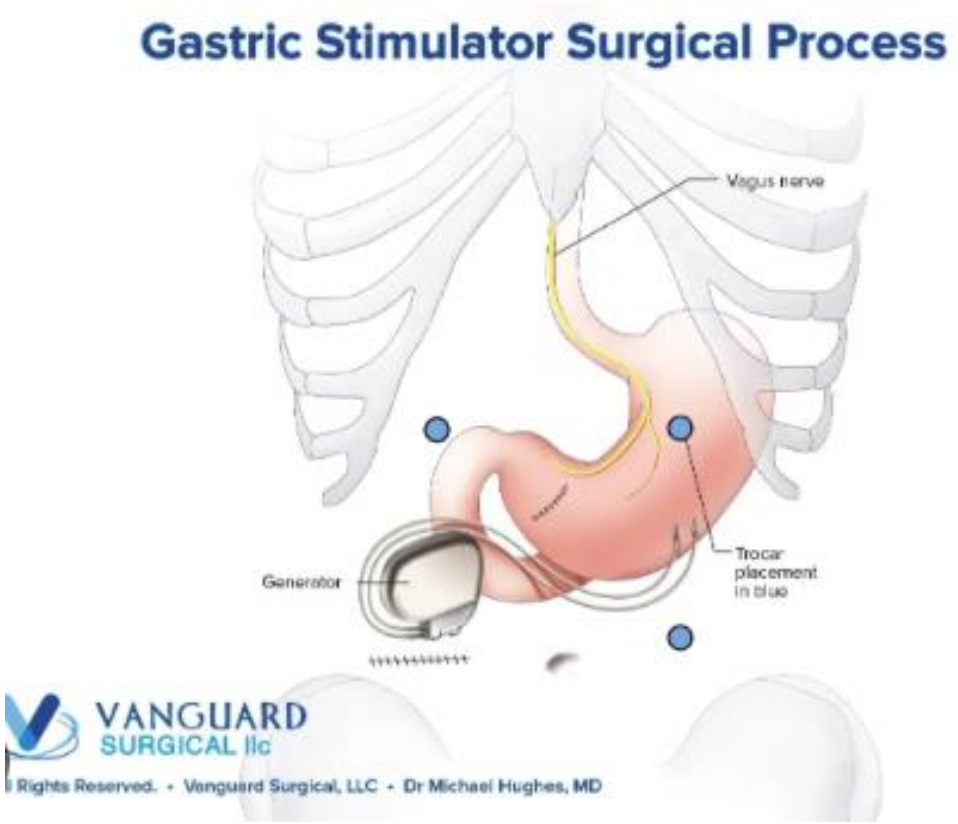
- Management of gastroparesis should be individualized.
- Small frequent meals, low fat, more liquid than solid
- It is difficult so, involve a dietitian
- Optimize glycemic control
- Adjust insulin, avoid gastric wise antidiabetics

Olausson EA, et al. Am J Gastroenterol. 2014;109:375–385.
Tornblom H. Diabetologia. 2016;59:409–413.
Calles-Escandon J, et al. PLoS One. 2018;13:e0194759.

Drug therapy

Tornblom H. Diabetologia. 2016;59:409–413.
Patterson D, et al. Am J Gastroenterol. 1999;94:1230–1234.
Jones KL, et al. Diabetes Care. 1999;22:339–344.
Lembo A, et al. Gastroenterology 151: 87-96 e86.
Manini ML, et al. Neurogastroenterol Motil 22: 42-49, e47-48.
Carbone F, et al. Am J Gastroenterol. 2019;114:1265–1274.

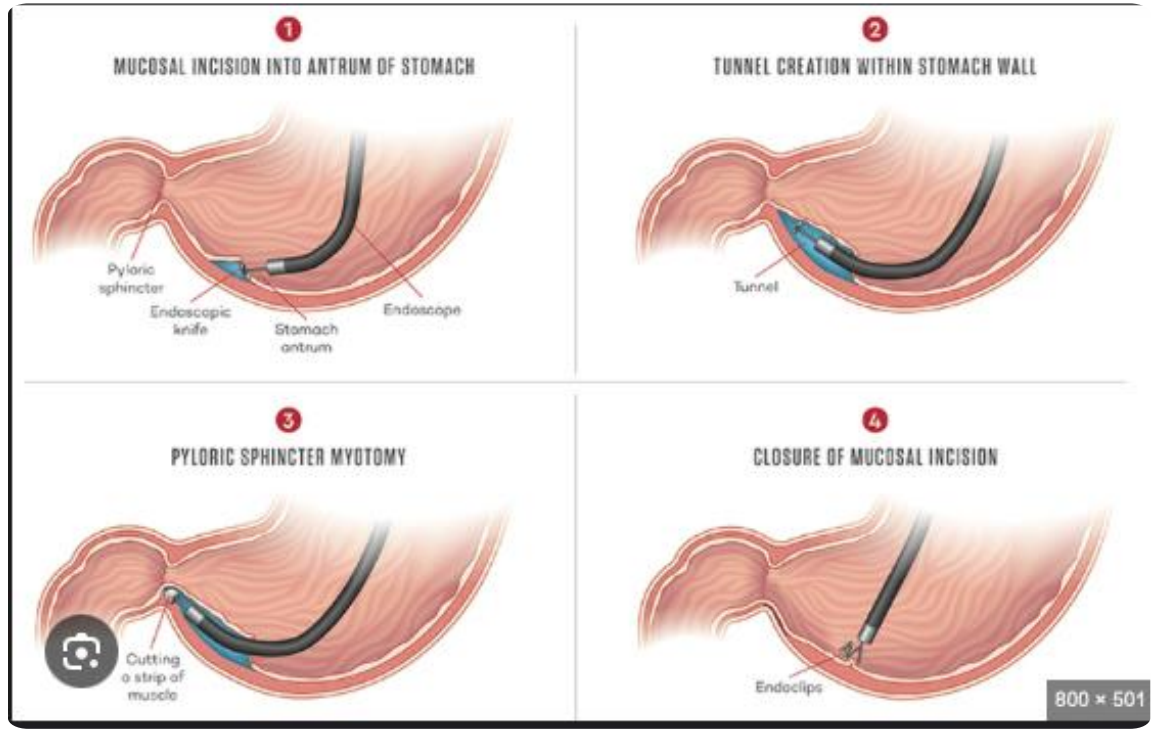
Prokinetic drugs:	Metocloperamide: FDA approved for short periods “12 weeks”
	Domperidone: the famous but cardiac concerns
	Erythromycin: but tachyphylaxis
Novel agents including	Ghrelin agonist: relamorelin
	5HT4 receptor agonist: velusetrag and prucalopride



Gastric Stimulator

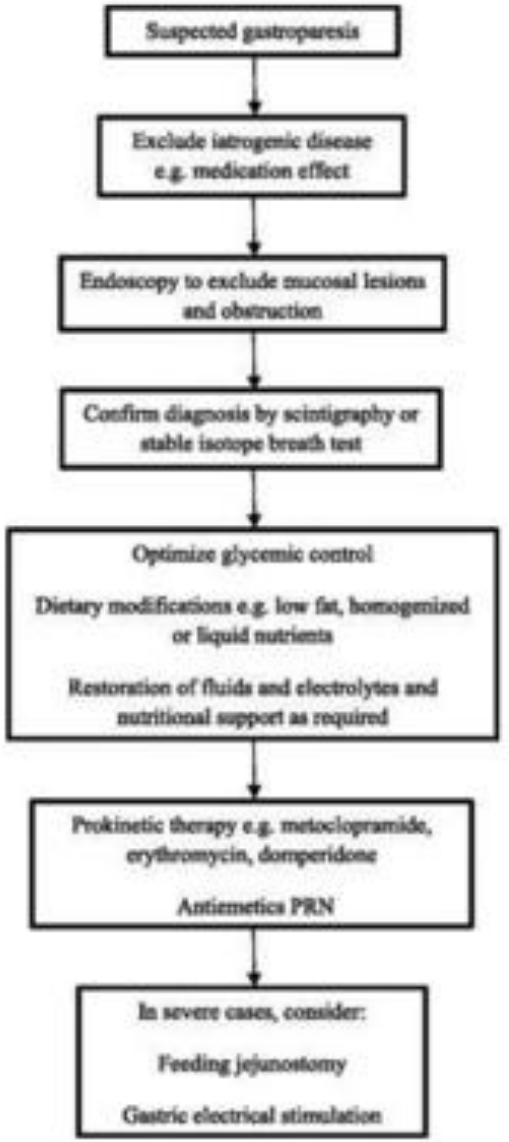
- A gastric stimulator is a small, implanted device that sends mild electrical pulses to the stomach muscles through two lead wires.
- Symptomatic improvement can be 50–60% with gastric electrical stimulation.

G-POEM



- Gastric peroral endoscopic myotomy (G-POEM) is a minimally invasive procedure that treats gastroparesis
- During the procedure, a therapeutic endoscopist uses a gastroscope to cut the muscles near the pyloric sphincter, permanently relaxing it to allow food to pass through.

Diabetic Gastroparesis Bottom-line



Du YT, et al. Diabetes Care. 2018;41:627–637.

Gall bladder

- Gall stones are more frequent in people with diabetes “risk factors for stones, such as intestinal dysmotility, obesity, and hyper TG, are more common in this group (esp. T2D)
- Diabetic cholecystoparesis: acute hyperglycemia inhibit GB motility
- Delayed gastric emptying = delayed GB emptying
- Some drugs may impair GB emptying e.g., GLP1 RA
- Dramatic weight loss after metabolic surgery may be contributor

Pazzi P, et al. Aliment Pharmacol Ther. 2000;14 Suppl 2:62–65.
Gielkens HA, et al. Scand J Gastroenterol. 1998;33:1074–1079.
Marso SP, et al. N Engl J Med. 2016;375:311–322.
Gether IM, et al. J Clin Endocrinol Metab. 2019;104:2463–2472.
Pineda O, et al. Obes Surg. 2017;27:148–153.

Small intestine

- SIBO:
  - ✓15% – 40% in T1D
  - ✓It is due to altered intestinal motility and partly due to impaired immunity
- Diabetic enteropathy with impaired intestinal motility in a way like gastroparesis
  - ✓Diagnosis of exclusion

Enteropathy workup

- Exclude diabetes and gut in same battle e.g., T1D and Celiac
- Exclude your fault: your antidiabetic drugs e.g., metformin, GLP1 RA, acarbose…
- Small intestinal manometry: limited to specialized centers.
- Scintigraphy can quantify small intestinal transit: uncertain.
- More recent technologies: ingestible wireless capsules
- SIBO: diagnosis by aspiration and culture

Treatment of enteropathy

Prokinetic agents used for gastroparesis, but much less well evaluated.

SIBO can be treated with antibiotics, such as rifamixin, amoxicillin-clavulanic acid or metronidazole.

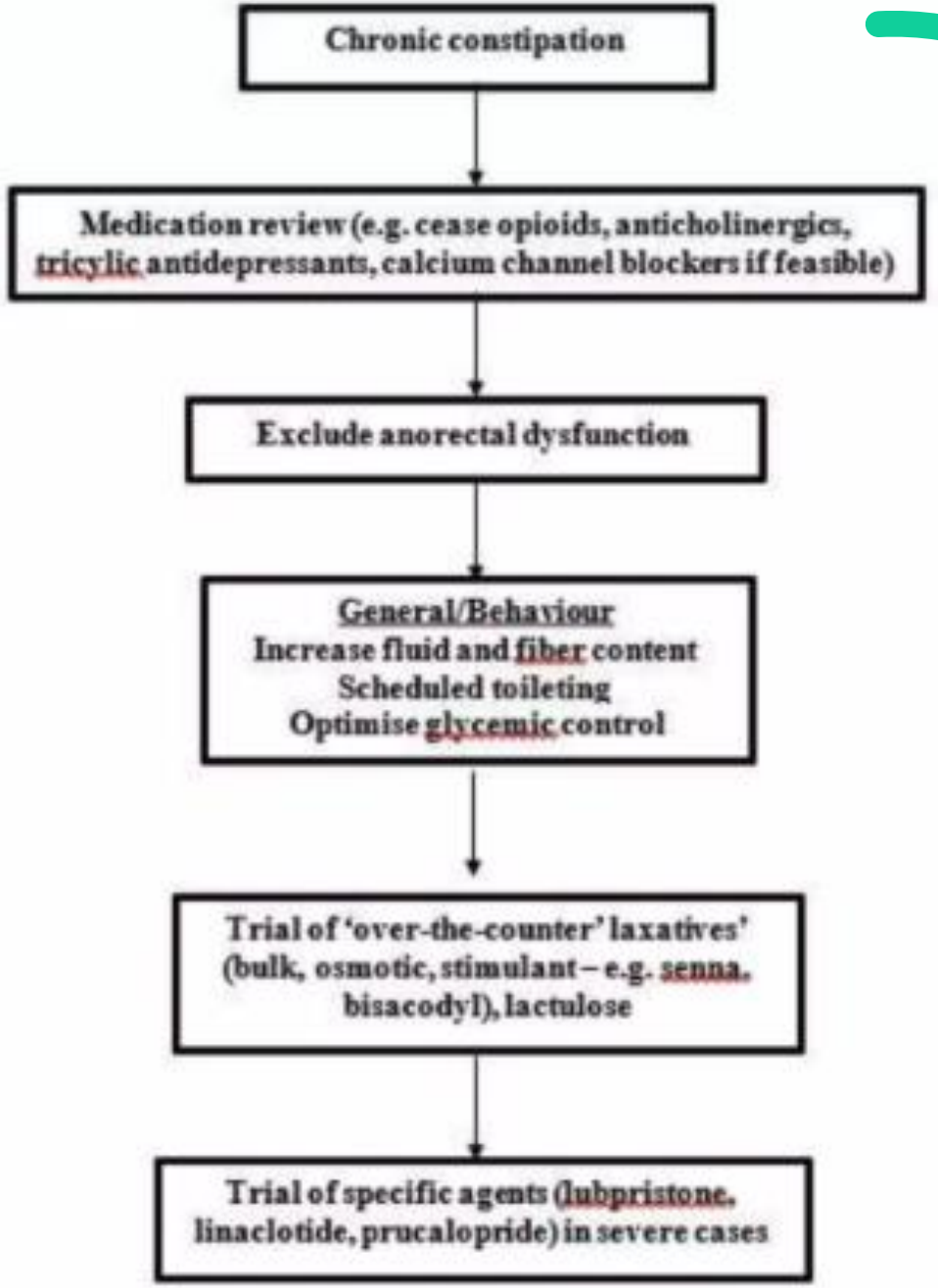
SIBO frequently relapses.

Diabetic constipation

- Multifactorial:
  - ✓Prolonged transit
  - ✓Autonomic neuropathy
- Validated techniques for evaluation include colonic transit scintigraphy and the use of radio-opaque markers and wireless motility capsules

Maleki D, et al. Arch Intern Med. 2000;160:2808–2816.
Prasad VG, et al. Indian J Gastroenterol. 2017;36:11–22.
Rao SS, et al. Neurogastroenterol Motil. 2011;23:8–23.

Chronic constipation in diabetes



Marathe CS, et al. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553219/

Diabetic diarrhea

Autonomic neuropathy

Large volume, painless, nocturnal, diarrhea with or without fecal incontinence.

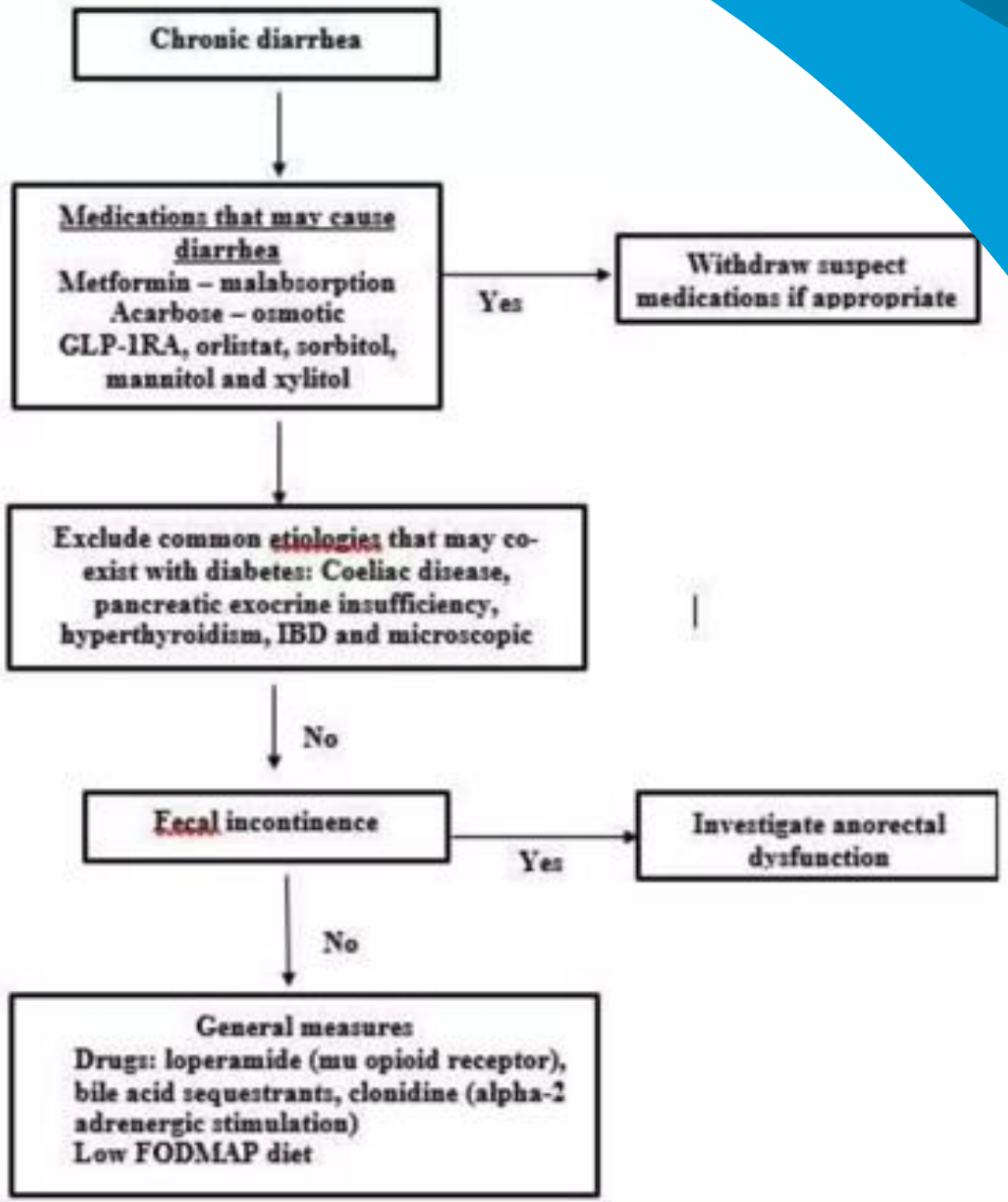
It is a diagnosis of exclusion

Diabetic diarrhea vs just incontinence

Remember antidiabetic drugs that may cause diarrhea: metformin (malabsorptive), acarbose (osmotic), and GLP-1 receptor agonists

Celik AF, et al. Am J Gastroenterol. 2001;96:1314–1316.
Marathe CS, et al. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553219/

Chronic Diarrhea in Diabetes



Marathe CS, et al. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK553219/

Type 1 Diabetes and Celiac disease

- Gut malabsorption and upset
- There is a genetic link between both
- 6% of T1DM patients have CD
- Symptoms of CD may be overlooked
- More T1D members in 1 family increases risk of CD

GLP1s and GI side effects

GLP-1GI side effects

- The following precautions and adverse effects pertain to glucagon-like peptide 1 (GLP-1) receptor agonists, used alone or in combination with a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist.
- The long-term safety of GLP-1 receptor agonists has not been established, as the majority of clinical trials are less than four years in duration.

Gastrointestinal

- The side effects of GLP-1-based therapies are predominantly gastrointestinal, particularly nausea, vomiting, and diarrhea, which are frequent.
- They occur consistently in trials in 10 to 50 percent of patients.
- In a network meta-analysis of 236 clinical trials, GLP-1 receptor agonists compared with oral agents were associated with greater adverse events leading to treatment discontinuation

Gastrointestinal

- When used for body weight reduction, GLP-1-based therapies have been associated with more severe gastrointestinal risks, including obstruction and symptomatic gastroparesis.
- Anesthesia guidelines recommend holding these therapies prior to elective intubation for presumed risk of aspiration.

Gastrointestinal

- Semaglutide and Tirzepatide also associated with gastrointestinal side effects.
- In a trial comparing Tirzepatide with semaglutide, gastrointestinal adverse effects were similar in the two groups (nausea 17.4 to 22.1 percent, diarrhea 11.5 to 16.4 percent, decreased appetite 5.3 to 8.9 percent
- Nausea may wane with duration of therapy and can be reduced with dose titration

Gastrointestinal

- While semaglutide and other GLP-1 agonists cause adverse events, such as nausea, vomiting, diarrhea, and a range of other GI symptoms, these effects of delayed gastric emptying are reported to be reduced after 20 weeks of use…

Pancreas

- Acute pancreatitis has been reported in association with GLP-1 receptor agonists.
- There are insufficient data to know if there is a causal relationship.
- Pancreatitis should be considered in patients with persistent severe abdominal pain (with or without nausea), and GLP-1 receptor agonists should be discontinued in such patients.
- If pancreatitis is confirmed, it should not be restarted.
- GLP-1 receptor agonists should not be initiated in a patient with a history of pancreatitis.

Pancreas

- In some trials, GLP-1 receptor agonists increased pancreatic enzymes (amylase and lipase) from baseline levels, although often remaining within the normal range.
- In one analysis, lipase and amylase levels increased above the upper limit of normal in the Liraglutide and placebo groups (51 and 32 percent of participants, respectively, for lipase and 29 and 23 percent, respectively, for amylase)
- These elevations did not predict risk of subsequent acute pancreatitis.

Pancreas

- After a review of available data, the US Food and Drug Administration (FDA) and the European Medicines Agency agreed that there was insufficient evidence to confirm an increased risk of pancreatic cancer with use of GLP-1-based therapies
- However, concerns remain and monitoring for and reporting of pancreatic adverse effects will continue.

Pancreatic Cancer and GLP-1RAs

October 29, 2024 | 2 min read SAVE

‘No observed increase’ in pancreatic cancer among patients with type 2 diabetes on GLP-1RAs

- Using deidentified electronic health records, Alchirazi and colleagues identified 4,950,000 patients with a history of type 2 diabetes between 2005 and 2020, of whom 245,532 were on GLP-1RAs. All patients were drug naive with no history of pancreatic cancer at baseline.
- The researchers compared GLP-1RAs with insulin, metformin, alpha-glucosidase inhibitors, dipeptidyl-peptidase 4 (DPP-4) inhibitors, SGLT2, sulfonylureas and thiazolidinediones, and matched patients 1:1 based on demographics, lifestyle factors, medical history and family history of disease, among others.

- According to results presented at the ACG Annual Scientific Meeting, the risk for pancreatic cancer was significantly lower among patients on GLP-1 RAs vs. insulin (HR = 0.56; 95% CI, 0.44-0.72), DPP-4 inhibitors (HR= 0.8; 95% CI, 0.73-0.89), SGLT2 inhibitors (HR = 0.78; 95% CI, 0.69-0.89) and sulfonylureas (HR = 0.84; 95% CI, 0.74-0.95).

"This study provides reassurance that there is no observed increase in the incidence of pancreatic cancer among patients using these GLP-1RAs."

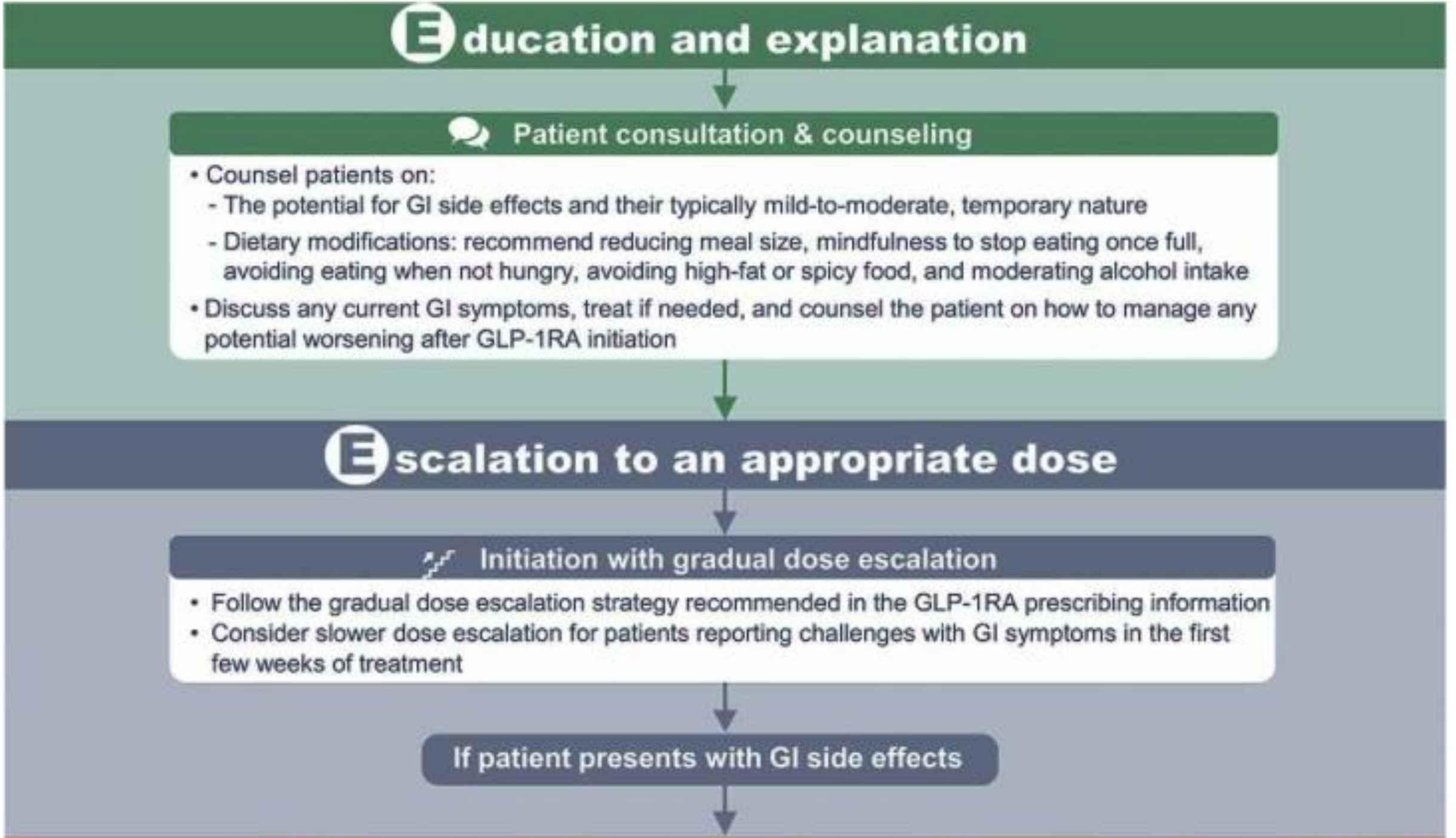
Khaled Alsabbagh Alchirazi, MD

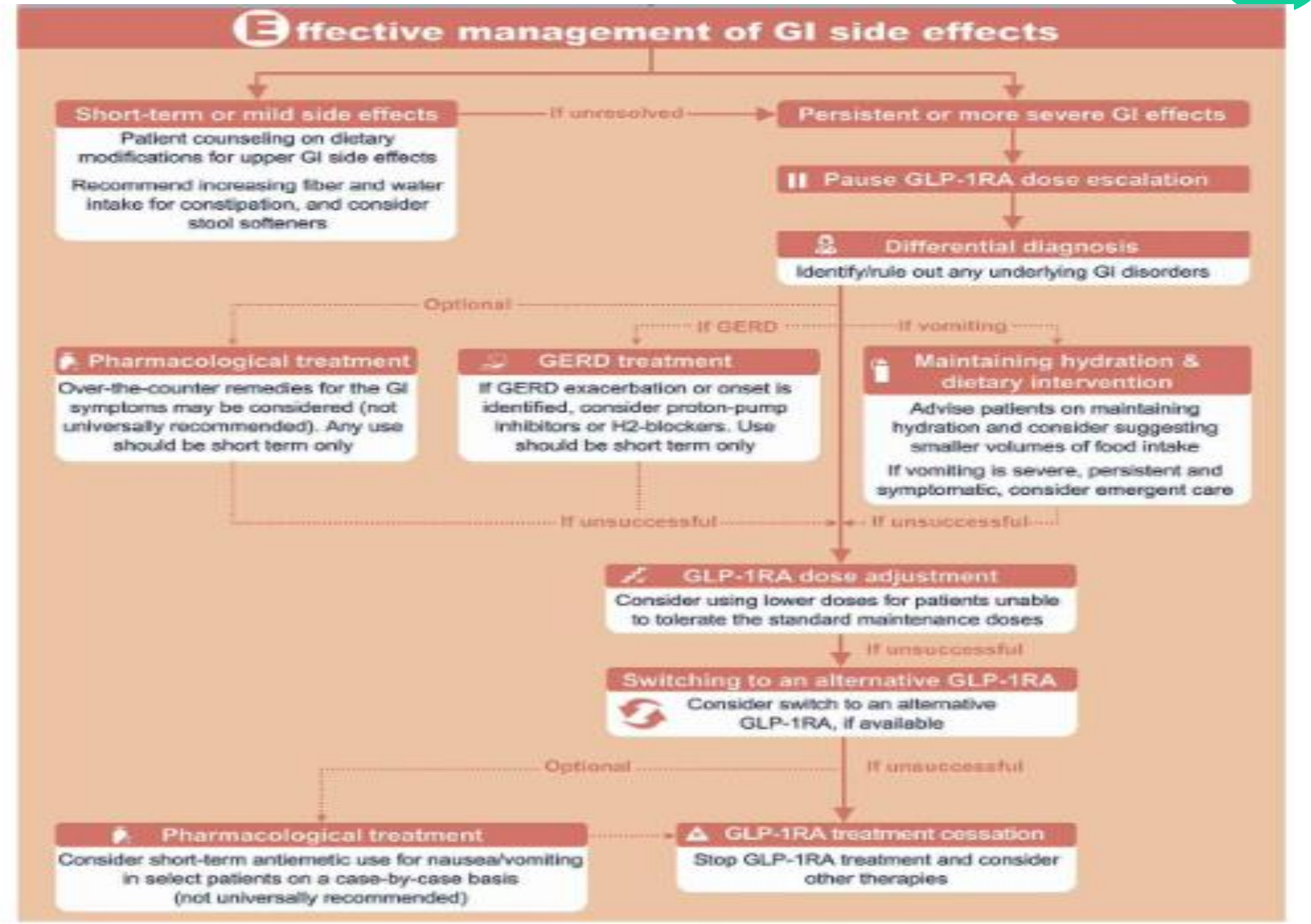
Key takeaways:

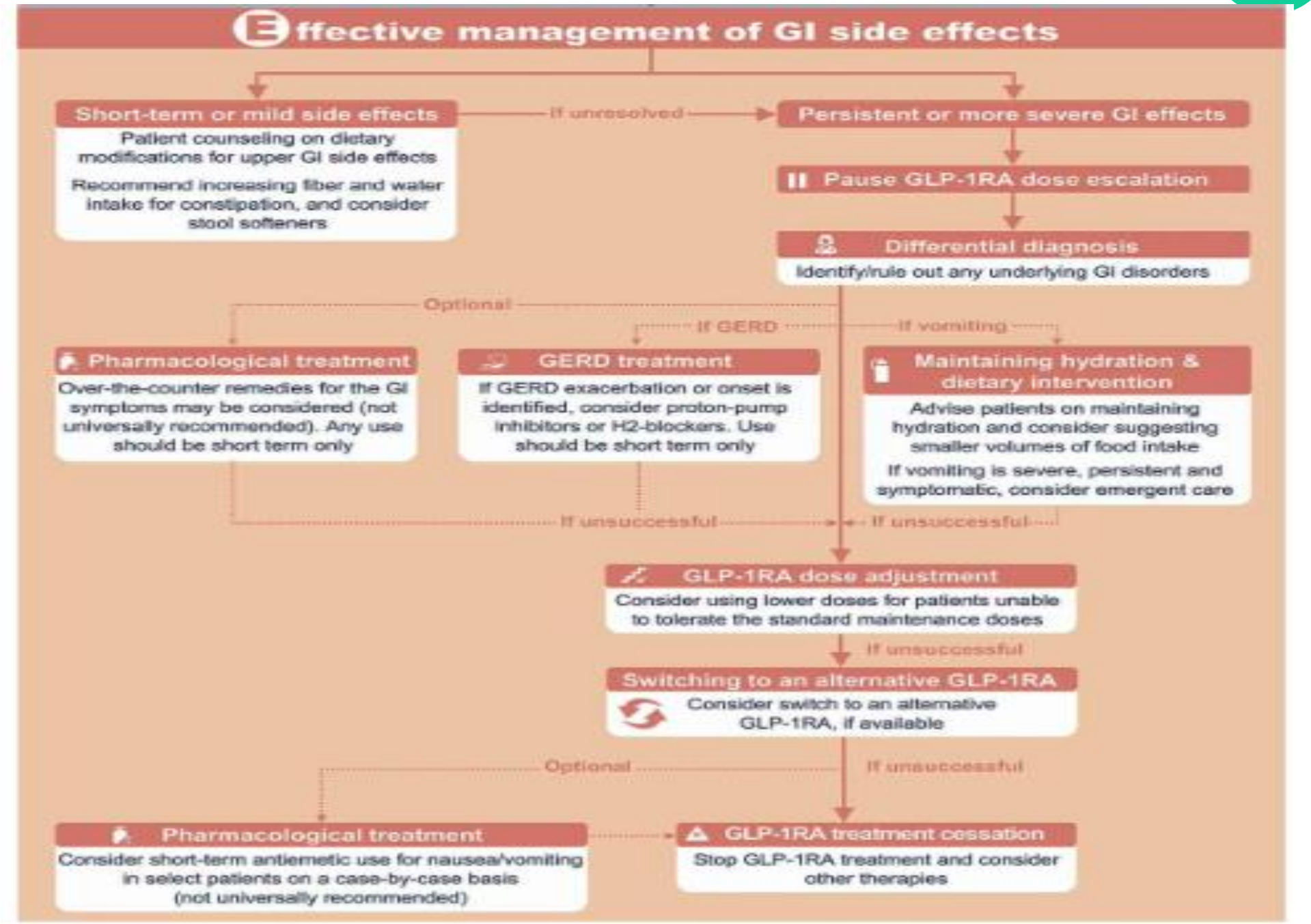
- Patients with type 2 diabetes on GLP-1RAs had a significantly lower risk for pancreatic cancer vs. those on other antidiabetic treatments.
- Results were consistent among those with obesity or overweight.

Gallbladder and Biliary Disease

- GLP-1 receptor agonist therapy has been associated with increased risk of gallbladder and biliary diseases including cholelithiasis and cholecystitis.
- In one meta-analysis of 76 trials, participants randomly assigned to GLP-1 receptor agonist treatment had an increased risk of the composite outcome of gallbladder or biliary diseases (event rate 1.58 versus 1.19 percent, relative risk [RR] 1.37, 95% CI 1.23-1.52)
- Use of GLP-1 receptor agonists specifically for weight loss, higher doses, and longer duration of treatment were all associated with greater risk.
- Elevated risk of acute cholecystitis with GLP-1 receptor agonist treatment has further been supported by a subsequently published postmarketing surveillance report


Education and explanation
Patient consultation & counseling
• Counsel patients on:
- The potential for GI side effects and their typically mild-to-moderate, temporary nature
- Dietary modifications: recommend reducing meal size, mindfulness to stop eating once full, avoiding eating when not hungry, avoiding high-fat or spicy food, and moderating alcohol intake
• Discuss any current GI symptoms, treat if needed, and counsel the patient on how to manage any potential worsening after GLP-1RA initiation
Escalation to an appropriate dose
Initiation with gradual dose escalation
• Follow the gradual dose escalation strategy recommended in the GLP-1RA prescribing information
• Consider slower dose escalation for patients reporting challenges with GI symptoms in the first few weeks of treatment
If patient presents with GI side effects


Effective management of GI side effects
Short-term or mild side effects
Patient counseling on dietary modifications for upper GI side effects
Recommend increasing fiber and water intake for constipation, and consider stool softeners
If unresolved
Persistent or more severe GI effects
Pause GLP-1RA dose escalation
Differential diagnosis
Identify/rule out any underlying GI disorders
Optional
If GERD
If vomiting
Pharmacological treatment
Over-the-counter remedies for the GI symptoms may be considered (not universally recommended). Any use should be short term only
GERD treatment
If GERD exacerbation or onset is identified, consider proton-pump inhibitors or H2-blockers. Use should be short term only
Maintaining hydration & dietary intervention
Advise patients on maintaining hydration and consider suggesting smaller volumes of food intake
If vomiting is severe, persistent and symptomatic, consider emergent care
If unsuccessful
If unsuccessful
GLP-1RA dose adjustment
Consider using lower doses for patients unable to tolerate the standard maintenance doses
If unsuccessful
Switching to an alternative GLP-1RA
Consider switch to an alternative GLP-1RA, if available
Optional
If unsuccessful
Pharmacological treatment
Consider short-term antiemetic use for nausea/vomiting in select patients on a case-by-case basis (not universally recommended)
GLP-1RA treatment cessation
Stop GLP-1RA treatment and consider other therapies


Effective management of GI side effects
Short-term or mild side effects
Patient counseling on dietary modifications for upper GI side effects
Recommend increasing fiber and water intake for constipation, and consider stool softeners
If unresolved
Persistent or more severe GI effects
Pause GLP-1RA dose escalation
Differential diagnosis
Identify/rule out any underlying GI disorders
Optional
If GERD
If vomiting
Pharmacological treatment
Over-the-counter remedies for the GI symptoms may be considered (not universally recommended). Any use should be short term only
GERD treatment
If GERD exacerbation or onset is identified, consider proton-pump inhibitors or H2-blockers. Use should be short term only
Maintaining hydration & dietary intervention
Advise patients on maintaining hydration and consider suggesting smaller volumes of food intake
If vomiting is severe, persistent and symptomatic, consider emergent care
If unsuccessful
If unsuccessful
GLP-1RA dose adjustment
Consider using lower doses for patients unable to tolerate the standard maintenance doses
If unsuccessful
Switching to an alternative GLP-1RA
Consider switch to an alternative GLP-1RA, if available
Optional
If unsuccessful
Pharmacological treatment
Consider short-term antiemetic use for nausea/vomiting in select patients on a case-by-case basis (not universally recommended)
GLP-1RA treatment cessation
Stop GLP-1RA treatment and consider other therapies

Thank you!

MONUMENT HEALTH