GI manifestations of D.M

M.Kazem Amirbeigy

Gastroenterologist

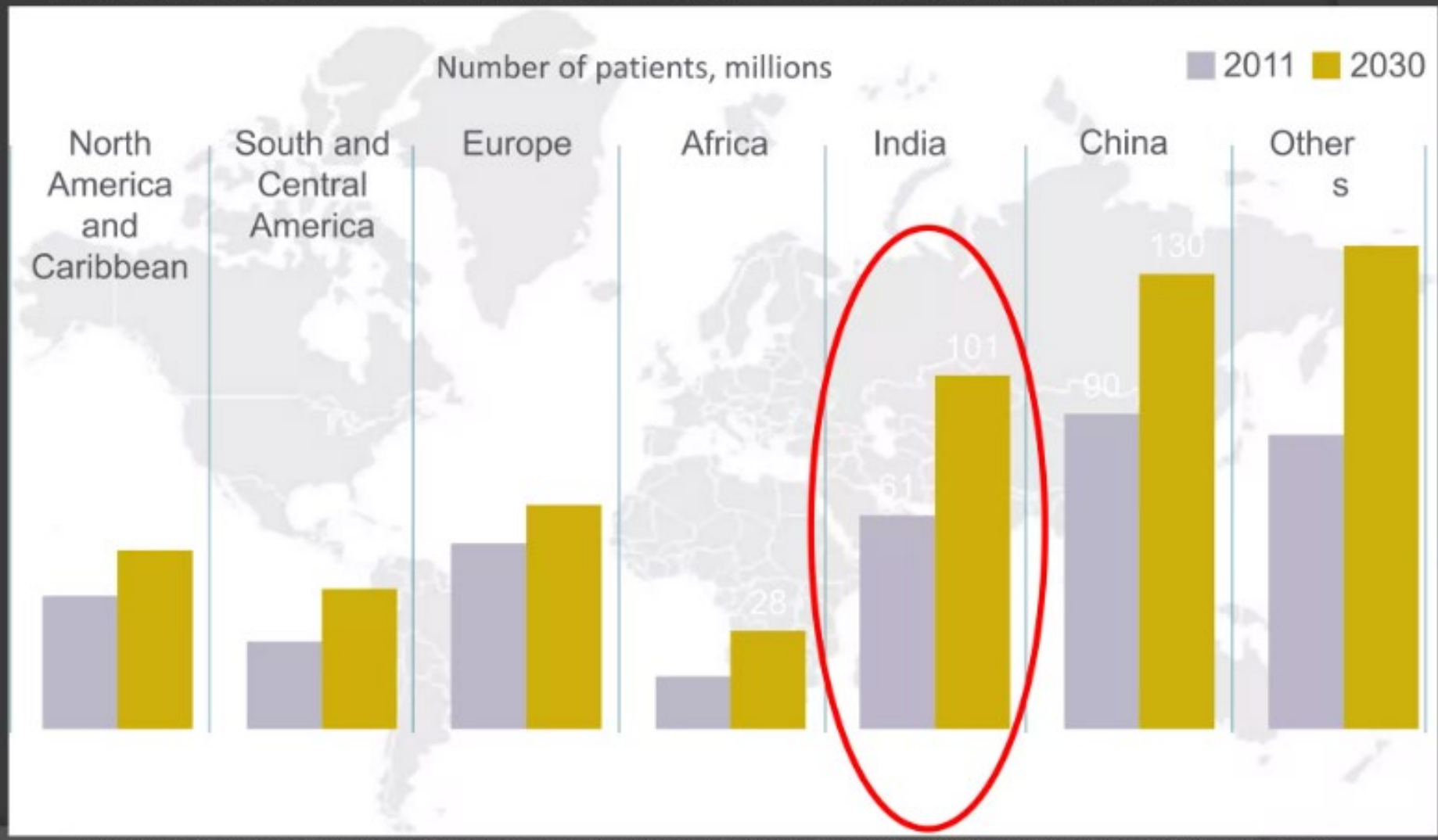
Shahid sadoughi medical university

Case 3- problem list

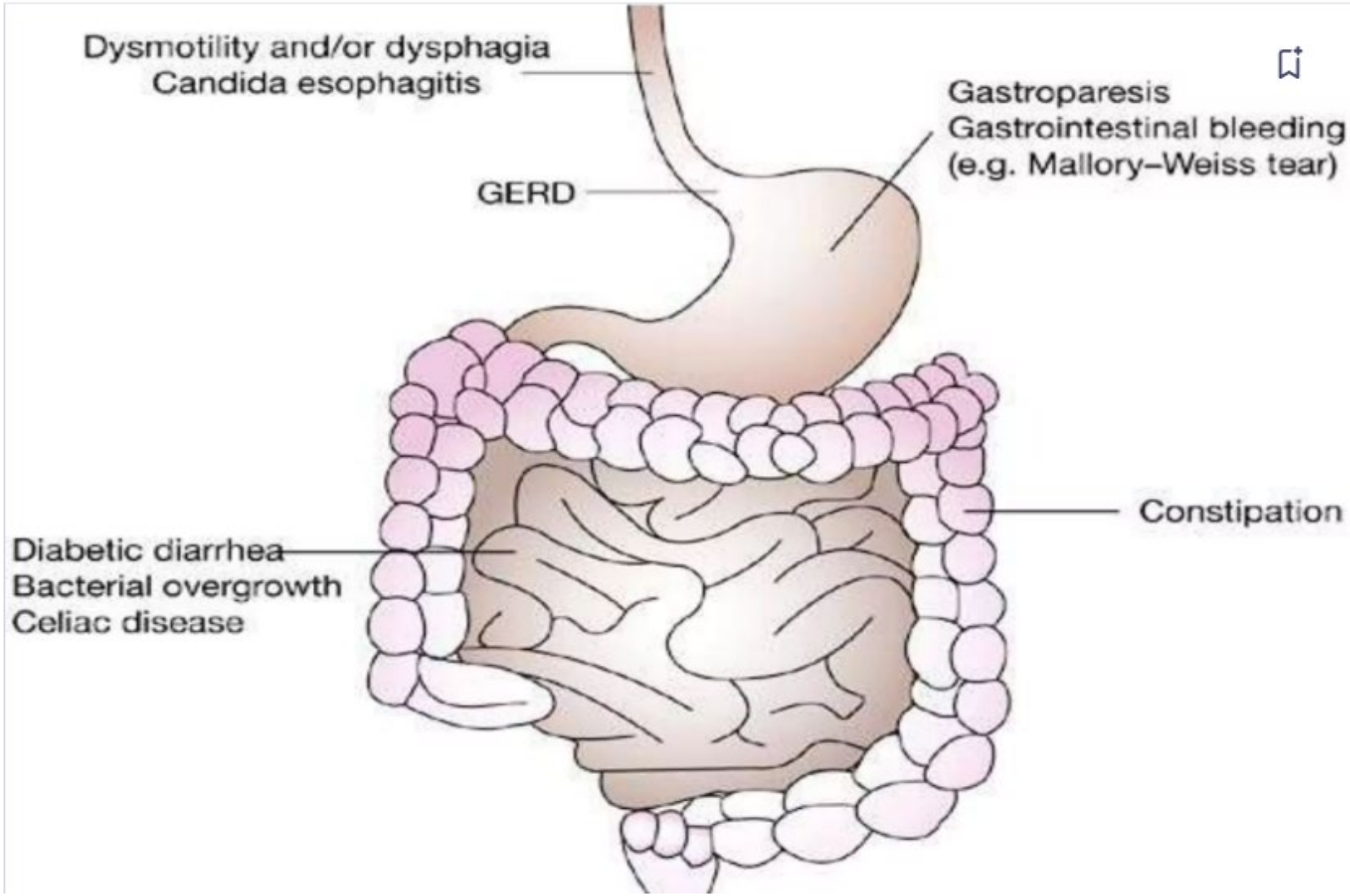
- A 48 years old man with D.M For 25 years
- Gastroparesis symptoms(nausea- paroxysmal vomiting-bloating – early satiety & normal UGI endoscopy)
- Diarrhea (watery 3-4 times/day)
- Muli nodular goiter with TSH=0.02

DM

The number of patients with diabetes worldwide is expected to increase from 366 million in 2011 to 552 million in 2030



International Diabetes Federation. IDF Homepage. International Diabetes Federation 2011. Available from: http://www.idf.org/.


Dysmotility and/or dysphagia
Candida esophagitis
GERD
Gastroparesis
Gastrointestinal bleeding
(e.g. Mallory–Weiss tear)
Diabetic diarrhea
Bacterial overgrowth
Celiac disease
Constipation

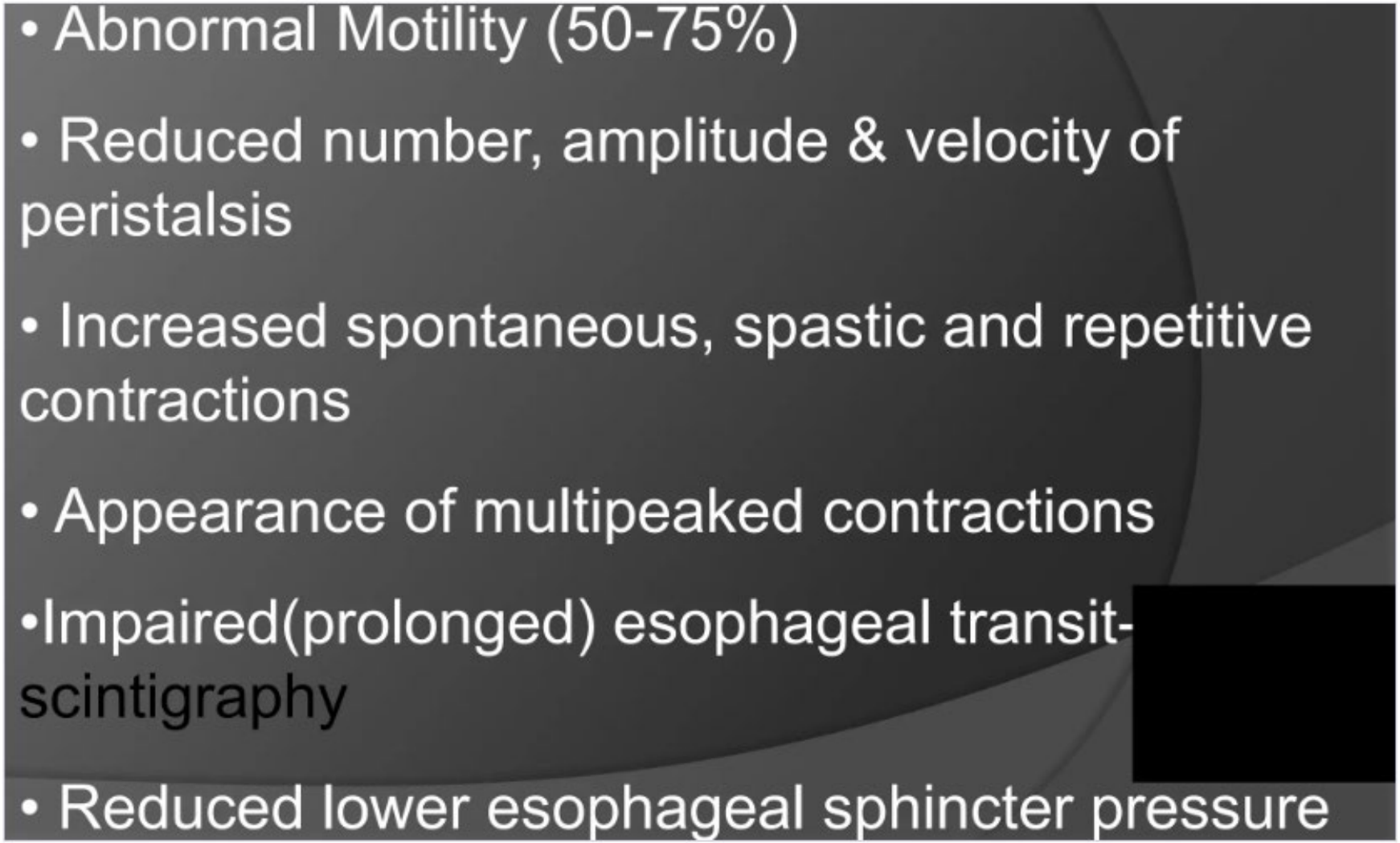
Most common problems

- Constipation
- Diarrhea
- Abdominal pain
- Nausea
- Vomiting

g for c.pub.network...

Esophagus

Download to read offline



Download to read offline

- Odynophagia
- ® Nystatin 1lakh U-3-5times/dy, Clotrimazole 10mg(troche) 5 times/dy or 500mg VT HS.
- Fluconazole- 200mg loading + 100mg/dy x 21dys





Stomach

Download to read offline

Type 1: Gastritis/Gastric Atrophy (5% to 10%).

Parietal cell antibodies (15% to 25%).

Pernicious Anemia (2.6% to 4%).

Reduced acid hence decreased ulcer incidence.

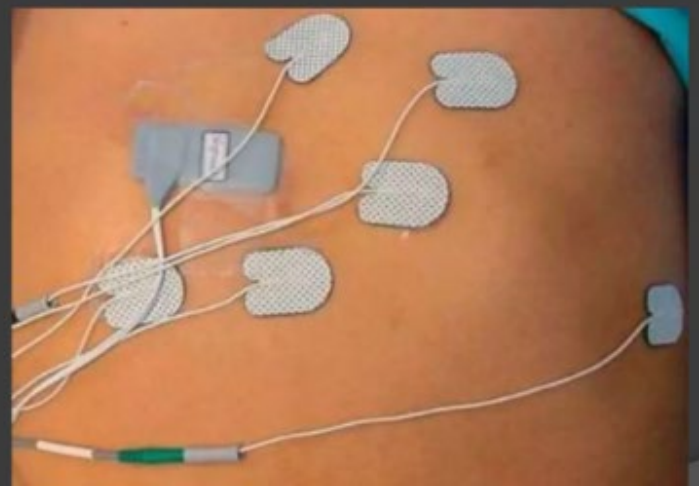
Increased risk of ulcer bleeding- microcirculatory changes that impair mucosal integrity.

GASTROPARESIS DIABETICORUM

- Seen in upto 60%
- Insidious nature, Rarely acute- similar to vagotomy
- Nausea, vomiting, pain, bloating, early satiety, flatulence, anorexia and postprandial regurgitation- 20%
- Changes in drug absorption
- Food retention- increase of bacteria toxins & fermentation products- hypermotility and diarrhoea
- Examination - succussion splash

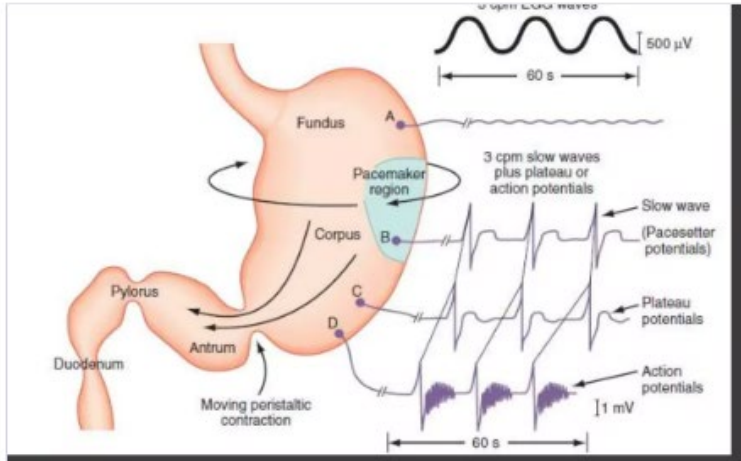
Diabetic gastroparesis （ D.G ）

- Scintigraphy- Solid and liquid emptying assessed
  Gastroparesis->60% @ 2hrs & >10% @ 4hrs.
- Saline loading- 800-1000ml.
- EGG- Increased frequency of antral dysrhythmias.
  Phase 3 MMC are absent →bezoars.



Diabetic gastroparesis （ D.G ）

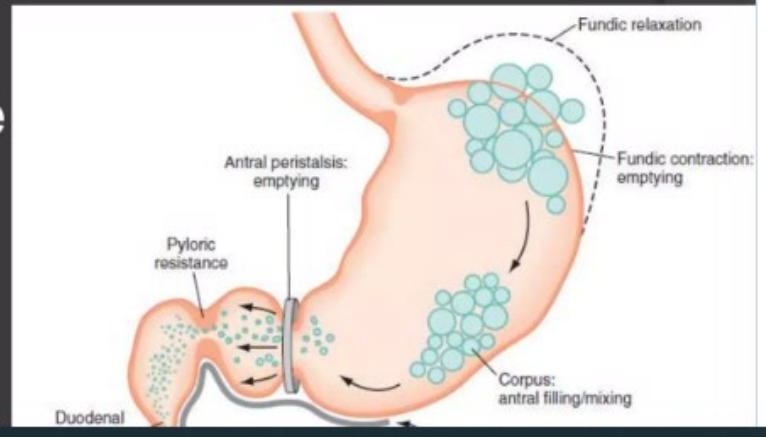
Download to read offline



Abnormal Gastroduodenal pressure

Fundal relaxation

Pylorospasm

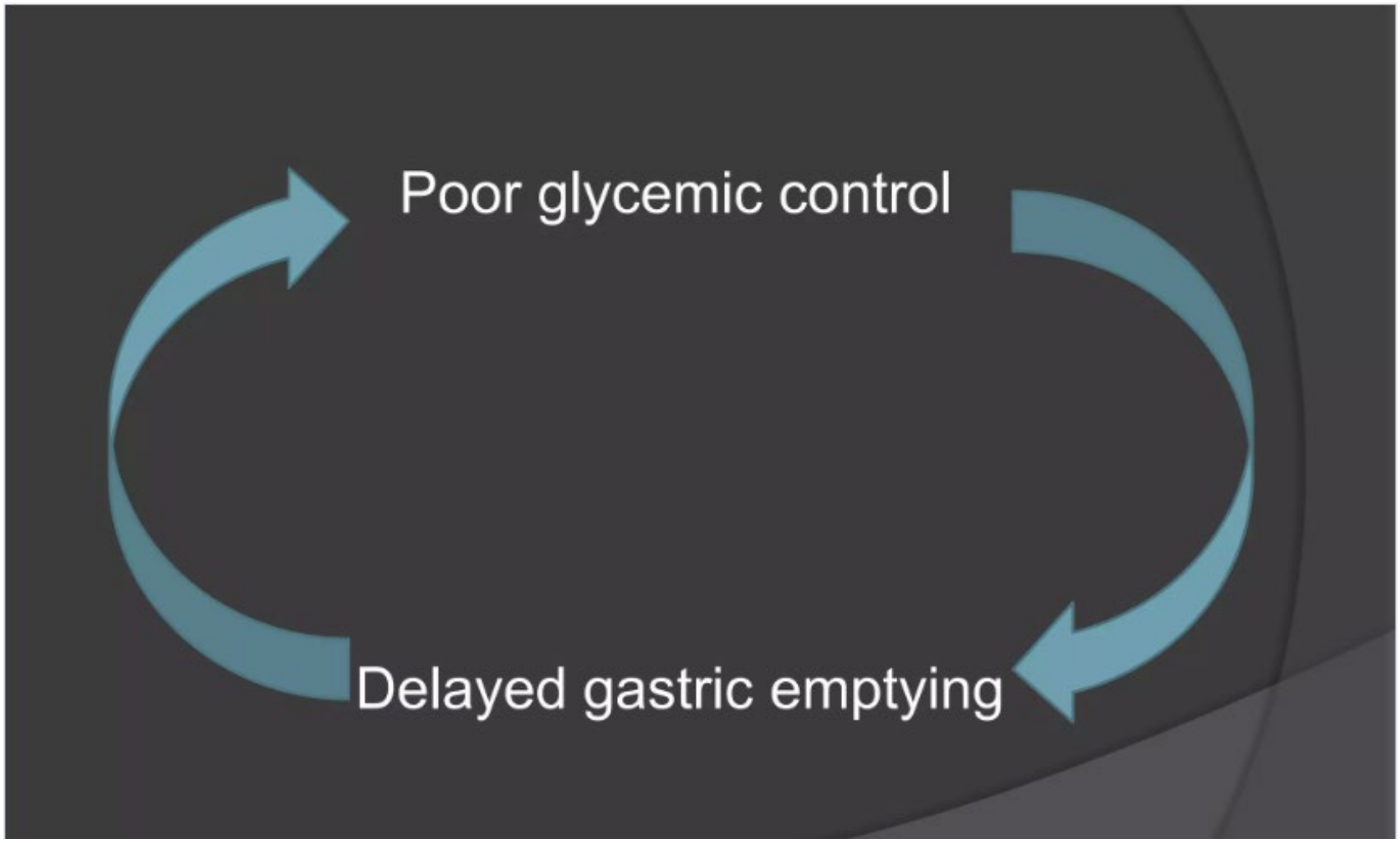


DIETARY CHANGES

- Small frequent meal, low-fat, low-residue & ↑ liquid content meals are best tolerated in patients with symptomatic gastroparesis
- Chewing food well, drinking non-carbonated liquids with meals & avoiding lying down for 2 h after a meal may assist with gastric emptying

INTRODUCTION CONT'D

- Mainstay of medical treatments includes
  - Modifying lifestyle & diet
  - Improving glucose control in diabetics
  - Prokinetic, anti-emetic & analgesic drugs
- Non-medical modalities
  - Acupuncture
  - Hypnotherapy
  - Gastric electric stimulation & surgical procedures
    Reserved for rare & severely refractory patients


Poor glycemic control
Delayed gastric emptying

PROKINETICS

Dompamine D2-R antagonists

- Metoclopramide & domperidone - equally effective in ↓ symptoms of diabetic gastroparesis

Metoclopramide

- D2 receptor antagonist & 5-hydroxytryptamine receptor 4 (5-HT4) agonist
- Prokinetic action & anti-emetic properties
- Provides prolonged symptomatic relief in gastroparesis
- US-FDA - approved for gastroparesis

PROKINETICS CONT'D

Metoclopramide cont'd

- Overall adverse central nervous system (CNS) effects of metoclopramide, e.g., somnolence, dystoni & reduction in mental acuity, can be severe
- Tardive dyskinesia can be irreversible & disfiguring - FDA black box warning in 2009
- Treatment beyond 3 months should be avoided in most cases

PROKINETICS CONT'D

Domperidone

- Anti-emetic & prokinetic effects
- Unlike metoclopramide, CNS reactions are uncommon because of less penetration of blood–brain barrier
- Rationally suitable for use in gastroparetic patients such as with Parkinson's disease
- Treatment - doses of 80–120 mg per day for up to 3 months is tried before considering as treatment failure
- US - FDA issued warning about cardiac safety - regarding QT prolongation
  - Intravenous dosage form - withdrawn due to cardiotoxicity

PROKINETICS CONT'D

Itopride

- Antiemetic & prokinetic properties
- Has D2 antidopaminergic & anti-ChE (ACh potentiating) activity, but very low affinity for 5-HT_4 receptor
- Very similar to domperidone & seems to be devoid of any cardiac toxicity or CNS side effects

Levosulpiride

- Dopamine D2 receptor antagonist
- Reported to improve gastric emptying & symptoms (nausea, vomiting & early satiety) in diabetic gastroparesis during 6 months of treatment

SEROTONERGIC 5-HT4 AGONISTS

Cisapride

- Mixed 5-HT4 agonist/5-HT3 antagonist
- ↑ acetylcholine release from enteric nervous system & directly ↑ smooth muscle contractions – ↓ gastric emptying time
- Withdrawn in 2000 - side effect of causing long QT syndrome

Mosapride

- Improves gastric emptying & symptoms of gastroparesis & improves glycemic control

MOTILIN RECEPTOR AGONISTS

Erythromycin

- Effect on gastroparesis - two pathways activating motilin receptors on cholinergic neurons & muscle
- Most effective intravenous prokinetic agent in acute setting - initial management of hospitalized patients with diabetic gastroparesis
- Rapid development of tolerance is seen - By 4 weeks of oral treatment
- Drawbacks - Potential to induce abdominal cramps, nausea & vomiting & to slow small intestinal transit

MOTILIN RECEPTOR AGONISTS CONT'D

Clarithromycin & azithromycin

- Promotilides & ↑ antral contractions
- Effect on motilin receptor requires metabolism by acid & this should be kept in mind while prescribing to patients with dyspepsia , there by potentially making drug less effective as a promotilide
- Fewer drug interactions than erythromycin, less incidence of QTc interval prolongation, a longer half-life & fewer untoward GI effects

ANTIEMETICS

Prochlorperazine

- D2 antagonist - one of most commonly used medicines for treatment of nausea in patients with gastroparesis
- Major side effects are sedation, extrapyramidal side effects

Granisetron transdermal form - effective for refractory nausea & vomiting in gastroparesis

Aprepitant

- Substance P antagonist & works by blocking neurokinin 1 (NK1) receptor
- Effective for refractory nausea in severe gastroparesis & is currently under investigation

GASTRIC ACID SUPPRESSION

- Stomach acid suppression plays important role for overall symptom management in gastroparesis
- Careful choice of acid-suppressing drugs can optimize gastroparesis symptom management
- Nizatidine - Histamine H2 receptor antagonist - demonstrated to hasten stomach emptying in patients with Parkinson's disease

CONT'D

Buspirone -5HT1A agonist

- Positive effect on gastroparesis symptomatic relief, even without evidence showing of gastric emptying in healthy volunteers
- In addition to ↓ in transient lower esophageal sphincter relaxation, which is major mechanism underlying gastroesophageal reflux disorder, this symptomatic relief might be due to fundic relaxation & ↑ gastric accommodation

Sumatriptan - 5-$HT_{1D/1B}$ agonist,

- Relaxes fundus & effective in functional dyspepsia

Both buspirone & sumatriptan have potential disadvantage of slowing gastric emptying

TARGETING PYLORIC FUNCTION

- Conceptually, gastric retention could be due to impaired relaxation of pyloric sphincter, which might be caused by a lack of normal inhibitory innervation through nitric-oxide-producing intrinsic neurons
- Nitric oxide exerts its effect through cyclic GMP as a mediator & sildenafil which protects second messenger from breakdown should mimic effects of nitric oxide release & relieve gastric retention
- Sildenafil did not improve emptying in pilot study of patients with diabetic gastroparesis, possibly because of its concurrent relaxatory action on fundus

TARGETING PYLORIC FUNCTION CONT'D

- Botulinum toxin A injected into pyloric area during endoscopy initially reported symptomatic improvement & acceleration of gastric emptying
- Two controlled trials did not demonstrate superiority over placebo

ANTIBIOTICS FOR TREATMENT OF BACTERIAL OVERGROWTH

- Gastric stasis can lead to bacterial overgrowth in stomach & intestine
- Patients with small intestinal bacterial overgrowth also present with symptoms similar to those of gastroparesis & various antibiotics used for bacterial overgrowth may also improve gastric motility
- Rifaximin has gained more recent attention since it is poorly absorbed & therefore works primarily in intestine with fewer potential side effects

Treatment of D.G

- Glycemic control- Depo-insulin to prevent hypoglycaemic episodes

- DIET MODIFICATION:

  Smaller/liquid meals, low-fat, low-fiber diet

  Jejunal tube feeding/ TPN

- MEDICATIONS-

  Prokinetics: Metoclopramide10to20mg, Erythromycin 125mgBD or TDS or IV200mg over5to10minutesTDS, Domperidone 10 to 30 mg.

  Antiemetics- (promethazine or prochlorperazine), scopolamine patch.

  Low-dose TCA

  5-HT3 receptor antagonists- odansetron, dronabinol

  Ghrelin- improves gastric emptying

Treatment of D.G

GES

A) Gastric pacing - improves gastric emptying

B) Neurostimulation - controls nausea/vomiting



Endoscopic therapy with injection of botulinum toxin into the pyloric sphincter

Gastric resection (Partial or complete) in medically refractory cases

Download to read offline

TABETIC PAIN



- sharp, sudden pain
- With nausea, vomiting, anorexia and weight loss- mimics intra-abdominal malignancy
- Diabetic *radiculopathy* of thoracic nerve roots
- The diagnosis- abnormal EMG of the anterior abdominal wall muscles

DIARRHEA

- Drugs- Metformin, ά-Glucosidase inhibitors ,sugarfree sweeteners.
- SIBO
- Pancreatic insufficiency
- Fast transit (and hyperthyroidism)
- Celiac disease(4%)
- Hormones- glucagon or somatostatin
- Autonomic neuropathy

Treatment

Download to read offline

- **Strict control of blood glucose**
- Broad spectrum antibiotics
- Vitamins, folic acid, liver extracts, bismuth, opiates, atropine
- Corticosteroids
- **Clonidine** (0.1 to 0.6 mg twice daily) stimulate intestinal absorption
- **Octreotide** (50 to 100 subcutaneously, BD) in refractory diabetic diarrhea
- **Codeine sulfate** (30 mg every six to eight hours),
- **Diphenoxylate** with atropine (Lomotil),
- **Loperamide**
- **Psyllium** hydrophilic mucilloid

D.M & celiac disease

- Coexist (4%)-shared HLA class II genes and non-HLA loci
- Found within 4 years of DM.
- Short stature, pubertal delay, - signs of vitamin deficit, anemia, losing weight and pigmentation,osteoporosis, and/or reproductive disorders
- Have poor glycemic control- hypoglycemic episodes, and microvascular complications.
- Small intestine which shows villous atrophy and abnormal superficial epithelium
- Malabsorbtion in diabetes-limited only to fats
- Respond to gluten free diet

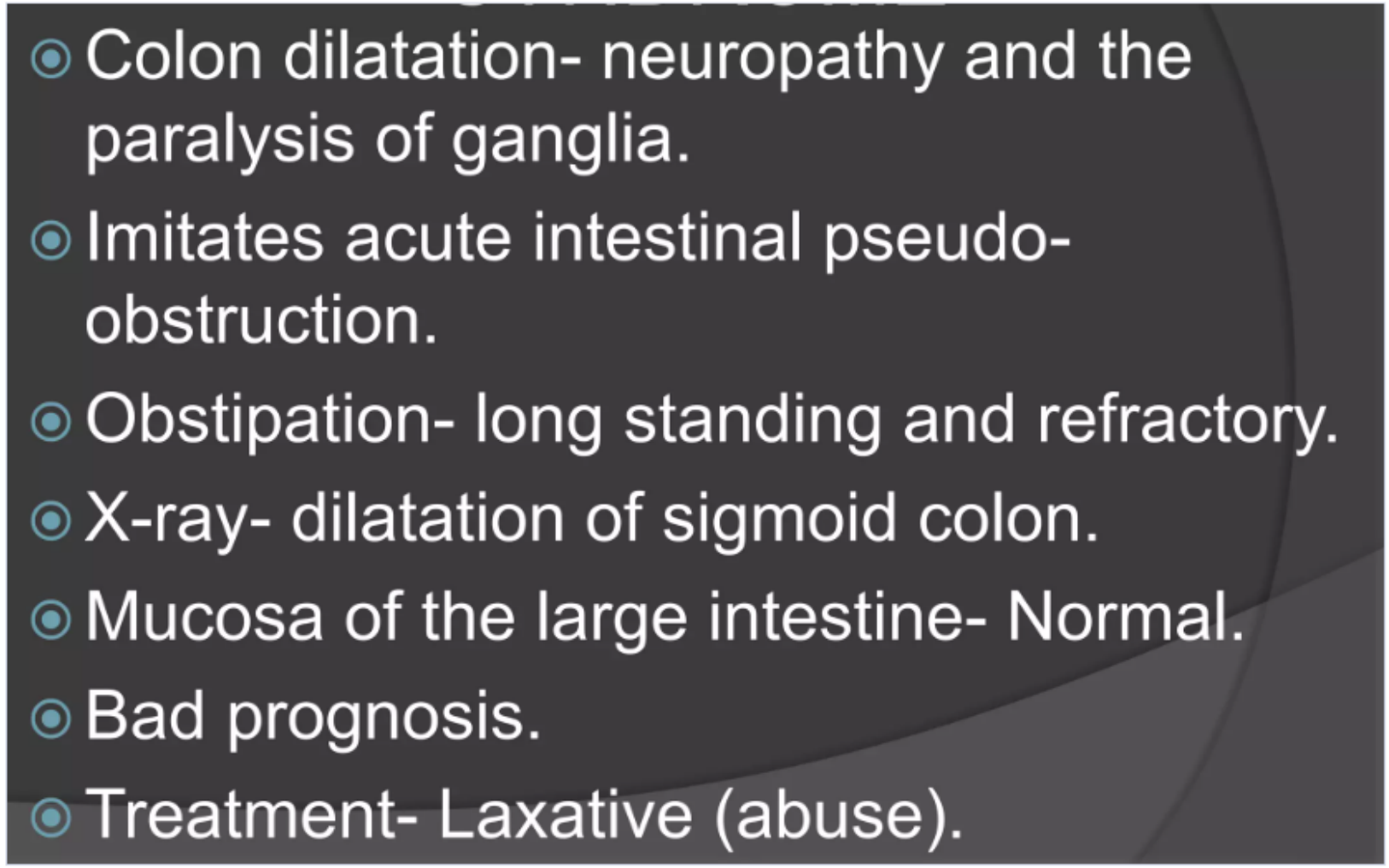
Large intestine

Download to read offline

- Constipation
- Impaired gastrocolic reflex and delayed colonic transit
- Ischemic colitis - luminal narrowing of submucosal arterioles.
- Neuropathy damages the motility.
- Equally frequent and severe without neuropathy
- Obstipation- nausea, vomiting, belching and bloating.

Megasigmoid syndrome

Download to read offline



Waiting for googleads.g.doubleclick.net...

Fecal incontinence

- The total stool volume is normal.
- Steatorrhea in 30%.
- Impaired internal anal sphincter resting tone and reflexive internal sphincter relaxation.
- Reduced sensitivity of the rectum to distension.
- Management:

  Antidiarrheal therapy

  Biofeedback training

  Sacral nerve stimulation

  Surgery

  In some patients incontinence remits spontaneously.

Diabetes-Liver/Biliary

HIGHER INCIDENCE OF ACUTE HEPATITIS B-1.4 vs 0.7 per 100,000 patients

HCV- patients have an increased risk of type 2 DM.
GALL BLADDER: acute cholecystitis postoperative complications are higher

GALLSTONES MORE FREQUENT (2X)

- lithogenic bile
- hypomotility
- prophylactic cholecystectomy.- not recommended

SOMATOSTATINOMA Triad- Gallstones, Diabetes, Diarrhea/Steatorrhea

STEATOSIS in upto 80%

DM is a risk factor for HCC.

Diabetes-NAFLD (MFLD)

Download to read offline

- Spectrum of disease:
  - Simple steatosis→steatohepatitis(NASH) → cirrhosis(20%).
  - Increase the risk of acute hepatic failure
- Risk Factors: female, diabetes, obesity, hyperlipidemia
- Fatty deposition, nuclear vacuolisation, cellular infiltration and fibriosis
- Cryptogenic cirrhosis → 70% obese/50% diabetic!!
- Cirrhosis of the liver may precede or cause diabetes→ glucose intolerant & 30%-60% develop DM

Treatment MFLD

- Slow/gradual weight loss
- Control diabetes/hyperlipidemia
- Pharmacologic treatment: TZD's, others
- Surgery:
  - Bariatric - improvement in 90%
  - Liver transplant(Cirrhotics)

pancreas

Download to read offline

- DM for more than 5 years
- Pancreatitis can produce diabetes
- Exocrine pancreas secretion- Deteriorates

- Diabetes and pancreatitis:
  Causes hyperglycemia
  May persist for several months
  Pancreatic calcifications
  Degenerative complications-less frequent

- Exocrine secretion-reduced volume & enzymes

Gall bladder

- Higher incidence- unexplained
- Defect in the cholinergic pathway
- Reduced α-adrenergic tone
- Deficiency of cholecystokinin receptors
- Arteriolar disease impairing muscle contraction
- Hyperglycemia
- Hyperinsulinemia

Carcinoma

- Insulin resistance→secondary hyperinsulinemia → ↓IGF-binding proteins → ↑IGF-1 & Growth hormone → cancer growth(Pancreas, liver & colon).
- Loss of weight and deteriorated glycoregulation.
- New onset diabetes >50 yrs.
- HbA1c > 7.5% → young age, more advanced tumor and poorer survival.
- Slow bowel transit time increase carcinogen exposure

Hyperthyroidism

- Diarrhea (small intestinal hypermotility-increase intestinal secretion due to intracellular CAMP-bile acid malabsorption)
- Minor histologic change in liver(transaminase elevation)
- Antithyroid drug cause hepatic injury.