Managing Gastrointestinal Complications of Diabetes Mellitus

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EDUCATIONAL OBJECTIVES

• Understand prevalence of gastrointestinal (GI) complaints in Diabetes Mellitus (DM)

• Understand co-existent conditions in DM affecting the GI system

• Appreciate all treatment options for GI issues related to DM
FACULTY Q&A

• We have little to offer patients with DM suffering from GI complaints – True or False?

• Pharmacologic treatments are the sole option that can be offered to diabetics with GI complaints – True or False?

• Coexistent conditions can worsen symptoms in these patients – True or False?
Worldwide Impact of Diabetes Mellitus (DM)

• Over 9% of the US population & more than 380 million people worldwide affected by DM

• Number likely to rise to almost 600 million by 2035

• Affects virtually every organ system with degree of involvement directly proportional to duration and severity of disease as well as comorbidities
Gastrointestinal (GI) Manifestations of DM

• Awareness is high, but GI complications are under-recognized and under-treated

• Diabetics are far more likely to experience GI symptoms compared with controls
GI Manifestations of DM

• GI organ systems influenced by DM
  • Oropharynx
  • Esophagus
  • Stomach
  • Small & Large Intestine
  • Anorectum
  • Liver

• Oncologic Concerns
Oropharyngeal Manifestations of DM

- Fungal infections
  - Up to 30% incidence of oral candidiasis
- Periodontal disease
  - Up to 60% incidence
- Mucosal ulcerations
- Xerostomia
- Aguesia
Esophageal Manifestations of DM

• Candidiasis
  • Odynophagia
  • Dysphagia
  • Heartburn-type pain
  • Bleeding (rare)

• Dyssmotility
  • Chest Pain
  • Dysphagia
  • Heartburn

• Gastroesophageal Reflux Disease (GERD)
Esophageal Manifestations of DM

• Dysmotility
  • Up to 63% prevalence
  • No difference between T1DM versus T2DM or between genders
  • Strong association with retinopathy
Esophageal Manifestations of DM

• Gastroesophageal Reflux Disease (GERD)
  
  • Up to 20% prevalence in the Western world in general population
  
  • Symptom prevalence in DM is up to 41% and strongly associated with peripheral neuropathy
  
  • Prevalence of erosive change is as high as 67% (neuropathy) and 33.3% (without neuropathy)
Gastric Manifestation of DM

• Gastroparesis
  • Objectively delayed gastric emptying in the absence of mechanical obstruction resulting in nausea, vomiting, early satiety, bloating, and/or upper abdominal pain

• 10 year incidence of symptomatic gastroparesis:
  • T1DM 5%
  • T2DM 1%
  • General population 0.2%

• Prevalence of symptomatic gastroparesis:
  • T1DM up to 65%
  • T2DM up to 30%
    • Early studies lacked benefit of intensive insulin therapy
Gastric Manifestation of DM

• Gastroparesis
  • 4:1 female predominance

• Risk factors:
  • Elevated HgbA1c
  • DM duration > 10 years
  • Presence of macro/microvascular complications
Gastric Manifestation of DM

• Gastroparesis
  • Weight loss may occur in up to 53% of patients but up to 24% may gain weight
  • 1/3 of patients have chronic symptoms with periodic exacerbations
  • 1/3 have chronic worsening symptoms
  • Succussion splash on bedside exam
Small & Large Intestine Manifestations of DM

- Enteropathy
- Small Intestine Bacterial Overgrowth (SIBO)
- Bile Acid Diarrhea
- Non-Tropical Sprue (Celiac Disease)
- Exocrine Pancreatic Insufficiency
Anorectal Manifestations of DM

- Incontinence

- Pelvic Floor Dyssynergia
Hepatic Manifestations of DM

• NAFLD

• NASH

• Glycogenic Hepatopathy
Oncologic Manifestations of DM

- Pancreatic Cancer
- Hepatocellular Carcinoma (HCC)
- Adenomatous Colon Polyps
- Colorectal Cancer
Mechanisms & Diagnosis of DM-related GI Complications

• Oropharyngeal and esophageal candidiasis
  • Candida normally colonize oral cavity of healthy patients
  • Hyperglycemia increases buccal mucin as well as glucose and decreases salivary lysozyme levels
  • Reflux-related inflammation weakens protective flora and weakens cellular barriers

• Periodontal disease
  • Compromised neutrophil function decreases adherence, chemotaxis, and phagocytic functions
Mechanisms & Diagnosis of DM-related GI Complications

• Esophageal Dysmotility & GERD
  • Sequelae of vagal (autonomic) neuropathy
    • Myenteric neurons
    • Interstitial cells of Cajal
    • Smooth muscle fibers
    • Structural remodeling of esophageal musculature
Mechanisms & Diagnosis of DM-related GI Complications

• Esophageal Dysmotility & GERD
  • Decreased amplitude and velocity of esophageal contractions
  • Reduced lower esophageal sphincter pressure
  • Increased number of transient lower esophageal sphincter relaxtions
  • Retrograde contractions
Mechanisms & Diagnosis of DM-related GI Complications

• Esophageal Dysmotility & GERD
  • Impaired clearance of esophageal liquid, food, secretions, and acid
  • Reduced sensitivity
    • Classic symptoms of heartburn and dysphagia are absent in a majority of patients due to damage of sensory afferent nerve fibers
  • Severity inversely proportional to glycemic control
Mechanisms & Diagnosis of DM-related GI Complications

• Esophageal Dysmotility & GERD
  • History
  • Endoscopic exam
  • pH probe (wireless vs catheter) +/- impedance
  • High resolution manometry +/- impedance
Mechanisms & Diagnosis of DM-related GI Complications

• Gastroparesis
  • Sequelae of inflammatory ganglia damage and dropout of vagal myelinated fibers
  • Abnormal myenteric neurotransmission
  • Impaired inhibitory NO-containing nerves
  • Damage to Interstitial cells of Cajal
  • Smooth muscle fibrosis
  • Abnormal macrophage-containing immune infiltrates
Mechanisms & Diagnosis of DM-related GI Complications

• Gastroparesis
  • Smooth muscle dysfunction

• Loss of normal migrating motor complexes

• Blunted antral contractions

• Pyloric spasm

• Poor meal accommodation

• Abnormal sensory feedback
Mechanisms & Diagnosis of DM-related GI Complications

• Gastroparesis
  • Likely a physiologic mechanism to slow release of foodstuffs into the small intestine based upon circulating levels of various constituents
    • Impaired medication absorption and episodes of unexplained hypoglycemia

• Tachygastria
  • Unexplained episodes of hyperglycemia
Mechanisms & Diagnosis of DM-related GI Complications

• Diagnosis of gastroparesis
  • Gastric emptying study (scintigraphy)
  • Upper endoscopy
  • Incidental finding of cross sectional imaging
  • Antroduodenal manometry
  • Must exclude rumination syndrome
Mechanisms & Diagnosis of DM-related GI Complications

• Small & Large Intestine
  • Enteropathy
    • Prevalence of autonomic (DM-related) diarrhea is up to 22%
      • Occult stool infection should always be excluded
    • Results from damage to myenteric nerve plexus due to autonomic neuropathy and fibrosis of intestinal muscular layers
  • Slow motility (versus dumping)
    • Sitz marker study
  • Increased nutrient diffusion distance resulting in disordered fluid transport and electrolyte exchange
Mechanisms & Diagnosis of DM-related GI Complications

- Small & Large Intestine
  - SIBO

  - Up to 60% incidence in DM

  - Maldigestion and/or malabsorption due to overabundance of bacteria or alteration in microbiome constituents resulting in enterocyte damage

  - Jejunal aspirate versus breath testing (hydrogen/methane)
Mechanisms & Diagnosis of DM-related GI Complications

• Small & Large Intestine
  • Bile acid-related
    • Reduced endogenous bile salt pool
      • Impaired ileal reabsorption from rapid small bowel transit
      • Bile acid deconjugation from SIBO
  • Medications
    • Metformin
    • Acarbose

• High FODMAPs diet
Mechanisms & Diagnosis of DM-related GI Complications

• Small & Large Intestine
  • Non-Tropical Sprue (Celiac Disease)
    • Upper endoscopy with small bowel biopsies
    • Tissue Transglutaminase/Anti-Endomysial Antibodies
    • HLA DQ-2/8 testing
  • Exocrine Pancreatic Insufficiency
    • Gas/Bloat
    • Weight loss
    • Abdominal pain
    • Steatorrhea
    • Fecal elastase/fat
    • CT/MRI/Endoscopic Ultrasound
Mechanisms & Diagnosis of DM-related GI Complications

• Anorectum
  • Fecal incontinence
    • Internal/External sphincter dysfunction secondary to autonomic neuropathy
    • Hyperglycemia can further inhibit external anal sphincter function and decrease rectal compliance
    • Voluminous stools overwhelm normal continence abilities
    • Anorectal dysfunction yields decreased sensation and reduced resting anal sphincter pressure
Mechanisms & Diagnosis of DM-related GI Complications

• Anorectum
  
  • Pelvic Floor Dyssynergia
    
    • Anorectal manometry
    
    • Balloon Expulsion Test
    
    • Defecography
Mechanisms & Diagnosis of DM-related GI Complications

• NAFLD
  • Hepatic manifestation of metabolic syndrome
  • Most common cause of chronic liver disease in North America
    • 30% of US population
    • Up to 87% of T2DM

• NASH
  • Up to 60% of T2DM
  • Need to exclude EtOH, steatogenic meds, or hereditary lipid disorder
  • Aside from progression to liver fibrosis and cirrhosis, HCC is dreaded complication that has been reported to occur in non-cirrhotic patients

• Glycogenic Hepatopathy
  • Hepatic manifestation of poorly controlled T1DM
Mechanisms & Diagnosis of DM-related GI Complications

• Oncologic Manifestations
  • Proposed mechanisms:

  • Insulin receptor and insulin-like growth factor 1 pathway
    • Elevated epidermal growth factor levels
      • Cell proliferation
      • Angiogenesis
      • Inhibited apoptosis
    • Elevated pro-inflammatory cytokines (IL-6)

  • Receptor for advanced glycation end products
    • Promotes inflammation and tumorigenesis
Treatment of DM-related GI Complications

• Oropharyngeal Candidiasis
  • Glycemic control
  • Good hydration
  • Anti-fungal treatments (topical and systemic)

• Periodontal Disease
  • Glycemic control
  • Strict oral hygiene with regular dental cleanings
Treatment of DM-related GI Complications

- Esophageal Candidiasis
  - Glycemic control
  - Avoid unnecessary/overaggressive acid-reduction
  - Anti-fungal treatments (topical and systemic)

- Dysmotility
  - Glycemic control
  - Acid suppression
  - Baclofen
  - Erythromycin
Treatment of DM-related GI Complications

• GERD
  • Glycemic control

• Weight loss
  • Exercise
    • 25-40 gram sugar restriction

• Avoidance of large meals

• Avoidance of meals within 4 hours of bedtime

• Avoidance of “trigger foods”

• Elevation of head of bed
Treatment of DM-related GI Complications

• GERD
  • Drink adequate fluids after pills and with meals

• H2 Blocker or Proton pump inhibitor

• Prokinetic agents
  • Metoclopramide
  • Domperidone
  • Erythromycin
Treatment of DM-related GI Complications

• Gastroparesis
  • Glycemic control

• 4-6 low fiber, low fat, low carb meals/day
  • Liquid-based meals in severe cases

• Avoiding meds that slow gastric emptying
  • Narcotics
  • Anxiolytics
  • Pramlintide
  • Exenatide
  • Liraglutide
  • THC
Treatment of DM-related GI Complications

• Gastroparesis
  • Prokinetic agents
    • Metoclopramide
    • Domperidone
    • Erythromycin
    • Haloperidol
  • Botox injection into pylorus during upper endoscopy
Treatment of DM-related GI Complications

• Gastroparesis
  • Gastric pacemaker
    • Extended benefits > 10 years have been reported yielding up to 80% reduction in nausea/vomiting
    • Improved nutritional status, metabolic dynamics, and quality of life
    • Decreased health care utilization
  • Surgery
    • Pyloroplasty has been reported to achieve 83% symptom reduction
    • Venting G-tube has shown mixed results
    • J-tube has been shown to reduce healthcare utilization
• TPN best suited for patients with severe gastroparesis complicated by severe small bowel dysmotility
Treatment of DM-related GI Complications

• Small & Large Intestine
  • Diarrhea
    • Glycemic control
  • Low FODMAPS diet
  • 25-40 gram sugar restriction
  • Decrease caffeine
  • Avoid smoking
Treatment of DM-related GI Complications

- Small & Large Intestine
  - Diarrhea
    - Rehydration
  - Electrolyte/vitamin/micronutrient replacement

- Medications
  - Loperamide
  - Lomotil
  - Clonidine
  - Cholestyramine
  - Octreotide
  - Codeine

- TPN may be needed in severe cases to avoid hypoglycemia as a result of insulin overwhelming impaired enteral nutrient delivery and/or delayed absorption
Treatment of DM-related GI Complications

- Small & Large Intestine
  - Constipation
    - Glycemic control
  - Hydration
  - Exercise
  - Fiber
- Medications
  - Stool softeners
  - Lubiprostone
  - Linaclotide
  - Minimize purgative laxatives
Treatment of DM-related GI Complications

• Small & Large Intestine
  • SIBO
    • Rifaximin (versus other antibiotics)
  • Probiotics
  • Prokinetics
  • Cyclic gut lavage
Treatment of DM-related GI Complications

• Anorectum
  • Incontinence
    • Glycemic control
  • Bulking agents
  • Medications

• Pelvic Floor Dyssynergia
  • Glycemic control
  • Diaphragmatic breathing
  • Biofeedback
Treatment of DM-related GI Complications

- NAFLD/NASH
  - Glycemic control

- Exercise

- 25-40 gram sugar restriction

- Weight loss (5-10% of total body weight)

- Control blood pressure and cholesterol
Treatment of DM-related GI Complications

• NAFLD/NASH (T2DM)
  • Meds
    • Vitamin E in non-diabetics
    • Statins
    • Metformin
    • Pioglitazone
    • GLP-1 analogues
      • Gastroparesis concerns
  • Bariatric surgery

• Bariatric endoscopy
Treatment of DM-related GI Complications

• Glycogenic hepatopathy (T1DM)
  • Glycemic control
  • Exercise
  • 25-40 gram sugar restriction
  • Weight loss
  • Control blood pressure and cholesterol
  • Insulin
Treatment of DM-related GI Complications

• Oncologic Concerns
  • Pancreatic CA
    • ≥3 first degree relatives with pancreatic cancer should be screened
  • Metformin (benefits may extend to HCC and CRC prevention)

• Elevated insulin levels and sulfonylurea use have been associated with increased risk of malignancy
Treatment of DM-related GI Complications

• Oncologic Concerns
  • HCC screening if known/suspected advanced fibrosis
    • Alpha Fetoprotein (AFP) and transabdominal ultrasound
    • Contrasted CT/MRI needed if AFP elevated

• Standard CRC screening guidelines
FACULTY Q&A

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FACULTY Q&A

• We have little to offer patients with DM suffering from GI complaints – False!

• Pharmacologic treatments are the sole option that can be offered to diabetics with GI complaints – False!

• Coexistent conditions can worsen symptoms in these patients – True!