

# 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)
- Dysmotility
  - 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 relaxations
  - 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
    - Liraglutamide
    - 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
    - $\geq 3$  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
    - Contrast 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!