The Impact of Obesity and Its Treatment on GI Disorders

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Disclosures

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Learning Objectives

• Discuss the GI disorders influenced by excess body fat with respect to their etiology and pathogenesis
• Assess the effects of weight loss on GI disorders and their risks
• Identify GI disorders that have occurred as a result of methods used to induce weight loss

Learning Objectives

Introduction

• Sometimes obvious, sometimes not, body weight and body fat distribution can strongly influence GI disorders
• The influence encompasses risk of occurrence, course of the disease once it has occurred, and response to treatments
• We will now discuss some of the obvious (and not-so obvious) GI conditions impacted by obesity and what is known about the effects of weight loss on these conditions

Medical Complications of Obesity

• Idiopathic intracranial hypertension
• Cataracts
• Coronary heart disease
• Diabetes mellitus
• Dyslipidemia
• Hypertension
• Gynecologic abnormalities
• Abnormal menses
• Infertility
• Poly cystic ovarian syndrome
• Osteoarthritis
• Phlebitis
• Venous
• Stasis
### Gastroesophageal Reflux Disease

- Prevalence is strongly correlated with increasing BMI
- Also correlated with distribution of fat
  - Abdominal obesity
  - Pregnancy
- Mechanical mechanism is most likely the primary etiology
- Weight loss has been shown to reduce symptoms

### Lower GI Tract

- Diverticular disease
  - Dietary fiber level inversely correlated to prevalence
  - Obesity increases risk; unclear if independent of diet
  - Weight loss does not clearly reduce risk or complications
- Colorectal cancer
  - Also likely a diet effect rather than a primary obesity effect

### Hepatobiliary Diseases

- Non-alcoholic fatty liver disease
- Gallbladder disease
  - Cholelithiasis: Classic risks = the 3 “Fs”
    - Increased risk with rapid weight loss
      - Bile saturation and gallbladder stasis
    - Preventive measures: fat in diet, bile-salt prophylaxis
- Gallbladder cancer
- Hepatocellular carcinoma

### Specific Dieting Problems: Gallstones

- Rapid weight loss and prolonged fasting are associated with a high risk of gallstone formation (gallbladder stasis, increased cholesterol saturation of bile)
- Prevention strategies: Dietary
  - Limitation of weight loss to a moderate rate (maximum of 1.5 kg/3.3 lb/week) may prevent gallstone formation (evidence level 2A)
  - Addition of 10 g fat to a low-calorie diet has also been shown to prevent gallstone formation at evidence level 1B evidence, probably because of enhanced gallbladder emptying
  - Placebo-controlled study: Addition of polyunsaturated fatty acids has prevented gallstone formation, although only 6-week follow-up (evidence level 2B)

### Specific Dieting Problems: Non-Alcoholic Fatty Liver Disease

- Extremely common
  - Incidence rising with obesity and T2DM
  - Often benign, but may appear as NASH and lead to fibrosis and cirrhosis, and even hepatocellular carcinoma
- Treatment remains challenging
  - Thiazolidinediones (pioglitazone) target insulin resistance and adipose tissue dysfunction or inflammation that promotes hepatic “lipotoxicity” in NASH
  - In non-diabetic patients with NASH, studies have reported variable degrees of histologic benefit with TZDs
- Weight loss generally improves NAFLD and NASH

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**BMI** = body mass index.

**NAFLD** = non-alcoholic fatty liver disease.

**NSAID** = non-steroidal anti-inflammatory drug.

**T2DM** = type 2 diabetes mellitus; **NASH** = non-alcoholic steatohepatitis; **FFA** = free fatty acids; **TG** = triglycerides; **TZD** = thiazolidinediones; **NAFLD** = non-alcoholic fatty liver disease.
Researchers from Seattle VA investigated whether dietary nutrient composition was associated with the subsequent development of cirrhosis or liver cancer in the United States using NHANES data. During follow-up of 13.3 years, 118 new patients with cirrhosis; 5 liver cancer—these individuals were more likely to be older, more obese with more central fat distribution, lower education, higher EtOH, and more males, with diabetes mellitus and non-whites. Diets high in protein and cholesterol were linked to a higher risk of hospitalization or death due to cirrhosis or liver cancer. Diets high in carbohydrates were associated with a lower risk. Diets high in protein and cholesterol were linked to a higher risk of hospitalization or death due to cirrhosis or liver cancer. Drugs blocking intestinal cholesterol absorption might reduce the progression of fatty liver disease, but prospective studies are lacking.

Obesity is associated with an increased risk of cancer in general. And certain GI/liver cancers in particular...

Patients who are obese are twice as likely to develop esophageal adenocarcinoma. Most studies have not observed increases in risk with obesity in squamous cell cancer of the esophagus. Diet does affect both types of esophageal cancer, with a higher intake of fruits and vegetables associated with reduced incidence. Aspirin and other NSAIDs are currently the most promising chemoprevention.

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Has been found to be associated with obesity, particularly among women. May be due to the higher frequency of gallstones among obese individuals. Gallstones are a strong risk factor for gallbladder cancer.
**Inflammation and Cancer**

- Chronic inflammation is associated with a high cancer risk
- Chronic inflammation produces:
  - Free radicals and aldehydes, which can induce deleterious gene mutations
  - Cytokines, growth factors, and transcription factors, which control the expression of suppressor genes, oncogenes and inducible NO synthase and COX-2
- The pro-cancerous outcome of chronic inflammation is increased DNA damage, DNA synthesis, cellular proliferation, disruption of DNA repair, inhibition of apoptosis, and promotion of angiogenesis and invasion
- Chronic inflammation is also associated with immunosuppression, which is also a risk factor for cancer

**Inflammation**

- Chronic disease states, especially cancer and heart disease, are associated with oxidative stress as a result of inflammation
- Oxidative stress leads to the formation of free radicals (O-)
- High dietary fat (especially saturated/ trans/omega-6 fats), simple sugars, and obesity increase inflammation and oxidative stress
- Omega-3 fatty acids have anti-inflammatory effects, suppress IL-1-beta, TNF-alpha, IL-6, and reduce cancer cell growth in culture
- Omega-3 PUFA and flavonoids could be used therapeutically against inflammation that is mediated by environmental pollutants (such as heavy metals and organics)

**Colorectal Cancer**

- Ca colorectum is more frequent in obese than lean, especially for men
  - Weaker or absent in studies of women
- Unlike for breast and endometrial cancer, estrogen appears to be protective vs that for colon cancer in women
- High fat and meat intakes are more common among those who are obese, and this increases bile acid production (damage DNA and colonocytes)
- Fatty diets increase oxidative stress, as does Fe in meats (catalyzes oxidative reactions), and carcinogenic heterocyclic amines found in cooked meats

**Risk Modifiers for Colorectal Cancer**

- Fiber: Soluble vs insoluble
  - Shortens GI transit time/contact with bile acids
- Fat and obesity
- Calcium
- Physical inactivity
- Fruits and vegetables
- Aspirin/NSAIDs
Colon Cancer and Diet

- Low fat, low red meat, high fruits and vegetables (RR, 0.48), and regular physical activity have major potential for primary prevention
- Calcium supplementation has been shown to reduce formation of premalignant lesions/adenomas
- Aspirin, NSAIDs, and selective COX-2 inhibitors have potential to reduce colorectal cancer and adenomas (in FAP, regress polyps)
- Issue of safety remains

Potential Complications of Surgical Weight Loss

- Mortality rate after discharge, possibly due to pulmonary emboli or arrhythmia (not yet certain)
- Acute complications
  - Hemorrhage, leaks, bowel obstruction, infection, blood clots
- Long-term complications
  - Nutritional deficiency: Fe and B vitamin
  - Neuropathies; especially from thiamine deficiency
  - Internal hernias
  - Gallstones
  - Nausea
- GI disorders associated with surgical weight loss
  - Marginal ulcers
  - Dumping syndrome
  - Hypoglycemia
  - B12 deficiency

What’s the “Take Home”?

- Obesity has a major influence on the GI tract and liver
- Obesity affects not only incidence and prevalence rates but also treatment efficacy and options
- The GI conditions related to obesity cover the gamut from gastroesophageal reflux disease to fatty liver to almost all types of GI cancer
- The mechanisms include mechanical/physiologic factors, inflammation-dependent pathways, and hormonal factors
- Weight loss can also result in GI complications, especially following bariatric surgery

Questions?