Definition, Pathogenesis, and Management of That Cursed Dyspepsia

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IM F1 김영기
Dyspepsia

- Umbrella term to refer number of nonspecific symptoms originate from UGI
- Minority: potentially life threatening ↔ Majority: functional
- Difficult to definition and manage functional dyspepsia (FD)

- Crean et al (1994), “Dyspepsia is episodic recurrent or persistent abdominal pain or discomfort, or any other symptoms referable to the upper alimentary tract, excluding bleeding or jaundice, of duration 4 weeks or longer, including abdominal pain/discomfort, heartburn or other manifestations of gastroesophageal reflux, anorexia, nausea and vomiting, flatulence or air eructation (belching, burping or aerophagy), early satiety or undue repletion after meals, abdominal distension or ‘bloating’

- Overlap? GERD, IBS
Functional dyspepsia (FD)

- Functional = “nonstructural” or “non-organic”
- No gold standard for the definition of FD
- Diagnosis of exclusion after exclusion of all organic causes
- Geographic variation: related in large part to *H.pylori* prevalence
- Problem of misunderstanding on the very symptoms of sufferer
- Physician bias: less commonly used in the US, where FD-type symptoms are designated as GERD.

  - Reflux type, ulcer type, dysmotility type, unspecified

  - **Post-prandial distress syndrome (PDS):** meal-induced dyspeptic symptoms; bothersome postprandial fullness; early satiety (+epigastric pain or burning that worsens with meals, on Rome IV) for ≥3 d/wk;
  - **Epigastric pain syndrome (EPS):** occurred in between meals; epigastric pain and/or burning for ≥1 d/wk.

- Excluded prominent heartburn or satisfied criteria for IBS

**Table 1. Rome III Functional Gastrointestinal Disorders**

A. Functional esophageal disorders
   - A1. Functional heartburn
   - A2. Functional chest pain of presumed esophageal origin
   - A3. Functional dysphagia
   - A4. Globus

B. Functional gastroduodenal disorders
   - B1. Functional dyspepsia
     - B1a. Postprandial distress syndrome
     - B1b. Epigastric pain syndrome
   - B2. Belching disorders
     - B2a. Aerophagia
     - B2b. Unspecified excessive belching
   - B3. Nausea and vomiting disorders
     - B3a. Chronic idiopathic nausea
     - B3b. Functional vomiting
     - B3c. Cyclic vomiting syndrome
   - B4. Rumination syndrome in adults

C. Functional bowel disorders
   - C1. Irritable bowel syndrome
   - C2. Functional bloating
   - C3. Functional constipation
   - C4. Functional diarrhea
   - C5. Unspecified functional bowel disorder

D. Functional abdominal pain syndrome

E. Functional gallbladder and Sphincter of Oddi (SO) disorders
   - E1. Functional gallbladder disorder
   - E2. Functional biliary SO disorder
   - E3. Functional pancreatic SO disorder

F. Functional anorectal disorders
   - F1. Functional fecal incontinence
   - F2. Functional anorectal pain
     - F2a. Chronic proctalgia
     - F2a1. Levator ani syndrome
     - F2a2. Unspecified functional anorectal pain
     - F2b. Proctalgia fugax
   - F3. Functional defecation disorders
     - F3a. Dyssynergic defecation
     - F3b. Inadequate defecatory propulsion

G. Functional disorders: neonates and toddlers
   - G1. Infant regurgitation
   - G2. Infant rumination syndrome
   - G3. Cyclic vomiting syndrome
   - G4. Infant colic
   - G5. Functional diarrhea
   - G6. Infant dyschezia
   - G7. Functional constipation

H. Functional disorders: children and adolescents
   - H1. Vomiting and aerophagia
     - H1a. Adolescent rumination syndrome
     - H1b. Cyclic vomiting syndrome
     - H1c. Aerophagia
   - H2. Abdominal pain-related functional gastrointestinal disorders
     - H2a. Functional dyspepsia
     - H2b. Irritable bowel syndrome
     - H2c. Abdominal migraine
   - H2d. Childhood functional abdominal pain
     - H2d1. Childhood functional abdominal pain syndrome
   - H3. Constipation and incontinence
     - H3a. Functional constipation
     - H3b. Nonretentive fecal incontinence

- Despite the fundamental change, sensitivity or specificity to identify FD was not different from previous criteria
FD: Rome IV (2016)

• FD should no longer be considered as a single disease entity but rather as a **spectrum** where there is significant **overlap** with GERD and IBS.

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<td><strong>D. Centrally Mediated Disorders of Gastrointestinal Pain</strong></td>
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<td>D1. Centrally mediated abdominal pain syndrome (CAPS)</td>
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<td>D2. Narcotic bowel syndrome (NBS)/Opioid-induced GI hyperalgesia</td>
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</tbody>
</table>

• Bothersome; occur more frequently than normal population
Epidemiology of FD

- Prevalence: 10~30% (problem of definition)
- Global pooled prevalence: 21%
- Western (ulcer-like, reflux-like) > Eastern (dysmotility like)
- SES tends to low in western, while high in Eastern.
- *H. pylori* eradication is more effective for Sx in Eastern.
- Higher economic impact in Western.
Pathophysiology of FD

Delayed gastric emptying
- Traditionally, thought to be one of the main players.
- 20~50% among dyspepsia sufferers
- 1.5 times slower on gastric emptying of solid than control subjects
- Symptom overlap between PDS and idiopathic gastroparesis
- Post-prandial fullness: related with delayed gastric emptying vs. other symptoms: not related with delayed gastric emptying
- Paradoxically rapid gastric emptying in small population
Pathophysiology of FD

**Impaired accommodation**
- Ingestion $\rightarrow$ vasovagal reflex $\rightarrow$ nitrergic nerve $\rightarrow$ fundus & HB relax
- Antrofundic reflex
- 40% in FD
- Early satiety: related with
- Barostat: gold standard, but invasive
- Drink challenge test: lower volume in FD
- US, SPECT, MRI

**Hypersensitivity**
- Barostat
- 34% in FD
- Postprandial epigastric pain, belching, weight loss
**Pathophysiology of FD**

**Duodenal hypersensitivity to acid and lipid**
- 59% of FD developed nausea during a brief period of duodenal acid perfusion
- Reduced clearance of exogenously administered acid from the duodenal bulb
- Directly via duodenal receptors and sensory nerves or indirectly through feedback changes in proximal gastric function
- Intraduodenal infusion of lipids sensitized the stomach to distention and provoked symptoms of fullness, discomfort, and nausea
Pathophysiology of FD

Postinfectious

- *De novo* development of FD following an enteric infection
- Early satiety, nausea, weight loss; symptoms were attributed to impaired accommodation resulting from dysfunction of gastric nitrergic neurons.
- *Salmonella enteritis*: the relative risk for the development of FD was 5.2
- *Giardia lamblia* infection has been shown to provoke visceral hypersensitivity and delay gastric emptying
Pathophysiology of FD

**Inflammation**
- PI-FD: CD8+↑, CD4+↓, MΦ ↑ in duodenum
- Not confined to PI-FD, mast cell ↑ in FD
- EC cells↑ in PI-FD
- Augmented expression of histamine, serotonin, and tryptase in gastric mucosal biopsy samples in FD
- Systemic inflammation↑
Duodenal eosinophilia (not gastric)
- OR for the FD in subjects with high duodenal bulb Eo counts was 11.7
- Early satiety, postprandial fullness: 2nd portion
- Abdominal pain: bulb & 2nd portion
- Related with PDS and allergy
Pathophysiology of FD

**H. pylori infection**
- via a variety of disturbances in acid secretion, motility, and neuroendocrine signaling
- may influence gastric hypersensitivity (effect of inflammation)
Pathophysiology of FD

- Psychosocial: stress, anxiety, depression
- Diet: salty, hot
- Lifestyle: tobacco, alcohol, NSAID
- Ehlers-Danlos type III
Management of FD

- **Reassure** (must not belittle)
- **Diet:** Visceral adiposity, canned food, alcohol weekly, high fat, salt, fermentable oligosaccharides, disaccharides, monosaccharides, and polyols, carbonated drinks, hot spices
- **Antidepressants:** TCA (not SSRI); amitriptyline 50 mg qd > escitalopram 10mg (ulcer-like epigastric pain & normal gastric emptying)
- **Eradication of *Helicobacter pylori***: small population (10%) but significant
- **Prokinetic agents:** metoclopramide, domperidone, mosapride, cinitapride > domperidone in post-prandial fullness, early satiation, bloating itopride: meta-analysis, phase II, (not in phase III)
  acotiamide: phase II, large multicenter phase III in Japan (post-prandial distress, early satiation, bloating)
- **Enhancing gastric accommodation:** buspirone (post-prandial fullness, early satiation, bloating)
- **Nonpharmacologic therapies:** psychotherapy, acupuncture (high risk of bias)
- **Herbal medicine:** Iberogast (Germany), Rikkunshito (Japan), Menthacarin
- **Novel approaches:** cannabinoid-1 receptor, a novel target
Dyspepsia: a Clinical Guide

Uninvestigated dyspepsia

“Test and treat”
Works best if high background rate of *H pylori*

“Test and treat”
Works best if high background rate of *H pylori*

Endoscopy

Fails

Empiric PPI
Works best if reflux-type symptoms present

Fails

Negative

Functional dyspepsia
Options include: diet, prokinetics/neuromodulators, antidepressants, non-pharmacologic approaches
Driven by symptoms

Pain
Tricyclic antidepressant

Nausea
Anti-emetic

Early satiety, post-prandial fullness
Buspirone

Positive

Organic dyspepsia
Conclusion

- Dyspepsia is difficult to define and manage