MECHANISMS OF HUMAN DISEASE:
MALABSORPTION LECTURE

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This handout is intended as a narrative supplement to the first half of the lecture slides (up to the point of clinical signs/symptoms of malabsorption and specific disease states). It should improve contextual understanding of the process of digestion and absorption. It walks you through digestion and absorption starting from the mouth down to the colon. It provides a narrative summary to explain the slides in more detail. It also incorporates pathophysiology by highlighting specific diseases that affect the different stages and locations of digestion and absorption. It will be helpful to refer to the slides as you read through the handout—the diagrams and summaries will enhance your understanding of the text and vice versa. Reading the summary will be similar to attending the first part of the class lecture, and most of the concepts will be repeated.

DIGESTION AND ABSORPTION-A COMPLICATED JOURNEY

One can’t understand malabsorption if one doesn’t understand absorption. Absorption is generally divided into three phases:

1. Luminal Phase (processing of nutrients within the lumen of the intestinal tract beginning with the mouth and ending with the colon, also called digestion)
2. Mucosal Phase (taking nutrients from the intestinal lumen and transporting/processing them across the intestinal lining and into the body, also called absorption)
3. Transport Phase (moving the processed nutrients to distant targets for storage and utilization, also called assimilation). The transport phase will not be a focus of this lecture.

Like most physiological processes, digestion and absorption are highly complex, highly regulated processes involving multiple organ systems. A defect in any one of the systems can cause malabsorption.

ORGAN SYSTEMS INVOLVED IN DIGESTION, ABSORPTION, AND ASSIMILATION

Mechanical (Chewing, Trituration, Peristalsis)
Enzymatic/Chemical (amylase, HCL, pepsin, lactase)
Hormonal (CCK, peptide YY)
Structural (Villi, intestinal length, IC valve)
Transport proteins/barrier function (GLUT, desmosomes)
Microbiome (Vit K, fermentation)
Lymphatic (chyle transport)
Vascular (nutrient transport, tissue oxygenation)
Metabolic (mitochondria, glycogen storage/glycolysis)
Neurologic (control center)
Electric (gastric pacemaker waves)
Digestion begins in the mouth. One ingests food, and multiple neural mechanisms stimulate secretion of salivary amylase while muscles of mastication and deglutition physically breakdown the food into a bolus that is then passed into the oropharynx and down the esophagus. Two examples of a break-down in the process include Sjogren’s syndrome where there is lack of saliva and neuromuscular disorders that impair the complex swallowing reflex. Additional pathological processes such as Scleroderma or Chagas disease also impair digestion and absorption by hindering passage of food through the esophagus.

Digestion continues in the stomach, requiring an adequately functioning neurological, hormonal, electrical, and chemical system. The lower esophageal sphincter must open to allow passage of the food bolus from the esophagus into the stomach. Achalasia can impair this process. The fundus of the stomach must expand to accommodate the food bolus. Functional dyspepsia is thought to be, in part, due to inadequate fundal accommodation. Gastric muscles must propel the food toward the antrum where repeated electrical waves called migrating motor complexes (MMCs) stimulate trituration, the process by which the stomach grinds food into ever-smaller particles. Gastroparesis impairs both trituration and passage of stomach contents into the small intestine. Neuro-hormonal feedback mechanisms respond to the presence of food in the lumen by secreting hormones such as gastrin which then stimulate the release of HCL which activates pro-enzymes, aids in digestion and absorption of micronutrients, and provides anti-bacterial properties. Pepsinogen is a pro-enzyme which is activated by HCL into pepsin. Pepsin, along with pancreatic proteases, breaks down proteins. HCL also activates gastric lipase, thus initiating fat digestion. Intrinsic factor (crucial for absorption of vitamin B12) and gastric amylase (breaks down carbohydrates) are also secreted in the stomach. Pernicious anemia, which targets the cells that make intrinsic factor, prevents absorption of vitamin B12. Proton pump inhibitors, which raise the gastric pH, inhibit absorption of iron because iron absorption requires an acidic environment. Zollinger-Ellison causes excess secretion of gastrin which in turn causes excess secretion of HCL thus inactivating pancreatic enzymes and bile acids in the small intestine, leading to malabsorption of fats, carbohydrates, and proteins.

After digestion in the stomach, the food bolus (now called chyme), moves into the small intestine. The small intestine is the site of absorption of almost all micro and macro-nutrients (a notable exception is small chain fatty acids such as butyrate which can be absorbed directly by the colon and become an important source of energy in patients with short bowel syndrome). Numerous processes occur throughout the small intestine, and nutrients are digested and absorbed in different regions along the way. If one knows the site of absorption of the various nutrients (iron and calcium in the duodenum, B12 in the ileum, etc), one can predict the consequences of a loss of any specific intestinal segment.

When chyme enters the duodenum, neuro-hormonal and chemical mechanisms stimulate pancreatic and biliary secretions. Pancreatic enzymes (amylase, lipase, protease) breakdown complex carbohydrates, intact lipids and proteins into simple carbohydrates, hydrolyzed proteins (single peptides, di and tri-peptides), and fat products (mono/triglycerides, free fatty acids, glycerol, sterols, phospholipids). Brush border enzymes further digest the carbohydrates into simple sugars such as glucose which can then be absorbed through facilitated diffusion by various pumps (such as the GLUT-2 glucose transporter) or by passive diffusion across the membrane. Lack of the brush border enzyme lactase causes one of the most common disorders of malabsorption in the world (lactose intolerance). Intestinal infections such as viral gastroenteritis can also cause a reversible loss of brush border enzymes that temporarily results in diarrhea and malabsorption until the enzymes are replated.

Bile salts and phospholipids form micelles around long-chain triglycerides (13 to 24 carbon atoms) to move them to the mucosal barrier and facilitate passive diffusion into the cell. Small and medium-chain triglycerides (<6 and
6-12 carbon atoms respectfully) have a unique property in that they can be absorbed directly across the intestinal lining without the need of pancreatic enzyme digestion or micelle formation. While medium-chain triglycerides (MCTs) can be an important source of calories for patients with Exocrine Pancreatic Insufficiency, much of the public hype surrounding MCT’s (aiding in weight loss, brain function, energy, and longevity) is overblown. Given the central role of pancreatic enzymes in digestion and absorption, malabsorption and weight loss are central features of Cystic Fibrosis and Chronic Pancreatitis where secretion of pancreatic enzymes is impaired. Anything that blocks biliary ducts or causes cholestasis (e.g. Primary Sclerosing Cholangitis or cirrhosis) can cause the same problem. Steatorrhea (fatty diarrhea) is the classic symptom that results.

After micronutrients and macronutrients are broken down and packaged in the lumen, they must cross the small intestine mucous membrane in order to enter the body. The lining of the small intestine plays a crucial role. It is covered in microstructures called villi, literally “fingers” projecting into the lumen that provide 250 square meters of absorptive area in the span of up to 23 feet! That’s the size of a tennis court! The interface between the lumen and the villi is called the brush border. There are several layers to the brush border (refer to the lecture slides for a diagram), including the unstimred layer, glycocalyx, cell membrane, enterocyte cytoplasm, basal or lateral membrane, intercellular space, basement membrane, and the capillary/lymph vessel membrane. Nutrients pass through this barrier via passive diffusion (direct un-aided movement from the lumen into the cell), facilitated diffusion (use of membrane-bound pumps and transporters), or active transport (fat and protein movement from the cell through the lymphatics and portal system). Disorders at the brush border level such as lack of transporters [the rare Glucose transporter type 1 (Glut1) deficiency syndrome], inflammation that flattens villi (Celiac disease), infiltrative diseases that invade the villi (amyloidosis), or disorders causing lymphatic or venous outflow obstruction (congenital lymphangiectasia or portal hypertension in cirrhosis) can all cause varying degrees of malabsorption.

Micro and macronutrients are absorbed throughout the small intestine. Most divalent cations (iron, calcium) and water-soluble vitamins are absorbed in the duodenum; therefore, patients with Celiac disease (where there is significant damage to the duodenum) will commonly develop folate deficiency, iron deficiency and calcium malabsorption. Patients with H. Pylori infection also often display iron deficiency which is due to a combination of inflammation and the achlorhydric state in the stomach that inhibits iron absorption (iron absorption requires acid). H. Pylori carriers can also develop vitamin B12 deficiency, but Celiac patients only rarely display vitamin B12 deficiency. This is because Celiac disease does not usually affect the stomach, so the acidic environment is preserved, and the terminal ileum is rarely affected. Vitamin B12 absorption depends upon an acidic stomach environment, just as iron does, which is why H. Pylori infection can cause deficiencies of both nutrients.

The duodenum is also the main site of mixing of pancreatic and biliary secretions with chyme from the stomach. Surgical procedures that alter native intestinal anatomy (gastric bypass for weight loss, Whipple’s procedure for pancreatic cancer, liver transplant) can cause a significant degree of malabsorption by altering the location of mixing of chyme and secretions. After such surgeries, the chyme usually enters a section of the jejunum that has been anastomosed to the stomach, but the bile and pancreatic secretions do not enter the jejunum until much further downstream. This impairs the initial breakdown phase of fats, protein, and carbohydrates. Patients often develop bacterial overgrowth in the excluded limbs which further impairs absorption.

The jejunum is the “workhorse” of the small intestine and is the site of the majority of macro-nutrient (fat, protein, carbohydrate) absorption. Ninety percent of absorption occurs in the first 100 cm of the jejunum. As crucial as the jejunum is to absorption, one can tolerate loss of the jejunum (such as through trauma) relatively well because the ileum is able to adapt to perform the absorptive function of the jejunum. Unfortunately, the jejunum is not very adaptable, and loss of the ileum (the site of vitamin B12 and bile salt reabsorption) is more poorly tolerated.
The ileum comprises only 2/5 of the length of the entire small intestine; however, it has some very specific roles in digestion and absorption that cause great problems if it is removed or diseased. The Vitamin B12-intrinsic factor complex is absorbed in the distal ileum, and loss of the ileum such as in Crohn’s disease is a common cause of Vitamin B12 deficiency. The ileum also is the site of peptide YY secretion which mediates the “ileal brake” mechanism—when lipids reach the ileum, it releases peptide YY which signals the stomach and jejunum to slow down. Loss of the ileal brake contributes to diarrhea in short bowel syndrome and severe Crohn’s disease where large portions of the ileum have been removed or damaged. The ileocecal (IC) valve also provides a physical barrier between the small intestine (where there are few bacterial colonies to inhibit digestion) and the colon. Loss of the IC valve through surgery or disease (common in Crohn’s disease) can lead to small intestine bacterial overgrowth which also can cause malabsorption (primarily fat malabsorption through deconjugation of bile salts) and vitamin B12 deficiency (selectively consumption of vitamin B12).

While many people overlook the role of the colon in digestion and absorption, it can play an important role in disease where large portions of the small intestine have been removed. The colon is the primary site of water and electrolyte reabsorption-90% of the fluid that enters the colon will be reabsorbed. It can also adapt to loss of the small intestine by lengthening and dilating thus improving its absorptive capacity. It has a limited but important ability to absorb short chain fatty acids which are by-products of bacterial fermentation of carbohydrates. Indeed, butyrate is the primary fuel source for the colonocyte. Short bowel syndrome patients with at least part of their colon or most of their colon fair far better than short bowel syndrome patients with a jejunostomy or ileostomy because they are able to reabsorb most of the fluid losses.

The remainder of the slides from the lecture discuss the clinical manifestations of malabsorption, the evaluation of malabsorption, and specific disease states. This will be discussed in detail during the lecture.