Malabsorption

Digestion and Absorption

Carbohydrates

The digestion of carbohydrates begins in the mouth. The salivary enzyme amylase begins the breakdown of food starches into maltose, a disaccharide. As the food travels through the esophagus to the stomach, no significant digestion of carbohydrates takes place. The acidic environment in the stomach stops amylase from continuing to break down the molecules.

The next step of carbohydrate digestion takes place in the duodenum. The chyme from the stomach enters the duodenum and mixes with the digestive secretions from the pancreas, liver, and gallbladder. Pancreatic juices also contain amylase, which continues the breakdown of starch and glycogen into maltose and other disaccharides. These disaccharides are then broken down into monosaccharides by enzymes called maltase, sucrase, and lactase. Glucose and galactose are absorbed across apical membrane of enterocytes by secondary active transport via Na^+- glucose co-transporter , fructose is absorbed across apical membrane of enterocytes by facilitated diffusion

Protein

A large part of protein digestion takes place in the stomach. The enzyme pepsin plays an important role in the digestion of proteins by breaking them down into short peptides, short chains of four to nine amino acids. In the duodenum, other enzymes – trypsin, chymotrypsin, and elastase – act on the peptides, reducing them to smaller peptides. These enzymes are produced by the pancreas. Further breakdown of peptides to single amino acids is aided by enzymes called peptidase. The amino acids are absorbed into the bloodstream through the small intestine.

Lipids

Lipid (fat) digestion begins in the stomach with the aid of lingual lipase and gastric lipase. However, the bulk of lipid digestion occurs in the small intestine due to pancreatic lipase. When chyme enters the duodenum, the hormonal responses trigger the release of bile. Bile aid in the digestion of lipids, primarily triglycerides, through emulsification. Emulsification is a process in which large lipid globules are broken down into several small lipid globules. These small globules are widely distributed in the chyme rather than forming large aggregates. Lipids are hydrophobic substances. Bile contains bile salts, which have hydrophobic and hydrophilic sides. The bile salts'

hydrophilic side can interface with water, while the hydrophobic side interfaces with lipids, thereby emulsifying large lipid globules into small lipid globules.
Emulsification is important for the digestion of lipids because lipases can only efficiently act on the lipids when they are broken into small aggregates. Lipases break down the lipids into fatty acids and glycerides. These molecules can pass through the plasma membrane of the cell to enter the epithelial cells of the intestinal lining, then entering the lymphatic vessels. From there, they enter the blood.

Malabsorption

It is disorder of diminished intestinal absorption of one or more dietary nutrients. It can result from a defect in the nutrient digestion in the intestinal lumen or from defective mucosal absorption. Malabsorption disorders can be categorized into generalized mucosal abnormalities usually resulting in multiple nutrient malabsorption and specific nutrient malabsorption disorders (carbohydrate, fat, protein, vitamin, mineral malabsorption).

Malabsorption Disorders Associated with Generalized Mucosal Defect

1- Food- induced enteropathy
Gluten-sensitive enteropathy
Cow's milk intolerance

3- Congenital bowel mucosal defects
Microvillus inclusion disease

3- Infectious induced enteropathy
Parasitic infections, e.g. Giardia, cryptosporidium
Bacterial overgrowth
Tropical sprue
Postinfectious enteropathy

4- Protein-losing enteropathy
Lymphangiectasia (congenital and acquired)
IBD

5- Immunodeficiency disorders
Congenital immunodeficiency disorders
Acquired immune deficiency

6- Autoimmune enteropathy

7- Miscellaneous
Short bowel syndrome
Blind loop syndrome
Radiation enteritis
Protein–calorie malnutrition

Clinical manifestations

The common presenting features are diarrhea, abdominal distention, and failure to thrive and its sequels. The nutritional consequences of malabsorption are more dramatic in young children because the limited energy reserves and higher proportion of calorie intake being used for weight gain and linear growth. In older children, malnutrition can result in growth retardation, as is commonly seen in children with late diagnosis of celiac disease.

Diarrhea

It is the main clinical expression of malabsorption.

- Timing: onset of diarrhea in early infancy suggests a congenital defect.
- Onset of symptoms after introduction of a particular food into a child's diet can provide diagnostic clues, such as with sucrose in sucrase-isomaltase deficiency, celiac disease.
- The nature of the diarrhea may be helpful:
  a- explosive watery diarrhea suggests carbohydrate malabsorption.
  b- Loose and bulky stools are associated with celiac disease.
  c- Pasty, pale- yellowish, bulky, and offensive stools suggest an exocrine pancreatic insufficiency.
  d- In secretory diarrhea caused by disorders such as congenital chloride diarrhea, the stool is watery and voluminous and can be mistaken for urine.
- Stool color is usually not helpful; green stool with undigested foods and fruit can suggest rapid intestinal transit in toddler's diarrhea, which is a self-limiting condition unassociated with failure to thrive.

Appetite:

- Anorexia: villous atrophy or inflammation (celiac disease, post-infectious enteropathy)
- very good appetites: exocrine pancreatic insufficiency

Specific **findings on examination** can guide toward a specific disorder, e.g.

- Edema: protein-losing enteropathy,
- Digital clubbing: cystic fibrosis and celiac disease.
- Perianal excoriation and gaseous abdominal distention: carbohydrate malabsorption.
- Perianal and circumoral rash: acrodermatitis enteropathica.

Laboratory Evaluation of a Child Suspected with Malabsorption

Initial work-up should include:
a) stool microscopy for ova and parasites such as *Giardia,* and stool occult blood and leukocytes to exclude inflammatory disorders.
b) stool cultures and antibody tests for parasites.
c) A complete blood count including peripheral smear for microcytic anemia, lymphopenia (lymphangiectasia), neutropenia (Shwachman syndrome), and acanthocytosis (abetalipoproteinemia) is useful.

More-specific investigations can be planned by history, physical examination, and initial work- up. These include:

1- Carbohydrate malabsorption

1- Lactose malabsorption: congenital and secondary lactase deficiency
2- Congenital sucrase-isomaltase deficiency
3- Glucose galactose malabsorption

Investigations
1- Stool pH (less than 5.4)
2- Measurement of carbohydrate in the stool: Clinitest reagent that identifies reducing substances, is a simple screening test.
- An acidic stool with >2+ reducing substance suggests carbohydrate malabsorption.
3-Breath hydrogen test is used to identify the specific carbohydrate that is malabsorbed. After an overnight fast, the suspected sugar (lactose, sucrose, fructose, or glucose) is administered as an oral solution (1-2 g/kg, maximum 50 g). In malabsorption, the sugar is metabolized by the normal bacteria flora. One of the products of this process is hydrogen gas, which is absorbed and excreted in the breath. A rise in breath hydrogen of 20 ppm above the baseline is considered a positive test.

The child should not be on antibiotics at the time of the test, because colonic flora is essential for fermenting the sugar.

4- Small bowel mucosal biopsies can measure mucosal disaccharidase (lactase, sucrase, maltase) concentrations directly. In primary enzyme deficiencies the mucosal morphology is normal, while partial or total villous atrophy in secondary disaccharidase deficiency and revert to normal after mucosal healing.

2- Fat malabsorption

1- Abetalipoproteinemia
2- Lymphangiectasia
3- Cystic fibrosis
4- Shwachman-Diamond syndrome
5- exocrine pancreatic insufficiency
6- Protein–calorie malnutrition
7- Cholestatic liver disease

Investigations

1- Quantitative determination of fat malabsorption requires a 3-day stool collection for evaluation of fat excretion; cumbersome, expensive, and unpleasant to perform. simpler tests are often preferred. The coefficient of fat absorption (CFA) which is the percentage of absorbed fat in the diet is normally about 90%.

2- Acid steatocrit test: the reliable test.

3- Sudan stain of stool

4- Serum concentrations of vitamins A, D, and E and PT.

5- Evaluation of bile acid levels in duodenal fluid aspirate: when bile acid deficiency is suspected of being the cause of fat malabsorption.

3- Investigations for Protein-Losing Enteropathy

1- Hypoalbuminemia and urine for protein to exclude proteinuria.

2- Spot test for stool α1-antitrypsin: This serum protein is, unlike Albumin, resistant to digestion in the gastrointestinal (GI) tract. Excessive α1-antitrypsin excretion in the stool should prompt further investigations.

4- Investigations For Exocrine Pancreatic Function

1- Sweat chloride test: for cystic fibrosis

2- Fecal elastase-1: a sensitive, specific, and non-invasive test. It is unaffected by exogenous pancreatic enzyme treatment, and correlates well with exocrine pancreatic function tests. The measurement of this proteolytic enzyme in stool by ELISA.

3- Serum trypsinogen
4- The gold standard test for exocrine pancreatic function is direct analysis of duodenal aspirate.

5- Investigations For Intestinal Mucosal Disorders

Endoscopy and small bowel mucosal biopsy: multiple biopsies, because mucosal involvement can be patchy, especially in celiac disease and Lymphangiectasia. Congenital microvillus atrophy need electron microscopy.

The procedure for biopsy has many roles:

a- Histopathology.
b- To measure mucosal disaccharidase activities.
c- Duodenal aspirates: to measure pancreatic enzyme concentration and bile acid level.
d- Duodenal aspirates: for quantitative bacterial cultures and to demonstrate other infections such as *Giardia*.

6- Imaging procedures

Ultrasonography/ Plain radiographs with or without barium contrast studies: flocculations of barium and dilated bowel with thickened mucosal folds suggest diffuse malabsorptive lesions such as celiac disease. Thickened bowel in Lymphangiectasia.

Celiac Disease
(Gluten-Sensitive Enteropathy)

Clinical disorder results from gluten sensitivity of the intestine, it predominantly affects the proximal part of small intestine results in malabsorption. It is a permanent intolerance to gluten & withdrawal of gluten results in complete remission.

It doesn't present until gluten products have been introduced into the diet, it may present in infancy, children & adult, but the most common period of presentation is between 6 mo and 2 yr of age, and

Etiology and Pathophysiology

Celiac disease is a T-cell–mediated chronic inflammatory disorder with an autoimmune and genetic component. A genetic predisposition is suggested by the

family aggregation and the concordance in monozygotic twins, which approaches 100%. There is strongest association with human leukocyte antigen in more than 90%. Type 1 diabetes and other autoimmune diseases are highly associated.

The gluten present in wheat, barley, rye, & possibly oat, the activity of gluten resides in the gliadin fraction which is highly resistant to intraluminal and mucosal digestion; incomplete degradation favor the immunostimulatory effect by sensitization of the lymphocytes of the lamina propria and activation of innate immunity mechanisms before activation of the adaptive immune response.

Long term dietary exposure to gluten cause sensitization of the lamina propria lymphocytes lead to inflammatory process & damage of the mucosa with characteristic microscopical changes showing villous atrophy, crypt hyperplasia, irregular vacuolated surface epithelium with increased numbers of lymphocytes in the epithelial layer.

The lesion takes few wk – 2 yr of exposure to gluten to develop, & few month- 2 yr to change to normal on gluten free diet.

Incidence & Screening

Screening test by serological markers show the incidence of celiac disease varies with population, e.g. 1/ 4000 in Denmark & 1/ 150 in Ireland.

Screening tests indicate the asymptomatic cases form 5 -7 times the symptomatic patients.

Clinical features

The mode of presentation is vary considerably;

- Intestinal symptoms are common in children whose disease is diagnosed within the 1st 2 yr of life; failure to thrive, chronic diarrhea, vomiting, abdominal distention, muscle wasting, anorexia, and irritability are present in most cases. Occasionally there is constipation, rectal prolapse, or intussusception.
- Infants is often clingy, irritable, and unhappy.
- Digital clubbing can occur.
- As the age at presentation of the disease shifts to later in childhood, extra-intestinal manifestations, have increasingly become recognized, affecting almost all organs.

a- The most common extra-intestinal manifestation of celiac disease is iron deficiency anemia, unresponsive to iron therapy.
b- 10% of children referred to endocrinologists for growth retardation without an endocrine or overt gastrointestinal disorder.
c- Other manifestations: Nutritional deficiencies or abnormal immune responses may be responsible mechanism:
- Bone: Osteoporosis, arthritis and arthralgia
- CNS: Epilepsy with bilateral occipital calcifications, peripheral neuropathies, ataxia.
- Mouth: Dental enamel hypoplasia and aphthous stomatitis,
- Dermatological: alopecia, dermatitis herpitiformis, and erythema nodosum.
- Systemic: Cardiomyopathy and isolated hypertransaminasemia.

It is more commonly associated with other conditions type 1 diabetes, autoimmune thyroid disease, Addison disease, Sjogren syndrome, autoimmune cholangitis, autoimmune hepatitis, primary biliary cirrhosis, selective IgA deficiency, Down, Turner, and Williams syndromes.

Diagnosis

The diagnosis of celiac disease is based on a combination of symptoms, antibodies, HLA, and duodenal biopsy.

Symptomatic patients

- Serum anti-TG IgA antibodies + total IgA or IgG anti–gliadin antibodies.
a- If anti-TG2 Ab is negative and the others are normal, celiac disease is unlikely.
b- If positive anti-TG2 antibody levels <10 × upper limits of normal should undergo upper endoscopy with multiple biopsies.
c- In patients with positive anti-TG2 antibody levels at or >10 × upper limits of normal, blood should be tested for HLA and EMA (endomysial antibodies). If positive EMA antibodies and DQ2 or DQ8 HLA testing, the diagnosis of celiac disease is confirmed.

- Asymptomatic persons belonging to high-risk groups, celiac disease should always be diagnosed using duodenal biopsies.

Notes:

- Intestinal biopsy is the gold standard for diagnosis.

- The diagnosis is confirmed by an antibody decline and preferably a clinical response to a gluten-free diet.

- Gluten challenge and repetitive biopsies will only be necessary in selected cases in which diagnostic uncertainty remains.

- Many diseases may cause flat intestinal mucosa, e.g. Infections such as rotavirus enteritis & Giardia lamblia, undernutrition, cow's milk protein or soy protein intolerance.

- The anti-endomysiel IgA antibody test is relatively expensive; interpretation is operator dependent and prone to errors so that it has largely been replaced by anti-tissue transglutaminase IgA antibody tests, which are simpler to perform and have similar sensitivity and specificity.

Treatment

The only treatment for celiac disease is;

- lifelong strict adherence to a gluten-free diet, response occurs within a week with change in mood, increase appetite & wt & improvement of diarrhea. The data available so far seem to suggest that the threshold should be set to <50 mg/day, although individual variability makes it difficult to set a universal threshold. No long-term complications from a gluten-free diet have been recognized.
- periodic visits for assessment of symptoms and signs, growth, and adherence to the gluten-free diet with measurements of TG2 antibody levels.

Patients with celiac disease show increased long-term mortality, the risk rising with delayed diagnosis and/or poor dietary compliance. Non-Hodgkin lymphoma is the main cause of death. The long life strict GFD will reduce the risk.

Abetalipoproteinemia

Abetalipoproteinemia is a rare autosomal recessive disorder of lipoprotein metabolism. Patients have mutations of the microsomal triglyceride transfer protein

gene, resulting in absence of microsomal triglyceride transfer protein function in the small bowel. This protein is required for normal assembly.
It is associated with severe fat malabsorption from birth. Children fail to thrive during the 1st yr of life, with steatorrhea; stools that are pale, foul smelling, and bulky stool. The abdomen is distended and deep tendon reflexes are absent as a result of peripheral neuropathy, which is secondary to vitamin E (fat-soluble vitamin) deficiency. Intellectual development tends to be slow. After 10 yr of age, intestinal symptoms are less severe, ataxia develops, and there is a loss of position and vibration sensation with the onset of intention tremors unless vitamin E levels are maintained in the normal range. These latter symptoms reflect involvement of the posterior columns, cerebellum, and basal ganglia. In adolescence, atypical retinitis pigmentosa develops without adequate supplemental of vitamin E.

Diagnosis rests on the presence of acanthocytes in the peripheral blood smear and extremely low plasma levels of cholesterol (<50 mg/ dL); triglycerides are also very low (<20 mg/dL). Chylomicrons, low-density lipoprotein fraction, very-low-density lipoproteins are not detectable.

Specific treatment is not available. Large supplements of the fat-soluble vitamins A, D, E, and K should be given. Vitamin E (100- 200 mg/kg/24 hr) appears to arrest neurologic and retinal degeneration. MCTs can be used to supplement fat intake.

Microvillus Inclusion Disease
(Congenital Microvillus Atrophy)

Microvillus inclusion disease is an autosomal recessive disorder, which presents at birth with profuse watery secretory diarrhea with dehydration and failure to thrive. It is the most commonly recognized cause of congenital diarrhea. Light microscopy of the small bowel mucosa demonstrates diffuse thinning of the mucosa, with hypoplastic villus atrophy and no inflammatory infiltrate. Antenatal ultrasound scans usually show multiple fluid-filled dilated loops of bowel and polyhydramnios. Despite parenteral nutrition, the diarrhea continues and initial fluid management is difficult. The disease is fatal without long-term parenteral nutrition support. Nonetheless, most children die in infancy or early childhood. The somatostatin analog octreotide has been used as treatment and may reduce the volume of stool in some infants. Intestinal transplantation is the only definitive treatment for this rare disease.

Congenital chloride diarrhea

Belongs to the more common causes of severe congenital diarrhea, with prevalence in Finland of 1:20,000. It is caused by a defect of the gene, which encodes a Na-Cl /HCO3 exchanger within the apical membrane of ileal and colonic epithelium. This exchanger absorbs chloride and secretes bicarbonate into the lumen, neutralizing the acidity of gastric secretion.

Prenatal clinical signs of this disorder are a dilated small bowel that can mislead to a diagnosis of intestinal obstruction. Newborns with congenital chloride diarrhea present with severe life-threatening secretory diarrhea during the 1st few wk of life. Laboratory findings are metabolic alkalosis, hypochloremia, hypokalemia, and hyponatremia (with high plasma renin and aldosterone activities). Fecal chloride concentrations are >90 mmol/L and exceed the sum of fecal sodium and potassium. Early diagnosis and aggressive lifelong enteral substitution of KCl in combination with NaCl. The diarrheal symptoms usually tend to regress with age.

Acrodermatitis enteropathica

The congenital form of acrodermatitis enteropathica is caused by a mutation in the protein, normally expressed on the apical membrane, which enables the uptake of zinc into the enterocytes.

It manifests with severe deficiency of body zinc soon after birth in bottle-fed children or after weaning from breastfeeding. Clinical signs of this disorder are anorexia, diarrhea, failure to thrive, humoral and cell-mediated immunodeficiency (poor wound healing, recurrent infections), male hypogonadism, skin lesions (vesicobullous dermatitis on the extremities and perirectal, perigenital, and perioral regions, and alopecia), and neurologic abnormalities (tremor, apathy, depression, irritability, nystagmus, photophobia, night blindness, and hypogeusia). The zinc-dependent alkaline phosphatase and plasma zinc levels are low. Paneth cells in the crypt of the small intestinal mucosa show inclusion bodies. Acrodermatitis enteropathica requires long-term treatment with elemental zinc 1 mg/kg/day.