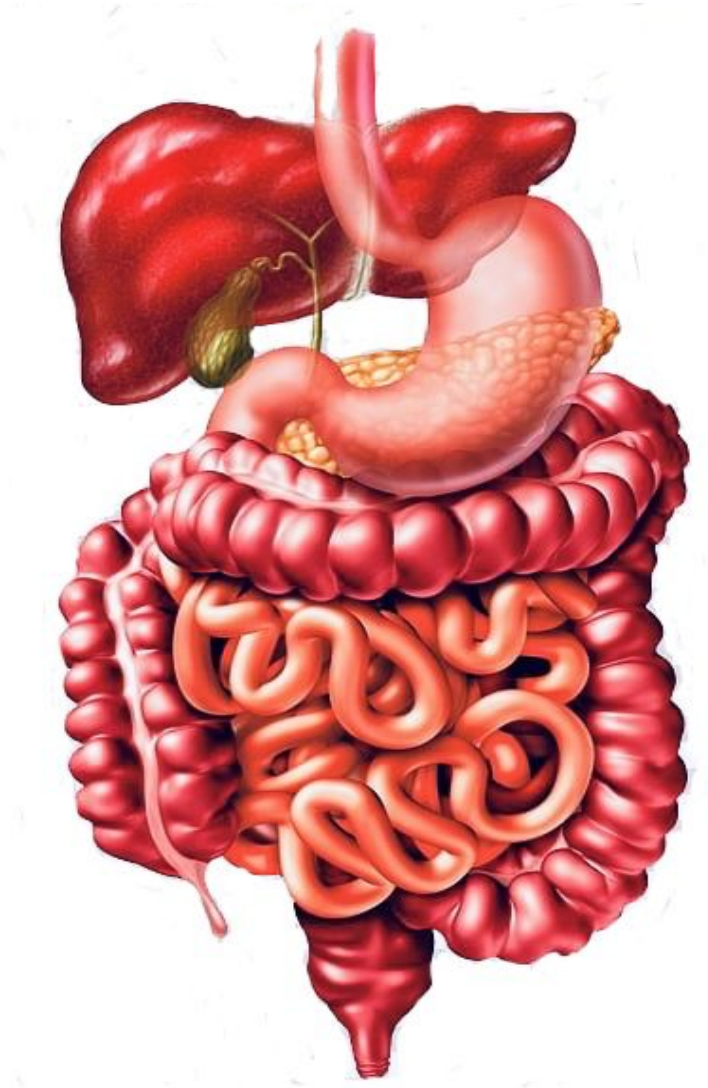
جامعة الملك سعود
King Saud University

MED437
KING SAUD UNIVERSITY

PATHOLOGY
TEAM 437

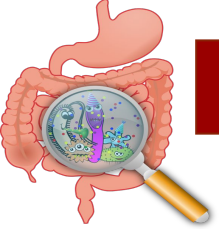


هذه المحاضرة هي تكريم لكل من يعمل ولا يكرّم،لكل من يعمل بالخفاء،لكل ايادي تدفعنا من ظهورنا لا نرى وجوه اصحابها

Please note:
This work is based on male slides except few points will appear pink

Diarrhea & Malabsorption

Content Explanation Notes Important



Objectives and there answers from Dr slides

Understand the physiology of fluid in small intestine

- 1.5 liter food
- 7 liters secretions and reabsorbed in small intestine
- 1.4 reabsorbed in large intestine

Describe the pathophysiology and causes of various types of diarrhea

- **Secretory**: Normal stool osmotic gap {bacterial toxin (E. coli , cholera) Endocrine tumours}
- **osmotic**: osmotic gap is high , {Malabsorption, osmotic laxatives}
- **Exudative**: blood and pus in the stool, { inflammatory bowel diseases, and invasive infections}
- **Motility-related**: {Irritable bowel syndrome (IBS)}

Define acute diarrhea and enumerate its common causes

- Less than 2 weeks
- **infections** (viruses, bacteria, helminths, and protozoa). **Food poisoning**

Define chronic diarrhea and enumerate its common causes

- More than one month
- Infection, post Infection malabsorption, Inflammatory bowel disease (IBD), cancer

Understand that the malabsorption is caused by either abnormal digestion or small intestinal mucosa

Know that malabsorption can affect many organ systems (alimentary tract, hematopoietic system, musculoskeletal system, endocrine system, epidermis, nervous system)

Celiac disease

immune reaction to gliadin fraction of the wheat protein gluten.

1.villous atrophy.

2.Crypt hyperplasia

3.Increased intraepithelial lymphocytosis

Lactose Intolerance

Low or absent activity of the enzyme lactase → Lactose not absorbed

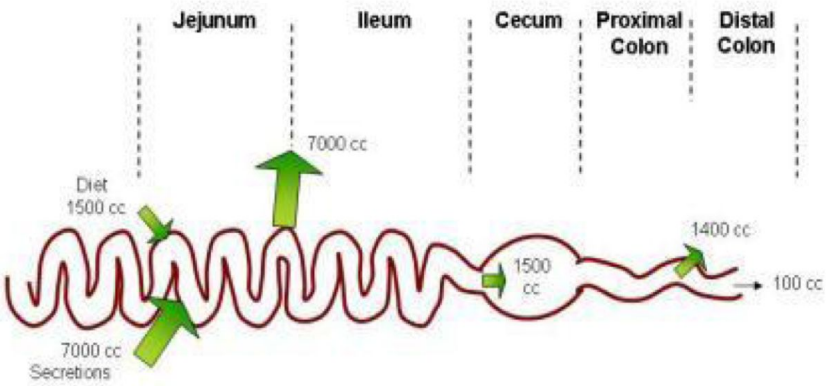
Lactose accumulate in colon

In colon:fermentation by bacteria → Gases

Understand the physiology of fluid in small intestine

Physiology of fluid and small intestine

*Approximately 8500 mL of fluid flow into the intestine daily :
1- from diet (1500mL).
2- Secretions (7000mL), EX (salivary, gastric, biliary, pancreatic, intestinal secretions).
3- Approximately (7000 mL) will be absorbed in the small intestines (most of the volume will be absorbed in the small intestines due to weaker tight junctions between enterocytes).
4- Approximately (1500 mL) cross the ileocecal valve.
5- The colon reabsorbed most of this fluid most of the fluid (1400 mL, but less than small intestines due to stronger tight junctions).
6- Finally, only (100mL) lost in the stool.



Fecal osmolality

As stool leaves the colon, fecal osmolality is = to the serum osmolality i.e. 290 mosm/kg.
when the osmolality increase the fecal osmotic gap increase.

Under normal circumstances, the major osmoles which create the osmotic effect are Na+, K+, Cl–, and HCO3 –.

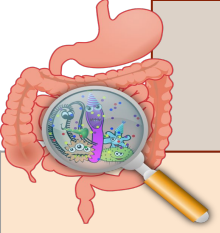
Fecal Osmotic Gap

290 mosm/kg H_2O - 2 ([Na^+] + [K^+])

Osmotic diarrhea: > 125

In case of osmotic diarrhea the gap will Formula used to be high due to assess the fecal abnormal increase in osmolality osmoles ** which in turn leads to osmotic diarrhea.

Notes



Describe the pathophysiology and causes of various types of diarrhea
((Secretory, osmotic, Exudative, Motility-related

Introduction to diarrhea

DEFINITION		CLASSIFICATION Based on duration!	IMPORTANCE		
		Acute 2 weeks	What happens	Prognosis	Mortality
WHO: 3 or more loose or liquid stool per day increased frequency	Abnormally high fluid content of stool >200-300 gm/day decreased consistency	Persistent 2-4 weeks	Loss of fluid through diarrhea can cause Dehydration and electrolytes imbalances and acid base imbalance	Easy to treat but if not treated may lead to death especially in children Due to dehydration	More than 70% of almost 11 million child deaths every year are attributable to a 6 causes **1-diarrhea** 2-malaria 3-neonatal infection 4-pneumonia 5-preterm delivery 6-lack of oxygen at birth
		Chronic 4 Weeks We should investigate here especially in children			

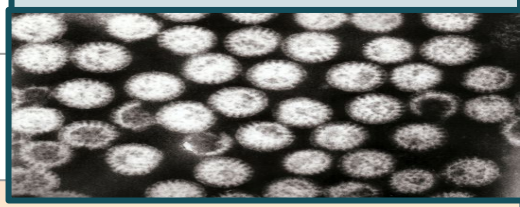
Types of diarrhea

Secretory	Osmotic	Exudative (inflammatory)	Motility-related
Normal stool osmotic gap < 100 mOsm/kg. (Isotonic stool)	Stool osmotic gap is high, > 125 mOsm/kg.		
-There is an increase in the active secretion. more than 7000cc. -Also Seen in endocrine tumours	Excess amount of poorly absorbed substances that exert osmotic effect water is drawn into the bowels diarrhea.	Presence of blood and pus in the stool.	Caused by the rapid movement of food through the intestines (hypermotility hyper-peristalsis).
High stool output. And lack of response to fasting The most common cause of this type of diarrhea is a bacterial toxin (E. coli, cholera) that stimulates the secretion of anions* not the bacteria itself but it's toxin. Bacteria toxin will stimulate secretion of small intestine only No RBC NO inflammation	Stool output is not massive and fasting improve the condition Can be the result of : A. Malabsorption in which the nutrients are left in the lumen to pull in water e.g. lactose intolerance B. Osmotic laxatives. Used for constipation but then the patient starts having diarrhea	Results from the outpouring of blood protein, or mucus from an inflamed or ulcerated mucosa Occurs with inflammatory bowel diseases, and invasive infections. Persists on fasting invasive Bacteria will invade mucosa and cause injury,inflammation, Blood.	Irritable bowel syndrome (IBS) القولون العصبي a motor disorder that causes abdominal pain and altered bowel habits with diarrhea predominating

Define Acute Diarrhea And Enumerate Its Common Causes

Etiology of acute diarrhea

Infections	Approximately 80% of acute diarrheas are due to infections (viruses, bacteria, helminths, and protozoa).	
Viruses	Viral gastroenteritis (viral infection of the stomach and the small intestine) is the most common cause of acute diarrhea worldwide.	**Rotavirus** Child get hospitalized because we Food poisoning Toxic or uncooked food like need to put him in IV line uncooked eggs, not washing hands (rehydration) the cause of nearly 40% of hospitalizations from diarrhea in children under 5
Food poisoning	Toxic or uncooked food like uncooked eggs, not washing hands before eating. Staph aureus toxins	
Drugs	Antibiotic, antidepressant, antacids Once we stop the drugs diarrhea stops.	



Antibiotic-Associated Diarrhea:

Acute Diarrhea occurs in 20% of patients receiving broad-spectrum antibiotics; about 20% of these diarrheas are due to Clostridium difficile.

How does Antibiotics cause Diarrhea?
Antibiotic can kill Flora in gut which help in digesting & synthesising B12 & K vit, but also give a chance of Clostridium difficile to overgrowth.change in normal flora

Tests useful in the evaluation of acute diarrhea

Acute diarrhea

Fecal leukocytes

Non-Present	Present
Non-Inflammatory diarrhea **Suggests a small bowel source or colon but without mucosal inju** osmotic gapنحسب	**Inflammatory diarrhea** **Suggests colonic mucosal damage caused by invasion** **1. shigellosis, salmonellosis, Campylobacter or Yersinia infection, amebiasis)** **2. toxin (C difficile, E coli).** **3. Inflammatory bowel diseases**

Notes

Define Chronic Diarrhea And Enumerate Its Common Causes

Etiology of chronic diarrhea:

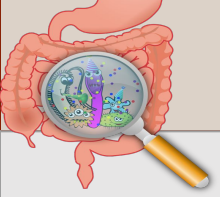
Infections
like Giardia lamblia In duodenum AIDS often have chronic infections of their intestines that cause diarrhea.. not the most common cause the most common is non infectious
Post-infectious
Following acute viral, bacterial or parasitic infections usually after traveling
Malabsorption
Colon cancer
Endocrine diseases.
Irritable bowel syndrome
Inflammatory bowel disease (IBD)

Complications:	**Leads to**
Fluids loss	Dehydration.
Electrolytes loss	Electrolytes imbalance
Sodium bicarbonate loss	Metabolic acidosis. If persistent it will lead to Malnutrition.

Tests useful in the evaluation of chronic diarrhea:

Stool analysis ova,parasites

+ve	-ve		
Infection	Stool fat test (normal <20%)		
	-ve		+ve
	Secretory	Non-infectious Inflammatory	Malabsorption



Understand That The Malabsorption Is Caused By Either Abnormal Digestion Or Small Intestinal Mucosa

Malabsorption Syndrome

- Inability of intestine to absorb nutrients adequately into the bloodstream.
- Impairment can be of single or multiple nutrients depending on the abnormality.

Physiology

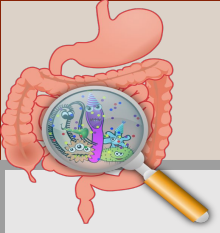
The main purpose of the gastrointestinal tract is to digests and absorbs nutrients (fat, carbohydrate, and protein), micronutrients (vitamins and trace minerals), water, and electrolytes. Mechanisms and Causes of Malabsorption

Mechanisms and Causes of Malabsorption Syndromes

There are many causes:

Inadequate digestion	Deficient bile salt	Primary mucosal abnormalities	Inadequate small intestine	Lymphatic obstruction
-Post gastrectomy -Deficiency of pancreatic lipase -Chronic pancreatitis - Cystic fibrosis -Pancreatic resection -Zollinger-Ellison syndrome	- Obstructive jaundice -Bacterial overgrowth -Stasis in blind loops, diverticula -Fistulas -Hypomotility states (diabetes) -Terminal ileal resection - Crohns' disease - Precipitation of bile salts (neomycin)	Celiac disease -Tropical sprue -Whipple's disease -Amyloidosis -Radiation enteritis -Abetalipoprote-inemia Giardiasis	-Intestinal resection - Crohn's disease -Mesenteric vascular disease with infarction -Jejunoileal bypass	-Intestinal lymphangiectasia -Malignant lymphoma Macroglobulinemia

Doctor didn't focus on this table ,the important is the next page :)



Understand That The Malabsorption Is Caused By Either Abnormal Digestion Or Small Intestinal Mucosa

Pathophysiology of malabsorption syndrome

Inadequate digestion	Or	Small intestine abnormalities	=	Malabsorption

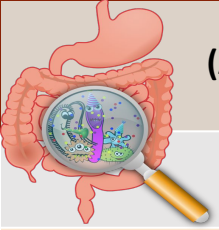
Inadequate digestion

Stomach	Postgastrectomy			
Pancreas	Deficiency of pancreatic lipase usually congenital			
	Chronic pancreatitis			
	Cystic fibrosis			
	Obstructive jaundice Usually associated with steatorrhea.			
	Pancreatic resection e.g in case of pancreatic tumor			
Bile	Obstructive jaundice Usually associated with steatorrhea.	Terminal ileal resection bile cycle		

Small intestine abnormalities

Mucosa	Tropical sprue	Giardiasis	Whipple's disease type of	Celiac disease
Inadequate small intestine short small intestines	Crohn's disease fibrosis shortens the small intestine	Intestinal resection		
Lymphatic obstruction	Intestinal lymphangiectasia	Malignant lymphoma		

Notes



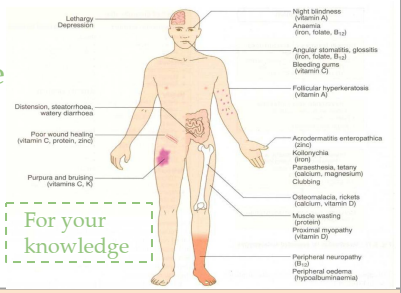
Know That Malabsorption Can Affect Many Organ Systems (Alimentary Tract, Hematopoietic System, Musculoskeletal System, Endocrine System, Epidermis, Nervous System)

Malabsorption syndrome

Clinical features

Depend on deficiencient nutrient :		
Protein	Muscle wasting swallowing or oedema	
B12, folic acid and iron deficiency	-Anaemia	-fatigue and weakness
Vitamin D and calcium	-Osteomalacia and osteoporosis	-Muscle cramp
Vitamin k and other coagulation factors	-Bleeding tendencies intracranial hemorrhage and bleeding under skin	

- There is increased fecal excretion of fat (steatorrhea) and the systemic effects of deficiency of vitamins, minerals, protein and carbohydrates.
- Steatorrhea is passage of soft, yellowish, greasy = fatty stools containing an increased amount of fat. It is diarrhea with fat. usually it has bad smell.
- Growth retardation, failure to thrive in children
- Weight loss despite increased oral intake of nutrients. because the nutrients are unabsorbed.



For your knowledge

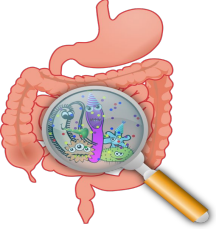
Diagnosis

There is no specific test for malabsorption but we have a guideline

Investigation is guided by symptoms and signs:

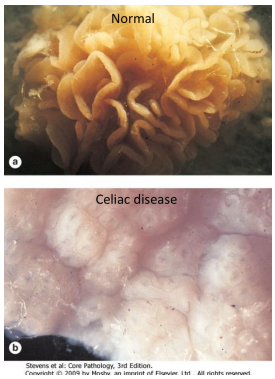
Fecal fat study to diagnose steatorrhea	Blood tests iron,vitamins and albumin	Stool studies	Endoscopy
			(Biopsy of small bowel) to exclude small intestine mucosa if normal that mean problem in bile or pancreas

Notes



Celiac Disease

What is it? (Abnormal small intestine mucosa)



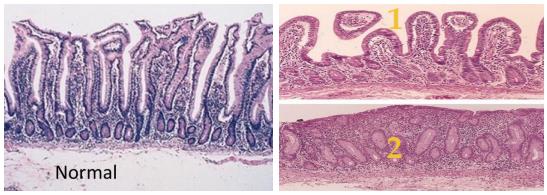
Endoscopy

- An immune reaction to gliadin, which is a fraction of the wheat protein gluten. gluten جزء بسيط من الـ gliadin
- Usually diagnosed in childhood-mid adult life.
- Patients have raised antibodies to gluten.
- Highly specific association with class II HLA (DQ2 or DQ8). And to a lesser extent, DQ8 (haplotype DR-4). HLA → Human leukocyte antigen, D → subtype of HLA and there are others (A,B,C).

Histology

- Mucosa is flattened with marked villous atrophy.[1]
- Crypt hyperplasia.[2] Normally crypts are short and small
- Increased intraepithelial lymphocytosis. This feature we use it for diagnosis, I will count for 100 enterocytes if the lymphocytes inside them ≥ 30 this is early celiac disease.

Are these changes reversible? yes, they are. It means if I take a biopsy after 1 month of gluten diet I can see the villi again



Clinical Features

GI symptoms that characteristically appear at age 9-24 months. Symptoms begin various times after the introduction of foods that contain gluten.

- In infants and toddlers: GI symptoms and failure to thrive.
- Childhood: Minor GI symptoms, inadequate rate of weight gain.
- Young adults: Anemia is the most common form of presentation.
- Adults and elderly: GI symptoms in the form of diarrhea are more prevalent

Diagnosis

- Clinical documentations of malabsorption.
- Increased fat in stool (Steatorrhea)
- Serologic tests for celiac disease, namely IgA antibodies to tissue transglutaminase (Anti-TTG-IgA).
- Small intestine biopsy demonstrate villous atrophy.
- Improvement of symptoms and mucosal histology on gluten withdrawal from diet, (Wheat, barley, rye). Other grains, such as rice and corn flour, do not have such an effect. diagnosis By endoscopy and stop him from wheat and then see the mucosa if it's better that mean he have celiac disease

Complications

- Osteopenia, osteoporosis.
- Infertility in women. due to hypoalbuminemia.
- Short stature, delayed puberty, anemia.
- Malignancies (intestinal T-cell lymphoma), 10 to 15% risk of developing GI lymphoma.

What malignancy is associated with celiac disease? T-cell lymphoma.

Pathogenesis of Celiac Disease

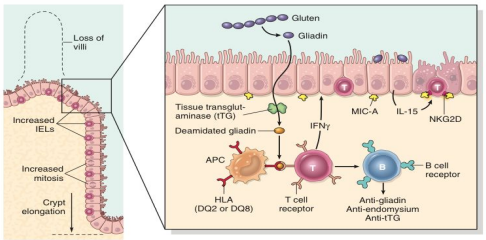
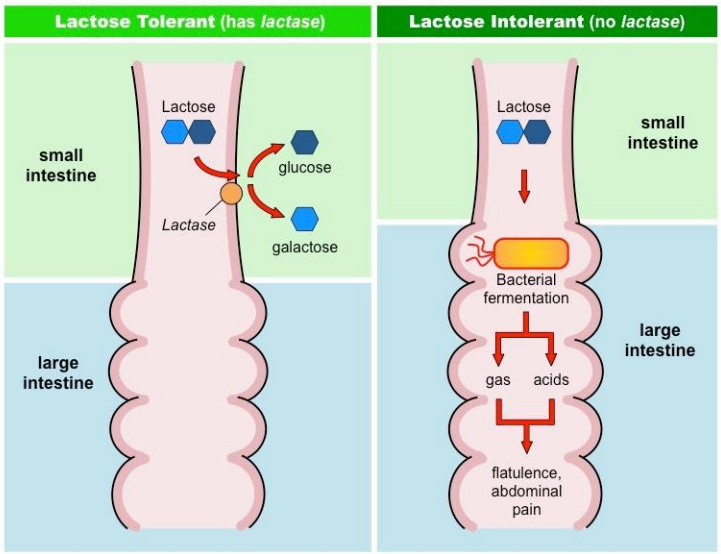


Fig. 15.21 The morphologic alterations that may be present in celiac disease, including varying degrees of villous atrophy, increased numbers of intraepithelial lymphocytes (IELs), and epithelial proliferation with crypt elongation *(left)*. A model for the pathogenesis of celiac disease *(right)*. Note that both innate and adaptive immune mechanisms are involved in the tissue responses to gliadin. CD4 T cells (producing IFNγ) are shown in lamina propria and CD8 T cells, expressing NKG2D receptor, in between epithelial cells.

Gluten is digested by brush border enzymes into gliadin. Gliadin is deamidated by tissue transglutaminase, then it's taken by macrophages, which are antigen presenting cells. They present them through HLA-DQ2 or DQ8 to CD4+ T Cells, which in turn recognize this and produce cytokines that damage the mucosa. They also stimulate B cells to produce antibodies against tTG and deamidated gliadin, which can be used to monitor the disease.

Lactose Intolerance



★ Lactose will go from small intestine → large intestine (there will be bacteria) and there will be fermentation with production of gases especially **hydrogen gas** which will lead to ↑ motility and irritation of the bowl and then lead to the symptoms (gases and pain).

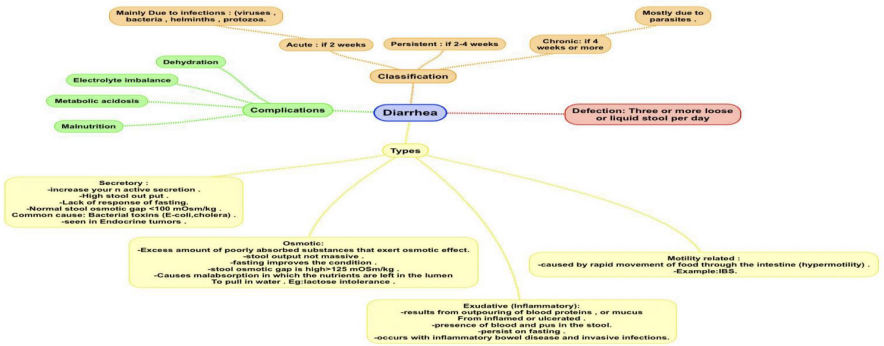
Normally, at the brush border of enterocytes in the small intestine, Lactose is metabolized to glucose and galactose by the enzyme Lactase. Any low or absent activity of the enzyme lactase will lead to **Lactose Intolerance**.

Causes	
Inherited lactase deficiency	**Acquired lactase deficiency**
1. **Congenital lactase deficiency,** extremely rare. 2. **Childhood-onset and adult-onset lactase deficiency:** Genetically programmed progressive loss of the activity of the small intestinal enzyme lactase, more common than (1). Lactase enzyme will be slightly lost with time.	It is transient, Secondary lactase deficiency due to intestinal mucosal injury by an infectious, allergic, or inflammatory process. eg, **Gastroenteritis**: Infectious diarrhea, particularly viral acquired lactase deficiency gastroenteritis in younger children, may damage the intestinal mucosa enough to reduce the quantity of the lactase enzyme.

Clinical	One hour to a few hours after ingestion of milk products: **Bloating** = abdominal gases**, abdominal discomfort, and flatulence.**
Diagnosis	1. Empirical treatment with A 3-week trial of a **diet that is free of milk** and milk products, which results in resolution of symptoms; is a satisfactory trial to diagnose lactose intolerance. **2. Hydrogen breath test: specific test** An oral dose of lactose is administered, the sole source of H_2 is **bacterial fermentation**; unabsorbed lactose makes its way to colonic bacteria, resulting in excess breath H_2. Increased exhaled H_2 after lactose ingestion suggests lactose malabsorption. In our blood circulation there's no H, so from where it will come? from the bacteria, so if there's unabsorbed lactose this allow for the colonic bacteria to ferment the lactose and produce the H ion → circulation → breath.

Summary

Diarrhea:



Malabsorption

1-Pathophysiology of malabsorption is inadequate digestion (BILE or PANCREAS) OR small intestine abnormalities (MUCOSA) .

2-The most diagnostic feature of malabsorption is STEATORRHEA and the clinical feature depend on the deficient nutrient.

3-Celiac disease is AUTOIMMUNE DISEASE that caused by producing antibodies against the fraction of GLUTEN (GLIADIN) by ingestion wheat , barley or flour .

4-CELIAC DISEASE under the microscope there will be VILLOUS ATROPHY And INCREASED INTRAEPITHELIAL LYMPHOCYTOSIS .

5-The most serious complication of celiac disease is INTESTINAL T-CELL LYMPHOMA .

6-LACTOSE INTOLERANCE could be INHERITED or ACQUIRED .

7-LACTOSE INTOLERANCE is diagnosed by HYDROGEN BREATH TEST Presence of HYDROGEN indicates BACTERIAL FERMENTATION .

Lactose Intolerance

- Deficiency/absence of the enzyme lactase in the brush border of the intestinal mucosa → Maldigestion and malabsorption of lactose.
- Unabsorbed lactose draws water in the intestinal lumen
- In the colon, lactose is metabolized by bacteria to organic acid, CO_2 and H_2; acid is an irritant and exerts an osmotic effect
- Causes diarrhea, gaseousness, bloating and abdominal cramps.

VI. LACTOSE INTOLERANCE

A. Decreased function of the lactase enzyme found in the brush border of enterocytes

1. Lactase normally breaks down lactose into glucose and galactose.

B. Presents with abdominal distension and diarrhea upon consumption of milk products; undigested lactose is osmotically active.

C. Deficiency may be congenital (rare autosomal recessive disorder) or acquired (often develops in late childhood); temporary deficiency is seen after small bowel infection (lactase is highly susceptible to injury).

VII. CELIAC DISEASE

A. Immune-mediated damage of small bowel villi due to gluten exposure; associated with HLA-DQ2 and DQS

B. Gluten is present in wheat and grains; its most pathogenic component is gliadin.

1. Once absorbed, gliadin is deamidated by tissue transglutaminase (tTG).
2. Deamidated gliadin is presented by antigen presenting cells via MHC class II.
3. Helper T cells mediate tissue damage.

C. Clinical presentation

1. Children classically present with abdominal distension, diarrhea, and failure to thrive.
2. Adults classically present with chronic diarrhea and bloating.
3. Small, herpes-like vesicles may arise on skin (dermatitis herpetiformis). Due to IgA deposition at the tips of dermal papillae; resolves with gluten-free diet

D. Laboratory findings

1. IgA antibodies against endomysium, tTG, or gliadin; IgG antibodies are also present and are useful for diagnosis in individuals with IgA deficiency (increased incidence of igA deficiency is seen in celiac disease).
2. Duodenal biopsy reveals flattening of villi, hyperplasia of crypts, and increased intraepithelial lymphocytes (Fig. 10.18). Damage is most prominent in the duodenum; jejunum and ileum are less involved.

E. Symptoms resolve with gluten-free diet.

1. Small bowel carcinoma and T-cell lymphoma are late complications that present as refractory disease despite good dietary control.

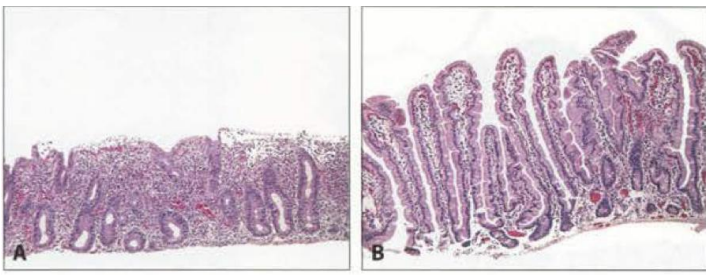


Fig. 10.18 Celiac disease. **A**, Flattened villi. **B**, Normal villi for comparison.

Questions

Q1 :which one of the following organisms may cause secretory diarrhea ?

A. Cholera
B. gonorrhea
C. s.aureus
D. l.monocytogenes

Q2:lactose intolerance may cause which type of diarrhea ?

A. osmotic
B. secretory
C. inflammatory
D. motility related diarrhea

Q3: If there is a patient suffers from diarrhea for the last 3 weeks , we can classify this condition as :

A. Chronic diarrhea
B. Acute diarrhea
C. Persistent diarrhea

Q4:A 10-month-old, previously healthy male infant develops a severe, watery diarrhea 2 days after visiting the pediatrician for a routine checkup. The most likely diagnosis is

A. Rotavirus infection
B. Enterotoxigenic
C. coli infection
D. Entamoeba histolytica infection

Q5 : all of the following are causes of acute diarrhea except:

A. Viral gastroenteritis
B. Food poisoning
C. Inflammatory bowel disease
D. Antibiotic-Associated Diarrhea

1-A 2-A 3-C 4-A 5-C

Questions

Q1 :malabsorption diarrhea is classified as?
(A) Chronic invasive
(B) Acute invasive
(C) Chronic osmotic
(D) Acute osmotic

Q2:which of the following is NOT a chronic malabsorptive disorder?
(A) celiac disease
(B) pancreatic insufficiency
(C) Crohn disease
(D) GERD

Q3:Which of the following is a symptom of malabsorptive disorders?
(A) they might have anemia due to pyridoxine, B12 and folate malabsorption
(B) they might have bleeding due to vit K malabsorption
(C) they might have tetany due to calcium malabsorption
(D) all of the above

Q4(from robbins) :which of the following is not a step of Celiac pathogenesis?
(A) Gluten is digested into amino acids and peptides including including "Gliadin" which will get deamidated by "tTG"
.(B) it will interact with HLA-DQ2/HLA-DQ8 of the antigen presenting cells which will present it to CD4 leading to cytokines release
(C) B-Cell activation leading to generation of antibodies against tTG , Gliadin and CD8 will enterocytes who expresses surface MIC-A
(D) all of the above are true

Q5 A 4-year-old girl is brought to the physician because her parents noticed that she has been having pale, fatty, foul-smelling stools. The patient is at the 50th percentile for height and 10th percentile for weight. Her symptoms respond dramatically to a gluten-free diet. Which of the following is the most likely diagnosis?
(A) Celiac sprue
(B) Cystic fibrosis of the pancreas
(C) Ménétrier disease
(D) Tropical sprue

1-C 2-D 3-D 4-D 5-D

كل الشكر والتقدير للجهود العظيمة
من قبل أعضاء فريق علم الأمراض الكرام.

قادة فريق علم الأمراض

فايز غياث الدرسوني

شيرين العكيلي

اعضاء فريق علم الأمراض

راكان محمد الغنيم
سلطان ناصر الناصر
عادل عبدالعزيز السحيباني
حسن محمد العريني
تركي عيد الشمري
عبدالجبار اليماني
عبدالله المعيذر
منصور العبرة
خالد العقيلي
تركي آل ينهار
سعد الفوزان
عبدالاله الدوسري

مها العَمري
مجد البراك
بتول الرحيمي
منيرة المسعد
مشاعل القحطاني
رناد الفرم
غادة الحيدري
دانة القاضي
مها بركه

رزان الزهراني
لين الحكيم
عهد القرين
وجدان الشامري
غرام جليدان
ليلى الصباغ
ريناد الغريبي
نورة القاضي