DISORDERS OF ABSORPTION

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MECHANISMS OF ABSORPTION

Disease of the small intestine are frequently accompanied by alterations in intestinal fonction, this impaired function is seen as malabsorption syndrome.
It is important to distinguish between **digestion** and **absorption.**
Digestion involves the breakdown or hydrolisis of nutritients to smaller molecules to prepare the ingested substance for absorption

ANATOMIC AND PHYSIOLOGIC FACTORS:

-The intestine has an enormous surface are (200m2)
-Bowel motility is an important process which permits nutritients to remain in intimate contact with the intestinal cells and influences the continued movement of the nutritients into and along the absorbing channels.Two types of motility aid in this process;

The gross motility of the intestine
The motility of individual villi

-Capillaries to portal system and lymphatics

TYPES OF ABSORPTION

Four mechanisms have been considered in the transport of substance across the intestinal cell membrane

- Active transport; involves the transport of a substance across the cell against an electric or chemical gradient, requires energy and carrier mediated.
- Passive diffusion; Energy is not required, transport is with the electric or chemical gradient and the process is not carrier mediated.
- Facilitated diffusion; is similar to passive diffusion except that it shows evidence of beign carrier mediated.
- Endocytosis; is process akin to phagocytosis.

SITES OF ABSORPTION

- The proximal intestine is a major area for the absorption of iron,calcium,water soluble vitamins (folate) and fat.
- Sugars are absorbed in the proximal intestine as well as in the mid intestine.
- Aminoacids are absorbed primaryl in the middle of the small intestine or jejunum.
- The distal small intestine is the major absorptive area for the bile salts and vitamin B12.
- The colon is important for the absorption of water and electrolytes.

ABSORPTION OF SPESIFIC NUTRITIENS:

Carbonhydrate absorption:

Much of the carbonhydrate we ingest is in the form of starch, a complex polysaccaride.

Salivary and pancreatic amylase ⟶ starch ⟶ oligosaccarides and disaccarides
Brush border disaccaridases ⟶ disaccarides ⟶ monosaccarides

(Beta-galactosidase=*Lactase,* Alfa-galactosidase= *Sucrase,Maltase*)

Lactose ⟶ Glucose and Galactose
Sucrose ⟶ Glucose and Fructose
Maltose ⟶ Glucose and Glucose

Monosaccarides are then transported through the cell into the portal circulation. They absorbed by an active transport mechanism. Energy is required for the accumulation and movement of glucose into the cell (Na,K-ATP ase in the basolateral membrane)

Protein and aminoacid absorption:

-Dietary proteins undergo initial degradation in the stomach by pepsin. Complete hydrolysis is largely achieved by the action of pancreatic endopeptidases (trypsin,chymotrypsin and elastase) and exopeptitase (carboxypeptidase).
These enzymatic processes yield oligopeptides (3-6 aminoacids) ,dipeptides (2 aminoacids) and aminoacids (aa).There are oligopeptidase to split small peptides on the surface and in the cytoplasm of the mucosal cells. Digestion of proteins to aa. Occurs in three locations;

- -The intestinal lumen
- -The brush border
- -The cytoplasm of mucosal cells

-Absorption of aa. is rapid in the duodenum and jejunum but slow in the ileum. Sodium ions and energy are needed for the entry and concentration of aa. in the cell.
-Dipeptides are absorbed more rapidly.
-Most naturally occuring aa. are L-aminoacids
-Neutral aa. share a common carrier mechanism, tryptofan and alanine show competitive inhibition.
-Among dibasic aa. that appear to have a diagnostic transport mechanism are arginine,ornithine and lysine. The neutral aa. cysteine shares this mechanism.
-They is a separate transport system for glycine,iminoacids (proline,hydroxyproline) and dicarboxylic acids (glutamic and aspartic acids).
-In **cystinuria**,there is impaired absorption of cystine,arginine,ornithine and lysine.
-In **Hartnup** disease,defect in the transport of neutral aa. (tryptofan,phenylalanine and histidine) is found.
-In these genetic disorders uptake and absorption of dipeptides are normal.

Fat digestion and absorption:

-Most of the ingested dietary fats are in the form of long-chain triglycerides (C-16, C-18 fatty acids)
-The average man eats 80-160 g of fat daily provided almost half of the calories
-Eight phases have been defined in fat absorption;

1-Enzymatic hydrolysis of triglyceride in the stomach (Trybutyrase)
2-Emulsification to form small lipid particles
3-Enzymatic hydrolysis of trglyceride to yield fatty acids and monoglycerides
4-Dispersion of the relesed lipids into carrier transport system such as bile acid micelles
5-Diffusion across an unstirred layer of water immediately adjacent to the epithelial cell membrane and release of the lipid from the transport system
6-Absorption of lipid into the epithelial cell
7-İntracellular metabolism, re-esterification and formation of chylomicrons
8-Transport of chylomicrons across the basolateral membrane into lymphatic channels and finally into the blood.

-Digestion of triglyceride begins in the stomach.(Lingual lipase and gastric lipase)
-The entry of fat into the duodenum causes release of secretin and cholecystokinin which stimulate the flow of bile and pancreatic juice (Lipase)
-There are at least five additional lipases ;Milk lipase,pancreatic lipase,pankreatic colipase,phopholipase and nonspesific lipase(Cholesterol esterase)
-Colipase is essential for the activation of lipase
-The hydrolysis of triglycerides by pancreatic lipase is a complex process involving lipase, colipase and bile salts.
-Bile salts play an important role in the digestion and absorption of fat. 200-600 mg bile acids are synthesized daily from cholesterol in the liver.In humans; principal bile acids excreted are conjugates of cholic and chenodeoxycholic acide. Approximately 95% of bile salts entering the duodenum are reabsorbed in the terminal ileum and returned to the liver for re-excretion. 200-600mg bile salts excreted in the feces per day. During digestion and micelles formation the concentration of bile salts in the lumen is in the range of 5 to 15 mic mol/ml.
-Fatty acids and monoglycerides enter the micelles, forming mixed micelles. Triglyseride emulsion is turbid but mixed micelles containing bile salts, fatty acids and monoglycerides form clear solutions.
-After the forming of mixed micelles the lipids pass through an unstirred water layer covering the intestinal cell surface.Fatty acids and monoglycerides can enter the cell.
-Fatty acids and monoglycerides derived from long-chain triglycerides (C16-18) are promptly reesterified to triglycerides by enzymes of the endoplasmic reticulum. These triglycerides then interact with spesific apolipoproteins plus cholesterol and phospholipid to form chylomicrons and VLDL. These then are secreted into the lacteals and the intestinal lymph.
-Intestinal epithelial cells synthetize apoprotein I - IV and apoprotein B which are added as a coating around the chylomicron particle prior to its release from the cell. These proteins are necessary for secretion across the epithelial cell basolateral membrane.

-Fatty acids derived from medium chain triglycerides (C 8- C12) are not reesterified to triglyceride inside the epithelial cell and are not incorporated into lipoproteins.They rapidly enter the portal venous system
-Fatty acids derived from short chain triglycerides (C6- C8) are more soluble in water,can be absorbed directly through the epithelial cell membrane without solubilization in bile salt micelles.

Absorption of cholesterol and fat-soluble vitamins(A,D,E,K):

-Within the lumen, cholesterol esters from the bile and diet are hydrolyzed by pancreatic esterase. Only free cholesterol enters the intestinal cell, much of the cholesterol is reesterified and is then secreted primarly into lymph.
-Lipid soluble vitamins transported in the chylomicrons of the lymph. The absorption mechanisms of the fat soluble vitamins are not well understood.

Water and sodium absorption:

Water is absorbed from the small bowel and colon by a passive process that is dependent on absorption of other nutrients (particularly sodium) Absorption of sodium proceeds through a number of mechanisms;

- Absorption along the electrochemical gradient.
- Absorption stimulated by glucose and aa. absorption (only in the small bowel)
- Hydrogen – sodium exchange (enhanced by the presence of bicarbonate)
- Sodium - chloride coupling

There are significant differences in the net sodium conservation capabilities of the jejunum,ileum end colon.(Conservation increases distally)

Calcium absorption:

Ca is actively transported by the small intestine. This process is intimately linked to the active form of vitamin D (1,25-dihydroxycholecalciferol). The role of calcium binding protein and calmoduline in the absorption remains unclear.

Iron absorption:

-In the average western diet iron intake avarages 15 to 25 mg/d; iron absorption averages 0,5 to 1mg/d in man and 1 to 2 mg/d in women.The duodenum is principal site of the iron absorption.
-The transferrin receptor and duodenal ferritin in small intesinal mucosa cells appear to have a regulatory /inhibitory role in iron absorption.
-Organic iron in the form of hemoglobin is absorbed more effectively than iron from cereals and vegetables.Absorption of inorganic iron is increased by ascorbic acid.
-Presence of anemia,liver injury,pregnancy,idiopatic hemochromatosis may result in increased iron absorption.The presence of phosphates,carbonates and phytates in the lumen may lead to decreased absorption of inorganic iron.
-İmpaired absorption of iron is frequent in disorders involve the duodenel mucosa

Absorption of water soluble vitamins:

Folic acid
Folats exist in food conjugated with glutamyl peptides (polyglutamates). They must be deconjugated foat deconjugase to monoglutamates for absorption. Oral contraseptives, sulfasalazine,diphenylhydantoin,trimethoprim inhibit the absorption of dietary folate.
Thiamine and riboflavin appear to be absorbed by passive diffusion

Vitamin B12 (cobalamin)
-Cobalamin (Cob) found in animal protein is released from protein in the stomach by the acid and pepsin
-Cob. binds the R protein (cobalophilin) secreted by the stomach
-This complex is degraded by pencreatic proteases with in the duodenum,with release of Cob. to bind with gastric intrinsic factor(IF)
-'Cob + IF' complex passes down to distal 60 cm of ileum and binds to specific receptor on the brush border
-Cobalamin enters to ileal cell but IF does not.
-Transcobalamin II (TCII) picks up cobalamin in the ileal mucosa and promotes its uptake by tissues throughout the body
-'TCII + Cob' complex enters tissue via endocytosis

CLASSIFICATION OF MALABSORPTION SYNDROME

Inadequate digestion:
Postgastrectomy steatorrhea
Deficiency or inactivation of pancreatic lipase
- Exocrine pancreatic insuffiency
  - Chronic pancreatitis
  - Pancreatic carcinoma
  - Cystic fibrosis
  - Pancreatic resection
- Gastrinoma /Zollinger-Ellison syndrome)

Inadequate absorptive surface:
Intestinal resection or bypass
- Mesenteric vascular disease with massive intestinal resection
- Regional enteritis with multipl bowel resections
- Jejunuileal bypass

Gastroileostomy

Intestinal bacterial overgrowth:
Structural abnormalities producing stasis
- Multipl small bowel diverticula
- Strictures
  - Crohn disease
  - Radiation enteritis
  - Vasculitis

Billroth II resection vith afferent loop stasis
Multipl laparatomies resulting in bowel adhesion

Fistulas
Gastrocolic,gastroileal,jejunoileal,jejunucolic

Motor abnormalities resulting in hipomotility
Scleroderma
Amyloidosis
Diabetes mellitus
Hypothyroidism
Intestinal pseudoobstruction

Gastric hypochlorhydria / achlorhydria
Pernicious anemia
Subtotal gastrectomy
Prolonged use of proton pump inhibitors

Lymphatic obstruction:
Intestinal lymphangiectasia
Lymphoma
Retroperitonel fibrosis
Chronic enfections (Tbc)

Cardiovascular disorders:
Costictive pericarditis
Conjestive heart failure
Mesenteric vascular insufficiency
Vasculitis

Endocrin and metabolic disorders:
Diabetes mellitus
Hypoparathyroidism
Adrenal insufficiency
Hyperthyroidism
Gastrinoma
Carcinoid syndrome
Meduller thyroid carcinoma

Primary mucosal absorptive defects:
İnflammatory,infiltrative disorders or infections

Crohn's disease	Collagenous sprue
Amyloidosis	Whipple disease
Sclerodrema	Nonspesific ulcertaive jejunitis
Lymphoma	Mastocytosis
Radiation enteritis	Dermatitis herpetiformis
Radiation enteritis	Tropical sprue

Biochemical or genetic abnormalities

Celiac sprue	Disaccaridase deficiency
Hypogammaglobinemia	Abetalipoproteinemia
Hartnup disease	Cystinuria

Reduced intestinal bile salt concentration:

Liver disease (Parenchymal or cholestatic)

Anormal bacterial proliferation in the small bowel

Afferent loop	Blind loops
Strictures	Multipl divertical of small bowel
Fistulas	Hypomotility (DM,İntestinal pseudo obstr.)

Interrupted enterohepatic circulation of bile acids

- Ileal resection
- Ileal inflammatory disease (Crohn,Tbc,Yersinia)

Drugs (Sequestration or precipitation of bile salts)

- Neomycin
- Calcium carbonate
- Cholestyramine

TESTS USEFUL IN THE DIAGNOSIS OF MALABSORPTION

Stool fat:

-The qualitatif microscopic examination of a stool specimen with the Sudan III stain is of value and correlates well with the quantitatif determination of fecal fat.

-Normal fecal fat excretion is less than 6 g for 24 h. representing a coefficient of fat absorption of > 94 percent.

-Oral 14C triolein can be used as an effective test for fat absorption

-14C-Triolein breath test (14C-glycerol triolate⟶ radiolabeled CO2)

Xylose absorption:

-The most coomonly employed test of carbohytrate absorption

-Patient ingests 25g D-xylose. A 5-h urine xylose excretion of 4g (26mmol) or grteater is concidered normal

-A blood xylose level of 30mg/dl or greater indicates normal absorption.

-Low values may be obtained in renal insufficiency, ascites ,intestinal bacterial overgrowth,administration of aspirin and indomethacin.

-Abnormal D-xylose absorption is found most frequently in disorders affecting the mucosa of the proximal small intestine,such as celiac sprue and tropical sprue.

Gastrointestinal X-Ray studies:

-All patients with malabsorption should have radiographic examinations of small intestine

-Traditional findings suggesting a diagnosis of malabsorption include;

- -Fragmantation , segmentation and flocculation of barium
- -Thickened and nodular small intestinal folds
- -Presence of strictures,fistulas and small bowel diverticula

Small intestinal biopsy:

-The most commonly used instrument for obtaining biopsy is upper gastrointestinal endoscopy which largely superseded the sue of the Crosby cabsules.

Disorders associated with abnormalities in small bowel biopsy specimens:

Biopsy has diagnostic value (Diffuse lesions)

-**Whipple disease**; Lamina propria infiltrated with macrophage containing PAS positive glycoproteins

-**Abetalipoproteinemia**; Villus structure normal,epithelial cell vacuolated due to excess fat

-**Agammaglobuinemia;** Flattened or absent villi, increased lymphocyte infiltration, absence of plasma cells

-**Mycobacterium avium complex**

Biopsy may have diagnostic value (Patchy lesions)

-**İntestinal lymphoma**; Infiltration of lamina propria and submucosa with malignant cells

-**Intestinal lymphangiectasia**; Dilated lacteals and lymhatics in lamina propria, clubbed villi

-**Eosinophilic enteritis**; Diffuse or patchy eosinophilic infiltration in lamina propria and mucosa

-**Regional enteritis**; Noncaseating granüloma

-**Parasitic infestations**; Parasitic invasion of mocosa, adherence of trophozoites to mucosal surface as in giardiasis

-**Systemic mastocytosis**; Mast cell infiltration of lamina propria

Biopsy is abnormal but not diagnostic

-**Celiac sprue**; Shortend or absent villi hypertrophied crypts, demaged surface epithelium,mononuclear infiltration

-**Collagenous sprue**; Indistiguishable from celiac sprue, extensive subepitelial collagen deposition

-**Tropical sprue**; Lesion similar to celiac sprue with shortened or absent villi,lymphocyte infiltration

-**Folate deficiency**; Shortened villi,megalocytosis,decreased mitosis in crypts

-**Vitamin B12** deficiency; Similar to folate deficiency

-**Acute radiation enteritis**; Similar to folate deficiency

-**Systemic scleroderma**; Fibrosis around Brunner's glands

-**Bacterial overgrowth syndromes**; Patchy damage to villi and increased lymphocyte infiltration

Schilling test for Vitamin B12 absorption:

-1mg of vitamin B12 is injected IM immediately prior to giving of the radioisotope labeled Vit B12. Then 1mg of 57Co-cyanocobalomin is given orally,all urine collected for the next 24 hours and the radioactivity in a sample of the pooled urine is measured. With normal absorption and renal excretion, 7 percent or more of the radioisotope should appear in the urine over 24 hours.Less than this amount may indicate any of the abnormalities .

-The Schilling test is valuable in the differential diagnosis of malabsorption and is frequently carried out in three stages;

1-Without instrinsic factor
2-With intrinsic factor
3-After a course of treatment with antibiotics or antiinflammatory drugs
-Vitamin B12 absorption is frequently abnormal in patients with exocrine pancreatic insufficiency

Tests of bile salt absorption:
-14C-Glycocholic acid breath test
-Selenium-75 labeled homotaurocholic acid test
-Cholestyramine therapy

Tests for bacterial overgrowth:
-**Culture of intestinal aspirate**; Bacterial counts rarely exceed 10.000/ml in the jejunum or 100.000/ml in the ileum. (Coliform and other aerobic bacteria lactobacillus,bacteroides)
-**Glycocholic acid breath test;** (14C-glycocholic acid) The test result is considered abnormal if more than 4,5% of the administered radioactivity is excreted in the breath during the subsequent 6 hr. False negative results have been found in some 35% of patients
Bacteria ⟶ 14C-Glycocholic acid ⟶ 14C-Glycine ⟶ 14CO2

-14C D-xylose breath test
-Glucose hydrogen breath test; Ene-expiratory breath hydrogen concentrations ara measured before and at 30,60,90 and 120 min. after ingestion of 50mg dose of glucose. A peak hydrogen concentration that exceeds fasting levels by more than 20ppm is a more reliable diagnostic indicator.(Sensitivitiy-65%, specificity-90%).

Investigation of pancreatic exocrine function:

-**Intubation studies**; Stimulation test require the analysis of aspirated duodenal contents following activation of the pancreas,

1-Directly by IV administration of secretin and pancreozymine
Secretin ⟶ pancreatic fluid and bicarbonate
Pancreozymine ⟶ enzyme production
2-İndirectly, with the Lundth test meal.

-**Bentiromide (PABA) test;** This test is the best-studied of the tubeless tests of pancreatic function.It provides an indirect measure of chymotrypsin activity.

Chimotrypsin ⟶ 500mg oral NBT-PABA ⟶ PABA in urine as arylamines

A cumulative 6 hr arylamine excretion of less than 50 percent of that ingested as bentiromide is virtually diagnostic of pancreatic insufficiency.
Pancreatic supplements should be discontinued for at least five days before the test is performed.The test is not accurate when the serum creatinine level exceeds 2mg /dl.

-Imaging the pancreas; Ultrasonography should be initial investigation. When the findings ara not sufficient computed tomography (CT) is indicated. When US and CT fail to confirm chronic pancreatitis endoscopic retrograde cholangiopancreotography (ERCP) is particularly helpful. Detection of calcification on the direct abdominal graphy may suggest the presence of chronic pancreatitis.

Abnormal serum calcium,albumin,cholesterol,magnesium,iron, serum carotenes, vitamin A and prothrombin time values may be found in several malabsorptiv disease

DISORDERS OF MALABSORPTION

INADEQUATE DIGESTION

Liver and biliary tract disease:

- Acut viral hepatitis,exrtahepatic biliary tract obstruction,primary biliary cirrhosis,post necrotic cirrhosis

-Steatorrhea is due to impaired hepatic synthesis or excretion of conjugated bile salts ,resulting impaired formation of micellar lipid. These patients also may have impaired fat soluble vitamins resulting severe metabolic bone disease

-Patients with alcohol induced liver disease also may have exocrine pancreatic insufficiency

Postgastrectomy malabsorption:

-Steatorrhea is more common with a Billroth II than Billroth I type of anastomosis

-Decreased stimulus for the release of secretin and cholecystokinin (CCK) from the duodenum may result in a depressed pancreatic enzyme response

-İnadequate mixing of the pancreatic enzymes and bile salts secreted into proximal duodenum with the gastric contents entering the jejunum

-Stasis of intestinal contents in the afferent loop resulting bacterial proliferation

-The loss of the reservoir function of the stomach resulting in decreased intestinal transit time

INADEQUATE ABSORPTIVE SURFACE (Short bowel syndrome)

Extensive intestinal resection often results in the short-bowel syndrome.

-Massive intestinal resection following a vascular insult to the small intestine
-Regional enteritis with multiple bowel resections
-A jejunoileal bypass for morbid obesity
-Resection of the ileum and the ileocecal valve alone may induce severe diarhea and malabsorption,even though less than 30 percent of small intestine is resected
-Several measures are important in the management;

-The diet should contain at least 2500 kcal and consist primarily of carbohydrate and protein with fat restricted to less than 40 g/d.

-It is often necessary to provide vitamins and mineral supplements

-Spesific drugs are helpful in controlling diarrhea (antikolinergics,loperamide, codeine)

-Bile salt sequestering agent such as cholestyramine may helpful

-Supression of gastric hypersecretion

-Octreotide, a long acting somatostatin analogue reduces digestive secretions and may ameliorate the diarrhea.

-Total parenteral nutrition is frequently required during the firs 6 months after massive intestinal resection

MALABSORPTION DUE TO BACTERIAL OVER-GROWTH OF THE SMALL BOWEL

-The proximal small intestine is usually bacteriologically sterile because of three factors;

1-The acid milieu of the stomach
2-Intestinal peristalsis
3-Secretion of immunoglobulins into the intestinal lumen
4-Intact ileocecal valve

Pathophysiology

-Intraluminal deconjugation of bile salts and decreased intaluminal bile salt concentration

-Impaired intraluminal micelle formation

-Intestinal mucosal lesions due to microorganisms

Clinical manifestations

-Positive breath tests

-Moderate steatorrhea (15-30g fecal fat/d)

-Macrocytic anemia with a megaloblastic bone marrow

-Corection of steatorrhea and vitamin B 12 absorption by antibiotic therapy (Tetracycline,metronidazole,ciprofloxacine,trimethoprime,sulfomethoxazole)

Chronic intestinal pseudoobstruction:

Two main types can be detected;

-**Primary** or idiopathic intestinal pseudoobstruction

Three types were described; Myopathic, neuropathic and idiopathic types

-**Secondary** intestinal pseudoobstruction

Scleroderma,dermatomyositis,SLE,amyloidosis,diabetes mellitus,hypothyroidism Chagas disease, drugs, paraneoplastic (small cell lung cancer)

-Nausea,vomiting,abdominal pain,distention,constipation,intermittant diarrhea,urinary tract symptoms,dysphagia are primary clinical manifestations

-Solid nutrients must be restricted, ***cisapride*** may be helpful

Scleroderma:

-Impaired intestinal motility and jejunal pseudo diverticulosis

-Involvement of the intestinal wall by the disease (collagen deposition)

-Vascular ischemia

-Treatment with antibiotics and prokinetics may be beneficial

Tropical sprue:

Tropical sprue is a malabsorptive disorder of unknown cause affecting residents or visitors to tropical regions. It may have its onset months or even years after a patient has returned from the tropics.

-Etiology

-A nutritional deficiency
-A transmisible infectious microorganism
-A toxin elaborated by a microorganisms or contained in the diet

-Anorexia,diarrhea,weight loss,symptoms of anemia (iron,B12 and folate), sequela of nutritional deficiency, abdominal distention
-Absorption of fat,xylose and B12 is impaired
-Jejunal biopsy; Shortened and thickened villi, icreased crypt depth,increased infiltration of mononuclear cells in the lamina propria and epithelium,lesions may be patchy.
-Treatment with vitamin B12,folate and antibiotics have all been effective in inducing remission (Tetracycline or Ciprofloxacine)

Malabsorption in AIDS:

-Diarrhea and weigt loss occur frequently in patients with AIDS
-These symptoms are often duo to; Infections and small intestinal Kaposi sarcoma

DISORDERS ASSOCIATED WITH LYMPHATIC OBSTRUCTION

Whipple's disease:

-This is a rare disorder characterized clinically by artralgia, abdominal pain,diarrhea,progresive weight loss, low grade fever, increased skin pigmentation peripheral lymphadenopathy ,heart failure,endocarditis,uveitis,central nervous system manifestations ,dilated lacteals in the bowel wall and impaired intestinal absorption
-The diagnosis is established by demonstrating the presence in the mucosa of macrophages containing large PAS positive cytoplasmic granules and dilated lymphatics
-Electron microscopic studies revealed the presence of rod-shaped structures in and adjacent to the macrophages,epithelial cells and leukocytes (**Tropheryma Whippelii)**
-Therapy with antibiotics will usually induce clinical remission. Patients with whipple' disease should be treated with antibiotics, such as trimethoprim-sulfamethoxazole at least 1 year.

Intestinal lymphoma:

-Steatrorrhea is a manifestation of primary intestinal lymphoma.may be either primary or secondary to lymphoma elsewhere..The diagnosis should be suspected in patients with malabsorption with the following findings;

1- A malabsorption syndrome in which clinical and biopsy features resemble those of celiac sprue but in which there is an incomplete response to a gluten free diet.
2- The presence of abdominal pain and fever
3- Signs and symtoms of intestinal obstruction

-Mechanism of malabsorption in intestinal lymphoma may be related to several factors;

1-Diffuse involvement of the small intestinal mucosa
2-Involvement of the bowel wall with lymphatic obstruction
3-Localized stenosis with stasis of intestinal contents and bacterial overgrowth

-The majority of primary intestinal lymphoma are B-cell lymphomas, the main exception being the lymphomas that complicate coeliac disease,which are T-cell

lymphomas (Enteropathy associated T-cell lymphomas). Hodgkin's disease only rarely involves the intestine.
-Hepatomegaly,splenomegaly,palpable abdominal masses and peripheral adenopathy are usually not found.
-There may be a total absence of villi or lesser degrees of blunting and shortening of the villi in histologic examination.

-Western type intestinal lymphoma
Short primary lymphomatous lesions,usually present with obstructive symptoms or as a mass, any part of the intestine may be involved but the distal small intestine and stomach are the most common sites. The disease occurs predominantly in men and age of onset of symptoms is about 50 years. Perforation ,bleeding and intestinal obstruction are common terminal complications.
Treatment; Surgical resection and/or chemotherapy -radiotherapy

-Alpha chain disease (Mediterranean lymphoma)(PPIL):
Primary proximal intestinal lymphoma (PPIL) is arguably only pre-malignant in its early stages and should probably be considered seperately from other intestinal lymphomas.There is hyperplasia followed by neoplasia of Ig-A producing cells within the intestine, poosibly as a result of chronic antigenic stimulation. The malignant cells produce IgA heavy chains in excees without ligt chains.The alpha chains can be detected in blood and urine. Secretuar IgA fuction is defective.Anemia,abdominal pain,steatorrhea,weight loss and severe clubbing are main common symptoms.The disease occurs predominantly in young man in countries around the mediterrenean,in Africa,South America and the Far East.
Treatment; With tetracycline in early premalignant phase and with chemothrapy in malignant phase

Cardiovascular disorders:
Steatorrhea has been described in patients with chronic congestive heart failure,superior mesenteric artery insufficiency and costrictive pericarditis

INFLAMMATORY OR INFILTRATIVE DISORDERS

Regional enteritis:
Malabsorption in regional enteritis may result from several factors;
1-Interruption of the enterohepatic circulation of bile acids by ileal disease or resection
2-Deconjugation of bile salts due to bacterial overgrowth, in turn related to srictures and /or fistulas
3-Active inflammatory bowel disease causing impaired mucosal cell function
4-Inadequate absorptive surface resulting from intestinal resection or fistulas
5-Severe protein depletion producing impaired exocrine pancreatic function.
Treatment with sulfasalazine,corticosteroids and other immunosupresive drugs may be beneficial.

After ileal resection (less then 80-100cm) ⟶ Bile salts induced diarrhea (Cholerrheic diarrhea) may respond to teratment with cholestyramine

After ileal resection (more than 100cm) ⟶ Fat acids induced diarrhea.
Cholestyramine to make worse the diarrhea.

Chronic nongranulomatous ulcerative jejunoileitis:

This disorder characterized by abdominal abdominal pain,weight loss, fever, diarrhea, steatorrhea, hypoalbuninemia and protein loosing enteropathy. Findings mimic celiac sprue and regional ileitis.Glucocorticoid treatment has resulted in transient improvement.

Amyloidosis:

Amyloid is an insoluble glycoprotein complex that may be deposited in a wide variety of body trissues including all parts of the digestive tract. It is an amorphous fibrillar material that stains pink with HE and Congo red.

There are main six types of amyloidosis; Primary amyloidosis, amyloid with multipl myeloma or chronic infectious disease, heredofamilial amyloidosis sush as FMF, local amyloidosis,I diopathic amyloidosis of aging.

Gastrointestinal tract involvement is common in amyloidosis.Chief sites for amyloid deposits and potential consequences are;

1-In muscularis mucusa,which impairs mucosal absorption
2-In the walls of small blood vessel, which can produce ischemia and infarction
3-Within the muscle layer of the bowel wall,which can interrupt normal motility.

Diagnosis should be confirmed by mucosal biopsy (Gastric,small intestinal or/and rectal)

There is no specific therapy for amyloidosis. Colchicine, antibiotics and prochinetic agents may supply some benefit.

Raidation injury to the small bowel:

Extensive morphologic damage of the small intestinal mucosa often follows normal or excessive abdominal irradiation (>4500 – 5000 rad). Changes duo to radiation injury include ; decrease in crypt mitoses, shortened of the villi, megalocytosis of epithelial cells and inflammatory cell infiltration of the lamina propria. In some patients intestinal strictures due to vasculopathy , ischemia and intestinal lymphangiectasia may develop.

Treatment with antibiotics,pancreatic enzymes,gluten-free diet, glucocorticoids and opiates has limited success.

Eosinophilic enteritis:

Eosinophilic gastroenteritis is a disorder of the stomach,small bowel and colon that is of unknown etiology and is characterized by peripheral blood eosinophilia and eosinophilic infiltration of the gut wall without evidence of vasculitis. Three main patters have been identified;

1-Predominantly mucosal disease ⟶ Symptoms due to diarrhea,steatorrhea
2-Predominant muscle layer disease ⟶ Symptoms due to obstruction
3-Predominant subserosal disease ⟶ Symptoms due to ascites (with marked eosinophilia in the asitic fluid)
4-It should be emphasized that mixed clinical forms may also occur.

Food allergy is related to symptoms in less than 20 percent of patients. In such patients fasting serum IgE levels are often elevated.

Elimination diets are frequently ineffective and such patients may require prolonged glucocorticoid therapy to remain well. Ketotifen and cromolyn are also useful therapeutic adjuncts.

Dermatitis and malabsorption:

A malabsorption syndrome ,usually mild, has been reported in patients with a variety of dermatologic disorders including psoriasis, eczemotoid dermatitis and dermatitis herpetiformis. Histologis changes of small bowel mucosa resemble celiac sprue.

BIOCHEMICAL OR GENETIC ABNORMALITIES

Celiac sprue (Gluten induced enteropathy):

-70 percent of the cases are in women.
-The incidence in siblings appears to be many times higher than that in the general population.
-Incidence is variable between 0,05-0,2 % .
-Celiac sprue patients have an increased frequency (in 70-90%) of some serum histocompatibility antigens (HLA-DR3 and HLA-DQw2).The HLA antigens may be linked to immune response to peptides in gluten or to production of pathogenic antigliadin antibodies.
-Gluten and related substance gliadin are found especially in wheat. The alcohol-soluble fraction of gluten cosists of glutamine- rich gliadin polypeptides which can be fractioned into alpha,beta,gamma and delta subgroups; all four are toxic to celiac spure patients.Two theories have been proposed;

1-Toxic theory; Patients with celiac sprue lack a spesific mucosal peptidase so that gluten or its larger glutamine containing peptides ara not effectively hydrolized to smaller peptides.As a consequence toxic peptides might accumulate in the mucosa.

2-Immunologic theory; Gluten or gluten metabolites may initiate an immune reaction in the intestinal mucosa. İnteraction of T lymphocytes with crypt epithelium may be a primary event in the pathogenesis of the intestinal lesion.
-A possible role for adenovirus serotype 12(Ad12) in the pathogenesis of celiac sprue has been proposed on the basis of two observations;

There is aa.sequence homology between a portion of a-gliadin and viral protein (E16) and patients with untreated celiac disease have a much higher frequency of antibodies to Ad12 than treated celiac sprue patients and controls.

-Jejunal biopsy specimens from patients with celiac sprue show a characteristic lesion;

-There is blunting and flattening of the mucosal surface with villi either absent, broad and short

-The crypts are elongated and ratio of willi to crypt lenghts are reversed

-There is generally dense infiltration of inflammatory cells in the lamina propria

-The surface epithelium is altered with a cuboidal rather than normal columnar cells.

-These changes are usually most severe in the proximal small bowel.

-Similar changes have been described in other conditions including lymphoma, tropical sprue and hypogammaglobulinemia associated with malabsorption.

-Since the mucosa is damaged and altered in patients with celiac sprue,there may be decreased release of pancreotropic hormones (secretin and CCK).

-Diarrhea in celiac sprue patients is due to number of factors;

-Impaired absorption of salt and water from small intestine

-Net secretion of water form abnormal jejunal mucosa

-Net colonic secretion of water and electrolytes induced by unabsorbed fatty acids.

Most patients with celiac sprue will have a typical malabsorption syndrome characterized by weight loss, abdominal distention and bloathing, diarrhea, steatorrhea and abnormal results on test absorptive function .

-**There are established associations between celiac sprue and;** diabetes mellitus, selective IgA deficiency, primary sclerosan cholangitis primary biliary cirrhosis,ulcerative cholangitis and lymphocytic (or microscopic) colitis.

-Three criteria should be met for a definite diagnosis of celiac disease to be made;

1-Evidence of malabsorption

2-The presence of characteristic abnormal findings on biopsy specimens

3-Clinical,biochemical and histologic improvement after institution of a gluten free diet.

-**Endoscopic findings;** Mucosa may be atrophic, mottled or scalopped appearence, edematous

-**Antigliadin,antiendomysial and antireticulin antibodies** have been widely used in the diagnosis of celiac disease.Approximately 90 percent of patients with untreated celiac disease have IgA and/or IgG antigliadin antibodies and antiendomysial antibodies. Antibody titers frquently decrease after institution of a gluten free diet.

-A possible variant of celiac diseae is **collagenous sprue** which characteristically reveal a collagen deposition in the lamina propria in addition the other characteristic histologic findings of celiac sprue. Fatal ,unremitting malabsorption developed in a third of the patients with dense collagen deposition.

-80 percent of patients improve after institution of a gluten free diet. Symptomatic improvement usually occurs within a few weeks but improvement in the small bowel histologic characteristics may not occur for months.

-The patients must avoid all wheat, barley, rye and oats. Rice, corn,soy and the flours of these grains are acceptable.

-Recent studies indicate that oats, when ingested in quantities of about 50g/d, are safe for celiac sprue patients for a period of at least 6 to 12 months.

-Approximately 50 percent of patients with refractory sprue respond to glucucorticoids.

-If patient with celiac sprue does not respond to gluten-free diet, other possibilities or complicating factors must be considered;

1-The diagnosis is incorrect

2-The patient is not adhering strictly to the diet

3-There may be another concurrent disease, such as pancreatic insufficiency

4-Lactase deficiency may be present with resulting milk tolerance

5-The patient may have collagenous sprue

6-The patient may have developed intestinal lymphoma

7-The patient may have developed lymphocytic colitis

8-The patient may have ulceration of jejunum or ileum

9-A small number of patients show a markedly delayed response to gluten free diet with significant improvement occuring only after 24 to 36 months of therapy.

-A late and rare complication of ceilac disease is developing of esophageal adenocarcinoma

Systemic mastocytosis:

-Some evidence of malabsorption occurs in 30 percent of patients with systemic mastositosis

-Malabsorption is usually not severe

-Steatorrhea may be related to excessive gastric acid secretion ,infiltration of the mucosa with mast cells and eosinophils which release histamine and other mediators such as prostoglandins that can affect mucosal secretion, blood flow and intestinal motility.

-Treatment with histamine H1 and H2 receptor antagonists and cromolyn provides relief of diarrhea in some patients.

Disaccaridase deficiency syndrome:

-Lactase deficiency:

Since lactose is principal carbohydtrate of milk,s uch individuals show milk intolerance with symptoms of abdominal cramps,bloating or distention and diarrhea. It would appear that about 5 to 15 percent of the adult white population shows intestinal lactase deficiency but in African American, Bantus and Asians, the incidence is as high as 80 to 90 percent.

-Lactose cannot be hydrolysed and it passes into the colon where it is fermanted by bacteria producing volatile short chain fatty acids,H2 and CO2 which cause discomfort and diarrhea.

-Oral lactose tolerance test and hydrogen breath test may be useful in the diagnosis

-Approximately 70 percent of patients with primary lactose intolerance will respond to a lactose restricted diet while the remaing 30 percent will not because of **underlying irritable bowel syndrome.**

-Acquired lactase deficiency is often seen association with a variety of gastrointestinal disease,in many of which there is histologic evidence of mucosal damage.

-Deficiency of other disaccaridase; Damage to intestinal mucosa may produce decreased levels of other disaccaridases, such sucrose-isomaltase deficiency.

Hypogammaglobulinemia:

-This rare disorder is characterised by a markedly reduced or absent IgA and IgM antibodies in the serum and jejunal secretion. Chronic diarrhea,malabsorption and respiratory infections are common.

-The diagnose is made on measurement of serum ‘Ig’ and on intestinal biopsy which shows that plasma cells are reduced or absent and there may be nodules of lymphoid tissue **(nodular lymphoid hyperplasia)** .Some patients have histologic features of coeliac disease. Giardia intestinalis infestation is very common.

-Treatments involves control of giardiasis and if necessary regular parenteral replacement of immunoglobulins.

Abetalipoproteinemia:

-Inherited otosomal recessive disorder caused by impaired synthesis of lipoprotein (apoprotein-B, a major protein component of VLDL, LDL and chylomicrons) in the

intestinal epithelial cells.The disease has been reported mainly in Jewish and Mediterranean.
-Mucosal epithelial epithelial cells are able to esterify monoglyceride with free fatty acids to form triglycerides but are unable to further synthesize complex lipids. As a result the newly synthesized triglycerides and reseterified cholesterol accumulated in the cell.
-Diarrhea,abdominal distention, steatorrhea, neurologic symptoms, acanthocytosis in peripheric blood, retinitis pigmentosa cardiac arrhytmias may develop.Serum triglycerides are often less than 10mg/dL.Serum cholesterol and fat soluble vitamins may also be reduced. Betalipoprotein is absent completely in the serum .
-Histologically , the intestinal epithelial cells are filled with lipid droplets and there is pratically no lipid in the submucosa and lamina propria.also lymphatics are empty.
-The amount of long-chain triglyceride in the diet should be reduced and replaced with medium-chain triglyceride.

ENDOCRINE AND METABOLIC DISORDERS

Diabetes mellitus:

-When steatorrhea accompanies diabetes,it may be due to the presence of;
1-Exocrine pancreatic insufficiency
2-Coexisting celiac sprue (6% in Type I DM)
3-Abnormal bacterial proliferation in the proximal small bowel
4-Severe and uncontrolled diabetes
5-Mesenteric ischemia due to diabetic vasculopathy
-Several signs of autonomic neuropathy ,peripheral neuropathy and peripheral vascular disease are usually present.
-Different therapeutic apporoaches such as therapy with antibiotics, prochinetics, opioids, gluten free diet ,clonidine and oxybutyrine may be beneficial in the treatment of diabetic diarrhea.

Gastrinoma (Zollinger-Ellison Syndrome):

-ZE syndrome is characterized by recurrent, refractory and unusually located peptic ulcers due to gastrinoma
-Diarrhea occurs in up to one third of patients and may be presenting symptom in 10 percent of cases
-Factors contributing to diarrhea include;
1-Acidification and dilution of intestinal contents caused by gastric acid hypersecretion
2-Precipitation of glcine-conjugated bile salts due to low intraluminal pH
3-Alteration of the intestinal mucosa with ulceration and metaplasia
4-İmpaired fatty acid esterification and chylomicron formation.
-Therapy includes surgical removing of tumor in patients without methastasis and acid suppression with proton pump inhibitors (omeprazole,lansoprazole) in patients with methastasis

Carcinoid syndrome:

-Diarrhea is common but significant steatorrhea is unusual in the methastatic carcinoid syndrome.

-Episodic flushing, telangiectatic skin lesions, cyanosis, pellegra-like skin lesions, broncospasm and cardiac murmurs due to right sided valvuler lesions are other common symptoms of the disease.
The syndrome results from secretion of a variety of vasoactive substances that are potent intestinal secratogogues, including serotonin,histamine, catecholamines, prostoglandin and kinins.

Hyperthyroidism:
Mild to moderate steatorrhea and hypoalbuminemia have been repoted bur absorption of D-xylose and vitamin B12 frequently normal. Dercreased contact time between the nutritients and absorptive mucosa due to increased bowel movement may be responsible factor of diarrhea. Steatorrhea usually remits after successful treatment of hyperthyroidism.

Adrenal insufficiency:
Patients with adrenal insufficiency have been found to have steatorrhea that is corrected by therapy with adrenal glucocorticoids.

PROTEIN LOSING ENTEROPATHY

-Several mechanisms have been proposed for the passage of plasma proteins across the gastrointestinal mucosa in certain disease;

1-Plasma proteins may pass into the gastrointestinal tract through an inflamed or ulcerated mucosa; Inflammatory bowel disease.

2-Plasma proteins loss may occur as a result of disordered mucosal cell stricture; Celiac sprue.

3-Presence of increased lymphatic pressure; Granulomotous or neoplastic involvement of lymphatics.

4-Dilated lymph vessels in the mucosa may rupture through the surface epithelium, discharging their contents into the intestinal lumen; Idiopathic intestinal lymphangiectasia.

-Administration of radiolabeled macromolecules such as I or Cr-labeled serum albumin have been used the detection of protein loss. Alpha-1 antitrypsin which has same molecular weight as albumin(50.000) is resistant to proteolysis and when leaked into the intestinal lumen, is not degraded. (Normal loss is less than 2,6mg/g in stool)

Intestinal lymphangiectasia:
-This disorder is characterised by increased enteric loss of protein, hypoproteinemia, edema, lymphocytopenia, malabsorption and abnormal dilated lymhatic channels in the small intestine.
-IL is part of a generalized congenital disorder of the lymphatic system.
-In adults apprx. **1500 ml** of lymp ,containing 79g fat and 50g albumin, passes through the thorasic duct each day.
-Three lines of evidence support the concept of intestinal leakage of lymph in intestinal lymphangiectasia;

1-Chlous fluid has been recovered from the duodenum

2-Retrograde passage of contrast material from retroperitonel lymphatics into the duodenum and jejunum

3-Significant steatorrhea may persist after completely fat-free diet.

The disease affects primarly children and young adults. Patients have edema, chylous effusions and diarrhea, hypoproteinemia (both albumin and globulin), mild steatorrhea, lymphocytopenia (due to loss of these cells from lymph).
-The diagnosis is established by; small intestinal biopsy and demonstrating of increased enteric protein loss using radiolabeled macromolecules. Jejunal mucosa characteristically reveal dilated and telangiectatic lymphatic vessels in the lamina propria and submucosa.
-A low fat diet and substitution of medium-chain triglycerides for dietary long-chain triglycerides must be recommended.

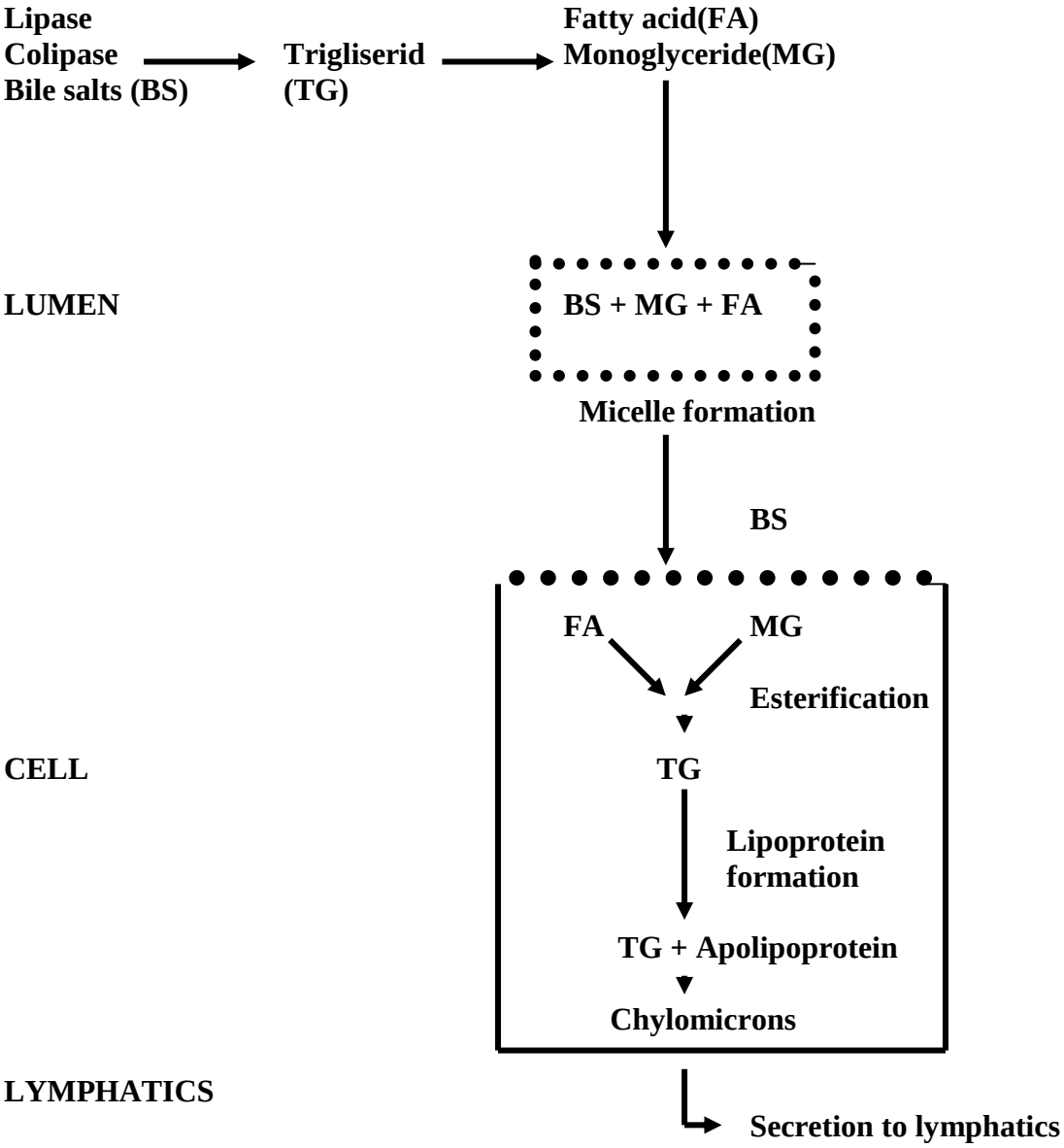
DİSORDERS ASSOCIATED WITH PROTEIN LOSING ENTEROPATHY

Stomach;
- Gastric carcinoma
- Menetrier's disease
- Atrophic gastritis
- Postgastrectomy syndrome

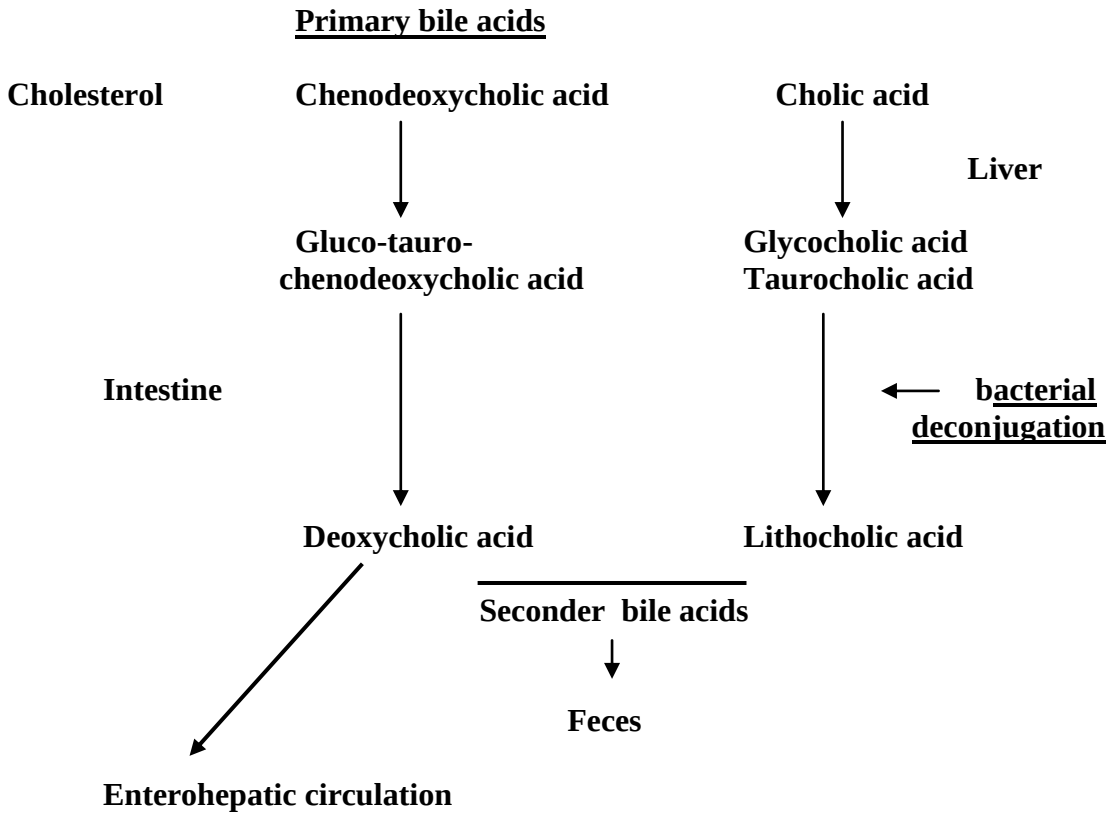
Small intestine
- Intestinal lymphangiectasia
- Celiac sprue
- Tropical sprue
- Whipple's disease
- Lymphoma
- Intestinal Tbc.
- Acute infectious enteritis
- Scleroderma
- Jejunal diverticulosis
- Allergic gastroenteropathy (Milk allergy)
- Eosinophilic gastroenteritis
- Bacterial overgrowth

Colon
- Colonic neoplasm
- Ulcerative colitis
- Granulamatous colitis

Heart
- Congestive heart feilure
- Constrictive pericarditis
- Cardiomyopathy



Scheme of intestinal digestion, absorption,esterification and transport of dietary triglycerides.



Schema of hepatic and intestinal metabolism of bile salts and enterohepatic circulation

PATHOPHYSIOLOGIC BASIS FOR SYMPTOMS AND SIGNS IN MALABSORPTIV DISORDERS

Symptoms or Sign	Pathophysiology
Gastrointestinal	
Generalized malnutrition and Weight loss	Malabsorption of fat,carbohydrate and protein, loss of calories, anorexia
Diarrhea	Impaired absorption or increased secretion of water and electrolytes; unabsorbed dihydroxy bile acids → decreased absorption of water and electrolytes; excess load of fluid and electrolytes presented to the colon may exceed its absorptive capacity (4 lt/d)
Flatus	Bacterial fermentation of unabsorbed carbohydr.
Glossit,heilosis,stomatitis	Deficiency of iron,vitamin B12,folate and other Vitamins
Abdominal pain	Distention or inflammation of bowel,chronic pancreatitis
Genitourinary	
Nocturia	Delated absorption of water,hypokalemia
Azotemia,hypotension	Fluid and electrolyte depletion
Amenorrhea, ↓ libido	Protein depletion and caloric starvation → Secondary hypopituitarism
Hematopoietic	
Anemia	Impaired absorption of iron,vitamin B12,folat and pyridoxine
Hemorrhagic phenomena	Vitamin K malabsorption → PTA ↓
Musculosceletal	
Bone pain	Protein depletion → impaired bone formation → Osteoporosis Calcium malabsorption → demineralization of bone → osteomalacia, Vitamin D malabsorption
Osteoarthropathy	Cause uncertain
Tetany, paresthesis	Calcium malabsorption → hypocalcemia Magnesium malabsorption → hypomagnesemia
Weakness	Anemia,electrolyte depletion (Hypokalemia)
Nervous system	
Night blindness	Impaired absorption vitamin A
Xerophthalmia	Vitamin A deficiency
Peripheral neuropathy	Vitamin B12, thiamine deficiency
Skin	
Eczema	Cause ucertain
Purpura	Vitamin K deficiency
Follicular hyperkeratosis and dermatitis	Deficiency of vitamin A, zinc, essential fatty acids and other vitamins