CHAPTER 26

Digestion, Absorption, & Nutritional Principles

Second Part

OBJECTIVES

After studying this chapter, you should be able to:

- Understand how nutrients are delivered to the body and the chemical processes needed to convert them to a form suitable for absorption.
- List the major dietary carbohydrates and define the luminal and brush border processes that produce absorbable monosaccharides as well as the transport mechanisms that provide for the uptake of these hydrophilic molecules.
- Understand the process of protein assimilation, and the ways in which it is comparable to, or converges from, that used for carbohydrates.
- Define the stepwise processes of lipid digestion and absorption, the role of bile acids in solubilizing the products of lipolysis, and the consequences of fat malabsorption.
- Identify the source and functions of short-chain fatty acids in the colon.
- Delineate the mechanisms of uptake for vitamins and minerals.
- Understand basic principles of energy metabolism and nutrition.

Chapter 26 digestion absorption and nutritional principle	• digestion and absorption of carbohydrate • protein and nucleic acid • lipids

- **Digestion begins** in the **stomach**
- **Some peptide linkages** are **cleaved** by **pepsin**
- **Pepsin** is synthesized and secreted as **inactive pepsinogen** (proenzyme) by **chief cells** and **activated** by gastric **HCl**
- **Pepsinogen I** is found **ONLY** in the **fundus** and **body** glands (**acid secreting glands**)
- **Pepsinogen II** found in fundus, body and **pyloric glands**
- Maximal **acid secretion correlated** with **pepsinogen I** level.

Role of pepsin:

- **Hydrolyzes** the **bonds** between **aromatic amino acids** such as **phenylalanine** or **tyrosine** and **a second amino acid**
- Yielding **polypeptides** of very **diverse sizes**
- Optimum **pH** for activity is **1.6-3.2**
- When the **pH** increase to **4-6.5** (when mixed with pancreatic juice) in the duodenum and jejunum it **rapidly inactivated**

PROTEIN DIGESTION

Protein digestion begins in the stomach, where pepsins cleave some of the peptide linkages. Like many of the other enzymes concerned with protein digestion, pepsins are secreted in the form of inactive precursors (**proenzymes**) and activated in the gastrointestinal tract. The pepsin precursors are called pepsinogens and are activated by gastric acid. Human gastric mucosa contains a number of related pepsinogens, which can be divided into two immunohistochemically distinct groups, pepsinogen I and pepsinogen II. Pepsinogen I is found only in acid-secreting regions, whereas pepsinogen II is also found in the pyloric region. Maximal acid secretion correlates with pepsinogen I levels.

Pepsins hydrolyze the bonds between aromatic amino acids such as phenylalanine or tyrosine and a second amino acid, so the products of peptic digestion are polypeptides of very diverse sizes. Because pepsins have a pH optimum of 1.6–3.2, their action is terminated when the gastric contents are mixed with the alkaline pancreatic juice in the duodenum and jejunum. The pH of the intestinal contents in the duodenal bulb is 3.0–4.0, but rapidly rises; in the rest of the duodenum it is about 6.5.

Role of pancreatic endopeptidases(trypsin, chymotrypsin, elastase, mucosal enterokinases and brush border peptidases

- The **polypeptides** formed by digestion in the stomach are further **digested** by **pancreatic proteolytic** enzymes and **intestinal mucosal enzymes**
- **Endopeptidases** act at **interior bonds** in the peptide molecules and **digest polypeptide** into **dipeptide** or **tripeptide** chains
- **Endopeptidases** are **synthesized** in the pancreas as **inactive** enzymes (precursors or proenzymes) and **activated** in their site of action (intestine) by **brush border enterokinases**
- **Trypsinogen** is converted into active **trypsin** by **enterokinases** in the duodenum
- **Enterokinase** contain **41**% **polysaccharides** that **prevents it from digesting itself before it can exerts its effect**
- **Trypsin** then converts proenzymes (**trypsinogen**, **chymotrypsinogen**, **proelastase**, **propeptidases**) into **active ones** (autocatalytic reaction).
- **Enterokinase** deficiency occurs as a **congenital** abnormality and leads to **protein malnutrition**

Role brush border peptidases:

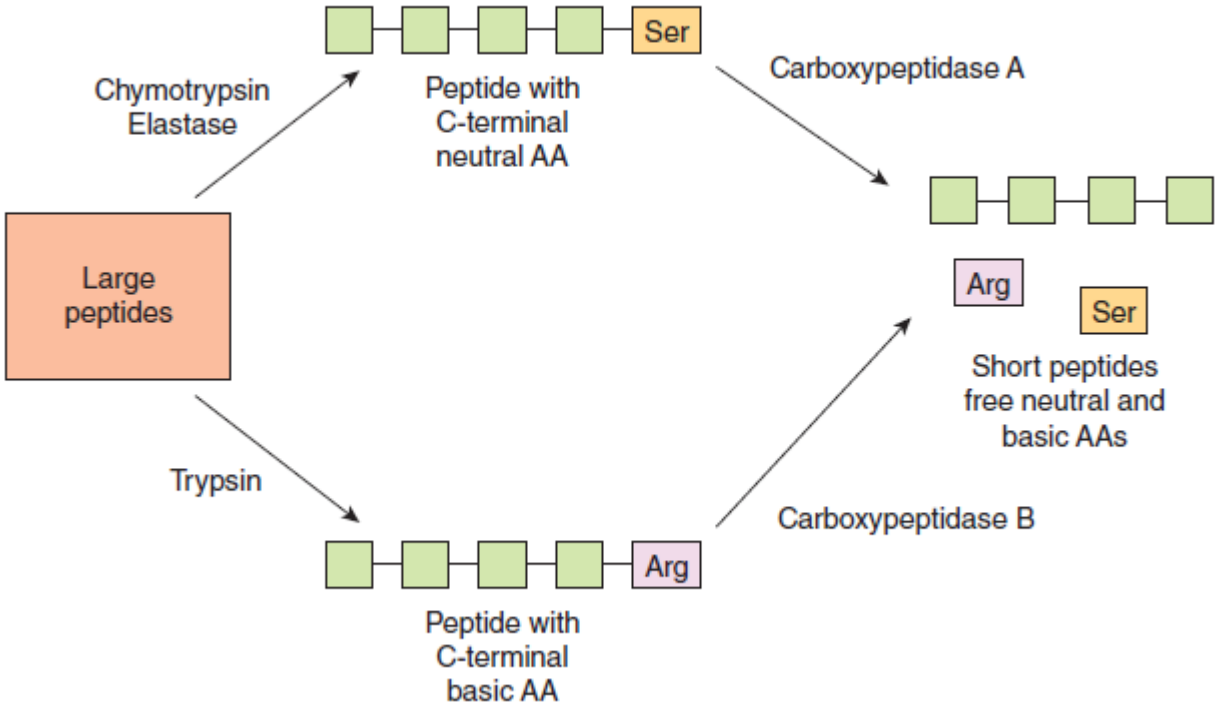
1. **Aminopeptidases**: split peptide chain **from amino terminal**
2. **Carboxypeptidases**: split peptide chain **from carboxyl terminal**
3. **Dipeptidases**: split **2 amino acids peptide into 2 amino acids**

- Some **di- and tri-peptides** are **transported** into **enterocytes** and **hydrolyzed** there into **amino acids** by **intracellular peptidases**
- The intracellular amino acids then **transported** into the **blood**
- Thus, the **final digestion of polypeptides** occurs in 3 locations: **intestinal lumen**; **brush border**; and the **cytoplasm** of **enterocytes**

In the small intestine, the polypeptides formed by digestion in the stomach are further digested by the powerful proteolytic enzymes of the pancreas and intestinal mucosa. Trypsin, the chymotrypsins, and elastase act at interior peptide bonds in the peptide molecules and are called **endopeptidases.** The formation of the active endopeptidases from their inactive precursors occurs only when they have reached their site of action, secondary to the action of the brush border hydrolase, **enterokinase** (Figure). The powerful protein-splitting enzymes of the pancreatic juice are secreted as inactive proenzymes. Trypsinogen is converted to the active enzyme trypsin by **enterokinase** when the pancreatic juice enters the duodenum. Enterokinase contains 41% polysaccharide, and this high polysaccharide content apparently prevents it from being digested itself before it can exert its effect. Trypsin converts chymotrypsinogens into chymotrypsins and other proenzymes into active enzymes (Figure 26–3). Trypsin can also activate trypsinogen; therefore, once some trypsin is formed, there is an auto-catalytic chain reaction.

Enterokinase deficiency occurs as a congenital abnormality and leads to protein malnutrition.

Some free amino acids are liberated in the intestinal lumen, but others are liberated at the cell surface by the aminopeptidases, carboxypeptidases, endopeptidases, and dipeptidases in the brush border of the mucosal cells. Some dipeptides and tripeptides are actively transported into the intestinal cells and hydrolyzed by intracellular peptidases, with the amino acids entering the bloodstream. Thus, the final digestion to amino acids occurs in three locations: the intestinal lumen, the brush border, and the cytoplasm of the mucosal cells.


Ser
Chymotrypsin
Elastase
Peptide with
C-terminal
neutral AA
Carboxypeptidase A
Large
peptides
Arg
Ser
Short peptides
free neutral and
basic AAs
Trypsin
Carboxypeptidase B
Arg
Peptide with
C-terminal
basic AA

Amino acid transporters

- They are **7**
- **5** of which are requiring Na+ (**Na^+-amino acid** cotransporters)
- **2** of which are **requiring Cl^-**

Peptide transporters

- **Di-** and **tri-peptides** cross apical membrane of enterocytes **via H+ dependent peptide transporter 1** (**PepT1**)
- In **enterocytes**, di- and tri-peptides are **hydrolyzed** by intracellular peptidases and **free amino acids** are released
- Intracellular **amino acids transported out** of **enterocytes** across basolateral membrane by **5 transporters** (**facilitated diffusion**) into portal blood
- **Absorption** of **amino acids** is **rapid** in **duodenum** and **jejunum**
- Little absorption existed in ileum (all are absorbed above it)

Source of digested intestinal proteins

- **50%** from **ingested** proteins in the **food**
- **25%** from proteins of the digestive juice
- **25**% from desquamated mucosal cells

Rate of digestion and absorption

- 95-98% digested and absorbed
- 2-5% escape digestion and absorption and subsequently some of which is digested by colonic bacteria
- **All protein** in the **stools** is **NOT** of dietary origin **BUT** from **bacteria** and cellular debris

The activity of brush border peptidases :

1. **Increased** by **resection** of part of the ileum
2. Altered in **starvation**
3. Subjected to **hemostatic regulation**

ABSORPTION

At least seven different transport systems transport amino acids into enterocytes. Five of these require Na^+ and cotransport amino acids and Na^+ in a fashion similar to the cotransport of Na^+ and glucose (Figure 26–3). Two of these five also require Cl^-. In two systems, transport is independent of Na^+.

The dipeptides and tripeptides are transported into enterocytes by a system known as PepT1 (or peptide transporter 1) that requires H^+ instead of Na^+ . There is a very little absorption of larger peptides. In the enterocytes, amino acids released from the peptides by intracellular hydrolysis plus the amino acids absorbed from the intestinal lumen and brush border are transported out of the enterocytes along their basolateral borders by at least five transport systems. From there, they enter the hepatic portal blood.

Absorption of amino acids is rapid in the duodenum and jejunum. There is a little absorption in the ileum in health, because the majority of the free amino acids have already been assimilated at that point. Approximately 50% of the digested protein comes from ingested food, 25% from proteins in digestive juices, and 25% from desquamated mucosal cells. Only 2–5% of the protein in the small intestine escapes digestion and absorption. Some of this is eventually digested by bacterial action in the colon. Almost all of the protein in the stools is not of dietary origin but comes from bacteria and cellular debris. Evidence suggests that the peptidase activities of the brush border and the mucosal cell cytoplasm are increased by resection of part of the ileum and that they are independently altered in starvation. Thus, these enzymes appear to be subject to homeostatic regulation.

Allergy to proteins:

1. **Crustaceans**, **mollusks** and **fish** – **common** offenders
2. **Legumes**, **cow's milk** and **egg white** – **frequent**

- **Allergy** to proteins **DO NOT** occurs in **most** individuals
- It **occurs** in **some** individuals as a **genetic** suitability
- **Absorption** of **protein antigens** (from bacteria and viruses) **takes place in** large micofold cells (**M cells**) specialized intestinal epithelial cells that overlie aggregates of Peyer patches (lymphoid tissue)
- **M cells pass** the **antigen** to **lymphoid cells** and the **lymphocytes** are **activated**
- **Activated lymphoblasts** then inter blood BUT they later **return** to the **intestinal mucosa** and other epithelia and **secrete IgA** in response to **second exposure** to the **same antigen**

Certain foods are more allergenic than others. Crustaceans, mollusks, and fish are common offenders, and allergic responses to legumes, cows' milk, and egg white are also relatively frequent. However, in most individuals food allergies do not occur, and there is an evidence for a genetic component in susceptibility.

Absorption of protein antigens, particularly bacterial and viral proteins, takes place in large **microfold cells** or M cells, specialized intestinal epithelial cells that overlie aggregates of lymphoid tissue (Peyer patches). These cells pass the antigens to the lymphoid cells, and lymphocytes are activated. The activated lymphoblasts enter the circulation, but they later return to the intestinal mucosa and other epithelia, where they secrete IgA in response to subsequent exposures to the same antigen.

- **Nucleic acids** **split** into **nucleotides** in intestine by **pancreatic nucleases**
- The **nucleotides** then split into **nucleosides** and **phosphoric acid** by **mucosal surface enzymes**
- The **nucleosides** then **split** into **sugar** and **purine** and **pyrimidine** bases
- The **bases** are absorbed by **active transport**
- **Nucleosides** also absorbed by **secondary active** and **passive nucleoside transporters** in apical membrane of enterocytes

NUCLEIC ACIDS

Nucleic acids are split into nucleotides in the intestine by the pancreatic nucleases, and the nucleotides are split into the nucleosides and phosphoric acid by enzymes that appear to be located on the luminal surfaces of the mucosal cells. The nucleosides are then split into their constituent sugars and purine and pyrimidine bases. The bases are absorbed by active transport. Families of equilibrative (ie, passive) and concentrative (ie, secondary active) nucleoside transporters have recently been identified and are expressed on the apical membrane of enterocytes.

Digestion:

1. **Lingual lipase (in some species):** secreted by Ebner glands on the dorsal surface of the tongue
2. **Gastric lipase (in human):** secreted by stomach

Both are of little quantitative significance for lipid digestion and can NOT significantly digest lipids in case of pancreatic lipase deficiency. BUT generate FFA that signals to most distal parts of GIT such as causing CCK release

3. **Pancreatic lipase:** of quantitative significant for lipid digestion

Pancreatic lipases

- Released **in response** to **CCK** hormone
- CCK released when GI mucosa is **stimulated** by **free fatty acids** generated by **lingual** or **gastric lipase**.
- **Digest** triglycerides or triglyceroles (**TG**) - Most digestion occurs **in duodenum**
- **Acts** on the **1-** and **3-bonds** of TG with **very ease**
- **Acts** on the **2-bond** with **very slow rate**
- The **result** is liberation of free fatty acids (**FFA**) and 2-**monoglycerides (or 2-monoglyceroles). Acts** on **fat** that have been **emulsified**
- Its activity is **facilitated when** an amphipathic helix that covers the active site like a **lid** is **bent back**

Pancreatic colipase

- **Binds** to the **-COOH-terminal** domain of lipase and **facilitates** the **opening** of the **lid**
- Secreted as **proenzyme** and **activated** by **trypsin**
- **Critical** the **lipase** action; it **allow** lipase to remain **associated with droplets** of dietary lipids **even in the presence of bile acids**

LIPIDS

FAT DIGESTION

1. A lingual lipase is secreted by Ebner glands on the dorsal surface of the tongue in some species, and the 2. stomach also secretes a lipase (Table 26–1). They are of little quantitative significance for lipid digestion other than in the setting of pancreatic insufficiency, but they may generate free fatty acids that signal to most distal parts of the gastrointestinal tract (eg, causing the release of CCK).

Most fat digestion therefore begins in the duodenum,

3. pancreatic lipase being one of the most important enzymes involved. This enzyme hydrolyzes the 1- and 3-bonds of the triglycerides (triacylglycerols) with relative ease but acts on the 2-bonds at a very low rate, so the principal products of its action are free fatty acids and 2-monoglycerides (2-monoacylglycerols). It acts on fats that have been emulsified. Its activity is facilitated when an amphipathic helix that covers the active site like a lid is bent back. Colipase, a protein with a molecular weight of about 11,000, is also secreted in the pancreatic juice, and when this molecule binds to the –COOH-terminal domain of the pancreatic lipase, opening of the lid is facilitated. Colipase is secreted in an inactive proform and is activated in the intestinal lumen by trypsin. Colipase is also critical for the action of lipase because it allows lipase to remain associated with droplets of dietary lipid even in the presence of bile acids.

Cholesterol esterase (4% of protein in pancreatic juice):

- secreted by pancreas and activated by bile acids and hydrolyze
1. **Cholesterol esters**
2. **Esters of fat soluble vitamins**
3. **Phospholipids**
4. **Triglycerides (less active – pancreatic lipase is 10-6 times more active)**

- A similar enzyme found in human milk

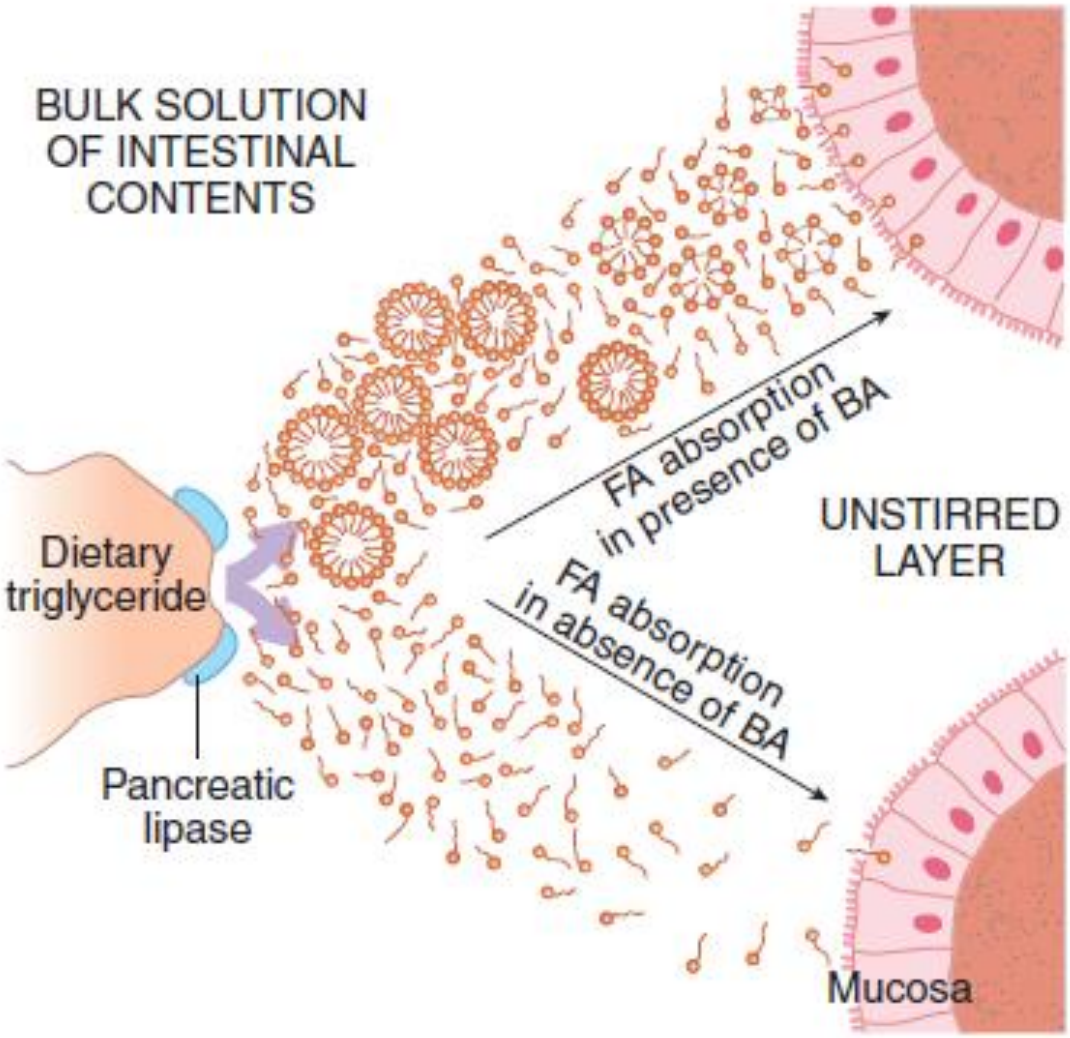
Absorption

- **Fats** are **insoluble** in GI fluid and **require continuous stirring** to reach intestinal mucosa and be absorbed (**un implacable**)
- Instead, fats are finely **emulsified** in small intestine by the detergent action of **bile acids**, **phosphatidylcholine** and **monoglycerides**
- The **high concentration** of **bile acids** interact spontaneously with lipids to **form cylindrical micelles**
- Micelles aggregate **takes up fatty acids**, **monoglycerides**, **cholesterol** and other **fat soluble materials** in their hydrophobic **centers**
- **Micelle** formation **stabilizes** the **lipids** and **provides a mechanism for their transport into the enterocytes**
- **Micelles move** along their conc. gradient through the unstirred layer **to** the **mucosal cells**
- The **lipids** in the micelle **diffuse out of the micelles** and a **saturated solution** of lipids is **maintained** in **contact** with **mucosal cells**

Another pancreatic lipase that is activated by bile acids has been characterized. This 100,000-kDa **cholesterol esterase** represents about 4% of the total protein in pancreatic juice. In adults, pancreatic lipase is 10–60 times more active, but unlike pancreatic lipase, cholesterol esterase catalyzes the hydrolysis of cholesterol esters, esters of fat-soluble vitamins, and phospholipids, as well as triglycerides. A very similar enzyme is found in human milk.

Fats are relatively insoluble, which limits their ability to cross the unstirred layer and reach the surface of the mucosal cells. However, they are finely emulsified in the small intestine by the detergent action of bile acids, phosphatidylcholine, and monoglycerides. When the concentration of bile acids in the intestine is high, as it is after contraction of the gallbladder, lipids and bile acids interact spontaneously to form **micelles** (Figure). These cylindrical aggregates take up lipids, and although their lipid concentration varies, they generally contain fatty acids, monoglycerides, and cholesterol in their hydrophobic centers. Micellar formation further solubilizes the lipids and provides a mechanism for their transport to the enterocytes. Thus, the micelles move down their concentration gradient through the unstirred layer to the brush border of the mucosal cells. The lipids diffuse out of the micelles, and a saturated aqueous solution of the lipids is maintained in contact with the brush border of the mucosal cells (Figure).

Lipids collect in the micelles, with cholesterol in the hydrophobic center and amphipathic phospholipids and monoglycerides lined up with their hydrophilic heads on the outside and their hydrophobic tails in the center. The micelles play an important role in keeping lipids in solution and transporting them to the brush border of the intestinal epithelial cells, where they are absorbed.


BULK SOLUTION
OF INTESTINAL
CONTENTS
FA absorption
in presence of BA
UNSTIRRED
LAYER
Dietary
triglyceride
FA absorption
in absence of BA
Pancreatic
lipase
Mucosa

Recall: lipids are FFA, TG and cholesterol

- **Traditional theory say**: lipids are absorbed by **passive diffusion**
- **Recent theory say**: lipids are absorbed by **carrier mediated transport** as well
- **Cholesterol** and **plant sterols** are **exported back** into the lumen **after absorption**; this **limits** their oral **bioavailability**

Absorption of FFA less than 10-12 carbon:

1. **Across apical membrane**: by **passive** diffusion
2. **Across basolateral membrane**: **diffuse** out of the enterocytes into portal blood and circulate as **FFA**

Absorption of FFA more than 10-12 Carbone:

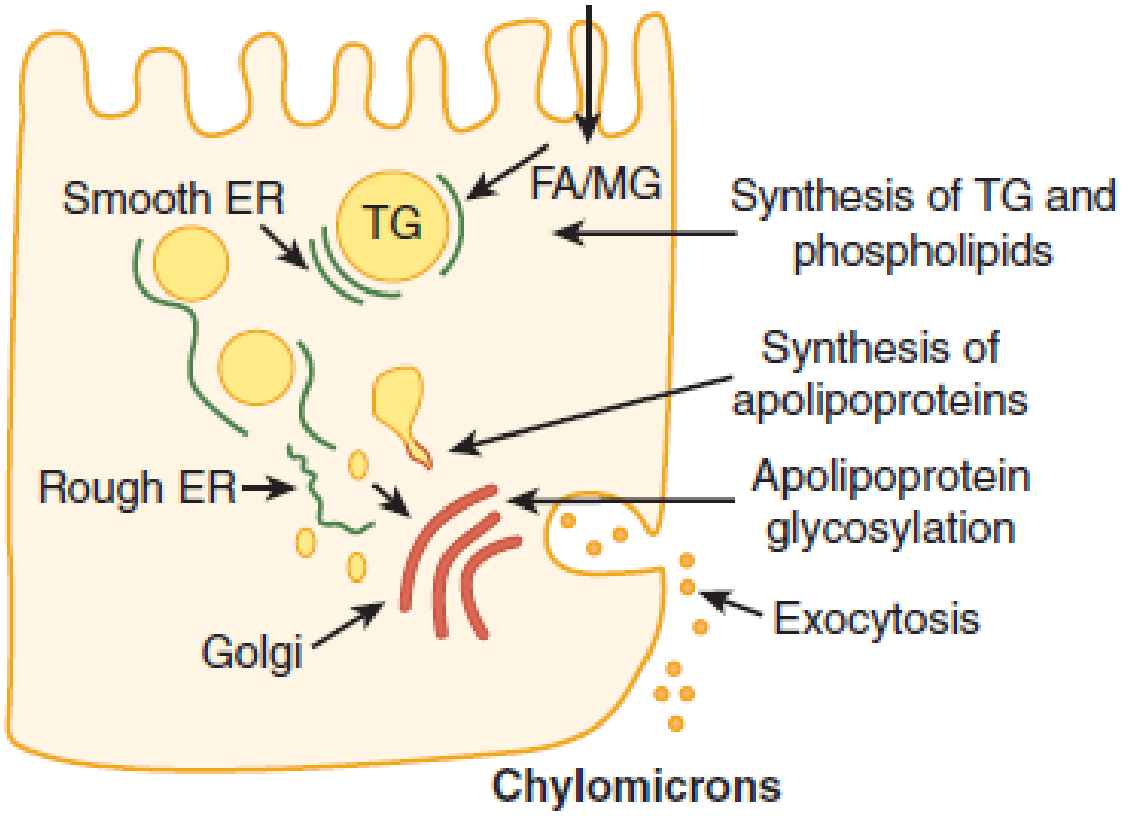
1. **Across apical membrane**: by **passive** diffusion
2. **Across basolateral membrane**: as **chylomicrons**

- Inside enterocytes and 10-12C FFA are **re-esterified** to **TG** and **coated** with **lipoprotein** (protein, cholesterol and phospholipid coat).
- The **lipoprotein** and the **inside** lipids (**FFA**, **TG** and **cholesterol**) called **chylomicron**.
- Chylomicron are of **large size** that **can NOT** pass through the junctions between capillary endothelial cells **SO** they **pass** into **lymphatic** channels

FAT ABSORPTION

Traditionally, lipids were thought to enter the enterocytes by passive diffusion, but some evidence now suggests that carriers are involved. Inside the cells, the lipids are rapidly esterified, maintaining a favorable concentration gradient from the lumen into the cells (Figure). There are also carriers that export certain lipids back into the lumen, thereby limiting their oral availability. This is the case for plant sterols as well as cholesterol.

The fate of the fatty acids in enterocytes depends on their size. Fatty acids containing less than 10–12 carbon atoms are water-soluble enough that they pass through the enterocyte unmodified and are actively transported into the portal blood. They circulate as free (unesterified) fatty acids. The fatty acids containing more than 10–12 carbon atoms are too insoluble for this. They are reesterified to triglycerides in the enterocytes. In addition, some of the absorbed cholesterol is esterified. The triglycerides and cholesterol esters are then coated with a layer of protein, cholesterol, and phospholipid to form chylomicrons. These leave the cell and enter the lymphatics, because they are too large to pass through the junctions between capillary endothelial cells (Figure).


Smooth ER
TG
FA/MG
Synthesis of TG and phospholipids
Synthesis of apolipoproteins
Rough ER
Apolipoprotein glycosylation
Golgi
Exocytosis
Chylomicrons

TG formation inside enterocytes

- Mostly by acylation of **absorbed 2-monoglycerides** with **2** FFA in **SER**
- Some bY acylation of **glycerophosphate** (from glucose metabolism) with **3** FFA in **RER**
- **Partial acylation** of **glycerophosphate** give **glycerophospholipids** that participate in **chylomicron** formation
- **Acylation** of **glycerophosphate** and **lipoprotein formation** occurs in **RER**
- **Glycation** (**carbohydrate addition**) occurs in **Golgi** apparats
- Finished **chylomicrons extruded** by **exocytosis** from **basolateral membrane** of enterocyte

- **Absorption** of **long-chain FA** is **greatest** in duodenum and jejunum (**upper small intestine**); BUT appreciable amount also absorbed in ileum (**lower small intestine**)
- On **moderate** fat **intake** about **95% or more** of ingested fats are **absorbed**
- **At birth** the **process** of **fat absorption** is **NOT** fully **mature**; SO **infants fail to absorbed 10-15% of ingested fats** causing them **more susceptible** to the **ill** effects of disease processes that reduce fat absorption

In mucosal cells, most of the triglyceride is formed by the acylation of the absorbed 2-monoglycerides, primarily in SER smooth endoplasmic reticulum. However, some of the triglyceride is formed from glycerophosphate, which in turn is a product of glucose catabolism. Glycerophosphate is also converted into glycerophospholipids that participate in chylomicron formation. The acylation of glycerophosphate and the formation of lipoproteins occur in RER rough endoplasmic reticulum. Carbohydrate moieties are added to the proteins in the Golgi apparatus, and the finished chylomicrons are extruded by exocytosis from the basolateral aspect of the cell.

Absorption of long-chain fatty acids is greatest in the upper parts of the small intestine, but appreciable amounts are also absorbed in the ileum. On a moderate fat intake, 95% or more of the ingested fat is absorbed. The processes involved in fat absorption are not fully mature at birth, and infants fail to absorb 10–15% of ingested fat. Thus, they are more susceptible to the ill effects of disease processes that reduce fat absorption.

ABSORPTION OF IRON

- Amount **lost** from the body is **relatively small**
  1. **In men:** **0.6**mg/day – largely in stool
  2. **In premenopausal women:** variable larger loss and twice as men – loss (**1.2**mg/day) during menstruation
- Iron **loss** is **unregulated**
- Iron **store** is **regulated** by **change the rates of absorption** from intestine
- **Daily intake ~ 20mg**
- **Daily absorbed** normally **3-6% of the ingested** amount
- However; the **amount absorbed equals only** to the **losses**

In adults, the amount of iron lost from the body is relatively small. The losses are generally unregulated, and total body stores of iron are regulated by changes in the rate at which it is absorbed from the intestine. Men lose about 0.6 mg/d, largely in the stools. Premenopausal women have a variable, larger loss averaging about twice this value because of the additional iron lost during menstruation. The average daily iron intake in the United States and Europe is about 20 mg, but the amount absorbed is equal only to the losses. Thus, the amount of iron absorbed is normally about 3–6% of the amount ingested.

Factors affect iron absorption

1. **Dietary factors**: **phytic acid** in **cereals reacts** with iron to form **insoluble compounds** as do phosphates and oxalates
2. **Oxidation state:**
   - Most **dietary** iron is in **ferric (Fe^{3+},** oxidized) form
   - Iron **absorbed** only in **ferrous (Fe^{2+}**, reduced) form
   - **Reductase** enzyme is **associated** with **DMT1** (iron transporter) in the **brush** border of **enterocytes**
3. **Role of gastric secretions and vitamin C:**
   - **Dissolve** iron and **permit** it to form **soluble** complex with **ascorbic acid** (vitamin C) and others that **aid** its **reduction** to form **Fe^{2+} form**
   - Partial **gastrectomy frequently** causes **iron deficiency anemia**
4. **DMT1 availability:**
   - **All** iron absorption occurs in **duodenum** via **DMT1**.

Fate of absorbed iron

1. **Some** is **store** in **ferritin** and the **remainder** is **transported out** of enterocytes **via** basolateral membrane **ferroportin 1** (**associate with hephaestin "Hp" protein that facilitate basolateral transport**)
2. **In plasma**, Fe^{2+} is converted to Fe^{3+} and **bound** to **transferrin** (iron transporter protein; which has **2 iron-binding sites**. Normally transferrin is about **35% saturated with iron**

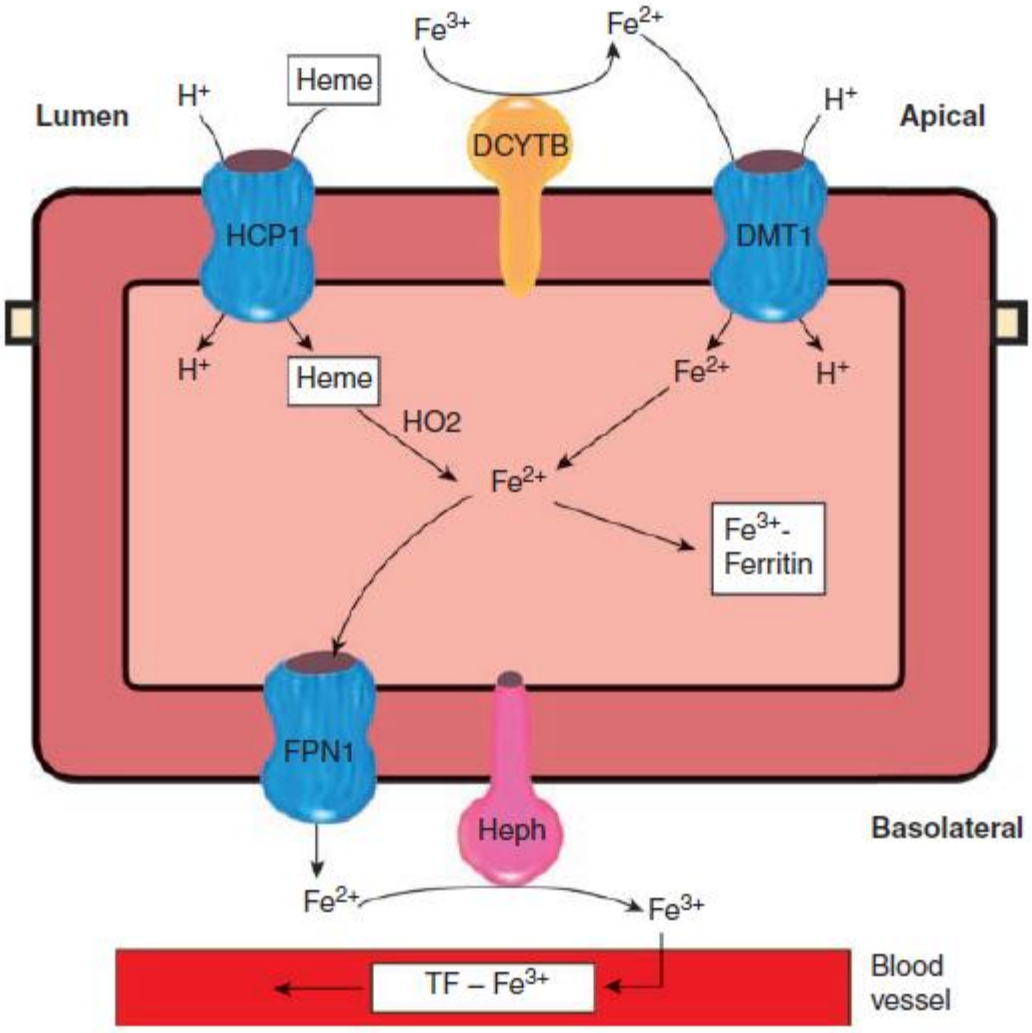
Normal plasma iron:

- **Men**: **130ug/dL**
- **Women**: **110ug/dL**

Various dietary factors affect the availability of iron for absorption; for example, the phytic acid found in cereals reacts with iron to form insoluble compounds in the intestine, as do phosphates and oxalates.

Most of the iron in the diet is in the ferric (Fe^{3+}) form, whereas it is the ferrous (Fe^{2+}) form that is absorbed. Fe^{3+} reductase activity is associated with the iron transporter in the brush borders of the enterocytes (Figure). Gastric secretions dissolve the iron and permit it to form soluble complexes with ascorbic acid and other substances that aid its reduction to the Fe^{2+} form. The importance of this function in humans is indicated by the fact that iron deficiency anemia is a troublesome and relatively frequent complication of partial gastrectomy.

Almost all iron absorption occurs in the duodenum. Transport of Fe^{2+} into the enterocytes occurs via divalent metal transporter 1 (DMT1) (Figure). Some is stored in ferritin, and the remainder is transported out of the enterocytes by a basolateral transporter named **ferroportin 1**. A protein called **hephaestin (Hp)** is associated with ferroportin 1. It is not a transporter itself, but it facilitates basolateral transport. In the plasma, Fe^{2+} is converted to Fe^{3+} and bound to the iron transport protein **transferrin**. This protein has two iron-binding sites. Normally, transferrin is about 35% saturated with iron, and the normal plasma iron level is about 130 µg/dL (23 µmol/L) in men and 110 µg/dL (19 µmol/L) in women.


Fe3+
Fe2+
Heme
H+
Lumen
DCYTB
H+
Apical
HCP1
DMT1
H+
Heme
Fe2+
H+
HO2
Fe2+
Fe3+-
Ferritin
FPN1
Heph
Basolateral
Fe2+
Fe3+
TF – Fe3+
Blood
vessel

Iron Heme:

1. **Heme binds** to apical **transporter** in **enterocytes** and is **carried into cytoplasm**
2. **Heme oxidase** 2 (HO-2) **removes Fe^{2+}** from heme and **added** it to **intracellular pool**

Distribution of body iron:

- **7%** in **Hb**
- **3%** in **myoglobin**
- **90%** in **ferritin** (in enterocytes and other cells)

Ferritin:

- Apoferritin is a **globulin protein** made up of **24 subunits**
- **Apoferritin** + iron = ferritin
- Ferritin is readily **visible** under **electron microscope**
- Ferritin has been **used** as a **tracer** in studies of **phagocytosis** and related phenomena
- Ferritin in **lysosomal membranes** may aggregate in **deposits** that contain as much as **50% iron** (called **hemosiderin**)

Intestinal absorption of iron is regulation by 3 factors

1. Recent **dietary intake** of iron
2. State of **iron store** in the body
3. State of **erythropoiesis** in bone marrow

Heme binds to an apical transport protein in enterocytes and is carried into the cytoplasm. In the cytoplasm, HO-2, a subtype of heme oxygenase, removes Fe^{2+} from the porphyrin and adds it to the intracellular Fe^{2+} pool.

Seventy percent of the iron in the body is in hemoglobin, 3% in myoglobin, and the rest in ferritin, which is present not only in enterocytes, but also in many other cells. Apoferritin is a globular protein made up of 24 subunits. Ferritin is readily visible under the electron microscope and has been used as a tracer in studies of phagocytosis and related phenomena. Ferritin molecules in lysosomal membranes may aggregate in deposits that contain as much as 50% iron. These deposits are called **hemosiderin.**

Intestinal absorption of iron is regulated by three factors: recent dietary intake of iron, the state of the iron stores in the body, and the state of erythropoiesis in the bone marrow. The normal operation of the factors that maintain iron balance is essential for health (Clinical Box 26–2).

Disorders of Iron uptake

1. Iron **deficiency** causes **anemia**
2. Iron **overload** causes **hemosiderosis**

CLINICAL BOX 26–2

Hemosiderosis

- **Occurrence**: Hemosiderosis **commonly seen** in **hemochromatosis**
- **Effect**: Large amount of hemosiderin can **damage tissues**
- **Characteristics**:
  1. Skin pigmentation
  2. Pancreatic damage with diabetes (Bronze diabetes)
  3. Liver cirrhosis
  4. High incidence of hepatic carcinoma
  5. Gonadal atrophy

Types: (1) **hereditary** or (2) **acquired**

1. Hereditary hemochromatosis

- **Cause**: mutation of HFE gene (common in white population) located in chromosome 6
- HFE gene is **closely related** to **HLA-A locus**
- **HFE** coded for protein that **inhibits expression** of duodenal **DMT1** that participate in iron absorption
- **Mutation** in **HFE** causes individuals to **absorbed excess** amounts of **iron**

*HFE protein = Human homeostatic iron regulator protein or **High FE^{2+}**.*

HLA-A: Human leukocyte antigen (a major HCM complex specific to humans)

1. Acquired hemochromatosis

- **Cause**: when **iron-regulating** system is **overwhelmed** by **excess** iron **loads** due to **chronic destructions** of **RBCs**, **liver diseases**, **repeated blood transfusion**

Treatment of hemochromatosis

- Early diagnosis increase life expectancy
- Treated by repeated withdrawal of blood
- Iron chelation (Deferoxamine or deferasirox)

MULTIPLE-CHOICE QUESTIONS

For all questions, select the single best answer unless otherwise directed.

1. Maximum absorption of short-chain fatty acids produced by bacteria occurs in the

   A. stomach.
   B. duodenum.
   C. jejunum.
   D. ileum.
   E. colon.

2. A premenopausal woman who is physically active seeks advice from her primary care clinician regarding measures she can take to ensure adequate availability of dietary calcium to ensure bone health later in life. Which of the following dietary components should enhance calcium uptake?

   A. Protein
   B. Oxalates
   C. Iron
   D. Vitamin D
   E. Sodium

3. A decrease in which of the following would be expected in a child exhibiting a congenital absence of enterokinase?

   A. Incidence of pancreatitis
   B. Glucose absorption
   C. Bile acid reabsorption
   D. Gastric pH
   E. Protein assimilation