Fat malabsorption … Back to basics

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Oct/17/07

Fat structure

- Chemically, fats are generally tri-esters of glycerol and fatty acids = Triglycerides

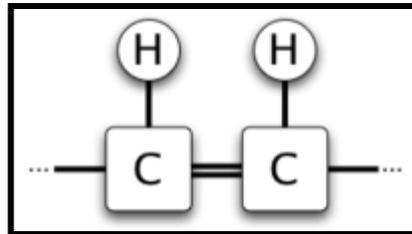triglyceride   + 3 H₂O → glycerol   fatty acids

Fat structure

- The more carbon atoms there are in any fatty acid, the longer its chain will be → a higher melting point.

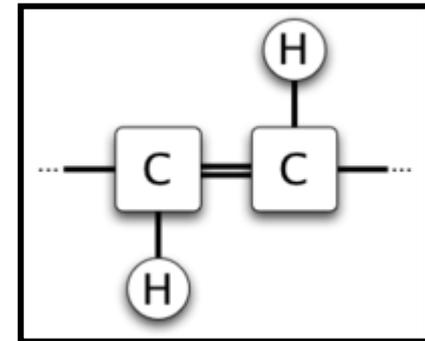- Long chains also yield more energy per molecule when metabolized (trough breaking down C-H bond).

Fat structure

Fat structure
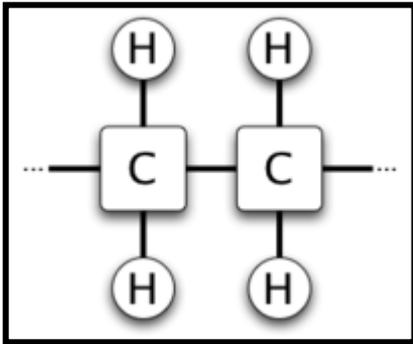
Saturated fat -
saturated carbon atoms
(each with 2 hydrogens)
joined by a single bond

Cis- Unsaturated FA -
unsaturated carbon atoms
(each with 1 hydrogen)
joined by a double bond.
Cis configuration (naturally
occurring).

Trans unsaturated FA-
unsaturated carbon atoms
(each with 1 hydrogen)
joined by a double bond.
Trans configuration

Fat structure

- Trans unsaturated fats are particularly bad because the double bond allows the fat molecules to assume a linear conformation which leads to efficient packing (i.e., plaque formation).

- Cell membranes of mammals have a higher composition of polyunsaturated fat and a lower composition of monounsaturated. Higher polyunsaturated membrane content gives greater membrane fluidity and functionality

Quick facts about fat absorption

- Dietary fat is the most difficult nutrient to absorb. It depends on all the 3 phases for its absorption.

- Most dietary lipids are absorbed in the proximal two thirds of the jejunum.

- Normally, more than 94 percent of dietary fat is absorbed in children > 1 year of age

- Physiologic steatorrhea of the newborn

Quick facts about fat absorption

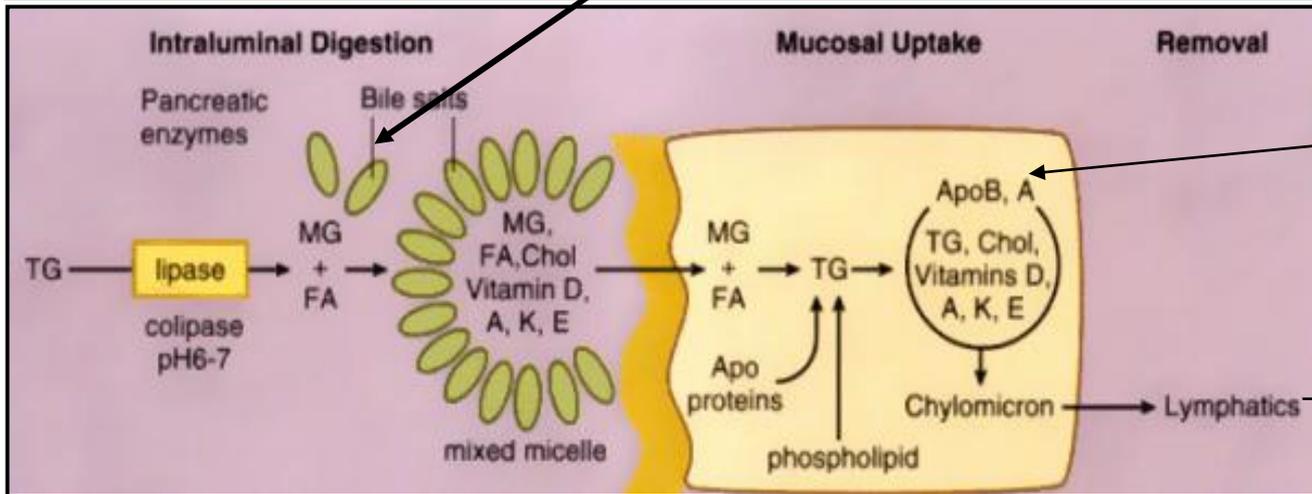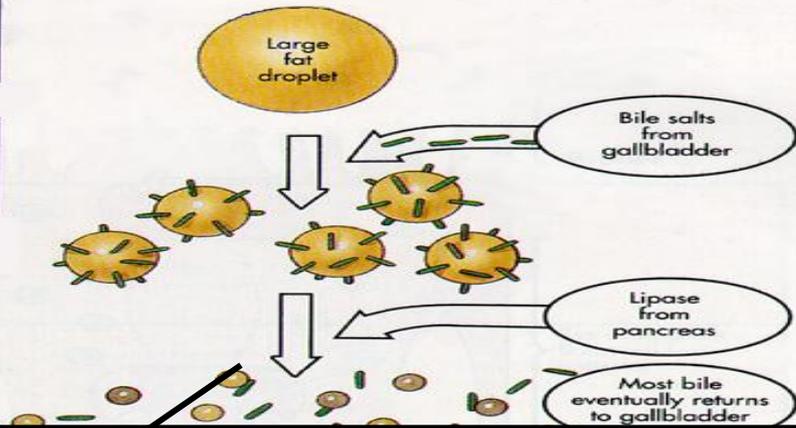**Three steps are required for normal nutrient absorption**:
- Luminal processing
- Absorption into the intestinal mucosa
- Transport into the systemic circulation

- Malabsorption can result from defects in each of these three phases.

- One or more mechanisms may exist concurrently.

- Thus, while the clinical sequelae may be the same, the underlying pathophysiology and treatment may be different.

Digestion and Absorption

Large fat droplets enter small intestine after meal

Bile salts emulsify fats into smaller particles

Lipase breaks down fat into fatty acids and monoglycerides

Large fat droplet

Bile salts from gallbladder

Lipase from pancreas

Most bile eventually returns to gallbladder

Intraluminal Digestion | Mucosal Uptake | Removal

Pancreatic enzymes

Bile salts

Apo B 48

ApoB, A

TG — lipase — MG + FA — mixed micelle — MG, FA, Chol, Vitamin D, A, K, E — MG + FA — TG — TG, Chol, Vitamins D, A, K, E — Chylomicron — Lymphatics

colipase pH6-7

Apo proteins

phospholipid

Liver to be repacked in VDRL,LDL

Pancreas enzymes

Two factors optimize the effect of pancreatic enzymes:

1- The entry of gastric hydrogen ions into the duodenum stimulates the release of secretin, which enhances pancreatic bicarbonate secretion.
→ This raises the intraluminal pH to approximately 6.5, which is optimal for pancreatic enzyme activation & BS micelle formation.

→ Diseases that substantially decrease duodenal pH, such as Zollinger-Ellison syndrome, can selectively inhibit fat absorption)

2- Bile salts :

Pancreas enzymes

- The activity of pancreatic lipase depends upon the presence of another enzyme, <u>colipase</u>, which <u>facilitates attachment</u> to triglyceride droplets and <u>prevents bile salts from deactivating</u> pancreatic lipase.

- Dietary and biliary phospholipids and cholesterol are further hydrolyzed by the action of <u>phospholipase A2</u> and <u>pancreatic cholesterol esterase.</u>

BSs

- BS themselves remain in the intestinal lumen, eventually reaching the <u>terminal ileum</u> where they are actively reabsorbed (95 % of the total secreted BSs), enter the portal circulation, and are then re-secreted into bile.

- This cycle is known as the enterohepatic circulation.

BSs

- BSs need to reach to a specific level in intestine (called critical concentration level= 5-15 nM) to be able to form micelles.

- <u>Decrees in achieving this level</u> can happen with
  - Decreased BS synthesis (sever liver disease)
  - Decreased BS delivery (cholestasis) or
  - Removal of luminal BSs (bacterial overgrowth, TI disease /resection, cholestryramine therapy)

Major Categories and Causes for Fat malabsorption

- **Intraluminal - maldigestion**
  - Defective bile secretion
  - Obstructive biliary or cholestatic liver disease
  - Pancreatic insufficiency (Pancreatitis, cystic fibrosis, Shwachman-Diamond syndrome, Johnson-Blizzard syndrome, and Pearson syndrome)
  - Bacterial overgrowth

- **Mucosal - malabsorption**
  - Celiac disease
  - Crohn's disease
  - Infection – bacteria, parasites
  - Intestinal resection –short gut; reduced mucosal SA, impair BS absorption
  - Abetalipoproteinemia

Major Categories and Causes for Fat malabsorption

- **<u>Transport into the circulation</u>**

  - Lymphangiectasia (reflux of the absorbed fat into intestinal lumen because obstructed lymph flow)

Presentation .. Clinical hints

- Steatorrhea is a soft, pasty, foul-smelling stools.

- Stool is not watery because <u>undigested TGs</u> form large emulsion droplets with little osmotic force which, in contrast to FA, do not stimulate water & electrolyte secretion in the colon.

- Significant steatorrhea usually associated with fat absorption coefficient being < 50 %.

Presentation .. Clinical hints

- Steatorrhea of mucosal disorders are less sever than that of exocrine pancreatic insufficiency (most of the mucosal disorders affect mainly proximal SB & presence of other accessory pathways make mucosal disorders less sever)

- Overt steatorrhea in pancreatic insufficiency does not occur until approximately 90 percent of glandular function has been lost

Presentation .. Clinical hints

- Fat malabsorption does <u>not always cause diarrhea</u>. It may present only with picture of fat soluble vitamins deficiency (Rickets, bleeding …)

- <u>Wt loss</u> (insufficient energy intake due to the high energy value of dietary lipids) with <u>increase appetite</u> trying to compensate

- Isolated fat malabsorption are extremely rare, so, other features of malabsorption may coexist …osmotic diarrhea, hypoalbunemia

Diagnostic
tests of fat malabsorption

72-hour fecal fat collection

- <u>It is a quantitative measurement</u> of fat absorption

- The patients need to consume a normal amount (80-100 g/d) of fat before and during the collection.

- A three days collection is ideal because it reduces errors and variability that may occur if a shorter collection period is used.

- Normal fat absorption depends on age. It is lower in neonates and improves throughout the first year of life to the reference range levels of 95% or higher.

72-hour fecal fat collection

- Moderate fat malabsorption ranges from 60-80%.
  Fat absorption of less than 50% indicates severe malabsorption.

- <u>FALS POSITIVE</u>; fecal fat excretion can be moderately increased in <u>diarrheal diseases even without fat malabsorption</u>.

- Values of up to 14 g/day have been reported in volunteers in whom diarrhea was intentionally induced and in patients with a stool weight of greater than 1000 g/day.

  (Fine, KD, and Fordtran, JS. The effect of diarrhea on fecal fat excretion. Gastroenterology 1992; 102:1936)

72-hour fecal fat collection

- Thus, a <u>modest increase in</u> fecal fat excretion in a patient with diarrhea <u>does not necessarily indicate malabsorption</u> <u>as the primary cause</u> and other tests should be performed to identify the cause of the diarrhea.

- Importantly, quantitative fecal fat determination <u>does not discriminate between causes</u> of steatorrhea, as there may be considerable overlap in values.

Other tests

- Acid steatocrit test and Sudan III stain of stool and Near Infrared Reflectance Analysis (NIRA).

- More easily and more quickly than a 72-hour fecal fat determination

- None has yet replaced the 72-hour collection.

Sudan III stain

- Normally, a stool sample should show only a few drops of red-orange stained fat under the microscope.

- If properly performed, a Sudan stain on a spot sample of stool can <u>detect more than 90 percent</u> of patients with <u>*clinically significant* steatorrhea</u>.

- Variability in the performance and interpretation of the test limit its overall sensitivity and reliability
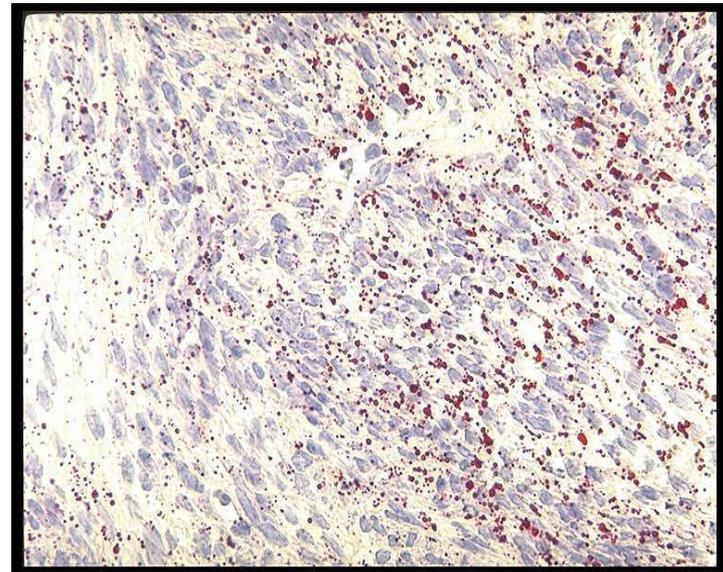
Due to its simplicity it is used for screening

Acid steatocrit test

- The acid steatocrit (a gravimetric assay performed on a <u>spot stool sample</u>) may provide an accurate and simplified method for detecting steatorrhea on a spot stool specimen.

- A study evaluating this technique found a sensitivity of 100 percent, specificity of 95 percent and PPV of 90 percent compared to a 72-hour fecal fat collection as the gold standard (Amann, et al. Am J Gastroenterol 1997; 92:2280)

Near Infrared Reflectance Analysis (NIRA)

- A method depend on measurement of the scattered radiation in the near infrared (spectrometry).

- It is performed in <u>less than1min</u> without further processing of the stool or using a chemical agents

- <u>NIRA advantages:</u>
  - equally accurate &
  - less time-consuming than a 72-hour fecal fat collection
  - allows for simultaneous measurement of fecal fat, nitrogen, and carbohydrates in a single sample.

- It may become the procedure of choice for evaluating fat malabsorption (used frequently in Europe).

Tests for
specific causes of
fat malabsorption
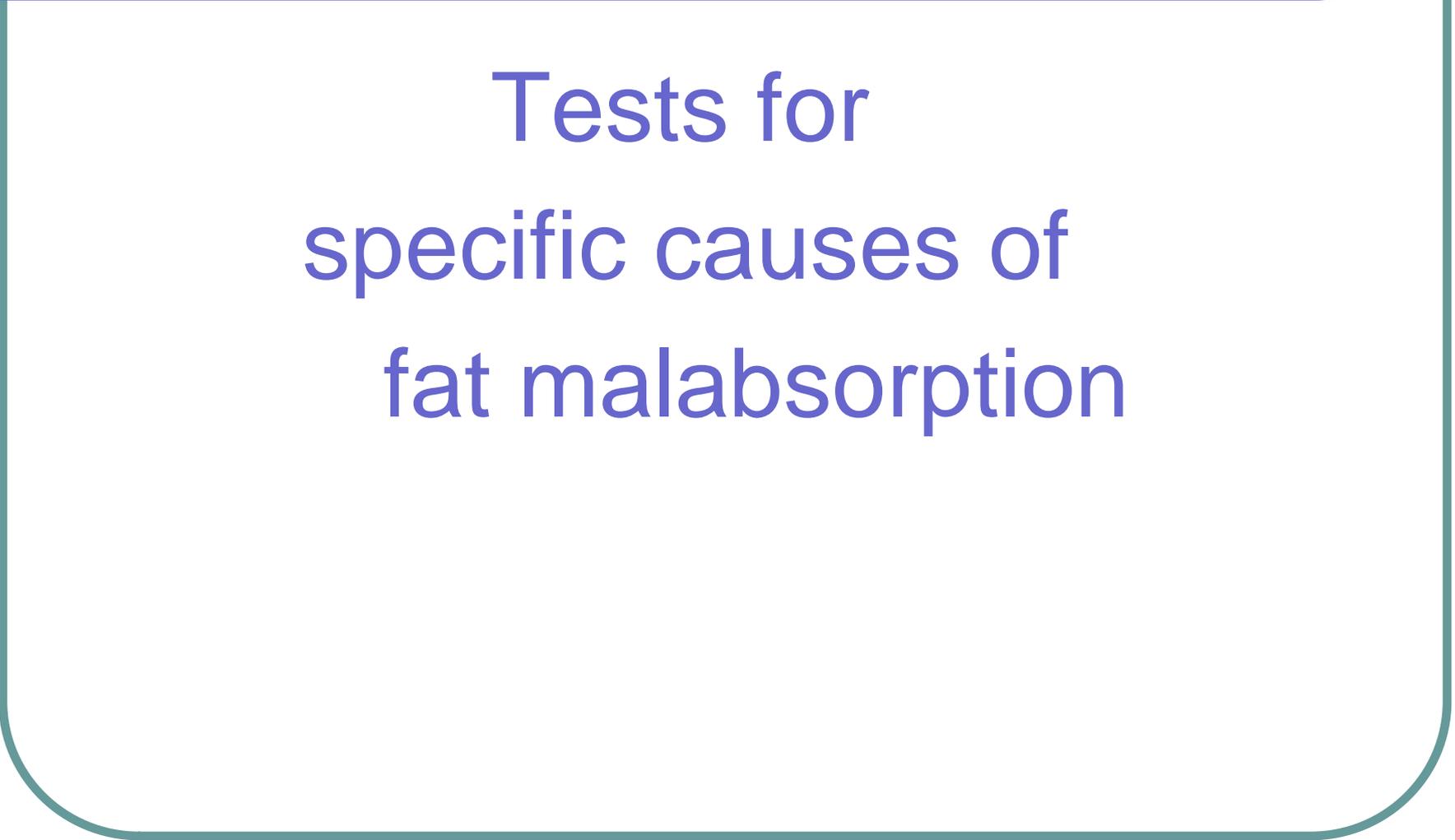
D-xylose test

- If the 72-hour fecal fat collection results demonstrate fat malabsorption, the <u>D-xylose test is used to document the integrity of the intestinal mucosa</u>.

- D-xylose absorbed primary in proximal intestine by facilitated diffusion.

- Approximately half of the absorbed D-xylose is excreted in urine, <u>unmetabolized</u> (the normal test).

D-xylose test

- If <u>Urinary excretion is less than normal</u>, it indicates either a reduced or damaged mucosal surface area (eg, surgical resection, celiac disease), or a luminal factor (eg, bacterial overgrowth)

- Cases of pancreatic insufficiency usually result in normal urinary excretion because the absorption of D-xylose is still intact.

Pancreatic Function tests

- **Direct tests** involve the stimulation of the pancreas through the administration of a meal or hormonae (secretin) after which underline duodenal fluid is collected and analyzed to quantify normal pancreatic secretory content (ie, enzymes, and bicarbonate).

- Only a few specialized centers perform these tests

Pancreatic Function tests

- **<u>Indirect pancreatic function tests ;</u>**
Low fecal chymotrypsin & Elastase 1 (remain relatively stable during transport through the gastrointestinal tract)

  - Indirect tests measure the consequence of exocrine insufficiency (maldigestion).

  - <u>Advantages:</u> simpler and easier to perform than direct tests

  - <u>Disadvantages:</u> their main role appears to be in diagnosis of <u>advanced PEI</u> since they are much less sensitive than direct tests for diagnosis of earlier stages of PEI.

Indirect tests

- Using the direct pancreatic function test as reference standard, Chymotrypsin sensitivity is approximately 85 percent for advanced PEI, but only 49 percent for mild and moderate PEI

  [Niederau, C, Grendell, JH. Diagnosis of chronic pancreatitis. Gastroenterology 1985; 88:1973.].

Indirect tests

- **Pancreatic elastase-1** appears to be more stable than chymotrypsin during intestinal transit.

- Using direct pancreatic function testing as reference standard, fecal elastase-1 has approximately 100 percent sensitivity for severe, 77 to 100 percent for moderate, and 0 to 63 percent sensitivity for mild PEI. Specificity is approximately 93 percent.

Summary

- Digestion & absorption of fat depends on many auxiliary molecules other than enzymes & carriers. This includes BS, colipase, FABP and apolipoproteins.

- Fat malabsorption alone is rare & need to look to the other associated nutrient malabsorption.

- 72 hrs stool collection is still the standard test for fat malabsorption diagnosis.

- Johanson-Blizzard syndrome is an extremely rare ectodermal dysplastic disorder characterized by aplasia or hypoplasia of alae nasi, midline scalp defects, growth retardation, varying degrees of mental retardation, hypothyroidism, exocrine pancreatic insufficiency and congenital deafness. This condition is supposed to be an autosomal recessive disorder.

- Pearson syndrome is currently recognized as a rare, multisystemic, mitochondrial cytopathy. Its features are refractory sideroblastic anemia, pancytopenia, defective oxidative phosphorylation, exocrine pancreatic insufficiency, and variable hepatic, renal, and endocrine failure.