

Overview of Malabsorption

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Malabsorption can affect macronutrients (eg, proteins, carbohydrates, fats), micronutrients (eg, vitamins, minerals), or both, causing excessive fecal excretion, nutritional deficiencies, and GI symptoms. Malabsorption may be global, with impaired absorption of almost all nutrients, or partial (isolated), with malabsorption of only specific nutrients.

Pathophysiology

Digestion and absorption occur in three phases:

- Intraluminal hydrolysis of fats, proteins, and carbohydrates by enzymes—bile salts enhance the solubilization of fat in this phase
- Digestion by brush border enzymes and uptake of end-products
- Lymphatic transport of nutrients

The term malabsorption is commonly used when any of these phases is impaired, but, strictly speaking, impairment of phase 1 is maldigestion rather than malabsorption.

Pancreatic enzymes (lipase and colipase) split long-chain triglycerides into fatty acids and monoglycerides, which combine with bile acids and phospholipids to form micelles that pass through jejunal enterocytes. Absorbed fatty acids are resynthesized and combined with protein, cholesterol, and phospholipid to form chylomicrons, which are transported by the lymphatic system. Medium-chain triglycerides are absorbed directly.

Unabsorbed fats trap fat-soluble vitamins (A, D, E, K) and possibly some minerals, causing deficiency. Bacterial overgrowth results in deconjugation and dehydroxylation of bile salts, limiting the absorption of fats. Unabsorbed bile salts stimulate water secretion in the colon, causing diarrhea.

Carbohydrates

The pancreatic enzyme amylase and brush border enzymes on microvilli lyse carbohydrates and disaccharides into constituent monosaccharides. Colonic bacteria ferment unabsorbed carbohydrates into CO₂, methane, H₂, and short-chain fatty acids (butyrate, propionate, acetate, and lactate). These fatty acids cause diarrhea. The gases cause abdominal distention and bloating.

Proteins

Gastric pepsin initiates digestion of proteins in the stomach (and also stimulates release of cholecystokinin that is critical to the secretion of pancreatic enzymes). Enterokinase, a brush

border enzyme, activates trypsinogen into trypsin, which converts many pancreatic proteases into their active forms. Active pancreatic enzymes hydrolyze proteins into oligopeptides, which are absorbed directly or hydrolyzed into amino acids.

Etiology

Malabsorption has many causes (see [Causes of Malabsorption](#)). Some malabsorptive disorders (eg, celiac disease—see [Celiac Disease](#)) impair the absorption of most nutrients, vitamins, and trace minerals (global malabsorption); others (eg, pernicious anemia) are more selective. Pancreatic insufficiency causes malabsorption if 90% of function is lost. Increased luminal acidity (eg, Zollinger-Ellison syndrome) inhibits lipase and fat digestion. Cirrhosis and cholestasis reduce hepatic bile synthesis or delivery of bile salts to the duodenum, causing malabsorption. Other causes are discussed elsewhere in this chapter.

Causes of Malabsorption

Mechanism	Cause
Inadequate gastric mixing, rapid emptying, or both	Billroth II gastrectomy
	Gastrocolic fistula
	Gastroenterostomy
	Biliary obstruction and cholestasis
	Cirrhosis
	Chronic pancreatitis
	Cholestyramine-induced bile acid loss
Insufficient digestive agents	Cystic fibrosis
	Lactase deficiency
	Pancreatic cancer
	Pancreatic resection
	Sucrase-isomaltase deficiency
Abnormal milieu	Abnormal motility secondary to diabetes, scleroderma, hypothyroidism, or hyperthyroidism
	Bacterial overgrowth due to blind loops (deconjugation of bile salts), diverticula in the small intestine

Mechanism	Cause
	Zollinger-Ellison syndrome (low duodenal pH)
	Acute intestinal infections
Acutely abnormal epithelium	Alcohol
	Neomycin
	Amyloidosis
	Celiac disease
	Crohn disease
Chronically abnormal epithelium	Ischemia
	Radiation enteritis
	Tropical sprue
	Whipple disease
Short bowel	Intestinal resection (eg, for Crohn disease, volvulus, intussusception, or infarction)
	Jejunioileal bypass for obesity
	Abetalipoproteinemia
	Addison disease
Impaired transport	Blocked lacteals due to lymphoma or TB
	Intrinsic factor deficiency (as in pernicious anemia)
	Lymphangiectasia

Symptoms and Signs

The effects of unabsorbed substances, especially in global malabsorption, include diarrhea, steatorrhea, abdominal bloating, and gas. Other symptoms result from nutritional deficiencies. Patients often lose weight despite adequate food intake.

Chronic diarrhea is the most common symptom and is what usually prompts evaluation of the patient. Steatorrhea—fatty stool, the hallmark of malabsorption—occurs when 7 g/day of fat are excreted. Steatorrhea causes foul-smelling, pale, bulky, and greasy stools.

Severe vitamin and mineral deficiencies occur in advanced malabsorption; symptoms are related to the specific nutrient deficiency (see [Symptoms of Malabsorption](#)). Vitamin B₁₂ deficiency may occur in blind loop syndrome or after extensive resection of the distal ileum or stomach. Iron deficiency may be the only symptom in a patient with mild malabsorption.

Symptoms of Malabsorption

Symptom	Malabsorbed Nutrient
Anemia (hypochromic, microcytic)	
Anemia (macrocytic)	Vitamin B ₁₂ , folate
Bleeding, bruising, petechiae	Vitamins K and C
Carpopedal spasm	Ca, Mg
Edema	Protein
Glossitis	Vitamins B ₂ and B ₁₂ , folate, niacin, iron
Night blindness	Vitamin A
Pain in limbs, bones, pathologic fractures	K, Mg, Ca, vitamin D
Peripheral neuropathy	Vitamins B ₁ , B ₆ , B ₁₂

Amenorrhea may result from undernutrition and is an important manifestation of celiac disease in young women.

Diagnosis

- Diagnosis typically clinically apparent from a detailed patient history
- Blood tests to screen for consequences of malabsorption
- Stool fat testing to confirm malabsorption (if unclear)
- Cause diagnosed with endoscopy, contrast x-rays, or other tests based on findings

Malabsorption is suspected in a patient with chronic diarrhea, weight loss, and anemia. The etiology is sometimes obvious. For example, patients with malabsorption due to chronic pancreatitis usually have had prior bouts of acute pancreatitis. Patients with celiac disease can present with classic lifelong diarrhea exacerbated by gluten products and may have dermatitis herpetiformis. Patients with cirrhosis and pancreatic cancer can present with jaundice. Abdominal

distention, excessive flatus, and watery diarrhea occurring 30 to 90 min after carbohydrate ingestion suggest deficiency of a disaccharidase enzyme, usually lactase. Previous extensive abdominal operations suggest short bowel syndrome (see [Short Bowel Syndrome](#)).

If the history suggests a specific cause, testing should be directed to that condition (see Figure: [Suggested evaluation for malabsorption](#)). If no cause is readily apparent, blood tests can be used as screening tools (eg, CBC, RBC indices, ferritin, vitamin B₁₂, folate, Ca, albumin, cholesterol, PT). Test results may suggest a diagnosis and direct further investigation.

Suggested evaluation for malabsorption.

Macrocytic anemia should prompt measurement of serum folate and B₁₂ levels. Folate deficiency is common in mucosal disorders involving the proximal small bowel (eg, celiac disease, tropical sprue [see [Tropical Sprue](#)], Whipple disease [see [Whipple Disease](#)]). Low B₁₂ levels can occur in pernicious anemia, chronic pancreatitis, bacterial overgrowth, and terminal ileal disease. A combination of low B₁₂ and high folate levels is suggestive of bacterial overgrowth, because intestinal bacteria use vitamin B₁₂ and synthesize folate.

Microcytic anemia suggests iron deficiency, which may occur with celiac disease. Albumin is a general indicator of nutritional state. Low albumin can result from poor intake, decreased synthesis in cirrhosis, or protein wasting. Low serum carotene (a precursor of vitamin A) suggests malabsorption if intake is adequate.

Confirming malabsorption

Tests to confirm malabsorption are appropriate when symptoms are vague and the etiology is not apparent. Most tests for malabsorption assess fat malabsorption because it is relatively easy to measure. Confirmation of carbohydrate malabsorption is not helpful once steatorrhea is

documented. Tests for protein malabsorption are rarely used because fecal nitrogen is difficult to measure.

Direct measurement of fecal fat from a 72-h stool collection is the gold standard test for establishing steatorrhea but unnecessary with gross steatorrhea of obvious cause. However, this test is available routinely in only a few centers. Stool is collected for a 3-day period during which the patient consumes 100 g fat/day. Total fat in the stool is measured. Fecal fat 7 g/day is abnormal. Although severe fat malabsorption (fecal fat 40 g/day) suggests pancreatic insufficiency or small-bowel mucosal disease, this test cannot determine the specific cause of malabsorption. Because the test is messy, unpleasant, and time consuming, it is unacceptable to most patients and difficult to do.

Sudan III staining of a stool smear is a simple and direct, but nonquantitative, screening test for fecal fat. Acid steatocrit is a gravimetric assay done on a single stool sample; it has a reported high sensitivity and specificity (using 72-h collection as the standard). Near-infrared reflectance analysis (NIRA) simultaneously tests stool for fat, nitrogen, and carbohydrates and may become the preferred test in the future; this test is currently available in only a few centers.

Measurement of elastase and chymotrypsin in the stool can also help differentiate pancreatic and intestinal causes of malabsorption; both are decreased in pancreatic exocrine insufficiency, whereas both are normal in intestinal causes.

The -xylose absorption test can be done if the etiology is not obvious; however, it is currently rarely used because of the advent of advanced endoscopic and imaging tests. Although it can noninvasively assess intestinal mucosal integrity and help differentiate mucosal from pancreatic disease, an abnormal -xylose test result requires an endoscopic examination with biopsies of the small-bowel mucosa. As a result, small-bowel biopsy has replaced this test to establish intestinal mucosal disease.

-Xylose is absorbed by passive diffusion and does not require pancreatic enzymes for digestion. A normal -xylose test result in the presence of moderate to severe steatorrhea indicates pancreatic exocrine insufficiency rather than small-bowel mucosal disease. Bacterial overgrowth syndrome can cause abnormal results because the enteric bacteria metabolize pentose, thus decreasing the -xylose available for absorption.

After fasting, the patient is given 25 g of -xylose in 200 to 300 mL of water po. Urine is collected over 5 h, and a venous sample is obtained after 1 h. Serum -xylose 20 mg/dL or 4 g in the urine sample indicates abnormal absorption. Falsely low levels can also occur in renal diseases, portal hypertension, ascites, or delayed gastric emptying time.

Diagnosing the cause of malabsorption

More specific diagnostic tests (eg, upper endoscopy, colonoscopy, barium x-rays) are indicated to diagnose several causes of malabsorption.

Upper endoscopy with small-bowel biopsy is done when mucosal disease of the small bowel is suspected or if the -xylose test result is abnormal in a patient with massive steatorrhea. Endoscopy allows visual assessment of small-bowel mucosa and helps direct biopsies to affected areas. Aspirate from the small bowel can be sent for bacterial culture and colony count to document bacterial overgrowth if there is clinical suspicion. Video capsule endoscopy (see [Video capsule endoscopy](#)) can now be used to examine areas of the distal small intestine that are beyond the reach of a regular endoscope. Histologic features on small-bowel biopsy (see [Small-Bowel Mucosal Histology in Certain Malabsorptive Disorders](#)) can establish the specific mucosal disease.

Small-Bowel Mucosal Histology in Certain Malabsorptive Disorders

Disorder	Histologic Characteristics
Normal	Fingerlike villi with a villous:crypt ratio of about 4:1; columnar epithelial cells with numerous regular microvilli (brush border); mild round cell infiltration in the lamina propria
Celiac disease (untreated)	Virtual absence of villi and elongated crypts; increased intraepithelial lymphocytes and round cells (especially plasma cells) in the lamina propria; cuboidal epithelial cells with scanty, irregular microvilli
Intestinal lymphangiectasia	Dilation and ectasia of the intramucosal lymphatics
Tropical sprue	Range from minimal changes in villous height and moderate epithelial cell damage to virtual absence of villi and elongated crypts with lymphocyte infiltration in the lamina propria
Whipple disease	Lamina propria densely infiltrated with periodic acid-Schiff–positive macrophages; villous structure possibly obliterated in severe lesions

Small-bowel x-rays (eg, small-bowel follow-through, enteroclysis) can detect anatomic conditions that predispose to bacterial overgrowth. These include jejunal diverticula, fistulas, surgically created blind loops and anastomoses, ulcerations, and strictures. Abdominal flat plate x-rays may show pancreatic calcifications indicative of chronic pancreatitis. Barium contrast studies of the small bowel are neither sensitive nor specific but may show findings suggestive of mucosal disease (eg, dilated small-bowel loops, thinned or thickened mucosal folds, coarse

fragmentation of the barium column). CT, magnetic resonance cholangiopancreatography (MRCP), and ERCP can establish the diagnosis of chronic pancreatitis.

Tests for pancreatic insufficiency (eg, secretin stimulation test, bentiromide test, pancreolauryl test, serum trypsinogen, fecal elastase, fecal chymotrypsin—see [Diagnosis](#)) are done if history is suggestive but are not sensitive for mild pancreatic disease.

The ¹⁴C-xylose breath test helps diagnose bacterial overgrowth. ¹⁴C-xylose is given orally, and the exhaled ¹⁴CO₂ concentration is measured. Catabolism of ingested xylose by the overgrowth of flora causes ¹⁴CO₂ to appear in exhaled breath.

The H₂ breath test measures the exhaled H₂ produced by the bacterial degradation of carbohydrates. In patients with disaccharidase deficiencies, enteric bacteria degrade nonabsorbed carbohydrates in the colon, increasing exhaled H₂. The lactose-H₂ breath test is useful only to confirm lactase deficiency (see [Diagnosis](#)) and is not used as an initial diagnostic test in the evaluation of malabsorption. The ¹⁴C-xylose and H₂ breath tests have replaced bacterial cultures of aspirates taken during endoscopy for diagnosis of bacterial overgrowth syndrome (see [Bacterial Overgrowth Syndrome](#)).

The Schilling test assesses malabsorption of vitamin B₁₂. Its 4 stages determine whether the deficiency results from pernicious anemia, pancreatic exocrine insufficiency, bacterial overgrowth, or ileal disease.

- Stage 1: The patient is given 1 mcg of radiolabeled cyanocobalamin po concurrent with 1000 mcg of nonlabeled cobalamin IM to saturate hepatic binding sites. A 24-h urine collection is analyzed for radioactivity; urinary excretion of 8% of the oral dose indicates malabsorption of cobalamin.
- Stage 2: If stage 1 is abnormal, the test is repeated with the addition of intrinsic factor. Pernicious anemia is present if intrinsic factor normalizes absorption.
- Stage 3: Stage 3 is done after adding pancreatic enzymes; normalization in this stage indicates cobalamin malabsorption secondary to pancreatic insufficiency.
- Stage 4: Stage 4 is done after antimicrobial therapy with anaerobic coverage; normalization after antibiotics suggests bacterial overgrowth.

Cobalamin deficiency secondary to ileal disease or ileal resection results in abnormalities in all stages.

Tests for less common causes of malabsorption include serum gastrin (Zollinger-Ellison syndrome), intrinsic factor and parietal cell antibodies (pernicious anemia), sweat chloride (cystic fibrosis), lipoprotein electrophoresis (abetalipoproteinemia), and serum cortisol (Addison disease).

To diagnose bile acid malabsorption, which may occur with diseases of the terminal ileum (eg, Crohn disease, extensive resection of terminal ileum), patients can be given a therapeutic trial of

a bile acid binding resin (eg, cholestyramine). Alternatively, the selenium homocholic acid taurine (SeHCAT) test can be done. In this test, ⁷⁵Se-labeled synthetic bile acid is given orally and, after 7 days, the retained bile acid is measured with a whole-body scan or gamma camera. If bile acid absorption is abnormal, retention is less than 5%.