6. SCREENING AND CONFIRMATION OF MALABSORPTION

Zdislava Vaníčková, Petr Kocna, Tomáš Zima

6.1 INTRODUCTION

6.1.1 DEFINITION OF MALABSORPTION

Malabsorption is a failure of normal absorption of nutrients and micronutrients regarding transport, digestion or absorption of nutrients in the gut. It differs from malnutrition, which is an inadequate food intake (1,2). Malabsorption can be generalized, affecting absorption of a range of nutrients, or specific, where the absorption of only a single nutrient is impaired. Principially three mechanisms are involved in pathophysiology of malabsorption: premucosal (luminal), mucosal and postmucosal (postabsorptive). Premucosal mechanisms lead to maldigestion, mucosal and postmucosal mechanism lead to real malabsorption (1,3,4).

6.1.2 CLINICAL SYMPTOMS

Main clinical symptoms are weight loss, abdominal pain, chronic diarrhea, bloating, steatorrhea, anemia, osteopathies and neuropathies. If the process affecting absorption is mild, malabsorption may stay clinically silent, as it is compensated by bigger food intake. In more severe cases it presents by one or more signs and symptoms of the malabsorptive state. Fat malabsorption usually presents by diarrhea, steatorrhea, weight loss, reduced triceps skin-fold

Table 6.1 Basic laboratory tests for investigation of malabsorption

Tests to seek evidence of malabsorption	Tests for course of malabsorption
Global tests Blood count Mean erythrocyte corpuscular volume Mean erythrocyte corpuscular hemoglobin Serum iron Serum ferritin Serum cobalamin Serum and red blood cell folate Prothrombin time Plasma proteins Serum electrolytes Liver enzymes Thyroid stimulating hormone Occult bleeding quantitative test in stool	**Infection markers** C-reactive protein Erythrocyte sedimentation rate Immunoglobulins Stool bacteriology/parazitology tests **Celiac disease** anti-tissue transglutaminase anti-deamidated-gliadin antibodies Beta carotene **Carbohydrate malabsorption** Hydrogen breath tests ^{13}C substrate labeled breath tests Xylose test **Fat malabsorption** 72-hour faecal fat collection Pancreatic elastase I in stool ^{13}C substrate labeled breath tests **Protein malabsorption** Alpha1-antitrypsin clearance in stool Bowel permeability tests

thickness, fat soluble vitamin deficiences (night blindness, dry eyes, osteomalacia and prolonged prothrombin time). Protein loss brings edema, reduced mid-arm muscle circumference, reduced creatin and creatinine: height ratio. Iron deficiency presents by glossitis, angular stomatitis and pallor; group B vitamins deficiency shows glossitis, magenta tongue, pellagra and peripheral neuropathy (1,3-7).
Major diseases involved in malabsorption are: celiac disease, Crohn's disease, lactose intolerance, small bowel lymphomas and intestinal infections, gastric and liver diseases, chronic pancreatitis, systemic diseases and neuroendocrine tumors.
Diagnosis is based on physical examination, physical history, imaging methods; routine and special laboratory tests (Table 6.1). The use of scoring systems like MUST (malnutrition universal screening tool) is advisable (4,8,9). MUST scoring system uses patient's height, weight, recent unplanned weight loss, considering effect of acute disease, to determine malabsorption risk and to manage it if present.

6.2 LABORATORY TESTS FOR MALABSORPTION

Laboratory tests can be divided according to biological material from which they are performed: blood (serum, plasma), stool and breath samples, while latter two can be assessed non-invasively and are suitable even for children and good for screening. From those pancreatic elastase I in stool is widely used to assess severity of exocrine pancreatic dysfunction and hydrogen breath tests to show suspected monosacharides and disacharides intolerance. Breath tests are summarized in Table 6.2 (10-13). In general hydrogen breath tests and ^{13}C-labeled substrate breath tests can be performed. For carbohydrate malassimilation both types can be used employing lactose, fructose, sorbitol, saccharose, D-xylose and starch. Small intestinal bacterial overgrowth can be objectified by glucose, lactulose, glycocholate and D-xylose breath tests. For orocaecal transit time assessment lactulose, inulin and lactoseureide as substrates are used. ^{13}C-labeled substrates are of great importance in exocrine pancreatic function assessment: ^{13}C-mixed triglycerides, ^{13}C-triolein and other substrates are widely used. Permeability tests are sometimes performed (14,15).

Table 6.2 Breath tests used in malabsorption screening and diagnosis.

Hydrogen breath tests substrates	**^{13}C-breath tests substrates**
Carbohydrate malabsorption	
Lactose	^{13}C-lactose
Fructose	^{13}C-fructose
Sorbitol	^{13}C-starch
Saccharose	^{13}C-saccharose
D-xylose	
Fat malabsorption	
	^{13}C-mixed triglycerides
	^{13}C-triolein
Small intestinal bacterial overgrowth	
Glucose	^{13}C-D-xylose
Lactulose	^{13}C-glycocholate
Orocaecal transit time measurement	
Lactulose	^{13}C-lactoseureide ^{13}
Inulin	

6.3 NORMAL BOWEL PHYSIOLOGY

Normal absorption relies on multiple processes, some starting as soon as food is seen, smelt and tasted. Chewing starts the physical transformation of food and secretions from the salivary glands, stomach, pancreas, liver and intestine dissolve components of the meal and lubricate its passage. Coordinated muscle function is needed to swallow the bolus, gastric motility is crucial for mixing food in the stomach and emptying the semi-liquid chyme into duodenum. Intestinal peristalsis propels and mixes nutrients during digestion and absorption. These processes are controlled by nerves and hormones (16,17). Reabsorption of secreted water, electrolytes and bile acids takes place in the distal intestine. Bacterial action releases some further nutrients that can be absorbed in the colon (4).
For adequate digestion exocrine secretion of enzymes is essential. Digestive enzymes are also present on brush-border apical membrane and cytoplasm of the enterocyte. Main enzymes involved in digestion of macronutrients are shown in Table 6.3 (4,18,19).
Proteolytic enzymes are produced as inactive precursors and intestinal brush-border enterokinase activates trypsinogen to trypsin, which then activates other pancreatic proteases. Important non-enzymatic secretions are hydrochloric acid from the stomach (stomach enzymes better work at lower pH) and bicarbonate present in pancreatic juice and bile (intestinal enzymes prefer alkali pH). Bile acids and phospholipids from the liver form micelles with ingested lipids and improve their absorption.

Table 6.3 Enzymatic digestion of macronutrients.

Site	Carbohydrates	Proteins	Lipids
Salivary glands	Salivary amylase		
Stomach		Pepsins	Gastric lipase
Pancreas	Pancreatic amylase	Trypsin Chymotrypsin Elastase Carboxypeptidases	Lipase Colipase Phospholipase Cholesterol esterase
Intestine	Orocaecal transit Sucrase Lactase Maltase	Enterokinase Aminopeptidases Endopeptidases Oligopeptidases Dipeptidylpeptidase	

Water absorption is regulated by absorption of major electrolytes (sodium, chloride). Sodium is co-transported with many other nutrients (glucose, amino acids), in ileum and colon specific mechanisms of sodium and chloride ions absorption exist.
Carbohydrates are relatively easily digested. Monosacharides are absorbed in duodenum and upper jejunum rapidly. Sucrose is split by sucrase to glucose and fructose. Lactose, the milk sugar, is broken down by lactase to galactose and glucose. Starches are longer to digest and absorb, dietary fiber precedes through small intestine almost unchanged (4,20).
For protein digestion numerous enzymes are present in brush-border membrane; after full or partial digestion amino acids, dipeptides, tripeptides and oligopeptides are absorbed and further digestion proceeds in the enterocyte cytoplasm (4,21).
Triglycerides and phospholipids are not completely digested but absorbed as monoglycerides and lysophospholipids together with free fatty acids. Cholesterol esters are digested to

cholesterol and fatty acids. Inside the enterocyte are re-esterified and apolipoproteins synthesis takes place. These are incorporated into chylomicrons and very low-density lipoproteins and secreted at the basolateral enterocyte membrane (4,22).
Minerals, vitamins and other micronutrients usually have specific absorptive transport mechanisms. Iron and calcium are more soluble in acidic conditions and are absorbed in proximal intestine. Cobalamin has to be bond with stomach intrinsic factor and has limited region of absorption in the terminal ileum (23-25). Conjugated bile acids are reabsorbed (26).

6.4 GENERALIZED MALABSORPTION VERSUS SPECIFIC MALABSORPTION STATES

6.4.1 GENERALIZED MALABSORPTION

Generalized malabsorption commonly results from small intestine diseases, but pancreatic diseases and other organ diseases can be involved. Major intestinal findings are summarized in Table 6.4.

Table 6.4 Mechanisms of intestinal malabsorption.

Condition	Mechanisms
Short bowel syndrome	Loss of absorptive area Loss of digestive enzymes Rapid transit
Celiac disease	Reduced absorptive area due to villous atrophy Reduced enterocyte digestive enzymes Impaired intestinal hormonal secretion
Crohn's disease	Loss of functioning intestinal area Bypassed gut Small intestinal bacterial overgrowth
Lactose intolerance	Normal genetic non-persistence of lactase Secondary forms from mucosal injury
Bile acid malabsorption	Secondary to impaired bile acids reabsorption Overproduction in primary bile acids diarrhea
Infections	Reduced brush border enzymes Metabolic effects on enzyme and nutrients Villous atrophy, lymphangiectasia

Short bowel syndrome

Short bowel syndrome occurs when there is insufficient functioning bowel to meet individual's needs for macronutrients, salt and water from an ordinary diet, without artificial supplementation. This usually occurs when less than 200 cm of functioning bowel remains. The most common causes in children are congenital disorders and volvulus resulting in small bowel resection, in adults these are Crohn's disease and mesenteric vascular occlusion (1,4).

Coeliac disease

Celiac disease is chronic autoimmune condition in genetically susceptible individuals triggered by dietary gluten. There is a wide scale of disease severity: from clinically silent to severe malabsorption. Concomitant anemia and osteoporosis are usual, small intestine lymphomas and adenocarcinomas are rare. Association with other autoimmune diseases like

type 1 diabetes mellitus (27) and autoimmune thyreopathies is described (28). Diagnostically anti-tissue transglutaminase (IgG tTGA) and anti deamidated-gliadin (IgG DGP) plasma antibodies are recommended, and small bowel biopsy is performed.

Crohn's disease

Crohn's disease is a chronic inflammatory bowel disease that can affect any part of digestive tract; small bowel is involved in 70% of cases. Genetic susceptibility plays an important role. Major features in pathogenesis are gut microflora, mucosal permeability and host immunity. Malnutrition in Crohn's disease is multifactorial: anorexia, increased energy expenditure and reduced intestinal absorption. In patients with extensive small bowel involvement, picture similar to short bowel syndrome occurs, both macro- and micronutrients being malabsorbed together with imbalances in water and electrolyte metabolism. Terminal ileum is involved often; therefore cobalamin and bile acids are malabsorbed.

Laboratory tests include routine tests and special antibodies determination: pANCA (perinuclear anti-neutrophil antipody) and ASCA (anti-Saccharomyces cervisiae antipody). Colonoscopy and imaging methods are being involved (4,6,29).

Whipple's disease

Whipple's disease is a systemic disease caused by Gram-positive bacterium Tropheryma whipplei. Except of bowel disease affects joints, nervous and cardiovascular systems. Due to blocked lymphatics mostly postabsorptive malabsorption is present. Diagnosis is based on typical histological findings in small bowel biopsy: lamina propria populated by periodic acid-Schiff-positive foamy macrofages, PCR analysis is available (1).

Other infectious causes

Acute or chronic infection underlies many cases of malabsorption in developing world; similar conditions may affect travelers to such countries.

Acute tropical sprue follows acute (mostly viral) infections; chronic tropical sprue is probably associated with chronic bacterial infection of the upper gastrointestinal tract. Generalized malabsorption is often combined with specific folate malabsorption; diagnosis is made upon histology in small bowel biopsy.

Giardiasis is caused by upper small intestine colonization by trophozoite Giardia lamblia. Once established infestation by these leaf shaped microorganisms covering intestinal mucosa causes malabsorption by barrier effect, down regulation of brush-border enzymes is also present. Diagnosis is made from histological and microbiological observation in small bowel biopsy sample (1).

6.4.2 CARBOHYDRATE MALABSORPTION

Lactose intolerance

Lactose intolerance is most common type of malabsorption in Europe. Mucosal lactase concentrations are highest at birth and are essential for the absorption of energy from milk monosacharides. Lactase levels decrease following weaning during childhood in most populations (lactase non-persistance) resulting in intolerance of dairy products. Congenital defects are rare, secondary deficiency accompanies mucosal injury – like in celiac disease, giardiasis and radiation therapy. Undigested lactose reaches the colon where it is metabolized by bacteria, producing hydrogen, methane, and short chain fatty acids – this leads to symptoms of bloating, cramping and diarrhea. Diagnosis is based upon clinical findings,

exposition tests, hydrogen breath test, rapid test from biopsy and histology of small bowel sample (20,30-38).

Fructose intolerance

In general, fructose is less well absorbed than glucose and galactose. Malabsorption can be explained by low-capacity of carrier mediated facilitated diffusion, consumption of fructose without glucose and amino acids present in the same meal. In diagnosis, exposition and hydrogen breath tests are generally used (13,20,39).

6.4.3 FAT MALABSORPTION

Fat digestion and absorption is complex process with many organs involved, but chronic exocrine pancreatic insufficiency and lack of bile acids together with short bowel syndrome are the major causes of fat malabsorption. Tests available to uncover fat malabsorption are 72-hour fecal fat collection and fecal fat assessment (in Europe almost not used due to low compliance of patients and laboratories) and pancreatic elastase I in stool determination.

6.4.4 PROTEIN MALABSORPTION AND PROTEIN LOSING ENTEROPATHY

Protein losing enteropathies leading to protein malabsorption are rather the syndrome than single disease itself. Patient presents by hypoproteinemia and edemas in the absence of proteinuria, defects in protein synthesis or protein malnutrition. According to the type of mucosal alteration protein loosing enteropathy can be classified into three groups:

Mucosal ulceration occurs in ulcerative colitis, Crohn's disease, gastrointestinal carcinomas or peptic ulcer. *Non-ulcerated mucosa with evidence of altered permeability* is represented by celiac and Whipple's diseases and colagenous colitis. *Lymphatic dysfunction* presents either primary lymphatic disease or secondary to partial lymphatic obstruction.

Laboratory diagnosis is performed using alph1-antitrypsin clearance test from stool or tests using radio-labeled proteins (Gordon's test) (40).

6.4.5 MALABSORPTION OF SPECIFIC NUTRIENTS

Iron

Malabsorption is just one of the causes of iron deficiency, others are dietary inadequacy and low bioavailability, increased demands (childhood) and increased looses (cow's milk enteropathy, menstruation, hook worm infection, bleeding from polyps and tumors, Crohn's diesease). Iron intestinal malabsorption itself usually accompanies protein energy malnutrition where mostly mucosal mechanism is involved (24).

Vitamins

Thiamine (vitamin B_1) malabsorption occurs in states with diarrhea, dysentery, tropical sprue, ulcerative colitis. In some food are present thermo-labile thiaminases (raw fish) and thermo-stabile polyhydroxyphenols (coffee, tea, red cabbage, blueberries, blackcurrants etc.) that can impede thiamine absorption.

Riboflavine (vitamin B_2) absorption is decreased by deficiency of bile salts in patients with cirrhosis or hepatitis; biliary absorption increases when vitamin is taken together with food. Alcohol ingestion interferes with the absorption of dietary riboflavin by inhibiting the hysrolysis of food flavins to riboflavins as well as inhibiting its active transport mechanisms.

Vitamin B_6 (pyridoxol, pyridoxine, pyridoxamin vitaminers) in food is present as vitaminers phosphate. Prior absorption it has to be dephosphorylated by means of a membrane-bound alkaline phosphatase present in intestinal brush border (23).

Cobalamin (vitamin B_{12}) in nature is synthetsized exclusively by microorganisms and is present in animal but not plant products. Food cobalamin is attached to proteins and heating, gastric pepsin and hydrochloric acid action makes is available for binding to R-protein, from which it is released in the jejunum by pancreatic proteases, cobalamin binds to intrinsinic factor and proceeds to ileum where the complex has specific receptor. Main causes leading to malabsorption are pancreatic insufficiency and disease of the ileal region (Crohn's disease, Whipple's disease) (23,25). Diagnostically Schilling's test or novel ^{13}C labeled breath test can be performed (41).

Vitamin C is found almost exclusively in foods of plant origin. Gastrointestinal absorption of vitamin is fast and efficient, active carrier-mediated system has been described. With adequate intake malabsorptive states are extremely rare.

Fat soluble vitamins (A,D,E,K) are hydrophobic substances dissolved in the upper portion of gastrointestinal tract in the lipid phases and emulsions. Pancreatic lipase binds to the surface of fat droplets and catalyzes fat digestion; mixed micelles are formed, with the lipid core containing fat soluble vitamins. These micelles are small enough to gain close proximity to the microvillar surfaces of the intestinal mucosa and facilitating diffusion of fat soluble vitamins across enterocyte membrane. All fat soluble vitamins absorption can be affected by cholestasis, cystic fibrosis, chronic diarrhea, pancreatic insufficiency, Crohn's disease, small bowel resection, jejunal bypass and celiac disease (23).

Bile acids

Bile acids circulate in the neterohepatic circulation 4-6 times per day. Secondary malabsorption occurs when resected or diseased segment of terminal ileum reduces the proportion of reabsorbed bile acids, these then pass into the colon where they produce water and electrolyte secretion leading to diarrhea. When the pool of bile acids is significantly depleted, emulsification of fat in the small bowel is reduced, leading to fat malabsorption (4,40). Bile acids malabsorption can be investigated by selenium-75-homocholic acid taurine scans (26).

6.5 CONCLUSION

There are many diverse causes of malabsorption. Treatment depends on understanding mechanisms of malabsorption involved, identifying the cause by means of laboratory and imaging methods based tests and procedures and giving specific therapy where possible and available.

This artical is in the scope of the RVO-VFN64165/2012 and research programme of the Charles Unversity Prague PRVOUK-P25/LF1/2.

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