The KyberPlus System

Diagnostic Procedures for Clarifying Equivocal Intestinal Complaints

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Equivocal abdominal complaints are diagnosed more than 3 million times a year in Germany alone. It is seldom possible to definitively determine the triggering factors. Digestive disturbances may be due to liver, gallbladder, or pancreas disorders that lead to a deficit of digestive enzymes or bile acids. Nutrients of high molecular weight are no longer broken down into their basic components (maldigestion) but remain in the intestinal lumen, where they are broken down by bacteria or fungi.

However, digestive disturbances can also be due to impairment of the movement of nutrients from the intestinal lumen into the bloodstream and lymph system (malabsorption). In addition to inflammatory or diffuse chronic diseases of the small intestine (e.g., celiac disease, Crohn's disease, diverticulosis or diverticulitis, Whipple's disease, etc.) other factors such as diabetes mellitus, hyperthyroidism, or right ventricular heart failure can also be responsible.

This article introduces a new diagnostic system (KyberPlus) that makes it possible to ascertain the condition of the patient's digestion, mucosal immune system, and intestinal mucosa. In addition, this system provides a sure understanding of the most common diseases causing maldigestion or malabsorption. The sequence and parameters of the KyberPlus system are presented in Figure 1. The goal of the system is to create optimal prerequisites for understanding causative factors to be able to successfully treat the causes of illnesses that have often persisted for years or even decades. In the sections that follow, the diagnostic stages, the most important diseases, and the testing procedures involved in the KyberPlus system are described briefly.

Evidence of Digestive Disorders

A quantitative biochemical analysis of undigested food remnants in the feces is used as a screening procedure to indicate the presence of digestive disorders (Figure 2). It yields values for fats (neutral fat, long-chain fatty acids), nitrogen, carbohydrates, and water. Normally only small amounts of undigested food remnants are found in the feces. Daily elimination of fat and nitrogen is relatively constant. A healthy body eliminates a maximum of 7 g fat in 24 hours (3.5 g/100 g feces). Daily nitrogen elimination should not exceed 2 g (1 g/100 g feces) (Table 1). Pathologically high concentrations of fat and nitrogen in the feces point to digestive disturbances.[17, 20, 25] It is not possible to distinguish between maldigestion and malabsorption by means of this procedure (Figure 3).

Evidence and Consequences of Maldigestion

Exocrine pancreatic insufficiency and bile acid deficiency are the most frequent causes of maldigestion. When lipase activity is deficient in temporary or chronic pancreatic insufficiency, the signs of maldigestion are fatty stools and secondary malabsorption of fat-soluble vitamins, calcium, and vitamin B_{12}. Protein digestion is also often disturbed as a result of reduced trypsin and chymotrypsin activity.

Liver diseases can lead to disturbances in the synthesis, conjugation, or secretion of bile acids. Overgrowth syndrome, in which the small intestine is overgrown with microorganisms indigenous to the large intestine, also results in bile acid deficiency because conjugated bile acids are broken down by bacteria belonging to the faulty intestinal flora. As a result, fat absorption is disturbed and secondary malabsorption of fat-soluble vitamins occurs.

The presence of pancreas elastase 1 in the feces has proven to be a reliable laboratory indicator of exocrine pancreas insufficiency.[18, 19, 27] Diseases that lead to a deficiency of bile acids are diagnosed by determining the primary and secondary bile acids in the feces.

Evidence and Consequences of Malabsorption

Malabsorption can be confirmed by the presence of specific marker proteins in the feces, most importantly inflammation markers such as alpha$_1$-antitrypsin and lysozyme.

Many different diseases can cause malabsorption. The KyberPlus system aids in the diagnosis of the most frequent causes (Table 2). Disturbed nutrient absorption is often due to carbohydrate intolerances (e.g., lactose intolerance)[3, 15] or food allergies.[4] Diffuse chronic diseases of the small intestine, such as Crohn's disease or celiac disease, play a significant part.[7, 23] Overgrowth syndrome is also included in the Table because in addition to causing bile acid deficiency (maldigestion), it also causes damage to the intestinal mucosa (especially to the enterocytes), eventually leading to malabsorption of the products of food breakdown.[14]

Clarifying the Causes of Malabsorption

If malabsorption is present, further clarification of the causative factors is only possible by taking into account information supplied by the patient during case-taking. Detailed questioning of the patient must clarify whether the symptoms are

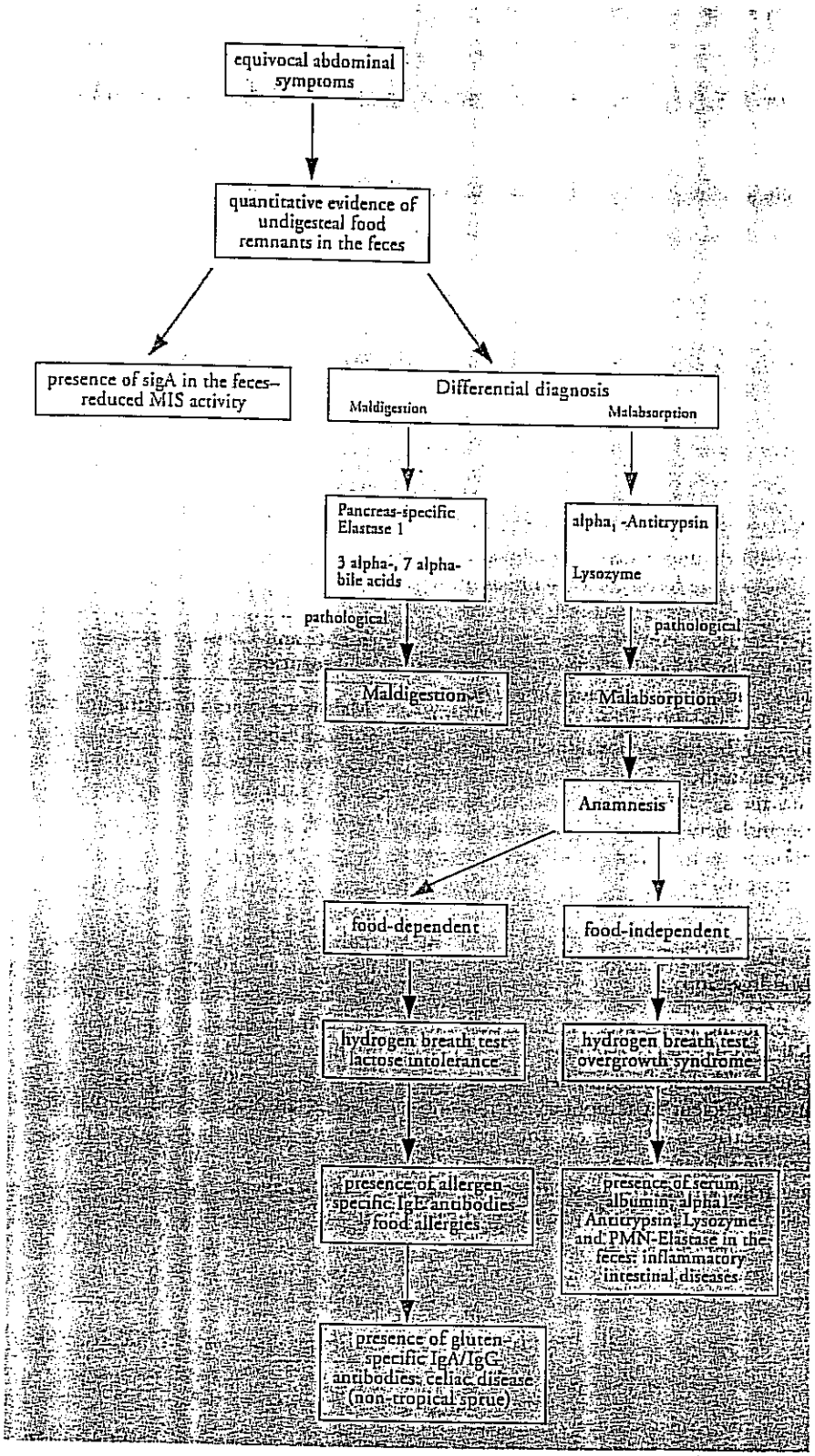

Figure 1: Diagram of the system of KyberPlus diagnosis. Pathological amounts of undigested food remnants in the feces point to digestive disturbances that can result from many different disorders or underlying illnesses. MIS = mucosal immune system.

food-dependent (carbohydrate intolerance, food allergies, celiac disease) or food-independent (overgrowth syndrome, inflammatory intestinal diseases).

Food-Dependent Diseases

Carbohydrate Intolerances

Many people develop gastrointestinal symptoms after ingesting certain mono- or disaccharides. Of all the carbohydrate intolerances, lactose intolerance (inability to digest milk sugar) is probably the most familiar (Figure 4). It is due to an enzyme defect (lactase deficiency). Approximately 15-20% of all Central Europeans are affected by it,[11] although the degree of intolerance varies greatly among individuals. Whereas normally 20-30 g lactose per day are tolerated, the tolerance threshold for patients with lactose intolerance is around 5-10 g. This corresponds to the lactose content of half a glass of cow's milk. In infrequent cases, no lactose at all is tolerated.

Lactose intolerance is seldom reported as such by patients, who often fail to make the connection between their intake of lactose-containing foods and symptoms such as sensation of fullness, nausea, cramp-like abdominal pains, bloating, and diarrhea.[8,9] A carbohydrate intolerance that has gone unrecognized for a long time, however, can place serious burdens on the large intestine and its flora (Table 3). Microbial fermentation of undigested carbohydrates undermine the integrity of the mucosa, with a resulting increase in susceptibility to food allergies.

Less well-known but much more common than lactose intolerance are intolerances to fructose, sorbitol, and xylitol, which are apparently based on reduced individual absorption capacity. Approximately one half to two thirds of the patients in question develop abdominal symptoms. The fructose intolerance discussed in this context is not to be confused with hereditary fructose intolerance.

In the KyberPlus system, carbohydrate intolerances are confirmed by means of a hydrogen breath analysis. By choosing the

appropriate sugar for testing, it is possible not only to confirm intolerance to lactose, but also to diagnose intolerances to fructose, sorbitol, or xylitol with certainty.

Food Allergies

The intolerances described above, which are based on enzyme defects or absorption disorders, must be distinguished from IgE-mediated food allergies.[28, 30, 31]

To confirm the presence of food allergies and to distinguish them from pseudo-allergic reactions, a diagnostic system was developed that detects over 90% of all clinically relevant food allergies. This was accomplished by choosing frequently appearing food allergens on the basis of a comprehensive search of the literature and consultations with experts in the field. The possibility of a food allergy is confirmed by a positive test result in the KyberPlus diagnostic system and largely eliminated by a negative result. A serum enzyme immune test (ELISA) is used to perform the analyses.

Gluten-induced Enteropathy (Celiac Disease)

Celiac disease is a disorder of the small intestine that is induced by specific grain proteins (gliadin) found in wheat, rye, barley, and oats. Genetic factors foster the development of the disease. Caucasians are especially susceptible (1:300 to 1:1000). Celiac disease is accompanied by characteristic atrophying of the villi of the small intestine, which ultimately leads to an absorption disorder throughout the small intestine.[7, 16, 26] In the long run, therefore, untreated celiac disease leads to malnutrition.

In addition to the form with fully developed clinical symptoms, recent studies have discovered much more common latent forms of the disease with less overt clinical symptoms. Symptomatology is atypical when morphological changes in the mucosa are less pronounced.[6, 26] Frequent loose bowel movements and equivocal abdominal complaints are reminiscent of irritable bowel syndrome. Iron-deficiency anemia and defects in tooth enamel can accompany latent celiac disease.

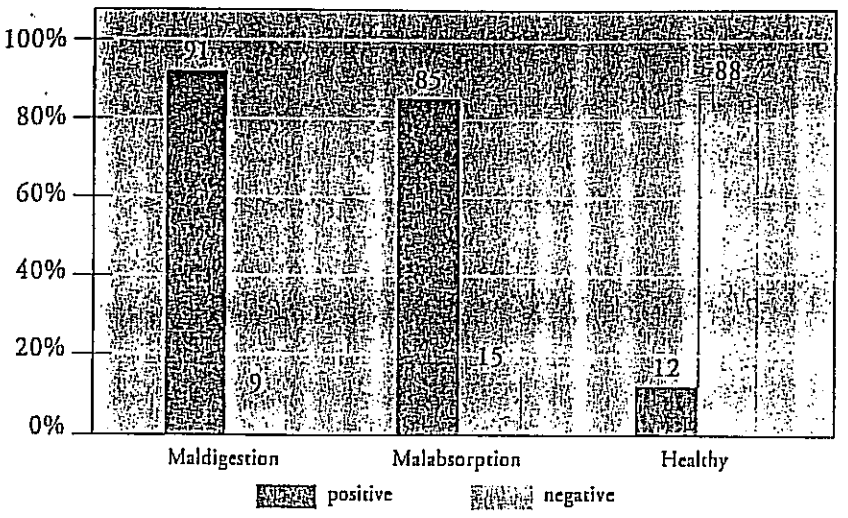

Figure 2: The suitability of quantitative analysis of digestive remnants in the feces as an indicator of digestive disorders was investigated on the basis of 200 patients with known maldigestion or malabsorption and 80 healthy subjects. Pathological presence of digestive remnants in 91% of patients with known maldigestion and 85% of patients with known malabsorption indicates a high level of reliability for the procedure.

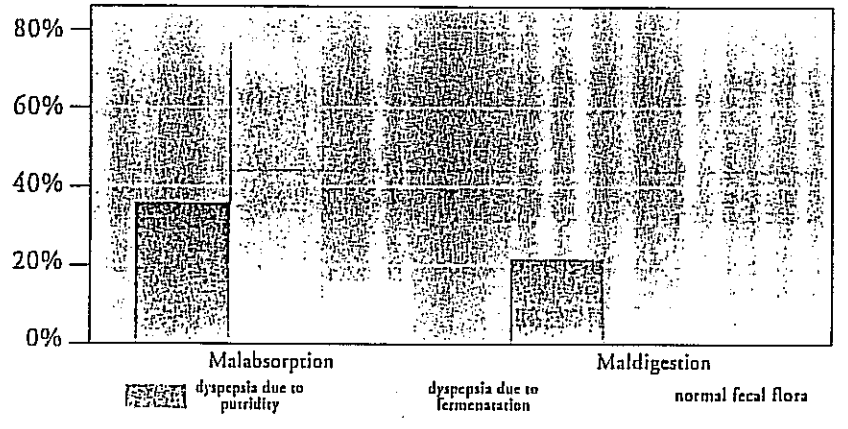

Figure 3: Frequency of maldigestion and malabsorption in 300 patients with equivocal abdominal symptoms.

Fat elimination	<3.5 g/100 g feces
Nitrogen elimination	<1.0 g/100 g feces
Carbohydrate elimination	<1.0 g/100 g feces
Water elimination	75-85 g/100 g feces

Table 1: Normal values for water and digestive remnants in feces.

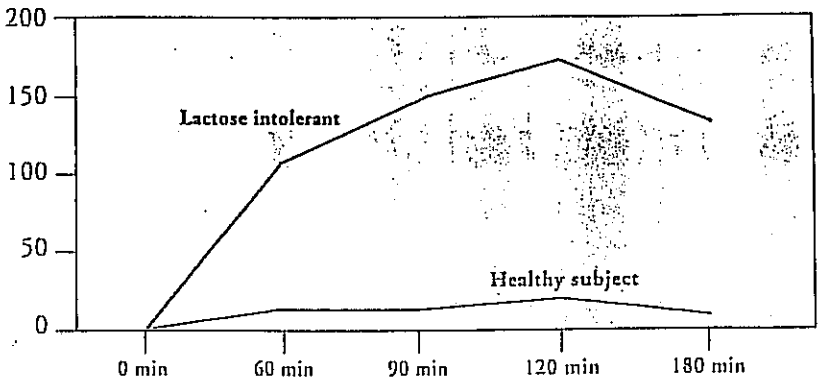

Figure 4: Results of hydrogen breath analyses confirming lactose intolerance. Normally, lactose is broken down in the small intestine into the easily absorbed monosaccharides galactose and glucose. In lactose intolerance, lactose that has not been broken down enters the large intestine, where fermentation by the indigenous microflora results in hydrogen formation.

——— *Healthy subject*

——— *Patient with lactose intolerance*

Disease	Incidence % of total population	Age of Highest Incidence
Acute Enteritis	most frequent cause	none
Carbohydrate Intolerences	15-20% of adults	ages 2-15
Food Allergies	5-10%	children
	up to 27% of asthma patients	adolescents
	up to 30% of patients with atopic dermatitis	young adults
	40-60% patients whose parents have food allergies	
Overgrowth Syndrome	5%	adults
Celiac Disease	0.03-0.3% of adults	infants
Crohn's Disease	0.02-0.04%	ages 15-35

Table 2: Causes of malabsorption in order of incidence.

Patients with active celiac disease almost always have circulating anti-gliadin antibodies in their blood, with antibody titers correlating closely with the degree of mucosal damage. An enzyme immune test can determine the concentration of anti-gliadin IgA (or anti-gliadin IgG, if IgA is deficient) in the serum. Raised levels of antibodies suggest a diagnosis of celiac disease.

Food-Independent Diseases

Overgrowth of the Small Intestine

In healthy individuals, the upper and middle sections of the small intestines are only sparsely populated with bacteria. In overgrowth syndromes, large sections of the small intestine (and also the stomach, to some extent) are overgrown with microorganisms that suppress the indigenous intestinal flora of lactobacilli and enterococci. Anaerobic genera of bacteria such as Bacteroides, Bifidobacteria, or Clostridia increase tremendously.[13,14]

Overgrowth syndromes can be caused by reduced intestinal motility or passage disorders. Other relevant factors, however, include mucosal damage, liver or pancreatic disease, and reduced immune defenses.

Dysbiosis of the small intestines leads to decreased intestinal absorptive ability as a result of pathological changes in the intestinal mucosa. Malabsorption of important nutrients, therefore, is also a primary factor in the clinical symptomatology of the disease.[14] Undigested food remnants in the intestinal lumen are broken down by the bacterial flora, resulting in intraluminal gas formation that can cause bloating, flatulence, cramp-like abdominal pain, or bad breath. Microbial metabolites, which can affect osmosis, and unresorbed free bile acids can cause diarrhea. If some of these symptoms occur and the level of fat excreted in the feces is elevated, differential diagnosis of an overgrowth symptom should be considered. Through KyberPlus diagnostics, definitive diagnosis is possible by means of a hydrogen breath analysis[19] (Figure 5).

This test, like the H_2 breath test to confirm lactose intolerance, is based on a

provocation experiment. The test sugar is lactulose, a disaccharide that can only be metabolized by the intestinal flora, not by the human body. It is taken orally and enters the intestines, where it is normally broken down by the intestinal flora only after it enters the colon.[21] This releases hydrogen, which reaches the lungs by way of the blood and is then exhaled. After 60-90 minutes its presence can be detected in exhaled air. In the case of overgrowth syndrome, lactulose is fermented by the faulty intestinal flora already in the small intestine, and the increase in H_2 in the exhaled air occurs earlier, often after only 10-20 minutes.[1,12]

Chronic Inflammatory Intestinal Diseases

The main chronic inflammatory intestinal diseases are Crohn's disease and ulcerative colitis. In Crohn's disease, the severity of the malabsorption depends on the location and extent of the inflammation. Malabsorption affects primarily vitamin B_{12} (which is absorbed in the terminal ileum), the fat-soluble vitamins A, D, E, and K, folic acid, zinc, magnesium, calcium, and iron. Ulcerative colitis is frequently accompanied by iron-deficiency anemia.

A diagnosis of inflammatory intestinal disease is usually confirmed by means of endoscopic, histological, or radiological procedures whose invasive character is quite burdensome to the patient. Since inflammatory intestinal diseases are accompanied by characteristic histopathological changes in the intestines, it is possible to acquire information about the extent of these changes by means of a quantitative analysis of specific marker proteins in the feces.[2, 10, 22, 24] The parameters investigated under the KyberPlus diagnostic system—serum albumin, alpha$_1$-antitrypsin, PMN elastase, and lysozyme—are highly sensitive and specific (Table 4). With their help, it is possible to diagnose an inflammatory intestinal disease with certainty in its early stages and to assess its course. Invasive exploratory techniques can often be avoided.

Sugar	Incidence	Symptomatic	Pathophysiology
Lactose	15-22%	60-70%	Lactase deficiency (congenital, acquired)
Fructose	40-80%	50-70%	Reduced individual absorption capacity
Sorbose	50-100%	50%	Reduced individual absorption capacity
Xylose	12%	50%	Reduced individual absorption capacity
Glucose	very infrequent		Glucose carrier disorder (autosomal-recessive)
Trehalose	very infrequent		Trehalose defiency

Table 3: Incidence of carbohydrate intolerance in Germany.

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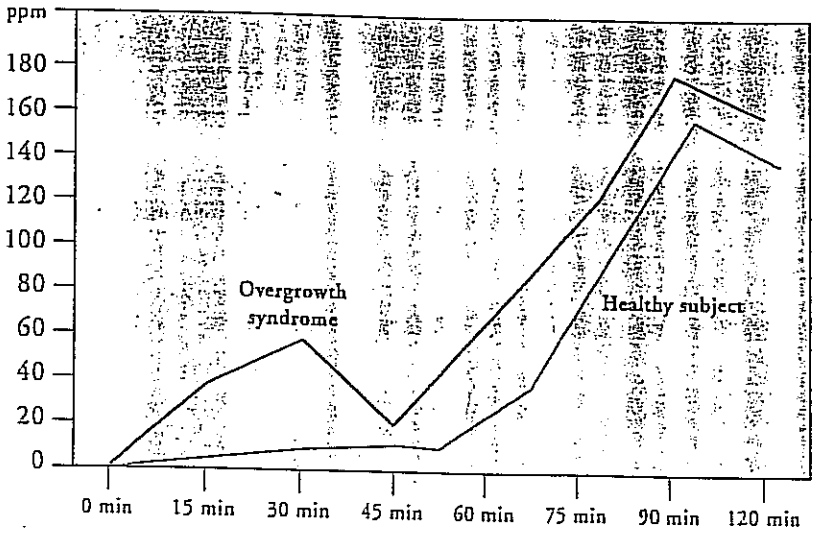

Figure 5: Hydrogen breath analyses in overgrowth syndrome. There is a very early clearly defined rise in exhaled hydrogen in the patient with overgrowth syndrome (—) in contrast to the healthy subject (—).

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Parameter	Histopathological correlate of elevated marker level
Serum albumin	intestinal bleeding and increased mucosal or vesicular permeability
alpha$_1$-Antitrypsin	permeability disorders of the intestinal mucosa
PMN-Elastase	granulocyte-mediated inflammatory reactions
Lysozyme	inflammatory reactions involving granulocytes, monocytes, and macrophages

Table 4: Marker proteins as indicators of inflammatory intestinal diseases.

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Note: For information on the KyberPlus system, please contact the author of this article. This diagnostic system is not available through Menaco or Heel Inc.