Carbohydrate malabsorption in patients with non-specific abdominal complaints

Peter Born

Peter Born, Department of Internal Medicine, Tirschenreuth District Hospital, Tirschenreuth 95643, Germany

Correspondence to: Professor Peter Born, MD, Department of Internal Medicine, Tirschenreuth District Hospital, St. Peter-Strasse 31, Tirschenreuth 95643,

Germany. peter.born@krankenhaus-tirschenreuth.de

Telephone: +49-9631-875204

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Abstract

Non-specific abdominal complaints are a considerable problem worldwide. Many patients are affected and many differential diagnoses have to be considered. Among these, carbohydrate malabsorption seems to play an important role. However, so far, only incomplete absorption of lactose is broadly accepted, while the malabsorption of fructose and sorbitol is still underestimated, although in many parts of the world it is much more frequent. Despite the success of dietary interventions in many patients, there are still a lot of unanswered questions that make further investigations necessary.

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Key words: Non-specific abdominal disorders; Carbohydrate malabsorption; Fructose; Sorbitol; Lactose; Dietary intervention

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INTRODUCTION

The incomplete absorption of carbohydrates may cause serious problems for the affected patients, and is a frequent cause of so-called non-specific abdominal complaints. Non-specific abdominal complaints are characterized by a lack of morphological or biochemical abnormalities in the affected patients^[1,2]. These complaints are a major problem throughout the world, with up to 30% of the population in Western countries being affected. Although only a minority seek medical attention, some 20%-50% of patients are referred to gastroenterologists so because of these non-

specific complaints^[2]. A study in Germany^[3] has reported similar data, with 30% of the population being affected. A quarter of the patients required medical treatment, and no other diagnosis could be established in two-thirds of the cases. Similar findings have been described in Africa^[4]; the rates appear to be lower in Asia, although they are still substantial, with a prevalence of up to 10% being reported^[5].

There is a wide range of symptoms; the predominant ones are pain, flatulence, constipation and diarrhea. These symptoms should always be distinguished from those such as anemia, weight loss, bleeding and fever, which may indicate more dangerous conditions^[6].

CARBOHYDRATE MALABSORPTION

Pathogenesis

Carbohydrates are a major source of calories in the diet. They may be ingested as monosaccharides, disaccharides, oligosaccharides or polysaccharides. During their passage from the mouth to the small intestine, they are broken down enzymatically until, in the small intestine, brush-border enzymes hydrolyze them into monosaccharides, which can be absorbed by various carrier systems^[7].

The most important carbohydrates that routinely cause clinical abdominal complaints are lactose, fructose, and the sugar alcohol sorbitol. Lactose has long been recognized as one of the most important nutrients, and fructose and sorbitol have become increasingly important following recommendations to increase fruit and vegetable consumption, and also as a result of their use as sweeteners in dietary preparations and so-called sugar-free sweets. Further disorders such as sucrase-isomaltase deficiency or lack of trehalase are rare or only of regional importance, and are not discussed in this paper, although in affected patients, diets free from these sugars are very successful.

Malabsorption may result from congenital or acquired defects of single transport systems (primary malabsorption), or from impairment of the epithelial surface of the small intestine, due to general intestinal diseases such as celiac disease or Crohn's disease, which impede the absorption of all carbohydrates (secondary malabsorption). In secondary malabsorption, treatment is directed at the underlying disease, and successful therapy can lead to the normalization of carbohydrate absorption. In primary malabsorption, selective interventions are necessary.

Lactose is split by the enzyme lactase (β -d-

galactosidase), derived from the brush border of the enterocytes, into galactose and glucose, which can be absorbed by a special carrier system. The most frequently associated deficiency is primary lactase deficiency in adults. In these patients, lactase activity gradually declines during early life, and symptoms may occur as early as late childhood. Congenital lactase deficiency is rare and already affects neonates^[8].

Several carriers, such as the GLUT family, are known to be involved in the transport of monosaccharides. GLUT-5 is the most important carrier currently known for the absorption of fructose. A deficiency in GLUT-5 leads to incomplete absorption or malabsorption of fructose^[9,10]. Sorbitol is only sparsely absorbed, and is therefore used therapeutically as an osmotic laxative. Absorption is thought to take place through passive diffusion^[11-13].

Congenital and acquired deficiencies are recognized. An important aspect is that the presence of glucose stimulates GLUT-5 activity, while sorbitol blocks it^[9]. These data from animal intestinal perfusion tests (in most cases rat jejunum) confirm previous clinical and experimental data, which show that addition of glucose to fructose in patients known to have fructose malabsorption can prevent malabsorption, and suppress the occurrence of the accompanying symptoms. In contrast, the presence of sorbitol may aggravate malabsorption and the symptoms^[13-17]. However, the mechanisms of carbohydrate absorption are still not completely understood.

There are also data that indicate an additional role for other factors in fructose metabolism, such as GLUT-2, which is capable of stimulating absorption^[10].

Prevalence

Lactase deficiency is the most common enzymatic defect worldwide, although there are considerable regional differences in its prevalence. The majority of people in Asia and Africa, as well as the aboriginal populations of America and Australia, are affected, while in Europe, there are very low rates (under 10%) in the north, with a strong increase (up to 70%-100%) in regions further south, such as in Italy and Turkey.

There have been many studies reporting high malabsorption rates for fructose and sorbitol. Depending on the dosage and concentration, the reported data are closely comparable. After the ingestion of 50 g fructose dissolved in 250 mL water (corresponding to the traditional lactose test), there are malabsorption rates of about 60%-70%^[15,18,19], while the rates are about 40% after a dosage of 25 g in 250 mL, the concentration now most commonly used^[14,20]. Similar values have also been documented in children^[21,22]. With regard to sorbitol, the test dosages used are less standardized, but even after an intake of 10 g, malabsorption rates can reach 100%^[12,19,23].

For all of these sugars, it should be noted that the malabsorption rates are quite similar in patients and healthy controls. While some 50% of those with malabsorption of fructose and sorbitol have no concomitant symptoms, the symptomatic rates for lactose malabsorption are much more varied, with only a few people being symptomatic in some populations, despite high malabsorption rates.

Symptoms

The clinical symptoms of carbohydrate malabsorption include flatulence, abdominal cramps and pain, diarrhea, and sometimes even headache, usually after the ingestion of a product containing the incompletely absorbed sugar. There are no symptoms specific for a single sugar. However, there are data showing that, in patients (mainly females) with fructose and sorbitol malabsorption, diet can improve not only gastrointestinal disturbances, but also mood^[24]. An association with reduced plasma levels of tryptophan has been discussed as a possible mechanism for this^[25].

The gastrointestinal symptoms are thought to be provoked by the increased osmotic load of the sugar, with an augmented intraluminal volume (water) and a consequent acceleration of intestinal passage. Gas production and diarrhea occur in connection with the bacterial flora in the colon, the unabsorbed sugar presenting as a substrate for increased bacterial fermentation. Moreover, the capacity of the colon to absorb the surplus water plays a role in the pathogenesis of diarrhea.

In view of these etiologic factors, it is of particular interest that many patients report that initial symptoms develop after an infection (mostly gastrointestinal) or after antibiotic therapy, although it must be assumed that malabsorption has been present since childhood. Irritable bowel syndrome (which probably often includes patients with carbohydrate malabsorption) has also been reported to develop in connection with infections, both inside and outside the gastrointestinal tract^[26,27]. In two small series, our own group has shown that the degradation of the malabsorbed sugar in stool cultures correlates with the occurrence of symptoms and a different pattern of short-chain free fatty acids^[28,29].

It may therefore be speculated that the symptoms of carbohydrate malabsorption depend on the pattern of the colonic flora. A further argument in favor of this view is the observation that, in volunteers in whom more than one type of malabsorption is detected, the symptoms occur either after each malabsorption or after none^[30].

Diagnosis

Carbohydrate malabsorption can be detected using direct or indirect methods. Using a cecal tube to measure the amount of unabsorbed sugar after oral ingestion is not practicable for routine purposes. Measurement of enzymatic activity in intestinal biopsies is a valuable tool for quantifying disaccharidase activity. It is therefore suitable for diagnosing lactase insufficiency, but is rarely used. Indirect methods are more widely used. Measurement of blood sugar after lactose ingestion was formerly a widespread method, but it declined in importance with the introduction of hydrogen exhalation tests. Direct measurement of ingested sugar in blood or urine is applicable for xylose.

By far the most frequently used method nowadays is the hydrogen exhalation test. After ingestion of the test sugar, the amount of hydrogen in the exhaled gas is measured. If there is incomplete absorption, part of

the ingested sugar passes into the colon, in which it is metabolized by bacteria into hydrogen, methane, carbon dioxide and free fatty acids. A small amount of hydrogen is absorbed and exhaled during the first passage through the lungs. An increase in hydrogen of more than 20 parts per million is considered to indicate malabsorption^[31-33]. The extent of the hydrogen increase does not correlate either with the patients' symptoms or with the degree of malabsorption^[34]. Hydrogen tests are only able to detect or exclude malabsorption. It should be pointed out that to avoid false-negative results, the presence of hydrogen-producing bacteria should be confirmed by carrying out a lactulose test (as lactulose is a disaccharide that cannot be absorbed by humans and therefore causes an increase in hydrogen). False-positive results due to bacterial overgrowth or accelerated orocecal transit can also be reduced with this test^[35].

Concomitant measurement of blood glucose may improve the accuracy of lactose tests and should be mandatory in all fructose tests, in order to detect rare cases of fructose intolerance, which may mimic the symptoms of fructose malabsorption, but can cause severe hypoglycemia and even death after the ingestion of fructose. There is also some evidence that parallel methane assessment may improve the accuracy of the hydrogen test, but the data are sparse and require further evaluation^[36]. The use of ¹³C exhalation tests also requires further evaluation^[37].

Therapy

Avoidance of the malabsorbed sugar is still the treatment of choice. In patients with lactose malabsorption, the addition of lactase (most conveniently in liquids) is an alternative, as well as the consumption of lactose-free milk products. Patients with fructose malabsorption can choose fruits and vegetables that have an equal ratio of fructose and glucose. In liquids, the addition of glucose can prevent malabsorption and its symptoms, but does not appear appropriate from the point of view of healthy nutrition. For sorbitol malabsorption, restricting sorbitol intake is the best method of preventing symptoms. In the same way that glucose can reduce malabsorption when administered along with fructose, adding sorbitol to fructose may aggravate the symptoms, and this should be taken into account when establishing the dietary regimen. For all sugars, small amounts are tolerated by most patients. Ingesting them along with or after other nutrients further improves tolerance.

The diet and its effects are often an important method of establishing a diagnosis of clinically relevant carbohydrate malabsorption. As mentioned above, many people are affected by malabsorption, but by no means are all symptomatic. Improvement after dietary adjustment and recurrence of symptoms when dietary errors occur is still the best way of confirming the diagnosis. There have been few studies that have documented the beneficial effects of dietary changes in patients with fructose and sorbitol malabsorption. In addition, there are methodological problems in all of these studies, including those by our own group. The diet itself is sometimes not clearly described; patient compliance with the diet is

difficult to assess; there are no control groups, so that the role of a placebo effect is difficult to assess; and there are inadequacies in the way in which the patients' dietary behavior is recorded.

Nevertheless, the available data are fairly consistent. In our own study, which had both prospective and retrospective parts (in order to assess the placebo effect), symptomatic improvement of 60%-100%, depending on the degree of patient compliance, was observed to a similar degree in both arms of the study^[38]. Fernandez-Banares *et al*^[39] have reported similar results and were able to show that the treatment effect was long-lasting, with the positive effects of the diet being maintained at 12 mo. Shepherd and Gibson have confirmed these data in a group of 62 patients^[40]. The largest study (so far available only as an abstract, so far as we are aware), including 1320 patients, documented an improvement after dietary changes in 87.5% of the patients^[41]. In a more recent study including 90 selected patients with non-specific abdominal complaints, we observed a high rate of carbohydrate malabsorption (lactose 34%, fructose 61%, and sorbitol 91%)^[42]. After dietary information had been provided, the patients reported significant improvement in 75% of cases, depending on the extent of compliance. The study by Ledochowski *et al*^[24], which has shown that dietary changes in patients with fructose malabsorption have a beneficial effect on gastrointestinal complaints and also on mood, as documented by improvements in depression score, has already been mentioned above. However, there are also contradictory data that show that only avoiding one sugar (with proven malabsorption) may not be sufficient for patients with irritable bowel syndrome^[43,44].

The phenomenon that patients with non-specific abdominal complaints frequently report improvement in their symptoms for several weeks after colonoscopy (thought to be due to bowel preparation with cleansing of the colon) underlines the possible role of bacteria in the colon. Treatments involving antibiotics^[45,46], attempts to reduce colonic bacterial fermentation^[47], and administration of probiotics^[48] therefore require further investigation.

Open questions

Although carbohydrate malabsorption appears to play an important role in patients suffering from non-specific abdominal complaints, there are several problems with this diagnosis that should not be overlooked. In the first place, diagnosis using hydrogen tests is still problematic, particularly if the increase is borderline. The threshold value of 20 p.p.m. requires further evaluation, as there may be significant variations in methane production in the colon, among other factors. Moreover, hydrogen tests are not capable of quantifying the amount of malabsorption. Symptoms do not always occur during the test, even in patients who are considered to be symptomatic. Assessing the clinical relevance of the diagnosis may therefore sometimes be difficult.

The etiology of the symptoms is not fully understood. If the data published by our own group, which show that symptoms occur after each malabsorbed sugar or after none (see above), are reproducible, it would theoretically mean that no patient should become symptom-free, since

physiological malabsorption of carbohydrates is essential for the colonocytes. Moreover, if the data showing that there is a beneficial effect of carbohydrate malabsorption on the short-chain free fatty acid ratio, and especially on the increase in butyrate, are confirmed^[29], this might also raise doubts about whether treatment is advantageous at all in the longer term.

CONCLUSION

Carbohydrate malabsorption is a common phenomenon not only in patients, but also in healthy individuals. In patients suffering from non-specific abdominal complaints, it is therefore very difficult sometimes to clarify whether the malabsorption that has been detected is definitely the cause of the symptoms. On the other hand, many patients with these symptoms and confirmed malabsorption appear to benefit considerably from dietary interventions, thus underlining the importance of diagnosing carbohydrate malabsorption. Another advantage of diagnostic work-up, including hydrogen exhalation tests, is that the results may provide evidence of other diseases that feature in the differential diagnosis of non-specific abdominal complaints, such as intestinal bacterial overgrowth or alterations in the orocecal transit times.

As pointed out above, however, there are still a considerable number of open questions in this field, so that further controlled studies are urgently necessary. The first step for the scientific community is to accept that, in addition to the widely accepted condition of lactose malabsorption, malabsorption of other sugars such as fructose and sorbitol also occurs and may be at least as important, or perhaps even more, than lactose malabsorption.

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