Mistakes in the management of carbohydrate intolerance and how to avoid them

Heinz F. Hammer, Johann Hammer and Mark Fox

Carbohydrates not absorbed in the small intestine are fermented by colonic bacteria to organic acids and gases[1] (e.g. carbon dioxide, hydrogen and methane), part of which is absorbed in the colon, the other part remaining in the lumen.[2,3] Large interindividual differences have been demonstrated for the production of such acids and gas.[4,5] Carbohydrate malabsorption can be diagnosed by using the hydrogen breath test, because the gases produced after administration of a provocative dose of carbohydrate are unique products of bacterial carbohydrate fermentation.[6,7]

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Fermentation products are thought to cause symptoms of bloating, abdominal pain, diarrhoea and nausea;[8] however, the role of the intestine in the pathogenesis of such symptoms is unclear in both adults and children.[9–11] Indeed, an important discrepancy between the degree of malabsorption and symptom severity has been established.[12,13]

Here, we discuss mistakes that are made when managing patients who have bloating, abdominal pain, diarrhoea and nausea, in whom carbohydrate malabsorption or intolerance have been diagnosed or are thought to contribute to the condition. The discussion focuses on lactose malabsorption, because of its well-known pathophysiology and high prevalence; however, similar mechanisms apply for intolerances to other poorly-absorbed fermentable, oligosaccharides, disaccharides, monosaccharides and polyols (sugar alcohols) (FODMAPs) and related artificial sweeteners. As treatment focuses on symptom relief, evaluation of complaints that are presumably related to carbohydrate ingestion has to place emphasis on symptom assessment.[14]

Mistake 1 Failing to distinguish food intolerance from food allergy

Many patients report having a reaction to food and that may be ascribed to an allergy; however, especially in adults, most food reactions are caused by intolerance. For practical purposes, patients have to be made aware of the difference between food allergy and food intolerance.

Food allergy is caused by an apparently dose-independent reaction of the immune system that can affect many organs and systems, and in some cases can be life threatening. By contrast, the symptoms and clinical consequences of food intolerance are dose dependent, generally less serious and are often limited to digestive problems.[15,16]

Mechanism	Example
Maldigestion, malabsorption	Absence of an enzyme needed for digestion (e.g. lactase deficiency)
Physiologically incomplete absorption	FODMAPs, magnesium
Dysregulated handling of bowel contents	IBS
Reaction to the products of digestion	Histamine, gas, short-chain fatty acids
Sensitivity to food additives or contents	Sorbitol, fructose, xylitol
Concurrent medical conditions	Previous surgery, concurrent diseases
Concurrent psychological conditions	Stress, psychological factors

Table 1 | Mechanisms involved in food intolerance.

Symptom development and severity in those with a food intolerance depends on the amount of the food ingested, the digestion and

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Heinz F. Hammer is Associate Professor at the Medical University Graz, Department of Gastroenterology and Hepatology, Graz, Austria. Johann Hammer is Associate Professor at the Medical University Vienna, University of Internal Medicine III, Department of Gastroenterology and Hepatology, Vienna, Austria. Mark Fox is Professor of Gastroenterology at the University of Zürich, Zürich, Switzerland and lead physician at Digestive Function: Basel, the Laboratory and Clinic for Motility Disorders and Functional GI Disease at Klinik Arlesheim, Arlesheim, Basel-Land, Switzerland.
Correspondence to: heinz.hammer@medunigraz.at

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assimilation of the food, and whether or not this process is tolerated. Different mechanisms that may be involved in food intolerance are shown in Table 1.

In the case of food allergy, the responsible allergen has to be completely avoided. By contrast, in the case of intolerance the focus is on reducing the intake of the offending food. In addition, drugs that assist the digestion of certain foods or treat underlying conditions can be administered as part of the medical treatment for those with a food intolerance.

Mistake 2 Not considering the mechanisms underlying the relationship between food ingestion and symptom development

Patients who notice abdominal symptoms after eating a particular food frequently consider that food to be the direct cause of symptoms, and may rely on its avoidance to treat their symptoms. However, in clinical practice, the association between food intake and symptom development may have different causal relationships (Table 2).[17,18] These relationships must be considered so that diagnostic evaluation and treatment of any underlying disease is not delayed.

In patients who are lactose intolerant, it may be unclear whether acquired primary lactase deficiency or another small intestinal disorder (e.g. chronic infection, coeliac disease or inflammatory bowel disease (IBD)) is responsible. Therefore, it may be necessary to exclude other malabsorptive disorders, especially if the patient's ethnic background is associated with a low prevalence of acquired primary lactase deficiency.

For practical purposes, food intolerances may have different functional or organic backgrounds, the clinical consequences of which range from being harmless nuisances to diseases requiring medical evaluation and treatment.[15,16]

Mistake 3 Assuming that the mechanisms underlying intolerance are completely understood

The typical symptoms of lactose malabsorption (i.e. abdominal pain, bloating, flatulence and diarrhoea) are generally attributed to bacterial fermentation of lactose in the large intestine. Fermentation products increase the osmotic gradient, causing water to shift into the lumen to restore an isotonic milieu[19] that may contribute to abdominal pain sensation and diarrhoea.[4] The gases released by colonic fermentation contribute to the sensation of bloating and to flatulence.[5]

Although colonic events have a major role in symptom generation, some symptoms develop rapidly, before intestinal contents have reached the colon. This may be a consequence of an overactive gastro-colic reflex or it may indicate that distension of the small intestine by fluids[20,21] can also contribute to some symptoms after a carbohydrate load. The latter mechanism is marked in the presence of small intestinal bacterial overgrowth (SIBO), in which fermentation and gas production occur already in the mid-gut.[22] Notwithstanding the above, the perception of bloating is not determined only by the amount of gas in the intestine.[5] Increased visceral sensitivity to the presence of gas is a very frequent finding in patients who have functional gastrointestinal disorders and complain of bloating.[23]

Practically speaking, it is important to remember that different factors are responsible for the development of symptoms in patients with carbohydrate malabsorption. The complex interplay between products of bacterial carbohydrate metabolism and the structures and functions of the gastrointestinal tract results in marked interindividual differences in the sensitivity to incompletely absorbed carbohydrates and symptom development.

Mistake 4 Not considering the role of all poorly absorbed, fermentable carbohydrates in patients with suspected carbohydrate intolerance

In addition to the commonly considered simple carbohydrates lactose or fructose, many other incompletely absorbed carbohydrates may reach the colon and be fermented by bacteria.[24,25] Indeed, the mechanisms by which lactose or fructose malabsorption lead to intolerance are shared by many other types of carbohydrate, including starch and nonstarch polysaccharides and FODMAPs.[20,25,26]

Reducing dietary FODMAPs in general can be recommended to patients who have a documented lactose or fructose intolerance but do not gain adequate relief on a diet free from lactose or fructose. Subsequently, individual foods are slowly reintroduced into the diet. Documenting individual intolerances can provide a focus on specific dietary components–thereby reducing the complexity of the diet and its potentially restrictive effect on costs, quality of life, long-term safety, nutritional adequacy and faecal microbiota.[18]

Mistake 5 Ignoring the possibility that comorbidities influence symptoms in patients with carbohydrate malabsorption

Abdominal pain, bloating and a variable bowel habit are nonspecific symptoms that can occur with various functional or organic diseases,

Causal relationship	Example	Clinical consequence
Food content is the cause of a disease	Food allergy, coeliac disease, alcoholic pancreatitis	Remove the offending food
Symptoms after food ingestion are a clinical manifestation of an underlying gastrointestinal, biliopancreatic or hepatic disease or abnormality	Biliary disease, irritable bowel syndrome (IBS), functional dyspepsia, small bowel obstruction, lactase deficiency	Detect and treat the underlying disease, reduce the offending food
Food contents stimulate or alter normal functions, possibly with the prerequisite of perturbed gastrointestinal function	Caffeine, fat, capsaicin (chilli), glutamate, histamine	Symptoms unrelated to a disease, reduce the offending food
Excessive ingestion of certain foods overwhelm normal physiologic absorptive capacities	FODMAPs, magnesium	Symptoms unrelated to a disease, reduce the offending food component

Table 2 | Causal relationships between food intake and the gastrointestinal tract in the pathogenesis of food-associated symptoms.

with or without carbohydrate malabsorption. In particular, intolerance of numerous foods is a hallmark of irritable bowel syndrome (IBS).[27] Potential comorbidities must be considered to better understand the treatment options for patients who have these symptoms.

Patient history may provide a clue towards understanding the pathogenesis of their symptoms. Those who have food intolerances with a defined aetiology, such as primary lactase deficiency, tend to have discrete symptoms that occur only after ingestion of the respective food. By contrast, those who have a functional aetiology, such as IBS, often complain of multiple gastrointestinal and other symptoms that change over time (e.g. dyspepsia, chronic headache and fibromyalgia).[28,29]

There is a large overlap between the occurrence of lactose malabsorption and IBS, both of which are common conditions worldwide. Altering dietary intake of fermentable carbohydrates, including lactose in patients with lactase deficiency, is known to alter symptoms in IBS.[30] In this condition, the risk of developing symptoms after lactose ingestion is related not only to the dose of lactose ingested but also to patient factors.[31] These factors include a history of abdominal surgery or recent gastrointestinal disease,[32] evidence of an activated mucosal immune system (e.g. increased mast cells in biopsy samples from the small intestine and colon),[33] the presence of SIBO[22] and colonic dysbiosis (as determined by excessive hydrogen production during a lactose hydrogen breath test [HBT]).[31,34] Psychosocial factors, such as the presence of psychological disease and/or high levels of 'life event stress', are also important.[32] Many of these factors, especially inflammation and anxiety, are associated with visceral hypersensitivity in patients with IBS.

In individuals with lactose malabsorption various somatic and psychosocial factors impact on the risk of symptom development after ingestion of small to moderate amounts of lactose (i.e. clinically relevant lactose intolerance). The shared aetiology of these conditions suggests that lactose intolerance is a form of functional bowel disease and, indeed, food intolerance is recognized as an important cause of symptoms in many IBS patients.[31]

In lactose or fructose intolerant patients whose symptoms persist while on an exclusion diet, other factors and diseases contributing to the pathogenesis of symptoms have to be considered and treated accordingly, typically the functional bowel disorders IBS and functional dyspepsia. A reduction of FODMAPs in the diet has been shown to reduce symptoms in patients with IBS.[35,36]

Mistake 6 Putting too much trust in breath testing

HBTs are the most commonly used tests for evaluating lactose malabsorption.[6] Diagnostic evaluation with the HBT and symptom assessment by questionnaire can be performed independent of the carbohydrate source or its chemical constitution, which makes it possible to also test for incomplete absorption of carbohydrates other than lactose.

A false-positive HBT, often characterized by a rapid increase in the concentration of hydrogen in the breath, can result from poor oral hygiene, SIBO or rapid intestinal transit.[6,37,38] Conversely, a false-negative HBT result occurs in at least 10% of patients because their colonic microbiome does not produce sufficient hydrogen to be detected by current technology.[6,39] If suspected, this can be confirmed by a lack of increase in breath hydrogen excretion in a lactulose HBT (lactulose being a disaccharide not digested by the small bowel).[39] In clinical trials, the measurement of methane in addition to hydrogen improves test sensitivity in hydrogen nonexcretors;[40,41] however, in practice, measurement of methane increases the cost and complexity of the test. False negatives may also occur if orocoecal transit time is prolonged and lactose enters the large bowel after the test is completed, usually after 3 hours.[39]

Interpreting the findings of breath studies is challenging in patients who report abdominal symptoms after carbohydrate ingestion without evidence of malabsorption (i.e. no increase in breath hydrogen). A study of fructose and fructose oligomers showed short-chain and long-chain carbohydrates had different effects in the small intestine and colon,[20] raising the possibility that symptoms after carbohydrate ingestion may occur without carbohydrates having to reach the colon (malabsorption).

Considering the pretest probability of lactase deficiency (according to ethnic background) is helpful. If the pretest probability of lactase deficiency is high, then the occurrence of typical symptoms 30–90 minutes after lactose ingestion may be sufficient to establish the diagnosis, and breath hydrogen may not need to be measured. Conversely, if the pretest probability of lactase deficiency is low, then it is probable that the symptoms represent a nocebo effect (i.e. an adverse response to a nonharmful stimulus) or that the symptoms are elicited in the small bowel without malabsorption being present.

It should also be noted that patients who report symptoms within a few minutes (<10 min) after ingestion of a test carbohydrate are likely to have functional dyspepsia triggered by gastric distention rather than a specific food intolerance.

Mistake 7 Misinterpreting lactase deficiency or lactose malabsorption as lactose intolerance

Various methods are available to assess the different parts of the process that leads from lactose maldigestion to the generation of symptoms (figure 1). These methods include genetic testing for lactase deficiency, determining lactase activity in biopsy samples taken from the small intestine, the HBT and symptom assessment.

A major limitation of the HBT is that after a provocative dose of a carbohydrate has been given symptom assessment is often inadequate. This means that the relationship between ingestion of the carbohydrate and symptom development is not established. The same is true for the other blood and biopsy tests listed above. These tests, therefore, establish lactose malabsorption, lactase deficiency or the genetic predisposition to lactase deficiency,[42] but they do not establish lactose intolerance, which is the main focus of clinical evaluation and treatment of symptomatic patients referred for testing. Furthermore, the HBT is usually performed with very high doses of the test carbohydrate and is not repeated with low doses that may be more relevant.

Given that genetic tests, enzyme activity testing of biopsy samples and breath tests only demonstrate enzyme deficiency, maldigestion or malabsorption, validated symptom assessment is required for assessment of clinically relevant intolerance. Suggestions for adhering to diets or using enzyme supplements (e.g. containing lactase or xylose isomerase[43]) should be limited to cases of documented intolerance, for which the relationship between ingestion of a carbohydrate and development of symptoms is validated.

Mistake 8 Relying on unvalidated symptom assessment

Documentation of intolerance is the main indication for dietary or drug treatment and symptom assessments during HBT measurements should be standardized to avoid bias.[8,12] Test-specific symptom questionnaires for the assessment of symptoms during breath tests have been developed and validated for both the paediatric and the adult populations.[11,44–46] These should be preferred to the use of unvalidated,[19] self-made symptom assessment[13] or generic gastrointestinal questionnaires that

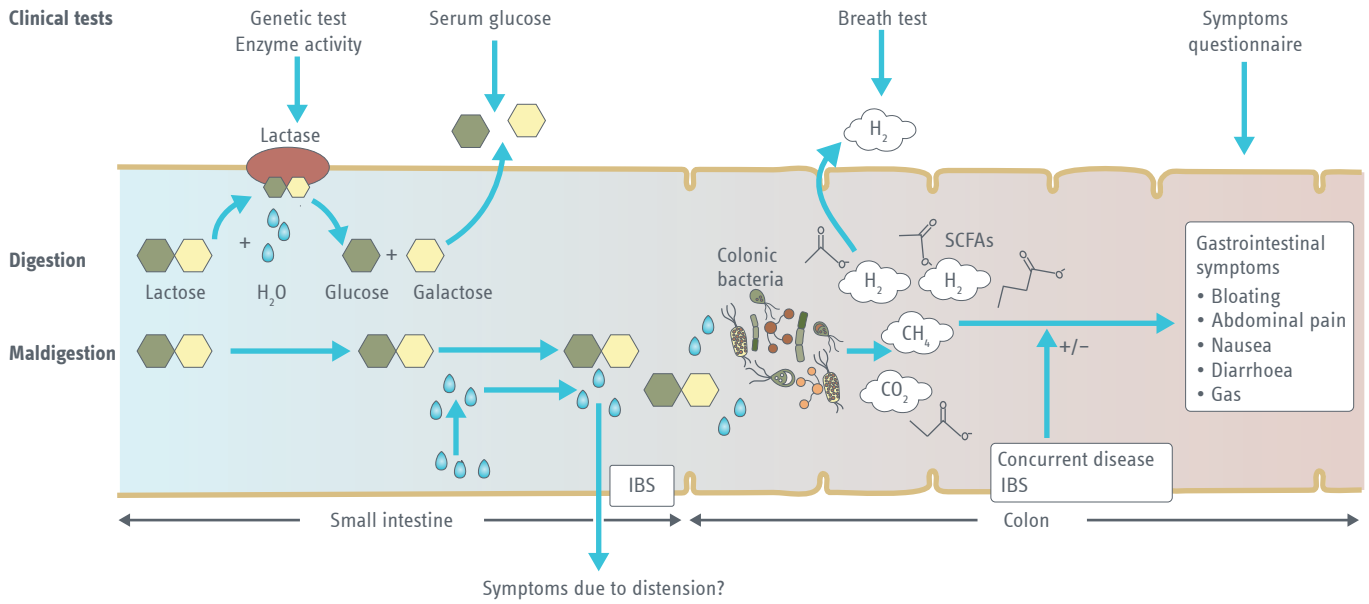

Figure 1 | Processes involved in lactose digestion, malabsorption and intolerance. In individuals with lactase persistence, lactose is digested by lactase to glucose and galactose, which are absorbed from the small intestine. Lactase activity can be measured in biopsy samples and genetic testing can detect mutations associated with lactase persistence. Glucose absorption can be demonstrated by a rise in serum glucose concentration. In individuals with lactase deficiency, lactose enters lower parts of the small and the large intestine along with water. Colonic bacteria then ferment lactose to generate gas and short-chain fatty acids (SCFAs). Absorbed hydrogen can be measured in the breath via the hydrogen breath test (HBT). The interplay with concurrent diseases, such as irritable bowel syndrome (IBS), leads to the development of gastrointestinal symptoms.

are not specifically targeted to the population to be studied and the topic of carbohydrate intolerance.[47,48]

Unvalidated symptom questionnaires should be avoided, as it is not known if these methods really measure what is intended and if the data are obtained in a consistent, uniform manner that can be compared to other centres. Limited confidence in the results impacts both the clinical interpretation of individual lactose breath test results—in terms of intolerance testing—and reliance on the results of scientific reports.

Mistake 9 Overlooking the dose dependency of symptom development

Patients sometimes assume that small amounts of lactose, for example those present as additives in drugs, cause symptoms of intolerance. Some pharmaceutical companies have recognised this as a potential market and advertise their drugs as being lactose free. As such, it is clinically relevant to understand the dose of lactose required to induce notable symptoms (i.e. intolerance).

Increasing the dose of lactose during a lactose challenge increases the number of individuals who report abdominal symptoms.[14] In one double blind study, ingestion of less than 10g lactose rarely induced abdominal symptoms in healthy controls, but 73% reported symptoms after ingestion of 40g lactose, which approximates the dose most often applied in clinical studies (35–50g). It should also be noted that when lactose malabsorbers ingest lactose with other nutrients, they usually tolerate the consumption of higher doses of lactose.[49]

Of the symptoms related to carbohydrate malabsorption, the pathophysiology of carbohydrate-induced diarrhoea is probably the best studied. Diarrhoeal response to a disaccharide load depends on the amount of malabsorbed carbohydrate.[4] The colon has a large capacity to absorb fermentation products and thus to avoid faecal excretion of osmotic loads.[19] This colonic salvage becomes saturated as the quantity of carbohydrates reaching the colon increases. For instance, in healthy individuals, ingestion of 45g of nonabsorbable disaccharide lactulose increased faecal water excretion only minimally. Only when greater than 80g lactulose was ingested, did significant diarrhoea develop.[3,19] The equivalent amount of lactose (45g) can be expected to be partially digested and absorbed in the small intestine even in lactose malabsorbers,[12] making it unlikely that this amount alone is responsible for severe diarrhoea.

Symptom development attributable to carbohydrate malabsorption depends on the amount of carbohydrate reaching the colon. Usually more than 10g of lactose has to be ingested to cause symptoms. When lactose is consumed in divided doses, even higher daily doses may be tolerated.[50] However, the consumed amount of different poorly absorbable carbohydrates from different sources, like dietary fibres or FODMAPs, may be enough to cause symptoms.

Mistake 10 Omitting professional dietary counselling and follow up

Patients for whom there is a clear association between symptoms and lactose ingestion should be educated about appropriate dietary restrictions. Individuals who develop symptoms only after ingestion of dairy products require only a lactose-reduced diet. However, as many carbohydrates other than lactose are incompletely absorbed by the normal small intestine,[24] and because dietary fibre is also metabolized by colonic bacteria, symptom persistence while on a lactose-reduced diet is not uncommon. Extending the diet to include global reduction of other poorly fermentable carbohydrates may be helpful for such patients.[35,51] In particular many patients with IBS and lactose intolerance require advice on a FODMAP-reduced diet rather than 'only' a lactose-reduced diet. Depending on local care provisions, this may be best served by well-trained dietitians, who can provide dietary counselling and follow up. Ideally, clinical decisions regarding dietary treatment should be supported by carbohydrate intolerance documented by the results of a structured

and validated assessment of symptoms after ingestion of the test carbohydrate.[11,44]

Patients should be informed that the doses of lactose usually consumed (up to a cup of milk) do not normally cause symptoms when ingested with a meal, even in IBS patients.[52]

If symptoms persist after ingestion of small amounts of dairy products, then the possibility of milk protein allergy, rather than lactose intolerance should be considered. Intolerance to fat is also prevalent in patients with functional gastrointestinal disorders and can be another reason why symptoms persist despite appropriate dietary restriction.[53,54]

Regular or daily consumption of lactose-containing food may be better tolerated than intermittent consumption.[14] Yogurt may be tolerated by such patients[55] and provide a good source of calcium. Alternatively, supplementation of dairy products with lactase of microbiological origin can be suggested.[56] The results of controlled studies on the use of lactose-reduced products or lactase capsules are, however, inconsistent.[14]

The rapid increase in the prevalence of obesity and guidelines that suggest limiting the consumption of simple sugars has increased interest in alternative sweeteners.[57] Some of these are poorly absorbed carbohydrates, such as sorbitol or xylitol, which may result in similar symptoms to fructose or lactose.

Dietary counselling must consider the supply of other nutrients, which may be affected by long-term adherence to a specific diet. For example, lactase deficiency may be a risk factor for the development of osteoporosis and bone fractures, either owing to the avoidance of dairy products[58] or interference with calcium absorption.[59] Patients for whom a lactose-reduced diet is recommended should be advised to add calcium from other dietary sources. Patients in whom a FODMAP-reduced diet is suggested should be made aware that there are limited data on the long-term safety of this diet, with respect to nutritional adequacy and effects on faecal microbiota. Professional dietary counselling can help patients to adapt their diet to the severity of their symptoms and assist them in meeting their long-term dietary needs and nutritional requirements.

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Your carbohydrate intolerance briefing

UEG Week

- "The low FODMAP diet: Selecting the right candidate" Presentation at UEG Week 2018 [https://www.ueg.eu/education/document/the-low-fodmap-diet-selecting-the-right-candidate/185141/].
- "Carbohydrate intolerance" Presentation at UEG Week 2017 [https://www.ueg.eu/education/document/carbohydrate-intolerance/155527/].
- "Breath testing for lactose intolerance is the way forward / Genetic testing for lactose intolerance is the way forward" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/breath-test-for-lactose-intolerance-is-the-way-forward-genetic-testing-for-lactose-intolerance-is-the-way-forward/109166/]
- "Food intolerance" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/food-intolerance/109281/].