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Fructose, trehalose and sorbitol malabsorption

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Abstract. **Carbohydrate malabsorption is a frequent clinical condition, often associated with abdominal symptoms. Although lactose represents the most commonly malabsorbed sugar, also other carbohydrates, such as fructose, trehalose and sorbitol may be incorrectly absorbed in the small intestine.**

Fructose malabsorption seems more common in patients with functional bowel disease, even if randomized and controlled studies on these topic were few and on small samples. Interpretation of breath hydrogen testing is difficult. In particular, neither studies comparing this test with a gold standard, nor validated doses and concentrations to be used, are available. Trehalose malabsoption due to trehalase deficiency represents a very rare condition and available studies do not support its relevance in clinical practice. Sorbitol absorption is dose and concentration related, and depends on the entity of intestinal absorption surface. Nevertheless, the finding of its malabsorption is not expression of a specific cause of intestinal bowel damage.

From available data, it is not possible to draw definite conclusions about clinical relevance of fructose, trehalose and sorbitol malabsorption, as well as, about diagnostic accuracy of commonly used tests to detect all these conditions. On the other hand, in patients who refer abdominal discomfort after ingestion of different carbohydrate-containing foods, a small intestinal bacterial overgrowth, should be promptly considered. This is because the large amount of intestinal bacteria may unspecifically ferment sugars, causing an abnormal H2 production and consequently a misleading diagnosis of sugar malabsorption.

KeyWords:
Fructose, Trehalose, Sorbitol, Malabsorption, Breath test.

Introduction

Carbohydrate malabsorption is a frequent clinical condition, often associated with abdominal symptoms. Although lactose represents the most commonly malabsorbed sugar and the most of studies are focused on this condition, also other carbohydrates, such as fructose, trehalose and sorbitol may be incorrectly absorbed in the small intestine.

Whether malabsorption of these sugars may be clinically relevant and may be detected by validate diagnostic techniques, will represent the topic of this paper.

It is well known that unabsorbed carbohydrates reaching the colon are fermented by the colonic microflora to short-chain fatty acids and to hydrogen, carbon dioxide and methane[1]. They also cause an increased osmotic load in the bowel lumen, leading to a greater secretion of electrolytes and fluids[1-2]. Sugar malabsorption does not necessarily result in the development of intolerance symptoms (e.g. abdominal bloating and pain, flatulence, nausea, borborygmi, diarrhea), the condition occurring, for example, only in about one third to half of lactose maldigesters[3].

Fructose

Fructose is a six-carbon monosaccharide that is ingested in three forms: pure monosaccharide; disaccharide, the sucrose, where fructose is complexed with glucose; and polymerized forms as oligosaccharides and polysaccharides[4]. Fructose is naturally present in fruits and vegetables, such as apples, peaches, prunes etc. It is also produced enzymatically from corn as high fructose corn syrup and this form of fructose is commonly used in many food sweeteners, soft drinks, diabetic and diet foods[5].

In the last years, there has been a marked rise in free frucose ingestion[4-6]. In general, the daily intake of fructose varies across the world, depending significantly on dietary habits and the use of fructose as a sweetener[5]. A United States Department of Agriculture study estimated that the annual consumption of fructose has risen from less than a ton in 1966 to 8.8 million tons in 2003[6].

Unlike other sugars such as sucrose or lactose, which are digested by sucrase or lactase enzymes produced by the intestinal brush border, fructose is not digested by a specific enzyme but is ab-

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sorbed, by a "diffusional pathway", dose and concentration related[4-6]. Fructose is transported by facilitated diffusion by GLUT 5[7], a protein able to drive net movement across the membrane through the energy of the solute concentration gradient. GLUT 5 is specific for fructose and cannot transport glucose or galactose[6]. When fructose is ingested in large quantities, the capacity of the gut to absorb fructose can be easily overwhelmed leading to fructose malabsorption and abdominal symptoms[4-7]. More recently, it has been shown that also GLUT-2, a transporter carrying glucose and galactose, may also be involved in fructose absorption by a paracelluar transport system involving opening of tight junctions[4,6]. GLUT-2 is constitutively found on the basolateral membrane, but, under specific conditions, it can also be expressed in the apical membrane[4]. It has been suggested that a way of altering the absorption of free fructose is to modulate the ability of small epithelial cells to insert GLUT-2 into the apical membrane in response to luminary dietary sugars; therefore, the co-ingestion of glucose or galactose considerably enhance fructose absorption[4,6].

Hydrogen breath tests have become a key tool in identifying those who malabsorb sugars. The principle of the test lies in unabsorbed carbohydrate reaching and being fermented by intestinal bacteria which generate hydrogen or methane. As regard fructose malabsorption, interpretation of breath hydrogen testing is difficult, since there are still several issues of concern[4]. Firstly, studies comparing breath test with a gold standard for fructose malabsorption (for example carrier levels), are lacking; then, both for dose and concentration to be administered, as well as, for the optimal cut-off, there is not a univocal opinion[4]. Moreover, there is a lack of information about the prevalence of incomplete absorption of fructose in the healthy population[4-6]. It has been estimated that a dose of 25 g at a concentration of 10% more closely approaches daily intake, whereas in the paediatric population a dose of 1 g/kg has been considered as appropriate[4]. It has been suggested that healthy subjects have the capacity to absorb up to 25 g of fructose, whereas many have incomplete absorption and intolerance with intake of 50 g of fructose[8]. Fructose malabsorption seems more common in patients with functional bowel disease, and can be present in up to 80% of cases[9,10]. However, randomized controlled studies on these topic were few and on small samples, and not showing a greater prevalence of fructose malabsorption among patients with irritable bowel syndrome (IBS) compared with healthy individuals[6], even if there is a consensus that symptoms are more frequent in this group[4-10]. As a consequences, the Rome Consensus Conference on "Methodology and indications of H_2-breath testing in gastrointestinal diseases" stated that fructose breath test is not recommended in clinical practice[11].

Trehalose

Trehalose is a disaccharide composed of two glucose molecules, found in mushrooms, algae and insect haemolymph[12]. Intestinal trehalase, a brush border enzyme, is a beta-galactosidase which catalyses the hydrolysis of trehalose to two glucose molecules for absorption. It is present throughout the small intestine with highest levels in the proximal jejunum[12-13]. Isolated trehalase deficiency represents an autosomic dominant condition, and occurs in at least 8% of the Greenland population[14]. Nevertheless, only three cases have been reported elsewhere, two of whom were first degree relatives.

The high concentration of trehalose in cryptobiotic plants is responsible for their remarkable ability to go through cycles of desiccation and rehydration without injury. This has led to interest by the food industry, as the addition of trehalose to foodstuffs improves the quality of dried food[12].

Up to now, only a study by Arola is available about trehalose malabsorption and H_2 breath test[13]. In this work, a 25-g oral trehalose load test was performed in 64 subjects. Trehalase activity was determined in serum and on a duodenal biopsy specimen and symptoms of intolerance were recorded. Intolerant subjects were best differentiated from tolerant subjects by changes in breath gases (hydrogen and methane) and duodenal trehalase/sucrase ratio. The change in breath gases correlated inversely with duodenal trehalase activity[13]. Nevertheless, no conclusive evidences are still available to support the trehalose H_2 breath test in clinical practice and, therefore, the performance of this test is not recommended[11].

Sorbitol

Sorbitol is a sugar alcohol widespread in plants, particularly in fruits and juice[15]. It is also produced synthetically for commercial purposes by the catalytic reduction of glucose and it is found in sweets, chewing-gum, dietetic food, and

drugs. It does not produce a rise in blood sugar when taken by mouth, and because of its sweetening power it is widely used as a sugar substitute in dietetic food and beverages and as a vehicle for suspending active drugs[15]. Sorbitol is poorly absorbed from the small intestine, as demonstrated by a dose as low at 5 g giving a positive response in more than 50% of subjects tested by H_2 breath testeath hydrogen analysis[15,16].

Sorbitol absorption occurs by a not mediated diffusion pathway, is dose and concentration related, and depends on the entity of intestinal absorption surface. In patients with malabsorption as a result of untreated coeliac disease, the ingestion of the smallest and least concentrated dose used, 5 g in a 2% solution, provoked a highly significant increase in H_2 excretion as compared with healthy subjects[15]. Corazza et al[15] found that all the untreated coeliac patients resulted as sorbitol malabsorbers and this, to a certain extent, was predictable as in villous atrophy and the consequent reduced intestinal surface to absorb sugars.

More studies[17] also suggested the use of sorbitol H_2 breath test in all subclinical/silent coeliac patients, since a strict correlation between cut-off value and histologic lesions. Moreover, sorbitol H_2 breath test was proposed[18] as a better diagnostic tool than antiendomysial antibodies in revealing histological recovery in the follow-up of coeliac patients after the start of gluten-free diet, due to its good correlation with histological damage. Finally, also in screening relatives of coeliac patients, it was proposed as a more effective diagnostic test than serological testing[19].

Therefore, sorbitol H_2 breath test should be effective in detecting small bowel damage with a relevant reduction of absorption surface, but it is not specific for any condition responsible for intestinal malabsorption. Therefore, as stated in the Rome Consensus Conference on " Methodology and indications of H_2-breath testing in gastrointestinal diseases", sorbitol H_2 breath test should not be recommended in clinical practice in both adults and children while its use may be indicated for research purpose[11].

Discussion

It has to been underlined that when a sugar, that is lactose, fructose, trehalose or sorbitol, is malabsorbed, the abdominal clinical picture is unspecific, often mimicking that of IBS, and it does not help for a specific diagnosis. Therefore, physicians and patients should pay attention to which foods are responsible for occurrence of symptoms, i.e. milk and dairy foods for lactose intolerance, or sweet and fruits for fructose or sorbitol intolerance, etc. Nevertheless, it is very common to find patients who refer abdominal discomfort, bloating and pain after ingestion of different carbohydrate-containing foods, such as bread, pasta, pizza, sweets etc. In these cases, a small intestinal bacterial overgrowth (SIBO) should be promptly considered. SIBO is characterized by a wide spectrum of manifestations, ranging from unspecific abdominal symptoms (e.g. bloating, abdominal discomfort, flatulence), very similar to those derived from sugar malabsorption, to less frequent severe generalized malabsorption and nutrient deficiency (diarrhea, steatorrhea, weight loss)[20]. In normal individuals, gut bacteria are primarily located in the colon and in the distal small intestine. In contrast, when SIBO is present, the bacterial population overgrowths proximally into the small intestine[21]. This shift in the fermentation site might lead to falsely abnormal sugar breath test, even in patients with normal absorption ability[21]. A study by Nucera et al[22] found a significant association between positivity to lactulose breath test (used for diagnosis of SIBO), and positivity to H_2 lactose, fructose and sorbitol breath tests. Moreover, the normalization of lactulose breath test one month after antibiotic treatment was associated with a normalization of the majority of previously positive lactose, fructose and sorbitol breath tests. Therefore, in presence of SIBO, the large amount of intestinal bacteria may unspecifically ferment sugars, causing an abnormal H_2 production and consequently a misleading diagnosis of lactose, fructose or sorbitol malabsorption.

The role played by intestinal bacterial flora (and eventually by SIBO) in the pathogenesis of IBS is controversial, with a prevalence of SIBO in patients with IBS fluctuating between 30% and 46%, as compared to 4% in healthy controls[23]. Moreover, antibiotic therapy also led to a significant improvement in IBS symptoms[23]. Pimentel et al showed that in a group of 202 IBS patients with a prevalence of SIBO of about 78%, after eradication therapy, 50% of subjects did not fulfill anymore Rome I criteria for diagnosis of IBS[24].

Therefore, from available data, it is not possible to draw definite conclusions about clinical relevance of fructose, trehalose and sorbitol malabsorption, as well as, about diagnostic accuracy of commonly used tests to detect all these conditions. It is

conceivable to advise physicians facing patients with unspecific abdominal symptoms, to consider the possibility of a SIBO, a more common condition, clinically relevant and susceptible of a specific therapy, before to prescribe useless diagnostic procedures and, most of all, dietetic restrictions.

Conflict of interest

The Authors declare that they have no conflict of interests.

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