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Hereditary Fructose Intolerance in a Pediatric Context

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Abstract: Carbohydrate intolerance is relatively common in childhood, but its diagnosis and management are still quite precarious. Hereditary fructose intolerance (HFI) is an autosomal recessive disease that results in deficiency of the enzyme aldolase B, which contributes to the onset of gastrointestinal and metabolic symptoms, triggered by the ingestion of foods high in fructose, sucrose or sorbitol. Methodology: For the accomplishment of such a study a search of the literature was done from August to September of the year 2018 with publication period of a maximum of 10 years. The theoretical reference was elaborated through the collection of relevant scientific articles on the subject, made in the electronic databases: Scientific Electronic Library Online (SciELO), Pubmed, EBSCOhost and CAPES, from descriptors generated by DeCS: "Fructose Intolerance"; "Child" and its correspondents in English. Thus, 81 articles were obtained and, from the title of the literature and its abstracts, were used. 19 Ademias, articles that were related to the topics covered in this study or whose sample was not composed by humans were also discarded. The diagnosis of HFI is based on the suggestive clinical picture initiated after the ingestion of the fructose, sucrose and sorbitol already mentioned, associated with the use of invasive and noninvasive examinations, but the confirmation is based on the response to the improvement of the symptoms after the restriction of the ingestion of such food, which constitutes the best therapy. Conclusion: Based on the consequences of inadequate management of HFI, it is of fundamental importance that the affected children have an early diagnosis, associated with an adequate nutritional monitoring, which enables an improvement in the quality of life of these individuals, besides preventing important repercussions such as renal and hepatic impairment.

Keywords: Hereditary Intolerance to Fructose, Child and Diet

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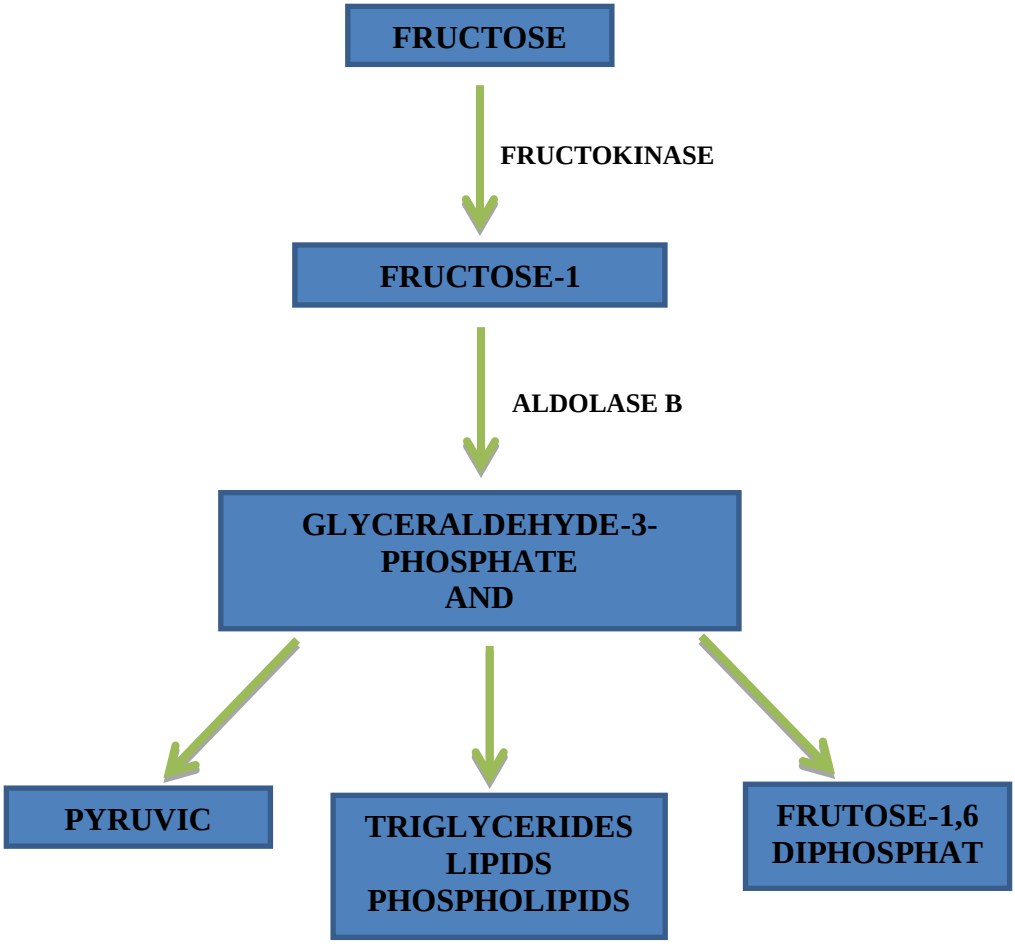
Introduction

Fructose is a carbohydrate, monosaccharide type, with molecular structure in the form of hexose, present in several foods routinely taken by the population, such as fruits, vegetables and honey; it is also used in the food industry in several products such as juices, sweets and sweetened products (Canani et al., 2016) (Mehta and Beg, 2018).

The intestinal absorption of fructose presents two main mechanisms, the first being a facilitated transport mediated by the Glut-5 protein (glucose transporter protein 5), which shows high affinity for fructose and low affinity for glucose, not depending on the action of insulin. The second mechanism has glucose-dependent co-transport, optimizing the absorption of fructose by up to 29%, when it is ingested as sucrose (disaccharide formed by the junction of fructose with glucose) or when ingested together with glucose (Tran, 2017) (Lozinsky et al., 2013) (Chumpitazi and Shulman, 2016).

After intestinal absorption, the fructose is transported through the basolateral enterocyte membrane with the aid of the Glut-2 protein (glucose transporter protein 2), reaching the bloodstream and then the liver through the portal circulation (Canani et al. 2016) (Lozinsky et al., 2013).

In the hepatocyte (Flowchart1), most of the fructose is phosphorylated at carbon 1, mediated by the enzymes ketokinase or fructokinase, but a smaller part is phosphorylated at carbon 6, through hexokinase, which has a higher affinity for glucose. The fructose-1 phosphate, by catalytic action of aldolase B, is cleaved in two trioses, dihydroxyacetone and glyceraldehyde-phosphate, which can follow three pathways: participate in the glycolytic pathway providing pyruvate and energy; be reduced to glycerol, necessary for the synthesis of triacylglycerols, phospholipids and other lipids; or be condensed to form fructose-1,6-diphosphate and form glucose or glycogen from it (Tran, 2017).



Flowchart 1. In the hepatocyte, fructose, through the action of the fructose kinase, is phosphorylated to fructose-1-phosphate, which is cleaved by aldolase B to form dihydroxyacetone phosphate and glyceraldehyde. Subsequently these intermediary metabolites can give rise to pyruvate; lipids, phospholipids and triglycerides; or form the fructose-1,6 diphosphate, which will participate in the formation of glucose and glycogen.

Some individuals may present with Hereditary Fructose Intolerance (HFI), a rare autosomal recessive genetic disorder characterized by the absence of the enzyme called aldolase B (fructose-1-6-diphosphatoaldolase) in the liver, kidney, and intestine. This enzyme catalyzes the phosphorylation of fructose to fructose-1-phosphate, conditioning its deficiency to the intracellular accumulation of fructose metabolites (Păcurar et al., 2017).

These patients present sensitivity to the high fructose diet, including sucrose and sorbitol (Chumpitazi and Shulman, 2016). Symptoms such as vomiting, nausea and sweating, associated with hypoglycemia and metabolic acidosis are characteristic in these patients and, when not treated properly, can have serious repercussions, mainly renal and hepatic insufficiency, and may lead to death (Filippeschi, N. Lopez and Maggiore, 2010) (Quintana et al., 2009).

Methods

For the development of such a study the literature was searched from August to September of the year 2018, with a maximum publication period of 10 years, in order to obtain more updated data.

The theoretical reference was elaborated by means of the collection of relevant scientific articles on the subject, made in the electronic databases: Scientific Electronic Library Online (SciELO), Pubmed, EBSCOhost and CAPES, from descriptors generated by DeCS: "Fructose Intolerance" and "Child" and their correspondents in English. Randomized and controlled trials were considered eligible, focusing on publications in English and Spanish. In addition, articles with irrelevant results, methodology not specified or that were not fully available, were also excluded from this study.

Based on this, 81 articles were obtained, and, from the reading of the title and its abstracts, 21 publications were selected, however 19 were used, due to the duplicity of 2 articles. In addition, scientific articles were used as criteria for inclusion in the clinical characteristics, diagnostic criteria, differential diagnoses and treatment of hereditary dysfunction related to hereditary fructose intolerance in the pediatric age group. Discarded articles that were not topics covered on this study or whose sample was composed of animals.

Discussion

HFI, also called fructose, is an enzymatic disorder with an autosomal recessive pattern, characterized by a breakdown in fructose metabolism, characterized by mutations in the ALDOB (aldolase B, fructosebisphosphate) gene, causing aldolase B deficiency, responsible for cleavage of the fructose-1-phosphate, in the kidneys, intestine and liver (Boghossian, Alahakoon and Tchan, 2017). Its incidence is approximately 1: 20,000 live births, with the same distribution between the sexes, and may vary according to the ethnicity studied (LI et al., 2018) (Bharadia and Shivpur, 2012).

The symptoms of these patients are usually triggered in infants, especially after the first six months, with the introduction of foods rich in fructose, sucrose or sorbitol,

such as fruits, juices, vegetables and honey (Coffee and Tolan, 2010) (Tsampalieros et al., 2008).

Due to the enzymatic defect of aldolase B, there is an accumulation of fructose-1-phosphate, which is osmotically active, producing acute symptoms such as abdominal distension, pain, cramps, vomiting and diarrhea. In addition, metabolic alterations such as hypophosphatemia, hyperlactatemia and hyperuricemia may be present due to the ability of fructose-1-phosphate to sequester phosphate and to eliminate adenosine triphosphate (ATP) and phosphate (El-Shabrawi and Kamal, 2011).

However, the occurrence of jaundice, pallor, hepatomegaly, changes in growth, seizures and shock, due to these metabolic alterations, are also described in the literature (Valadares et al., 2015). Another important repercussion is the decrease in the formation of glucose and glycogen, and interruption of gluconeogenesis and glycogenolysis, which can trigger severe episodes of hypoglycemia (Tran, 2017).

In addition, if not diagnosed early, people with HFI may progress with hepatomegaly, liver failure, renal dysfunction, coma and even death. (Coffee and Tolan, 2010).

The diagnosis is suspected in children with symptoms such as vomiting, diarrhea and abdominal distention, with no apparent cause, especially if there are episodes of postprandial hypoglycemia, which is often described as pre-prandial due to short feeding intervals in infants (Li et al., 2018). In addition, when such symptoms are accompanied by metabolic disorders (lactic acidosis), electrolytes, or even hepatic or renal dysfunction, clinical suspicion becomes even more relevant for the diagnosis of HFI (Tran, 2017).

The expired hydrogen test is part of the arsenal of tests that may aid in the diagnosis of fructose intolerance, whereby produced H2 is measured noninvasively in expired breath samples following the ingestion of a standardized dose of fructose dissolved in water (Canani et al., 2016). The test is considered positive by an increase of 20 ppm H 2 above the baseline value, twice consecutive, associated with symptoms such as abdominal discomfort after the test dose consumption (Sánchez-Ávila et al., 2016; Wilson and Hill, 2014).

However, a negative result does not exclude a satisfactory response to fructose restriction, therefore, hydrogen breath testing is not an appropriate diagnostic medium to predict diet response (Lozinsky et al., 2013). This test is based on the fact that normal intestinal flora metabolizes these sugars into short chain fatty acids and hydrogen. When the monosaccharide is not absorbed in the small intestine, this reaction occurs with

greater intensity and the hydrogen reaches the splenic venous circulation by diffusion through the intestinal wall, and is then transported through the portal system to the liver, systemic circulation and, finally, exhaled through the lungs, where high values of H2 are verified (Teitelbaum and Ubhrani, 2010; Mehta and Beg., 2018).

Diagnostic research also includes research on reducing substances in the urine or analysis of carbohydrates in the urine by thin-layer chromatography, which can identify urinary fructose. In addition, an examination such as thin-layer chromatography has a higher specificity than the presence of reducing substances in the urine, however, it is difficult to reach, being available only in reference laboratories, and it is useful to report the presence of fructose in the diet (Li et al., 2018).

The confirmatory diagnosis is based on the molecular analysis of the Aldob gene. If no mutation can be found despite a strong clinical and nutritional history suggestive of HFI, the demonstration of deficient aldolase activity (<10%) in the liver sample will confirm the diagnosis (Tran, 2017; Valadares et al., 2015).

Another test that presents good diagnostic accuracy is the intravenous fructose tolerance test; however, due to the risk of severe and possibly fatal metabolic effects induced by fructose infusion and the lack of availability of D-fructose for intravenous use, this test is being increasingly used (Tran, 2017).

Inborn errors of metabolism such as tyrosinemia, galactosemia, glycogen storage disorders and Wilson's disease are important diagnostic differences, so they deserve to be investigated. In addition, hepatitis, liver tumors, intrauterine infections and sepsis should also be considered (Valadares et al., 2015). Lactose intolerance can also be considered a differential diagnosis because it presents some unusual symptoms associated with food intake, with anamnesis, the hydrogen test expired and the therapeutic test with the suspension of lactose-rich foods the pillars for its diagnosis (Canani et al., 2016).

Some eating disorders present similar treatment to HFI, such as fructose malabsorption, which is a functional problem of the small intestine, triggered by a decrease in fructose absorption capacity, and may be caused by the excessive intake of fructose and consequent disorders in the intestinal microbiota or even to be secondary to an underlying intestinal disease such as celiac disease (Canani et al., 2016). Its symptoms are like those of the HFI, but with a lower intensity, being more related to emetic episodes, abdominal pain, bloating, abdominal distension and diarrhea after ingestion of foods rich in fructose, sucrose or sorbitol (Lozinsky et al., 2013). The test of expiratory hydrogen can be used to aid in the diagnosis, but the therapeutic test with the suspension

of foods rich in fructose presents a greater diagnostic and therapeutic accuracy (Yüce et al., 2016; Canani et al., 2016).

If there is evidence of HFI, according to clinical history and laboratory tests, a diet free of foods containing fructose, sucrose and sorbitol should be instituted in the diet of these children, which is the main form of treatment, which presents the best efficacy indexes (El Shabrawi and Kamal, 2011).

The established dietary goals are difficult due to the high concentration of fructose in foods eaten in children's daily life, such as fruits, vegetables, honey, infant formulas and pharmaceuticals, as shown in Table 1. However, medical and nutritional monitoring, as well as a good clarification of the parents, is fundamental for the adequate management of this disease. Levels considered to be a standard of fructose restriction in individuals with HFI have not been established, as some patients may reach levels that do not compromise (or regulate) liver and renal function, while others are symptomatic despite food restriction (El-Shabrawi and Kamal, 2011).

Children with HFI, if not diagnosed early, may present with metabolic disorders, gastrointestinal and systemic symptoms with important repercussions, and may often progress to hepatic and renal failure and even death, but if diagnosed early and presented good adherence to treatment, these individuals have a normal life with an excellent prognosis (Li et al., 2018).

Table 1. Foods Allowed and Not Allowed in Children with HFI

Foods	Allowed	Not allowed
Milk and derivatives	Sugar-free cow's milk, sugar-free white cheese and natural cheeses	Yogurt with fruits
Products of animal origin	Meat, fish, chicken and eggs	Sausages, (ham, pates,etc.)
Fruits	None	All fresh fruits, juices or canned
Vegetables	Pod, zucchini, green salad, spinach, celery, leek, asparagus, watercress and chives	Chickpeas, lentils, fava and dry peas
Sugar	Glucose, maltose and unsweetened cocoa	Sucrose, fructose, sorbitol, honey, chocolate and candies
Fats	Butter, margarine, bacon and lard	None
Beverage	Tea, coffee, mineral water and breast milk	Fruit juices, chocolate milk and dairy drinks with sugar

Source: Modified from:
(Canani *et al.*, 2016)

Conclusion

Thus, it can be concluded that HFI is an autosomal recessive disease, culminating with metabolic alterations involving the metabolism of fructose, due to a genetic alteration that affects the ALDOB gene, leading to a deficiency of the enzyme aldolase B.

As a result of these changes in fructose metabolism, patients with HFI may present with symptoms such as abdominal pain, vomiting, abdominal differentiation, diarrhea and metabolic disorders, after the ingestion of foods rich in fructose, sucrose and sorbitol. The early diagnosis becomes of extreme importance, which is characterized by the clinic of suggestive symptoms after the ingestion of such substances, associated with laboratory tests that contribute to the diagnosis.

The treatment consists in the restriction of the food intake with the presence of fructose and its derivatives, with the aim of improving the life qualities of the patients, besides avoiding unfavorable outcomes such as renal, hepatic and even death.

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