Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on Hereditary Fructose Intolerance (HFI), or aldolase B deficiency, and fructose malabsorption (intestinal fructose intolerance)

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Abstract

Hereditary Fructose Intolerance (HFI), also known as aldolase B deficiency, is an inherited metabolic disorder caused by the deficiency of that enzyme, which participates in the fructose metabolism in the liver, kidneys and small intestine. Aldolase B deficiency brings about the accumulation of fructose-1-phosphate in these organs, which can lead to a series of symptoms such as nausea, vomiting, abdominal pain, hypoglycaemia, liver dysfunction, kidney failure, growth retardation in children and even death, as a result of metabolic toxicity.

On the other hand, fructose malabsorption (intestinal fructose intolerance), a disorder that is in-

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creasingly frequent in our society, occurs when there is a deficiency, in the intestinal mucosa, of the transporter protein that allows its absorption in the small intestine, so that the excess of non-assimilated sugars passes to the colon, where the bacteria break them down forming acids, gas and water, which are what cause symptoms such as flatulence, abdominal pain/distension or diarrhoea.

These are disorders in which the metabolism and absorption of fructose, a sugar present in fruits, vegetables and honey, in sucrose or table sugar and in processed foods that contain sources of fructose, such as, for example, sorbitol, maltitol or glucose syrup, used in the food industry for their sweetening properties, are compromised.

Both conditions require dietary restrictions to control symptoms and prevent complications, which implies the elimination of fructose from the diet. However, this dietary restriction that involves eliminating, for example, fruits, vegetables and other sources of fructose, can lead to nutritional deficiencies and affect the quality of life of affected people. The lack of information on the fructose content and its sources in food labelling, especially of processed foods, poses a direct risk of accidental ingestion, with consequences that can be serious. Providing this information would be key to allowing consumers to make informed choices about the foods they buy and consume and, therefore, for the appropriate monitoring of an adequate fructose-restrictive diet.

The Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) concludes that, to improve the health and wellbeing of people with HFI and fructose malabsorption, it is important to educate and raise awareness among consumers, health professionals and the food industry about the health risks of these disorders; perform adequate personalised dietary guidance by competent health professionals in the field of nutrition; conduct research to understand the mechanisms and treatment of these conditions; and provide information on fructose and its sources, in food labelling, which allows people affected by these intolerances to safely choose foods. The fact that there is insufficient scientific evidence regarding the fructose intake levels that are safe for people with HFI or fructose malabsorption means that the limits of detection and quantification of analytical techniques can be a reference value to establish the conditions of use of a possible mention of the absence of fructose, and its sources, in the labelling of food products.

Key words

Fructose, Hereditary Fructose Intolerance, HFI, aldolase B, malabsorption, sugar, sources of fructose, sorbitol, food labelling.

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1. Introduction

Fructose is a sugar that is found naturally in fruits and vegetables, and in honey, as well as being part of the structure of sucrose (table sugar) that is used for its sweetening properties. Furthermore, there are other sources of fructose such as sorbitol; polyalcohols containing sorbitol in their structure (for example, isomalt, maltitol, lactitol); hydrogenated glucose syrups; or other sweeteners that are metabolised via the same metabolic pathway as fructose, as is the case with tagatose.

Hereditary Fructose Intolerance (HFI), or aldolase B deficiency, is a serious inherited autosomal recessive disorder that is due to a deficiency in the enzyme aldolase B (fructose 1,6-bisphosphate aldolase) responsible for metabolising exogenous fructose, provided in food, into glycolysis metabolites, primarily in the liver. The prevalence of this disorder varies depending on the population, but is estimated at approximately 1 in 20 000 to 60 000 births in Europe, being more common in certain regions due to founder mutations (Zugasti, 2009) (Bouteldja and Timson, 2010) (Gaughan et al., 2015) (Schrodi et al., 2015) (Buziau et al., 2020) (Singh and Sarma, 2022). The fundamental pillar of HFI management, which must be commenced after the definitive diagnosis, is the elimination of fructose, sucrose and sorbitol, or other sources of fructose, from the diet, including food additives, and medicines containing them (EFSA, 2005) (EMA, 2017).

On the other hand, fructose malabsorption (intestinal intolerance), a disorder that is increasingly frequent in our society, occurs when there is a deficit, in the intestinal mucosa, of the transporter protein that allows its absorption in the small intestine, so that the excess of non-assimilated sugars passes to the colon, where the bacteria break them down forming acids, gas and water, which are what cause symptoms (flatulence, abdominal pain/distension, diarrhoea, etc.). In this case, there are no prevalence data, but it is estimated at approximately 20 % of the population (Rumessen and Gudmand-Hoyer, 1998) (Choi et al., 2003, 2008) (Melchior et al., 2009).

Currently, Regulation (EU) No. 1169/2011 (EU, 2011) on the provision of food information to consumers does not include fructose or its sources in its Annex II, which lists substances or products that cause allergies or intolerances, or in its Annex III, which includes foods whose labelling must contain one or more additional particulars. Likewise, in the case of flavourings, neither Regulation (EU) No. 1169/2011 (EU, 2011) nor its specific regulations establish the obligation to include information on the sugars that may form part of their composition.

Hence, the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) has been requested to review the existing scientific information on HFI Intolerance or aldolase B deficiency and on fructose malabsorption, and to assess the possible risk for people who suffer from them associated with the lack of information regarding the sources of fructose in the foods they consume, in particular, processed foods, and the possible effects on their nutritional status arising from the limited diet that is suitable for them.

2. Fructose

2.1 Absorption and metabolism mechanism

Fructose is ingested through the diet (sugar naturally present in fruits, some vegetables and honey) and is absorbed in the small intestine through a specific transporter called GLUT5, located in

the apical membrane of intestinal cells or enterocytes (Dholariya and Orrick, 2022). Once inside, fructose passes into the bloodstream via another transporter, GLUT2, in the basolateral membrane, primarily targeting the liver, which is the central organ for its metabolism. In people with fructose malabsorption, the absorption capacity through GLUT5 is compromised, which causes not all the fructose to be absorbed. The fructose reaches the large intestine, where it is fermented by bacteria, giving rise to gastrointestinal symptoms such as bloating and diarrhoea (Ferraris et al., 2018).

The liver metabolises approximately 90 % of ingested fructose, and its metabolic pathway, known as the fructolysis pathway, differs from glycolysis (glucose metabolism) in several key respects:

a. Conversion to fructose-1-phosphate: In the liver, fructose is phosphorylated by the enzyme fructokinase (or ketohexokinase) to form fructose-1-phosphate. Fructokinase does not have a regulatory mechanism, which means that fructose can be rapidly metabolised. This is the basis for why patients with aldolase B deficiency suffer from hypoglycaemia when they consume it.
b. Division into triose phosphate: Fructose-1-phosphate is subsequently cleaved by the enzyme aldolase B into two trioses: dihydroxyacetone phosphate (DHAP) and glyceraldehyde. This step is crucial, since aldolase B is the deficient enzyme in people with Hereditary Fructose Intolerance (HFI). Glyceraldehyde is subsequently phosphorylated to glyceraldehyde-3-phosphate (G3P) by the enzyme triose kinase, using another ATP. Both DHAP and G3P are intermediates of glycolysis and can continue towards energy production or be converted into glucose by gluconeogenesis, depending on the body's energy requirements.
c. Energy production or lipid synthesis: Fructolysis intermediates (DHAP and G3P) enter the final stages of glycolysis to produce pyruvate. This can be converted to ATP through cellular respiration or, under conditions of excess energy, be channeled towards lipid synthesis (lipogenesis). The latter process is more common with fructose than with glucose, since the fructolysis pathway avoids the key regulatory control of phosphofructokinase-1 (a limiting point in glycolysis), which favours the accumulation of intermediates for fat production. This explains why excessive fructose consumption is associated with dyslipidaemia and hepatic steatosis.

2.2 Sources of fructose

For the purposes of this report, "sources of fructose" means all foods or products that provide fructose to the body, either as free fructose present in them, whether naturally or added; as fructose released following the digestion of sugars that include it in their structure (e.g. sucrose) or generated by biotransformation from precursors (e.g. sorbitol).

Fructose is naturally present in fruits, vegetables and honey, with varying concentrations according to the food matrix. In processed foods, it can constitute a relevant component in the form of glucose-fructose syrup (42 % fructose) or fructose-glucose syrup (55 % fructose), also known as high fructose corn syrup (HFCS), or sucrose (commonly known as table sugar) which is a disaccharide that, upon intestinal hydrolysis, releases glucose and fructose (Tappy and Lê, 2010).

In addition to dietary fructose, there are metabolic precursors capable of increasing systemic exposure to fructose. Sorbitol, a polyol widely used as a sweetener in products labelled as "sugar-free" and as an excipient for pharmaceutical use, is oxidised to fructose in the liver by the action

of the enzyme sorbitol dehydrogenase (Mayes, 1993). This conversion explains its ability to induce clinical symptoms in people with HFI or fructose malabsorption, even in the absence of free fructose in the diet (Gaughan et al., 2015).

On the other hand, tagatose deserves specific consideration. This is a monosaccharide structurally related to fructose, specifically an epimer of it, and its hepatic metabolism follows the same pathway as fructose, being phosphorylated by fructokinase (Levin et al., 1995). Consequently, tagatose is not tolerated by people with HFI, despite its frequent use as a low glycaemic index sweetener in products intended for populations with impaired glucose metabolism (Buemann et al., 2000a). Its presence may, therefore, represent an inadvertent source of metabolic exposure to fructose in these patients (Santer et al., 2016).

Finally, various components used in the food and pharmaceutical industry, such as additives, flavours and excipients, may contain traces of fructose or its sources, contributing to an unintended intake. The absence of detailed and specific information on fructose labelling increases the risk of exposure, particularly in processed foods. This reinforces the need for a thorough evaluation of the obvious and hidden sources of fructose in the dietary approach of patients with HFI or disorders related to its absorption.

2.2.1 Natural sources of fructose

Fructose is found naturally in a wide variety of plant-based foods, constituting an important supply of energy through the diet. The main sources include:

- Fruits: Apples, pears, mangoes, grapes, watermelons and bananas contain high levels of fructose. For example, an apple can contain between 5 and 7 grams of fructose per 100 grams (Ventura et al., 2011).
- Vegetables: Some vegetables such as onions, artichokes and asparagus have moderate amounts of fructose or fructans (fructose polymers) that are not digestible, but could aggravate the symptoms of fructose malabsorption (Shepherd and Gibson, 2006).
- Honey: Honey is essentially composed of different sugars, especially fructose and glucose, as well as other substances, such as organic acids, enzymes and solid particles derived from its collection (BOE, 2003b). It is a concentrated source of fructose, with approximately 40 % of its composition in the form of this sugar, which makes it unsuitable for people with HFI or severe malabsorption (Úbeda et al., 2024).

2.2.2 Other sources of fructose

Sometimes, foods do not contain fructose, but they do contain fructose precursors. Fructose precursors are compounds that, although not fructose itself, can be converted into this sugar in the body or released during its metabolism, representing a particular risk for people with HFI:

- Sucrose (table sugar): It is a disaccharide composed of glucose and fructose in a ratio of 1:1. Sucrose is broken down in the intestine into its individual components, releasing fructose. It is present in confectionery and pastry products and sugary drinks, representing a risk for people with HFI (Ali et al., 1998).

- Sorbitol: It is a polyalcohol ("sugar alcohol") present in "sugar-free" products such as chewing gum and sweets and also present in some medicines as an excipient. Sorbitol can be partially converted to fructose (1:1) in the liver via polyols, making it unsuitable for people with HFI (Bouteldja and Timson, 2010).
- Other polyols, such as maltitol, isomalt (also called isomaltose or isomaltitol) and lactitol, are used as sweeteners in low-calorie products. They are formed by the binding of a monosaccharide to a sorbitol molecule. Therefore, although their conversion to fructose is less direct than that of sorbitol, they are not well tolerated by people with HFI or fructose malabsorption (Latulippe and Skoog, 2011).

Additionally, there are food products containing fructose in their composition, such as:

- Glucose syrup, which is a viscous liquid sweetener obtained from the hydrolysis (breakdown) of starch, commonly from corn. It contains a mixture of glucose, maltose and other polysaccharides in varying proportions. Sometimes glucose is partially transformed into fructose to increase its sweetening power; in this way, it can contain a variable proportion of fructose, between 5 and more than 50 %. According to Royal Decree 1052/2003 (BOE, 2003a), if it contains more than 5 % fructose, it is called "glucose-fructose syrup" or "fructose-glucose syrup", depending on whether the proportion of glucose is higher than that of fructose or not. It is also commonly referred to as High Fructose Corn Syrup (HFCS).

  These products are widely used to improve texture, prevent sugar crystallisation and sweeten products such as soft drinks, baked goods, cereals, sweets, ice cream, confectionery and sauces. HFCS can contain between 42 % (HFCS 42) and 55 % (HFCS 55) of fructose. This makes it a significant, and often hidden, source in the diet (Ventura et al., 2011). For example, one can of soda can contain up to 15 grams of fructose from HFCS.
- Other syrups that are used as sugar substitutes, such as agave syrup or maple syrup, also contain fructose (Stuckel and Low, 1996) (Ozuna and Franco-Robels, 2022).
- Invert sugar: It is a liquid mixture of fructose and glucose, in a 1:1 ratio, obtained by breaking down (hydrolysing) sucrose. It is a very common ingredient in pastry, confectionery, bakery and ice cream products because it is sweeter than sucrose, helps retain moisture in baked products and prevents crystallisation in ice cream and candy (Singh et al., 2020).

A special case is that of tagatose: It is a simple sugar (monosaccharide), an isomer of fructose that is obtained mainly from galactose and is used as a sweetener. It has a sweet taste similar to sugar, but with fewer calories and a low glycaemic index. It is used in foods, such as baked goods and beverages. Tagatose is not suitable for people with HFI since it is metabolised in the liver through the same initial pathway as fructose. This involves phosphorylation by fructokinase to form tagatose-1-phosphate, which requires additional metabolism by aldolase B (Buemann et al., 2000b) (Izquierdo-García et al., 2020).

From a nutritional and clinical perspective, it is essential to consider the equivalences of fructose, since different sources of fructose can provide comparable amounts of free or potentially

bioavailable fructose after the digestive metabolism. This makes it difficult to accurately estimate the total load of fructose ingested (Gibson et al., 2007). The aforementioned substances have a highly variable absorption rate: for example, in the case of polyols, this has been estimated between 0 and 40 % (Izquierdo-García, 2019). On the other hand, there are no data on the yield of the reactions leading to the biotransformation of the absorbed fraction of said compounds into fructose. However, the estimate of the fructose equivalences of these compounds could be made assuming complete absorption and biotransformation, which provides a safer scenario for patients with HFI (Table 1).

Table 1. Fructose equivalences from the different sources of fructose for food use (maximum amount assuming complete absorption and biotransformation)

Compound	Amount of fructose (g) generated per gram of compound
Sucrose	0.53
Sorbitol (E 420)	0.99
Maltitol (E 965)	0.52
Isomalt (E 953)	0.25-0.52
Lactitol (E 966)	0.52
Glucose syrup	<0.05 (if it contains less than 5 % fructose) If it contains >5 % fructose, it should be referred to as "glucose-fructose syrup" or "fructose-glucose syrup"
Glucose-fructose syrup/ Fructose-glucose syrup	0.42 / 0.55 The ingredients commonly used in the food industry contain 42 % or 55 % free fructose. If an ingredient with a higher fructose content was used, the value would be higher, never exceeding 1 g.
Agave syrup	0.33-0.87 (depending on the raw material and the production process conditions)
Maple syrup	0.31-0.40
Invert sugar	0.51-0.53

In addition to being part of the sweeteners mentioned above, fructose can be found in or derived from other products such as:

- Additives and processing aids: In processed foods, some additives, such as stabilisers or preservatives, and processing aids, may come from sources that contain fructose or its precursors, although in smaller amounts. However, even small amounts can be critical for people with HFI.
- Natural and artificial aromas: Some aromas used in processed foods, such as those of fruit, may contain traces of fructose or its derivatives, particularly if they are derived from natural extracts. These ingredients are difficult to identify in labelling (Fedewa and Rao, 2014).
- Excipients in medicines: Syrups, chewable tablets, and pharmaceutical suspensions often contain fructose, sucrose, sorbitol, maltitol, or isomalt as sweeteners or stabilisers. For example, paediatric medicines frequently include these compounds, which could represent a risk (AEMPS, 2018) (Metabolic Guide, 2022).

2.3 Sweeteners that are not a source of fructose

Sweeteners that, due to their structure, are not a source of fructose and are tolerated by patients with aldolase B deficiency are: glucose, dextrinomaltose (also called maltodextrin or corn sugar) and glucose polymers. Also artificial sweeteners (acesulfame, alitame, aspartame, cyclamate, neotame or saccharin); peptides, such as thaumatin; glucoflavonoids, such as neohosperidine dihydrochalcone; or diterpene glycosides, such as steviol glycosides. Other sweeteners that also do not lead to fructose intake are erythritol, which is not metabolised in the body and is eliminated in the urine unaltered, or xylitol (birch sugar) which is metabolised by different pathways (Izquierdo-García et al., 2014) (AAIHF, 2023).

These sweeteners, which are not a source of fructose, are an alternative in the formulation of foods that could be consumed by people with HFI or fructose malabsorption.

2.4 Analytical determination of fructose

The presence of fructose or sources of fructose in food can be revealed by the analysis of compounds that, as indicated above, may constitute sources of fructose.

Liquid chromatography is a very common method in the analysis of soluble sugars (including fructose, sucrose or tagatose) and polyalcohols (such as sorbitol, maltitol, isomalt or lactitol) - it can be coupled to a differential refractometer detector (HPLC-RI), a pulse amperometric detector (HPAEC-PAD) or light scattering detection (HPLC-ELSD). These techniques can reliably measure fructose concentrations of 47.9, 2 and 0.33 µg/ml, respectively (Wang et al., 2021a, b) (Tiwari et al., 2023). Even better instrumental sensitivity parameters have been found using tandem mass spectrometry, coupled with liquid chromatography, capable of detecting fructose in amounts of 0.02 µg/ml. While all these methods provide highly accurate and precise results, as well as good specificity and sensitivity in the analyses to measure the content of these compounds, they pose a certain degree of analytical complexity. Generally, a previous phase of extraction in the appropriate medium (usually hydroalcoholic solutions), centrifugation, clarification, solvent changes, deproteinisation and interference elimination is necessary. They also require expensive equipment and need careful maintenance, balancing and calibration procedures.

To avoid these analytical difficulties, enzymatic methods have been developed, which are marketed in the form of analytical kits, and which also provide high sensitivity and specificity. Some of them are based on the application of several enzymes that act on fructose, with the formation of compounds that are measured using different techniques, such as spectrophotometry (limits of quantification of 2-5.6 µg/ml) or spectrofluorimetry (which can measure amounts as low as 0.072-0.130 µg/ml). Sorbitol and sucrose can also be analysed in food using specific kits, based on enzymatic reactions with the formation of coloured compounds, with a sensitivity close to 1 µg/ml. These methods provide high speed in the measurements. However, they sometimes also require sample purification to avoid the presence of interferences (for example, glucose, mannose or sulfites) (Lacorn and Hektor, 2025).

Hence, current techniques allow the analysis of fructose in food, with instrumental sensitivity parameters ranging between 0.02 and 50 µg/ml (chromatographic methods), and between 0.07 and

5.6 µg/ml (enzymatic kits). These values refer to the fructose concentration in the tested solution. Although the limits of detection and quantification in the food as consumed can be variable depending on the necessary sample preparation processes.

Currently, in Spain there are different techniques validated by accredited laboratories according to the UNE-EN ISO/IEC 17025:2017 standard (UNE, 2017), which allow the quantification of 0.05 % of fructose in foods, and even lower concentrations in certain matrices.

3. Hereditary Fructose Intolerance (HFI) or aldolase B deficiency

3.1 Definition, pathophysiology and management of HFI

Hereditary Fructose Intolerance (HFI), also known as aldolase B deficiency, is an inherited metabolic disorder caused by the deficiency of said enzyme, which participates in the fructose metabolism in the liver, kidneys and small intestine. More than 50 mutations in the ALDOB gene have been identified, the most frequent being A149P, A174D and N334K in Caucasian populations (Orphanet, 2026).

Aldolase B deficiency causes the accumulation of fructose-1-phosphate in these organs. This generates a series of symptoms such as nausea, vomiting, abdominal pain, hypoglycaemia and liver dysfunction, a result of metabolic toxicity. This accumulation interferes with other metabolic pathways, such as gluconeogenesis and glycogenolysis, causing hypoglycaemia and metabolic stress. In any event, it would appear that liver involvement can exist even in the "absence" of fructose intake. There are different clinical forms, with manifestations of greater or lesser severity, which can appear from early childhood, or later. However, in the long term all can lead to liver injury, kidney failure and even death, if not managed properly.

Symptoms of HFI usually manifest in childhood, often after the introduction, subsequent to weaning, of foods containing fructose or sucrose (such as fruits, juices or sweetened infant formulas). According to Ali et al. (1998), the symptoms can be classified as:

- Acute symptoms: After fructose intake, patients experience nausea, vomiting, abdominal pain, lethargy, hypoglycaemia and lactic acidosis. Hypoglycaemia is due to the inhibition of gluconeogenesis and glycogen hydrolysis by the accumulation of fructose-1-phosphate, which also reduces ATP levels in the liver.
- Chronic symptoms: Repeated or undiagnosed exposure can lead to liver failure (steatosis, cirrhosis), kidney failure (renal tubular acidosis) and growth retardation in children. In severe cases without treatment, FHI can be lethal (Metabolic Guide, 2022). Furthermore, hyperuricaemia and gout can occur (Singh and Sarma, 2022).

One notable aspect is that many patients develop a natural aversion to sweet foods or fruits from childhood, which can delay diagnosis if not thoroughly investigated.

In addition to the classic form, some patients have residual enzyme activity and may have a later clinical presentation with fewer symptoms. On the other hand, metabolic alterations have been described in people who carry the gene in heterozygosity before a high fructose intake, such as hyperuricaemia and insulin resistance, or hyperuricaemia and gout (Seegmiller et al., 1990) (Debray et al., 2021).

The diagnosis is confirmed by genetic tests, analysis of enzyme activity in liver biopsies or, in specific cases, supervised fructose tolerance tests (although these are less frequent due to the risks involved). HFI diagnosis requires a multidisciplinary approach combining clinical history, biochemical tests and genetic tests. Methods include:

- Clinical history: Identification of symptoms related to fructose or sucrose intake, especially in young children after weaning. It is usually accompanied by growth retardation.
- Biochemical tests: Detection of hypoglycaemia, lactic acidosis, hyperuricaemia, hypermagnesaemia and elevated liver transaminases after exposure to fructose. Hypoglycaemia does not respond when glucagon is administered. The fructose tolerance test, which involves administering a controlled dose of fructose and measuring metabolic responses, is rarely used due to the associated risks (Bouteldja and Timson, 2010).
- Enzymatic analysis: Measurement of aldolase B activity in liver or intestinal biopsies confirms the enzyme deficiency, although it is an invasive method.
- Genetic tests: ALDOB gene sequencing is currently the method of choice, since it identifies specific mutations with high sensitivity and specificity, allowing a definitive diagnosis without invasive procedures (Orphanet, 2026).

The differential diagnosis must rule out other causes of hypoglycaemia and liver dysfunction, such as galactosaemia or gluconeogenesis disorders.

The prevalence of this disorder varies according to the population, but is estimated at approximately 1 in 20 000 to 60 000 births in Europe, being more common in certain regions due to founder mutations (Zugasti, 2009) (Bouteldja and Timson, 2010) (Gaughan et al., 2015) (Schrodi et al., 2015) (Buziau et al., 2020) (Singh and Sarma, 2022).

The fundamental pillar of HFI management, which must be commenced after the definitive diagnosis, is the elimination of fructose, sucrose and sorbitol, or other sources of fructose, from the diet, including food additives, and medicines containing them (EFSA, 2005) (EMA, 2017).

Although there are no scientifically established and widely accepted tolerable levels of fructose intake for these conditions (EFSA, 2005), some authors indicate that the short-term administration (2 days) of 4.7 mg of fructose/kg of body weight/day could be safe and well tolerated by people diagnosed with HFI (Barshop et al., 2003). Other authors include the recommendation that the total amount of fructose ingested per day be less than 40 mg/kg b.w./day (Cox, 1991) (EFSA, 2005) (EMA, 2017) (Izquierdo-García, 2019) (Maiorana et al., 2020), and even some establish a stricter threshold of fructose intake (10 mg/kg b.w./day) (Cox, 1994) (EMA, 2017), although the spectrum of individual fructose tolerance in HFI seems to depend on age (babies are more sensitive than adults) and the respective genetic mutation (EFSA, 2005). In view of the need to standardise treatment, a fructose-free diet containing less than 1.5 grams of fructose per day has been recommended (Bell et al., 1987) (EFSA, 2005).

Although a strict diet without fructose or its sources is recommended during HFI treatment, some authors indicate that it is not clear whether small amounts of fructose in the diet can be tolerated nor the permissible limit of fructose that does not cause damage to the liver and kidneys (Singh and

Sarma, 2022). These authors note that it is possible that safe fructose intake limits may not be the case in asymptomatic patients with HFI. The latter is supported by the determination of Carbohydrate Deficient Transferrin (CDT) by isoelectric targeting among patients with HFI who followed a diet without fructose, sucrose and sorbitol (Di Dato et al., 2019). Di Dato et al. (2019) demonstrated a significant correlation between the amount of fructose consumed and the percentage of disialo-transferrin and the tetrasialo-transferrin/disialo-transferrin ratio. These authors suggested that the serum CDT profile could be considered a good tool to control fructose, sucrose and sorbitol intake. In addition, CDT determination could be used to identify the maximum daily fructose tolerance of each HFI patient. However, the lack of widespread availability of this tool and its high cost are the main obstacles to its application (Singh and Sarma, 2022).

3.2 Consequences of fructose consumption in people with HFI

Many products contain hidden fructose, which can trigger acute and severe episodes. This unintended exposure is one of the main causes of complications in patients with HFI (Úbeda et al., 2024).

In the United States, severe cases of liver failure have been documented in infants fed formula containing sucrose, without knowing that they were aldolase B deficient (Li et al., 2018). In Europe, follow-on formulas, as well as infant formulas made from hydrolysed proteins, may contain sucrose, which could at most generate up to 0.5-1 g of fructose per 100 ml of reconstituted end product (maximum levels according to Delegated Regulation (EU) 2016/127 [EU, 2016a]). This level is higher than the 40 mg/kg b.w./day set down by several authors as a recommended daily intake level in children (Cox, 1991), (EFSA, 2005) (EMA, 2017) (Izquierdo-García, 2019) (Maiorana et al., 2020), and could cause symptoms in infants with undiagnosed HFI. It has also been documented that the restriction of simple sugars can cause growth retardation, in patients with HFI, even in those who are clinically asymptomatic (Singh and Sarma, 2022).

Furthermore, in people with HFI, the fact that the intake of foods that are a source of fructose and also of essential vitamins (such as vitamin C), fibre and antioxidants is limited increases the risk of nutritional deficiencies and gastrointestinal problems such as constipation. This requires meticulous dietary planning and, in many cases, vitamin supplementation (Bonnardeaux and Bichet, 2020) (Mojica and Weinstock, 2022) (Pearl et al., 2022) (Scheinman, 2023) (Hijazi and Kishnani, 2025).

In addition, the need for a strict diet can lead to social isolation, food-related anxiety, and difficulties in settings such as schools or social events where fructose-rich foods are common. The stress of avoiding accidental intakes affects the emotional well-being of patients and caregivers (Metabolic Guide, 2022).

4. Fructose malabsorption (intestinal fructose intolerance)

4.1 Definition, pathophysiology and management of fructose malabsorption

Fructose malabsorption, also known as intestinal fructose intolerance, is a condition wherein the small intestine has difficulty absorbing fructose. Unabsorbed fructose then reaches the large intestine, where it is fermented by intestinal bacteria, producing gas, bloating, abdominal pain and diarrhoea.

Small Intestinal Bacterial Overgrowth (SIBO) deserves a special mention due to its relationship with fructose malabsorption since there is a rise in the bacterial load in the small intestine that can exacerbate these symptoms by increasing the fermentation of unabsorbed fructose, producing gas and short chain fatty acids (Gibson et al., 2007) (Bushyhead and Quigley, 2021). It has been seen that SIBO can cause or worsen fructose malabsorption by altering mucosal function and increasing carbohydrate fermentation, while fructose malabsorption can favour SIBO by providing an excess of substrate for bacterial growth and modifying the composition of the microbiota (Gibson et al., 2007) (Zhang et al., 2019). There are studies that have shown that the eradication of SIBO leads to a high rate of disappearance of fructose malabsorption, which suggests that SIBO may be a primary causal factor of malabsorption in many cases (Lin, 2004).

The main causes of fructose malabsorption include:

- Transporter deficiency: The absorption of fructose in the small intestine depends on the specific transporter GLUT5, located in the apical membrane of enterocytes. A limited capacity of this transporter, either due to individual variations or acquired factors, can reduce fructose absorption (Latulippe and Skoog, 2011).
- Alterations of the intestinal microbiota: Imbalances in the intestinal microbiota or conditions such as Irritable Bowel Syndrome (IBS) can affect fructose tolerance, increasing the likelihood of fermentation in the colon and of developing SIBO (Gibson et al., 2007).
- Excess intake: Even in healthy individuals, the intake of large amounts of fructose (especially without glucose, which facilitates absorption through GLUT2) can exceed the absorption capacity of the small intestine, resulting in transient malabsorption (Fedewa and Rao, 2014).

It is important to highlight that fructose malabsorption does not imply a metabolic intolerance as occurs in HFI, but a problem of intestinal transport, and its severity varies widely between individuals. Fructose malabsorption is primarily diagnosed by hydrogen breath tests. These detect hydrogen generated by bacterial fermentation of unabsorbed fructose in the large intestine. Fructose tolerance tests may also be performed, under medical supervision, to assess absorption capacity.

The most commonly used methods for diagnosis are:

- Clinical history: Identification of symptoms related to the intake of fructose-rich foods (such as, for example, fruits, soft drinks, products with HFCS). It is common for patients to report improvement by reducing the consumption of these foods.
- Hydrogen breath test: It is the standard non-invasive method. It consists of administering a controlled dose of fructose (usually 25-50 g) and measuring the hydrogen levels in the breath for several hours. A significant increase in hydrogen indicates bacterial fermentation of unabsorbed fructose in the colon, confirming malabsorption (Gibson et al., 2007). In paediatrics, due to the lower absorption capacity, it is advisable to use lower doses (0.5-1 g/kg b.w., maximum 25 g) to avoid false positives. It is essential to rule out SIBO, which can produce confusing results.
- Fructose tolerance tests: In some cases, the clinical and biochemical response after fructose intake is evaluated under medical supervision, although it is less common due to the discomfort it can generate.

The differential diagnosis must rule out other causes of gastrointestinal symptoms, such as coeliac disease, lactose intolerance or inflammatory bowel disorders, such as SIBO.

The symptoms of fructose malabsorption are primarily gastrointestinal and result from the fermentation of unabsorbed fructose by bacteria in the large intestine, which produces gases and osmotic by-products. According to Gibson et al. (2007), the most common symptoms include:

- Abdominal distension: Due to the production of gases such as hydrogen and methane.
- Abdominal pain or colic: Caused by intestinal distension and irritation of the mucosa.
- Diarrhoea: Result of the osmotic effect of unabsorbed fructose, which attracts water to the colon.

These symptoms usually appear between 30 minutes and 2 hours after the intake of fructose-rich foods and can vary in intensity depending on the amount consumed and individual tolerance. Although not life-threatening like HFI, fructose malabsorption can negatively impact daily well-being; it can also significantly affect quality of life and be associated with other conditions such as SIBO (Shepherd and Gibson, 2006).

Prevalence data do not exist, but it is estimated to be approximately 20 % of the population (Rumessen and Gudmand-Hoyer, 1998) (Choi et al., 2003, 2008) (Melchior et al., 2009).

Management of this disorder consists of restricting fructose intake in the diet, although the tolerance level varies from one person to another. Some people can tolerate small amounts of fructose while others need to avoid it altogether. The same as with HFI, accurate information on the fructose content in food is essential so that people with fructose malabsorption can control their symptoms.

Management focuses on reducing fructose intake and on dietary strategies adapted to individual tolerance. Unlike HFI, not all patients need to completely eliminate fructose from their diet. The main strategies include:

- Fructose restriction: Reducing the consumption of fructose-rich foods, such as certain fruits (e.g. apple, pear, mango), honey and foods processed with HFCS or sucrose. Tolerance varies and some individuals may consume small amounts without symptoms, although, as with people affected by HFI, tolerance threshold values have not been described in these patients (Latulippe and Skoog, 2011).
- Co-consumption with glucose: Glucose facilitates fructose absorption by enhancing the gradient through the GLUT2 transporter. Therefore, consuming fructose together with glucose (as in fruits with a low fructose/glucose index, e.g., bananas) can reduce symptoms in some cases (Gibson et al., 2007).
- Low FODMAP diet: Since many fructose-rich foods also contain other fermentable carbohydrates (FODMAP, Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols), a low-FODMAP diet, supervised by a competent healthcare professional, may be useful, especially in patients with concurrent IBS (Shepherd and Gibson, 2006).
- Food labelling education: Teaching patients to identify hidden sources of fructose in processed foods, such as HFCS, sucrose, and sorbitol in "sugar-free" products.

There is no specific pharmacological treatment for fructose malabsorption. However, in some cases probiotics are used to improve the intestinal microbiota, although with variable results.

4.2 Consequences of fructose consumption in people with fructose malabsorption

As in HFI, fructose malabsorption requires dietary restrictions that can affect the nutritional status of people who suffer from it. The elimination of fruits, certain vegetables and processed foods that can be sources of fructose, can lead to a deficiency of essential nutrients such as vitamins, minerals and fibre. It is important that people with these conditions are under the supervision of a competent health professional in the field of nutrition to ensure that they follow a healthy and balanced diet that meets their nutritional needs.

5. Food information provided to consumers

5.1 Regulations applicable to food labelling

Food labelling is the main means of communication between food producers and end consumers, constituting a key tool to allow the latter to make informed choices about the foods they buy and consume.

Pursuant to Regulation (EU) No. 1169/2011 on the provision of food information to consumers (EU, 2011), "labelling" means all "words, particulars, trademarks, brand name, pictorial matter, or symbols relating to food and placed on any packaging, document, notice, label, ring, or collar accompanying or referring to such food".

At national and European Union level, rules have been established to regulate both the labelling provisions that must include all foods in general, and those of a specific nature that regulate certain types of food.

5.1.1 European regulations

Regulation (EU) No. 1169/2011 (EU, 2011) includes the obligation to provide, on packaged foods, information on the list of ingredients, including additives and flavourings, as well as on any substance or product that causes allergies or intolerances, contained in Annex II, highlighting them typographically. However, fructose is not listed in that Annex.

Moreover, there are other provisions at Community level that regulate certain particulars relating to the absence or presence of substances that cause allergies or intolerances in foods, such as the presence of gluten (EU, 2014) or lactose (EFSA, 2010) for certain categories of foods, such as infant formulas and foods for special medical purposes (EU, 2016a, b).

On the other hand, Regulation (EC) No. 1333/2008 on food additives (EU, 2008a) establishes the Community lists of authorised additives, and, among the sweeteners and carriers that appear in said list, sorbitol (E 420), isomalt (E 953), maltitol (E 965) or lactitol (E 966) stand out, polyalcohols that, once metabolised in the body, are a source of fructose. Likewise, Regulation (EC) No. 1334/2008 on flavourings (EU, 2008b) includes the authorised Community list but does not establish the obligation to specify their composition or the carriers used and, therefore, does not make it compulsory to

include information on the sugars that could be part of their composition, such as fructose. On the other hand, Regulation (EC) No. 1924/2006 on nutrition and health claims made on foods (EU, 2006) states that, in commercial communications, whether in the labelling, presentation or advertising, of foods supplied as such to the end consumer, the nutritional claim "sugar-free" may be included, as well as any other claim that may have the same meaning for the consumer, if the product does not contain more than 0.5 g of sugars per 100 g or 100 ml, thus allowing a small amount of sugars, which could generate some confusion among consumers (Izquierdo-García, 2019).

However, to date, no specific regulation has been enacted on the claim related to fructose in food (or other sugars, polyols or other sources of fructose not tolerated by people with HFI or fructose malabsorption).

5.1.2 Spanish regulations

In the Spanish legal system, in addition to the direct application of Community legislation, specific provisions can be developed that specify aspects related to labelling.

However, at present, the regulations, aimed at the protection of the general population, do not include specific warnings for patients with metabolic intolerances, such as HFI, which can lead to risk situations if a critical reading of the labelling is not carried out.

Royal Decree 126/2015, of 27 February (BOE, 2015) establishes the mandatory food information to be provided in the case of non-packaged (non-prepacked) foods, including information on substances or products that cause allergies or intolerances in Annex II to Regulation (EU) No. 1169/2011 (EU, 2011). Although, as mentioned above, fructose does not appear in said Annex II.

On the other hand, it should be noted that, among the processing aids authorised and included in Royal Decree 773/2023, of 3 October, which regulates processing aids (BOE, 2023), there are some enzymes, used in "sugars" and "invert sugars", which act on them by isomerisation or hydrolysis mechanisms causing the appearance of fructose in the resulting product, without the presence of this sugar having to be informed to the consumer.

For its part, AESAN, in 2020, published an information note on HFI (AESAN, 2020a) wherein it was considered that, until there was a regulatory development in this area, a food operator could voluntarily use the expression "fructose-free" as long as it did not mislead the consumer, as indicated in Article 7 of Regulation (EU) No. 1169/2011 (EU, 2011). In particular, in this case, AESAN considered that this expression could be used voluntarily only in those foods that do not contain fructose or, of course, any other source of fructose.

And, in the same year, AESAN, in view of the lack of uniformity of criteria in the labelling of foods including the nutritional declaration "sugar-free" as an adapted declaration of "free from sugars", published an information note (AESAN, 2020b) stating that the term "sugars" should always be used for the purposes of mandatory particulars such as: name of the food, name as an ingredient in the list of ingredients and nutritional information, and, on the other hand, within the framework of Regulation (EC) No. 1924/2006 (EU, 2006), and with regard to the nutritional declaration "free from sugars", an adapted declaration such as "sugar-free" would have the same meaning for the consumer as "free from sugars" and would not mislead them, provided that the product, as sold to

the end consumer, does not contain sucrose or any other monosaccharide or disaccharide, since, otherwise, it would be misleading the consumer about the characteristics of the food.

Conclusions of the Scientific Committee

The reviewed scientific literature agrees that Hereditary Fructose Intolerance (HFI), or aldolase B deficiency, and fructose malabsorption represent significant challenges for people affected by these disorders due to the high presence of fructose in natural and processed foods.

Both are conditions that require dietary restrictions to control symptoms and prevent complications. However, the restrictive diets necessary to manage these conditions can lead to nutritional deficiencies and affect the quality of life of affected people.

Joint research efforts are required to establish safe levels of fructose intake, as well as to be able to offer adequate dietary guidance that mitigates nutritional risks.

To address the challenges faced by people with HFI and fructose malabsorption, it is essential to work on:

- Education and awareness-raising. There is a need to raise awareness among consumers, healthcare professionals and the food industry about the health risks of HFI and fructose malabsorption. This would help improve diagnosis, treatment, and support for people with these conditions.
- Dietary guidance. Individuals with HFI or fructose malabsorption should receive personalised dietary guidance from a competent healthcare professional. This would make it easier for them to follow a balanced diet that meets their nutritional needs and avoids deficiencies.
- Research. More research is needed to understand the mechanisms and treatment of HFI and fructose malabsorption. This would lead to better diagnosis and treatment strategies for these conditions.
- Food information. The lack of sufficient scientific evidence regarding the minimum fructose intake levels that are safe for people with HFI or fructose malabsorption means that dietary restriction plays a determining role, especially in people with HFI. Therefore, management measures such as the inclusion, in food labelling, of information on the fructose content and its sources are highly relevant, since they would make it easier for people affected by these disorders who could avoid consuming foods containing fructose. The lack of this information in labelling, especially of processed foods, poses a direct risk of accidental ingestion, with consequences ranging from gastrointestinal symptoms to serious complications in the case of HFI. This labelling would be key to allowing consumers to make informed choices about the foods they buy and consume and, therefore, for the appropriate monitoring of an adequate fructose-restrictive diet.

  The fact that there is insufficient scientific evidence regarding the fructose intake levels that are safe for people with HFI or fructose malabsorption means that the limits of detection and quantification of analytical techniques can be a reference value to establish the conditions of use of a possible particular of the absence of fructose, and its sources, in the labelling of food products, in a similar way as those established for lactose (AESAN, 2019). In Spain there are

accredited laboratories, in accordance with the UNE-EN ISO/IEC 17025:2017 standard, for the analysis of fructose using different techniques that allow the quantification of 0.05 % of fructose in food, and even lower concentrations in certain matrices. Given that dietary restriction plays a decisive role in preventing the problems associated with HFI, being able to base a possible particular of the absence of fructose and its sources on food labelling, in the lowest possible limits of detection and quantification, would offer a greater guarantee of safety for affected people. The analytical techniques used for this purpose should be robust, be accredited according to the UNE-EN ISO/IEC 17025:2017 standard for its application to different types of food matrices and be of widespread use by laboratories that provide service to the production and official control of food.

Proper food labelling, education, dietary guidance and research are essential to address these challenges and improve the health and well-being of people with HFI or fructose malabsorption.

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