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DISORDERS OF FRUCTOSE METABOLISM 2026: A SURVEY OF THE MOLECULAR, BIOCHEMICAL, AND PATHOPHYSIOLOGICAL BASES

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Abstract: Fructose is a monosaccharide widely present in the human diet, whose metabolism involves specific pathways predominantly in enterocytes, the liver, and the kidneys. Genetic alterations in the enzymes responsible for this metabolism can result in metabolic disorders with a variable clinical spectrum, particularly relevant during the neonatal and pediatric periods. Among these conditions, Hereditary Fructose Intolerance (HFI) stands out as an inborn error of metabolism with autosomal recessive inheritance caused by mutations in the ALDOB gene, as well as Essential Fructosuria, which results from deficiency of fructokinase (KHK) and is classically considered clinically benign. In HFI, aldolase B deficiency leads to the accumulation of fructose-1-phosphate, resulting in depletion of ATP and inorganic phosphate, with a direct impact on gluconeogenesis, glycogenolysis, and glycogenesis, culminating in severe hypoglycemia, hepatic and renal dysfunction, growth retardation, and risk of death when not diagnosed early. Advances in molecular genetics have enabled the identification of more than 60 pathogenic variants in the ALDOB gene, revealing broad genotypic and phenotypic heterogeneity, with clinical manifestations ranging from severe neonatal-onset disease to atypical or late-onset presentations in adolescents and adults. This review aims to compile and update current knowledge on the main disorders of fructose metabolism, with emphasis on HFI, addressing its pathophysiological mechanisms, genotype–phenotype correlations, the most frequent molecular variants. The biochemical and laboratory aspects of Essential Fructosuria are also discussed, highlighting its importance in the differential diagnosis with diabetes mellitus. Finally, the relevance of early molecular diagnosis, the use of targeted genetic panels, and the strict exclusion of fructose, sucrose, and sorbitol are emphasized as fundamental strategies to reduce morbidity and mortality, ensure appropriate genetic counseling, and enable individualized clinical management of affected patients.

Keywords: Fructose metabolism, Hereditary Fructose Intolerance, Essential Fructosuria, ALDOB gene variants.

Introduction

Fructose is a monosaccharide widely present in the human diet. It occurs naturally as a component of sucrose (β-D-fructofuranosyl-α-D-glucopyranose), which is found in fruits, honey, and vegetables. In addition, fructose is also used in its isolated form (β-D-fructose) as a sweetener and in industrialized foods, particularly as high-fructose corn syrup. Fructose absorption occurs predominantly in the enterocytes of the small intestine, where only a small fraction is metabolized locally. The majority of fructose metabolism takes place in the liver (approximately 70–80%) and, to a lesser extent, in the kidneys (Feinman & Fine, 2013; Stricker et al., 2021). Alterations in the enzymes involved in this metabolic pathway can lead to clinically relevant consequences, especially in pediatric populations. Clinical symptoms generally appear after the ingestion of fructose- or sorbitol-rich products, sorbitol being a polyol that can be metabolized into fructose, which are common in infant foods (Hallfrisch, 1990; Srikanth & Orrick, 2022). Consequently, the first manifestations may occur as early as the neonatal period. To date, two disorders of fructose metabolism have been well characterized: Hereditary Fructose Intolerance (HFI), an inherited disease caused by deficiency of the

enzyme aldolase B, resulting in the accumulation of fructose-1-phosphate, a highly toxic metabolite; and Essential Fructosuria, a benign metabolic disorder that may nonetheless lead to diagnostic confusion with diabetes mellitus (Ali et al., 1998; MARKS & SAMOLS, 1968; Schapira et al., 1972).

With advances in biotechnology, numerous genetic variants associated with these metabolic disorders have been identified over the past decades, many of which exhibit heterogeneous clinical manifestations (Lee et al., 2022). This scenario is particularly evident in HFI, in which neonatal symptoms may range from mild presentations to severe conditions, including chronic or even fatal clinical complications (Ali et al., 1998). These findings highlight the importance of early and more accurate diagnoses, capable of guiding individualized therapeutic approaches.

In this context, the objective of this review is to compile the currently available knowledge on genetic variants and their associated phenotypes in disorders of fructose metabolism, thereby increasing the visibility of the topic through the proposal of rapid variant identification panels (**Figure 2**). This approach aims to contribute to the development of earlier and more personalized therapeutic strategies. Such strategies are essential for appropriate clinical management, as well as for genetic and family counseling.

Fructose Metabolism

Fructose absorption occurs primarily in the small intestine, especially in the jejunum. Unlike glucose and galactose, fructose does not rely on sodium-dependent active transport. Its absorption mainly occurs through facilitated diffusion mediated by the GLUT5 transporter, located on the apical membrane of enterocytes. After entering the cell, fructose is released into the portal circulation via the GLUT2 transporter, which is present on the basolateral membrane (Koepsell, 2020). Approximately 70–80% of the absorbed fructose is rapidly metabolized in the liver due to the high expression of GLUT2 and the key enzymes involved in fructose metabolism, fructokinase, aldolase B, and triose kinase. Other tissues, such as the kidneys (particularly the renal cortex), skeletal muscle, brain, and adipose tissue, also metabolize fructose, but to a lesser extent, as this process is limited by lower expression levels of fructose transporters and metabolic enzymes (Hallfrisch, 1990).

After uptake via the GLUT2 transporter, fructose is rapidly phosphorylated by fructokinase, forming fructose-1-phosphate. This metabolite is then cleaved by aldolase B into dihydroxyacetone phosphate (DHAP) and glyceraldehyde. DHAP is converted into glyceraldehyde-3-phosphate by triose phosphate isomerase, while glyceraldehyde is phosphorylated by triose kinase, also producing glyceraldehyde-3-phosphate. Glyceraldehyde-3-phosphate can enter both glycolysis and gluconeogenesis, highlighting fructose as an important energy source (Hallfrisch, 1990; Mayes, 1993) (**Figure 1**). In addition, sorbitol plays a relevant role in fructose metabolism. This polyol, widely used as a sweetener in sugar-free candies and chewing gums (e.g., Trident), "diet" or "zero" products, pharmaceutical syrups, toothpastes, and mouthwashes, can be rapidly converted into fructose through a reaction catalyzed by sorbitol dehydrogenase, subsequently entering the fructolysis pathway (Sachs et al., 1993; Srikanth & Orrick, 2022).

Unlike glucose, fructose metabolism occurs independently of insulin and bypasses key regulatory steps of glycolysis, particularly the reaction catalyzed by phosphofructokinase-1. As a result, fructose is rapidly converted into fructose-1-phosphate by fructokinase, leading to an accelerated and poorly regulated production of phosphorylated trioses. This increased flux of metabolic intermediates may occur even in the absence of energy demand, promoting metabolic imbalances when fructose is consumed in excess. In addition, this mechanism contributes to the exacerbation of symptoms of HFI, as discussed below (Hallfrisch, 1990; Sachs et al., 1993).

Major Disorders of Fructose Metabolism

Hereditary Fructose Intolerance (HFI)

Hereditary fructose intolerance (HFI) is an inborn error of metabolism with autosomal recessive inheritance, caused by mutations in the ALDOB gene, which encodes the enzyme aldolase B. Deficiency of this enzyme leads to the accumulation of fructose-1-phosphate in tissues such as the liver, kidneys, and small intestine, interfering with essential energy metabolic pathways and resulting in depletion of ATP and inorganic phosphate. HFI was first described in the 1950s, when an association between fructose intake and episodes of severe hypogly-

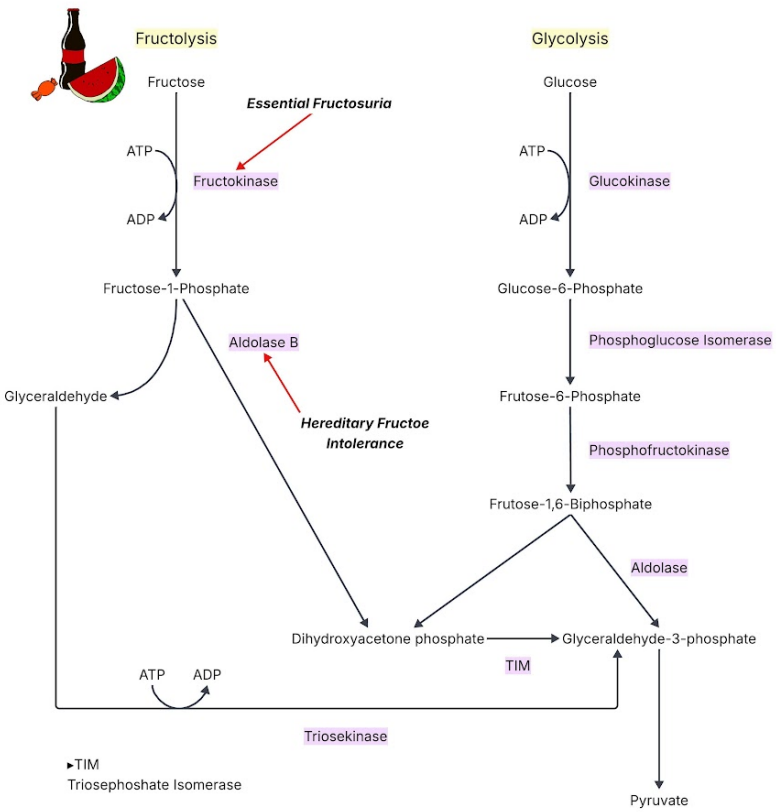

Figure 1 – Metabolic map of fructolysis and glycolysis. The red arrows indicate the enzymes that undergo mutations, giving rise to the respective metabolic disorders.

cemia in newborns was observed (Ali et al., 1998). Data from population studies and clinical databases indicate that the estimated global prevalence of the disease varies, with a commonly cited rate of approximately 1 case per 10,000 births when all pathogenic variants of the ALDOB gene are considered. In more extensively studied European populations, prevalence estimates range from 1 case per 20,000 to 1 per 30,000 live births (Coffee et al., 2010; Pinheiro et al., 2021; Santer et al., 2005) .

With advances in biotechnology, more than 60 pathogenic mutations in the ALDOB gene have been reported in the medical literature, and the severity of clinical manifestations is directly related to the residual activity of aldolase B. Symptoms usually appear after weaning, when foods containing fructose, sucrose, or sorbitol are introduced into the diet (Beyzaei et al., 2023; Coffee & Tolan, 2010; Pinheiro et al., 2021). Depending on the mutation, patients may present with mild manifestations or even remain asymptomatic during the neonatal period; however, in adulthood, the disease may present atypically, with nonspecific gastrointestinal symptoms and persistent hepatic abnormalities. In more severe forms of HFI, chronic exposure to fructose may lead to hepatomegaly, jaundice, liver failure, growth retardation, proximal renal dysfunction, spontaneous aversion to sweet foods, and acute hypoglycemic episodes. Without appropriate treatment, these cases may progress to death, particularly in infants (M. S. Kim et al., 2020; Odièvre et al., 1978; Schulte & Lenz, 1977) .

Because fructose tolerance tests are not recommended due to the risk of severe adverse events, the diagnosis of HFI relies on the combination of a suggestive clinical history and compatible laboratory findings. Currently, molecular genetic testing is considered the gold standard for diagnosis, as it enables direct identification of mutations in the ALDOB gene, although it is associated with longer turnaround times (A. Y. Kim et al., 2020; Úbeda et al., 2024). In this context, a more precise understanding of the biochemical and pathophysiological differences among genetic variants allows for earlier and more effective treatment, leading to more favorable prognoses in both newborns and adults (Odièvre et al., 1978; Úbeda et al., 2024).

Biochemical Bases of HFI

Pathogenic mutations in the ALDOB gene, that reduce or abolish the activity of the enzyme Aldolase B, lead to the accumulation of fructose-1-phosphate in hepatocytes, proximal renal tubular cells, and enterocytes (Cox, 1994; Cross, Cox, et al., 1990; Cross et al., 1988; Davit-Spraul et al., 2008). The main consequence of this accumulation is the sequestration of inorganic phosphate (Pi), resulting in depletion of free cytosolic phosphate. This process triggers profound metabolic consequences, as inorganic phosphate is essential for ATP regeneration. The resulting reduction in ATP levels leads to a state of cellular energy deficiency, which particularly affects the liver, the central organ of energy homeostasis. ATP depletion impairs fundamental processes involved in the maintenance of glycemia, including gluconeogenesis, glycogenesis, and glycogenolysis. As a consequence, following the ingestion of fructose, sucrose, or sorbitol, the liver loses its ability to release glucose into the circulation, explaining the severe hypoglycemic episodes observed in HFI. This condition is further exacerbated

by the fact that fructose-1-phosphate acts as a potent inhibitor of hepatic phosphorylase, a key enzyme in glycogenolysis (Bouteldja & Timson, 2010; Debray et al., 2021). In addition, depletion of ATP and inorganic phosphate reduces the activity of key gluconeogenic enzymes, such as fructose-1,-6-bisphosphatase, further compromising the liver's ability to mobilize glycogen and produce glucose, particularly during fasting or after fructose intake (Bian et al., 2022). Chronic accumulation of fructose-1-phosphate also induces direct hepatocellular injury, which is associated with mitochondrial dysfunction and increased oxidative stress. ATP depletion impairs energy-dependent antioxidant systems, favoring lipid peroxidation and hepatic inflammation. These mechanisms explain the progression of severe disease variants to hepatomegaly, elevated transaminase levels, hepatic steatosis, fibrosis, and, if untreated, cirrhosis (Dong et al., 2024; Li et al., 2025).

Accelerated degradation of adenine nucleotides, triggered by decreased ATP levels, also leads to increased production of uric acid. The conversion of AMP to uric acid results in hyperuricemia, a frequent biochemical finding in HFI. In addition, fructose competes with uric acid for renal excretion, further exacerbating its elevation in plasma levels (Lubawy & Formanowicz, 2023; Zhang et al., 2022). This combination of alterations contributes to manifestations such as metabolic acidosis and, in some cases, nephropathy. Accumulation of fructose-1-phosphate in the kidneys exerts a direct toxic effect on proximal tubular cells, leading to clinical findings such as aminoaciduria, phosphaturia, renal tubular acidosis, and urinary loss of glucose and bicarbonate. In the gastrointestinal tract, the presence of unmetabolized fructose contributes to symptoms such as vomiting, abdominal pain, and diarrhea, particularly in infants after the introduction of fructose-containing foods (Úbeda et al., 2024).

Acute manifestations observed in patients with more severe disease variants, in addition to those previously described, may progress to profound hypoglycemia, leading to lethargy and seizures (Douillard et al., 2020; Úbeda et al., 2024). Chronic exposure to sucrose, fructose, or sorbitol may also result in hepatomegaly, jaundice, liver failure, growth retardation, proximal renal dysfunction, and spontaneous aversion to sweet foods. In the absence of appropriate treatment, hereditary fructose intolerance may progress to death, particularly in infants. However, strict elimination of fructose, sucrose, and sorbitol from the patient's diet interrupts the pathophysiological cascade, allowing for significant functional recovery, especially when the diagnosis is established early (Úbeda et al., 2024).

Mutations in the ALDOB gene

HFI is caused by biallelic mutations in the ALDOB gene, located on chromosome 9 (9q21.3-q22.2), which is predominantly expressed in the liver, kidneys, and small intestine. Although classically described as a single clinical entity, HFI exhibits wide genetic and phenotypic heterogeneity (Brooks' And & Tolan2, 1994; Chi et al., 2007; Tolan, 1995). Advances in molecular genetics have enabled the identification of more than 60 pathogenic variants in the ALDOB gene, revealing substantial molecular diversity underlying the disease and accounting for varying degrees of clinical severity. Variants associated with HFI can be classified according to their molecular effects (**Table**

1), including **missense mutations**, which result in the substitution of critical amino acids; **nonsense mutations**, which introduce premature stop codons; small insertions or deletions leading to **frameshift mutations**; and **splicing variants** that affect messenger RNA processing (Brooks' And & Tolan2, 1994; Coffee & Tolan, 2010; Cross, Stojanov, et al., 1990; Davit-Spraul et al., 2008; Esposito et al., 2010; Santamaria et al., 1996; Santer et al., 2005).

These variants result in a structurally altered protein that may remain functional but exhibits reduced stability of the enzymatic tetramer. Such alterations can compromise the active site of aldolase B, leading to decreased affinity of the enzyme for its substrate. In addition, electrostatic instability caused by specific mutations may reduce the catalytic potential of the enzyme, resulting in varying degrees of enzymatic deficiency (Tolan, 1995). The genotype–phenotype correlation in hereditary fructose intolerance is not absolute; however, mutations that lead to complete loss of enzymatic activity tend to be associated with more severe clinical manifestations. In contrast, variants that retain residual activity are associated with greater phenotypic variability (Úbeda et al., 2024) (**Table 1**). In this context, environmental factors, such as the age at which fructose is introduced into the diet and the amount consumed, also significantly influence the patient's final phenotype (Debray et al., 2021). Therefore, accurate identification of genetic variants associated with HFI is essential for secure diagnostic confirmation, avoiding inappropriate and potentially dangerous fructose challenge tests. Moreover, this knowledge enables appropriate family genetic counseling, as well as effective prenatal and neonatal diagnosis (Janssen et al., 2025; Úbeda et al., 2024).

Although the treatment of HFI is the same regardless of the specific genetic variant, consisting of strict restriction of fructose, sucrose, and sorbitol, genetic characterization allows prediction of clinical severity, implementation of closer monitoring in cases associated with severe variants, and more precise guidance for family members. This is particularly important because early diagnosis, even in variants associated with severe clinical presentations, is linked to a favorable prognosis (Úbeda et al., 2024). The following section will specifically address the main molecular variants associated with HFI, highlighting the most frequent mutations as well as the most extensively studied severe variants. This approach aims

Variant Type	Molecular Effect	Impact on Aldolase B	Expected Clinical Severity
Missense mutations	Substitution of critical amino acids	Partial reduction of enzymatic activity	Mild to moderate, depending on residual activity
Nonsense mutations	Introduction of premature stop codons	Truncated, nonfunctional protein	Severe
Small insertions/ deletions (indels)	Frameshift and altered reading frame	Loss of functional protein	Severe
Splicing variants	Altered mRNA processing	Reduced or absent protein expression	Variable, often moderate to severe

Table 1: Types of ALDOB gene variants, molecular effects, impact on Aldolase B, and expected clinical severity

to support the implementation of targeted genetic panels (**Figure 2**), facilitating rapid and reliable diagnosis of HFI, especially in settings where full ALDOB gene sequencing, considered the diagnostic gold standard, is unavailable or associated with prolonged turnaround times.

Most Frequent variants of ALDOB gene

Four mutations in the ALDOB gene account for the majority of HFI cases (**Table 2**): the missense variant p.Ala150Pro, responsible for approximately 53–64% of global cases; the missense variant p.Ala175Asp, accounting for about 16%; the missense variant p.Asn335Lys, representing approximately 5%; and the frameshift variant p.Asn120LysfsTer32, accounting for roughly 4.6%. Together, these four variants comprise more than 80% of pathogenic alleles reported in several studied cohorts (Cross, Stojanov, et al., 1990; Davit-Spraul et al., 2008; Esposito et al., 2010; Santamaria et al., 1996; Tolan, 1995).

Missense mutations represent the majority of reported cases and generally affect highly conserved regions of aldolase B (**Table 2**). These alterations result in the substitution of a single amino acid, potentially impairing the enzyme's catalytic function or its affinity for the substrate (Davit-Spraul et al., 2008; Santamaria et al., 1996; Tolan, 1995).

The **p.Ala150Pro** variant, also described as A149P, depending on the numbering system used, is considered the classic form of HFI and is the most prevalent mutation, particularly in European populations, accounting for more than half of reported pathogenic alleles (Pinheiro et al., 2021; Santer et al., 2005). This substitution introduces a proline residue into a structurally critical region of the protein, causing distortion in aldolase B folding and compromising the formation of the functional tetramer, thereby leading to significant conformational insta-

Protein Variant	Alternative Nomenclature	Mutation Type	Estimated Frequency	Molecular Impact
p.Ala150Pro	A149P	*Missense*	~53–64%	Conformational instability and near-complete loss of enzymatic activity
p.Ala175Asp	A175D	*Missense*	~16%	Direct alteration of the catalytic site
p.Asn335Lys	N335K	*Missense*	~5%	Significant reduction in catalytic efficiency
p.Asn120LysfsTer32	N120Kfs	*Frameshift*	~4.6%	Truncated protein and complete loss of function

Note. Estimated frequencies are based on published population data. Variant nomenclature follows Human Genome Variation Society (HGVS) protein-level recommendations.

Table 2: Major protein variants, mutation type, estimated frequency, and molecular impact

bility. Although this variant retains very low residual activity, it is not completely inactive; nevertheless, it is generally associated with severe clinical manifestations, which may be milder when present in compound heterozygosity with less severe variants (Brooks' And & Tolan2, 1994; Santamaria et al., 1996; Tolan, 1995). Symptoms typically arise in early childhood following the introduction of fructose, sucrose, or sorbitol into the diet. Typical clinical manifestations include recurrent vomiting after fructose ingestion, symptomatic hypoglycemia (with lethargy, sweating, and seizures), severe abdominal pain, spontaneous aversion to sweets and fruits, and failure to thrive. Laboratory findings commonly include postprandial hypoglycemia, elevated transaminases, hyperuricemia, metabolic acidosis, hypophosphatemia, and reduced activity of pathways such as gluconeogenesis and glycogenolysis. In compound heterozygous individuals, the phenotype is generally intermediate and may result in a later diagnosis. Regardless of genotype, however, early dietary exposure to fructose significantly exacerbates the clinical presentation (Esposito et al., 2010).

The missense variant **p.Ala175Asp** is one of the most extensively studied and directly affects the catalytic site of aldolase B. This substitution introduces a negatively charged residue, altering its interaction with fructose-1-phosphate and resulting in a marked reduction in catalytic activity, even when the overall protein structure remains relatively stable. Approximately 5–15% of residual enzymatic activity is preserved, which may attenuate metabolic toxicity and is generally associated with milder forms of HFI. This residual activity allows minimal fructose tolerance and may lead to delayed diagnosis, occurring in late childhood, adolescence, or occasionally adulthood. Clinical manifestations include abdominal pain after ingestion of fructose or sucrose, occasional nausea and vomiting, abdominal distension, intermittent diarrhea, and postprandial fatigue (Ali et al., 1994; Coffee & Tolan, 2010; Cross, Cox, et al., 1990; Nchez-Gutirrez et al., 2002). Unlike the p.Ala150Pro variant, hypoglycemia is usually mild or sporadic, and severe episodes are rare. Patients may exhibit partial aversion to sweets and fruits, typically less pronounced than in the classic phenotype, and some individuals maintain moderate fructose intake until diagnostic evaluation. Laboratory findings may show mild or transient elevations in AST and ALT, mild hyperuricemia, generally normal serum phosphate levels, and hypoglycemia only after high fructose intake. In compound heterozygosity (A175D combined with a severe mutation), the phenotype ranges from intermediate to severe, depending on the allele in trans (Ali et al., 1998; Beyzaei et al., 2023; M. S. Kim et al., 2020; Úbeda et al., 2024).

The **p.Asn335Lys,** also described as N334K, mutation is a less frequent missense variant located in the C-terminal region of the enzyme, which is involved in structural stability and distant from the catalytic site (Cross, Stojanov, et al., 1990). This alteration causes a mild electrostatic change, preserving approximately 15–30% of residual enzymatic activity. This variant is generally associated with milder phenotypes, strongly influenced by dietary fructose load (Ali et al., 1994; Coffee & Tolan, 2010; Ferri et al., 2012; Nchez-Gutirrez et al., 2002). Diagnosis often occurs during adolescence or adulthood, frequently incidentally or after evaluation of nonspecific symptoms,

reflecting a high potential for underdiagnosis. Clinical manifestations include mild abdominal discomfort after excessive fructose intake, abdominal bloating, flatulence, and occasional nausea. Hypoglycemia is absent or extremely rare. Most patients do not exhibit marked aversion to sweets or fruits, and many maintain a regular diet for years. Laboratory findings typically show normal or slightly elevated AST/ALT, normal glycemia, and absent or mild hyperuricemia, with preserved renal function. In compound heterozygosity (N335K combined with a severe mutation), the phenotype is generally intermediate and determined by the more severe allele (Beyzaei et al., 2023; M. S. Kim et al., 2020; Úbeda et al., 2024).

The **p.Asn120LysfsTer32** variant is a classic frameshift mutation introducing a premature stop codon, resulting in a truncated and nonfunctional protein, consistent with complete aldolase B deficiency (Choi et al., 2012). It is frequently associated with early and severe clinical manifestations. Symptoms typically arise in infancy, shortly after the introduction of fructose, sucrose, or sorbitol into the diet (infant formulas, juices, or fruits). Patients present with recurrent vomiting, severe nausea, abdominal pain, and feeding refusal, often accompanied by spontaneous aversion to sweets and fruits. Metabolic disturbances are acute and include severe hypoglycemia, due to inhibition of gluconeogenesis and glycogenolysis, associated with lethargy, sweating, tremors, and, in untreated cases, seizures. Metabolic acidosis may occur during crises. Hepatic involvement includes hepatomegaly, elevated AST, ALT, and bilirubin levels, rapid development of hepatic steatosis, and risk of acute liver failure if dietary exposure persists. Proximal tubular dysfunction may also occur, with aminoaciduria, proteinuria, and renal tubular acidosis in more severe cases. Without early diagnosis and intervention, affected patients are at high risk for acute liver failure, growth retardation, and death during childhood (Beyzaei et al., 2023; M. S. Kim et al., 2020; Úbeda et al., 2024) .

Feature	p.Ala150Pro (A150P)	p.Ala175Asp (A175D)	p.Asn335Lys (N335K)	p.Asn120LysfsTer32 (N12C) (N120Kfs)
Mutation type	Missense	Missense	Missense	Frameshift
Structural location	α-helical region	Near catalytic site	C-terminal region	Truncating variant
Molecular impact	Severe conformational instability	Moderate catalytic impairment	Mild electrostatic alteration	Truncated protein
Aldolase B activity	<5%	5-15%	15-30%	Absent (0%)
Clinical phenotype	Classic, severe	Intermediate / mild	Mild / atypical	Classic, severe
Age at onset	Infancy	Late childhood / adolescence	Adolescence / adulthood	Infancy
Hypoglycemia	Frequent and severe	Occasional	Rare	Frequent and severe
Hepatic involvement	Hepatomegaly, increased AST/ALT	Mild or intermittent alterations	Minimal or absent	Severe hepatopathy
Renal involvement	Tubular dysfunction	Rare	Absent	Tubular dysfunction
Risk of metabolic crises	High	Moderate	Low	Very high
Dietary response	Strict fructose	Strict restriction	Low	Strict lifelong restriction

Figure 2 - Proposal for a genetic panel for the rapid identification of IHF variants in locations where genetic testing is unavailable or where results are very delayed. Variants are presented using HGVS protein-level nomenclature, and its respective abbreviation, on the horizontal axis. On the vertical axis, the characteristics and symptoms of HFI.

Essential Fructosuria

Essential Fructosuria is a rare inborn error of carbohydrate metabolism, traditionally considered clinically benign. Its medical relevance is not related to clinical manifestations, which are absent, but rather to its importance in differential diagnosis, particularly due to the possibility of confusion with diabetes mellitus in urinary screening tests. From a biochemical perspective, Essential Fructosuria results from deficiency or functional absence of the enzyme fructokinase (ketohexokinase, KHK), which is mainly expressed in the liver, kidneys, and small intestine (**Figure1**) (Asipu et al., 2003; Bonthron et al., 1994). This enzyme catalyzes the initial step of fructose metabolism, converting fructose into fructose-1-phosphate. When KHK is absent or deficient, fructose absorbed from the gastrointestinal tract is not properly metabolized. Consequently, it remains in its free form in the bloodstream and is excreted unchanged in the urine (Dholariya & Orrick, 2022; Petersen et al., 1992).

Basis of Diagnostic Confusion

The main historical source of diagnostic confusion related to Essential Fructosuria is associated with the use of nonspecific urinary glucose tests, widely employed before the dissemination of modern enzymatic methods. Classical tests such as Benedict's test, Fehling's test, and Clinitest detect reducing sugars, a chemical group that includes not only glucose but also fructose, galactose, lactose, and pentoses. Fructose, being a reducing monosaccharide, can reduce cupric ions (Cu^{2}) to cuprous ions (Cu) in these chemical assays, producing a positive result for "sugar in the urine". Thus, individuals with Essential Fructosuria may present a positive urinary sugar test after ingesting fruits, juices, or sucrose-rich foods. When blood glucose is not simultaneously measured, this finding may lead to an erroneous suspicion of diabetes mellitus. This confusion is particularly relevant in historical contexts, in regions with limited access to modern laboratory methods, or in older occupational and school screening programs. It may also occur during the initial evaluation of asymptomatic children with glycosuria detected by nonspecific methods (Alberti et al., 2023; Başkan et al., 2016; Benedict, 1909; Inzucchi, 2012).

Pathophysiological Differences

Although both conditions may present with sugar in the urine, their pathophysiological mechanisms are entirely different. In diabetes mellitus, glycosuria results from persistent hyperglycemia that exceeds the renal tubular reabsorption threshold for glucose. In Essential Fructosuria, blood gluco-

Aspect	Diabetes Mellitus	Essential Fructosuria
Blood Glucose Level	Elevated	Normal
Renal Transport Mechanism	SGLT2 saturation	Limited passive transport
Renal Threshold	Exceeded	Not applicable
Type of Urinary Sugar	Glucose	Fructose
Systemic Symptoms	Present	Absent
Classical tests	Positive	Positive

Table 3: Comparison Between Diabetes Mellitus and Essential Fructosuria

se levels are normal, and there is no insulin resistance or deficiency in insulin secretion. Fructose is freely filtered by the glomeruli and poorly reabsorbed by the renal tubules, leading to its urinary excretion. Therefore, the absence of classic diabetes symptoms, such as polyuria, polydipsia, weight loss, and fatigue, combined with normal plasma glucose levels should raise suspicion that a non-glucose reducing sugar is responsible for the positive urinary result (Cloete, 2021; Dholariya & Orrick, 2022; Inzucchi, 2012). Below is a quick comparison table between diabetes and Essential Fructosuria.

Clinical Impact of Diagnostic Confusion

Although Essential Fructosuria does not cause organic damage, confusion with diabetes mellitus may lead to unnecessary clinical and psychosocial consequences, including excessive ordering of complementary tests, incorrect labeling of the patient as diabetic, unjustified restrictive dietary recommendations, significant anxiety for patients and their families, in pediatrics, diagnostic errors may also result in avoidable invasive investigations or hospitalizations, particularly when recent dietary history is not considered (Herzer & Hood, 2010; Hurwitz & Sheikh, 2009; Program & Maxwell, 2018; Tareen & Tareen, 2017). Currently, the use of glucose-specific urine dipsticks based on the enzyme glucose oxidase virtually eliminates this confusion, as these strips do not react with fructose (Alberti et al., 2023). When necessary, diagnostic confirmation can be achieved through urinary sugar chromatography or molecular testing to identify variants in the KHK gene (Bonthron et al., 1994).

Final Considerations

Disorders of fructose metabolism, although relatively rare, have clinical relevance that is disproportionate to their prevalence, particularly in pediatric and neonatal settings. HFI stands out as a potentially severe and even fatal inborn error of metabolism when not recognized early, whereas Essential Fructosuria, despite being clinically benign, remains diagnostically important due to its potential to be confused with other metabolic conditions, especially diabetes mellitus.

Throughout this review, it has become evident that HFI exhibits broad genetic and phenotypic heterogeneity, strongly influenced by the type of variant in the ALDOB gene and the degree of residual aldolase B activity. Frameshift and nonsense mutations are consistently associated with more severe, early-onset presentations, carrying a high risk of profound hypoglycemia, liver failure, and death in the absence of immediate dietary intervention. In contrast, missense variants with residual enzymatic activity may allow milder or atypical phenotypes, often diagnosed later in life, underscoring the need for greater clinical awareness of these non-classical presentations.

Understanding the biochemical basis of HFI demonstrates that the accumulation of fructose-1-phosphate and the consequent depletion of ATP and inorganic phosphate constitute the central axis of its pathophysiology, integratively explaining the hepatic, renal, metabolic, and neurological manifestations observed in affected patients. This knowledge reinforces the therapeutic rationale for strict exclusion of fructose, sucrose, and sorbitol, a simple yet highly effective measure capable of interrupting the pathological cascade and providing an excellent

prognosis when instituted early. Furthermore, identifying the most frequent ALDOB variants enables the development of targeted genetic panels, particularly useful in settings where full gene sequencing is not readily available or has prolonged turnaround times. Such an approach facilitates rapid diagnosis, family screening, genetic counseling, and, most importantly, the prevention of potentially lethal dietary exposures in at-risk newborns.

Regarding Essential Fructosuria, although it poses no direct clinical risk, its accurate recognition remains crucial to prevent diagnostic errors, unnecessary investigations, and negative psychosocial consequences resulting from a false suspicion of diabetes mellitus. Knowledge of its biochemical basis, combined with modern and specific laboratory methods, virtually eliminates this diagnostic confusion.

In summary, advances in the molecular and biochemical understanding of fructose metabolism disorders highlight the importance of integrating genetics, clinical evaluation, and laboratory diagnosis. Investing in early diagnostic strategies, professional education, and the implementation of targeted genetic testing is essential to improve clinical management, reduce morbidity and mortality in HFI, and ensure safe and appropriate follow-up for patients and their families.

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