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Review article

From Definition to Therapy: A Comprehensive Article Review of Galactosemia

Amjed Torki Al-Rudaini[1]*

ABSTRACT

Galactosemia is a medical disorder that affects the body's ability to metabolize galactose. After infants ingest galactose from breast milk or formula, those with the condition can develop a life-threatening illness accompanied by feeding problems. Infants with galactosemia can be identified through newborn screening programs (NBS) or by symptoms that appear in the first weeks after birth. If untreated, infants may suffer kidney and liver damage, develop cataracts, and experience severe infections. Some countries offer newborn screening programs to help with the early detection and treatment of galactosemia. This article review aims to define galactosemia, its types, signs and symptoms, diagnosis, and ways it can be prevented or managed.

Keywords: Galactosemia, Metabolic Disease, Genetic Disorder, Newborn Screening Programs, Therapeutic Strategies

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1. INTRODUCTION

Galactosemia was first described by von Reuss in the early 1900s [1]. It is a hereditary disorder of carbohydrate metabolism that prevents the conversion of galactose, a sugar found in milk, which is a primary source of nutrition for newborns, into glucose, the body's main energy source [2]. Louis Leloir received the Nobel Prize in Chemistry for discovering the galactose breakdown process. The Leloir pathway involves three enzymes that metabolize galactose: galactokinase (GALK), galactose-1-phosphate uridyltransferase (GALT), and uridine diphosphate (UDP)-galactose 4-epimerase (GALE). If these enzymes are deficient, galactose builds up in the body, leading to galactosemia [1].

Galactosemia is an autosomal recessive genetic disorder of galactose metabolism caused by a deficiency of galactose-1-phosphate uridyltransferase, the second enzyme in the main pathway of galactose metabolism, known as the Leloir pathway, with an incidence of 1 in 16,000 to 60,000 live births. Galactose-1-phosphate (Gal-1-P), galactonate, and galactitol are accumulated as a result [4,5].

2. Galactosemia Types

The galactosemia can be classified as either classic, clinical, or biochemical:

Classic galactosemia is an allelic, autosomal-recessive inherited disorder of galactose metabolism [6]. After consuming galactose through breast milk or neonatal feeding, a significant deficiency of the enzyme galactose-1-phosphate-uridyltransferase (GALT; EC 2.7.7.12) leads to a potentially fatal disease in newborns. The only current treatment is a galactose-restricted diet, which does not prevent long-term issues but highlights the key signs in affected neonates. Regardless of illness during the neonatal period, many patients face long-term challenges even with timely or early treatment due to familial or neonatal screening [6,7].

* Correspondence: Dr. Al-Rudaini AT. E-mail: amjed.torki@sc.uobaghdad.edu.iq
Department of Biology, College of Science, University of Baghdad, Baghdad, Iraq
Full list of author information is available at the end of the article.

Untreated newborns with classic galactosemia may face hemorrhage, liver damage, feeding difficulties, growth failure, and Escherichia coli sepsis, among other potentially deadly outcomes. Even with prompt treatment starting early in life, children with classic galactosemia remain at higher risk for developmental delays, speech issues (such as childhood apraxia of speech and dysarthria), and motor function abnormalities. However, suppose a lactose-restricted diet is administered during the first ten days of life. In that case, neonatal symptoms typically resolve quickly, and risks like liver failure, sepsis, and neonatal death can be prevented. Most women with typical galactosemia experience early ovarian insufficiency [7,8]. Additionally, tremors are among the most common symptoms in patients with galactosemia [9].

Clinical variant galactosemia in untreated newborns can lead to potentially fatal complications, including feeding difficulties, failure to grow, liver damage such as cirrhosis, and bleeding. This condition has been observed in native Africans and African Americans in South Africa. Individuals with clinical variant galactosemia may be missed during newborn screening (NBS) because their breath tests appear normal, and their hypergalactosemia is less severe than classic galactosemia. A lactose-restricted diet during the first 10 days of life typically prevents severe newborn problems [7].

Biochemical variant galactosemia, specifically Duarte variant galactosemia, is an example of the disease's biochemical variation, which many people believe to be a harmless, non-disease condition [10].

3. The importance of galactose in health

Galactose is an essential carbohydrate for cell metabolism, acting as a precursor for glycosylation and aiding in energy production and storage across various human tissues [11]. It is a six-carbon reducing monosaccharide ($C_6H_{12}O_6$). Many living organisms require galactose, a carbon 4 (C-4) epimer of glucose, as a carbon source for producing anaerobic energy and synthesizing glycan. After digestion, galactose can be quickly absorbed into the bloodstream, where it supports glycosylation, energy formation, and other crucial metabolic processes [12].

Galactose is a naturally occurring aldohexose that mostly exists in the D-configuration and can be found in complex carbohydrates (oligosaccharides and polysaccharides), glycolipids, and glycoproteins, both as free and bound forms. Galactose combined with glucose to produce lactose as a disaccharide, which is found in the majority of bovine milk and acts as an important source of energy for newborns [13,14].

Lactose, found in milk and dairy products, is the most well-known dietary source of galactose. Lactose is broken down into glucose and galactose by lactase in the intestinal lumen after consumption. Galactose is transported across the enterocyte brush border membrane by the sodium/glucose co-transporter SGLT1, while it crosses the enterocyte basolateral membrane via the GLUT2 transporter through facilitated diffusion. It is carried by blood through the portal veins to the liver, the primary site of galactose metabolism, where the low-affinity, high-capacity GLUT2 enzyme absorbs it [15]. After being consumed, galactose enters the body and begins its metabolic journey in the lumen of the intestine, where it is absorbed by the villi's endothelial cells via the sodium-glucose linked transporter type I (SGLT1) [16].

Following that, galactose is released into the bloodstream via the glucose transporter type 2 (GLUT2), which is located on the membrane of enterocytes [16]. Galactose reaches the liver through additional GLUTs after passing through the portal vein. The liver stores most of the galactose consumed; only a tiny amount reaches other organs like the brain or the mammary glands, where it is used to manufacture lactose or amino acids [12]. The most significant amount of galactose is metabolized in the liver, skeletal muscles, and other target organs through three main pathways: (a) in the Leloir pathway, galactose undergoes glycosylation or glycolysis, (b) it is then converted to galactonate, which undergoes further metabolism to enter the pentose phosphate pathway, and (c) it is reduced to galactitol, which is subsequently eliminated by the kidneys (figure 1) [11].

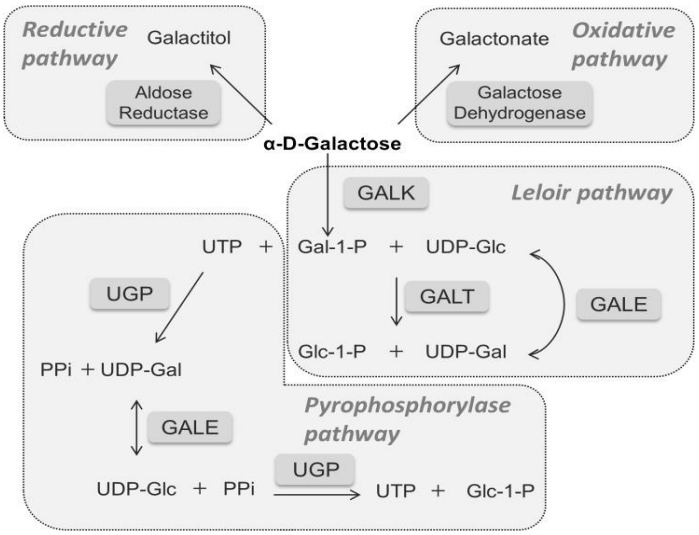

Fig. 1 Major pathways for galactose metabolism

4. Galactose and glycosylation in humans

From simple organisms, including bacteria, to plants and animals, galactose metabolism is highly conserved and generally occurs through the Leloir pathway. In 1948, L.F. Leloir first described this pathway, which consists of four enzyme steps that ultimately modify the C-1 position of galactose, changing its stereochemical configuration [17,18]. Galactose can be converted into UDP-α-D-galactose (UDP-Gal) and used as a glycosylation precursor or transformed into UDP-α-D-glucose (UDP-Glc), which then participates in glycogen synthesis or glycolysis depending on tissue type and energy needs. The initial step involves converting β-D-galactose into its stereoisomer α-D-galactose through the enzyme galactose mutarotase (GALM) [17,19].

Wallenfels and colleagues discovered GALM in E. coli in 1965 [20], but it wasn't until 2003 that its human homolog gene and protein were identified [21]. The human GALM protein is a 342- amino-acid β-sheet "sandwich" characterized by an active site in an open cleft. This contrasts with its bacterial counterpart, which functions as a monomer [21, 22]. Besides galactose, GALM can (with varying efficiency) modify the anomeric forms of lactose, D-glucose, maltose, D-xylulose, and L-arabinose [23].

The second step of the Leloir pathway involves galactokinase (GALK) phosphorylating D-galactose to form α-D-galactose 1-phosphate (Gal 1P) Galactokinase (GALK) is a protein consisting of 400 amino acids that is associated with the GHMP (Galacto, Mevalonate, Phosphomevalonate, and Homoserine) kinase superfamily. Though the complete three-dimensional structure of human GALK has not been fully elucidated, a crystal structure of GALK from *Lactococcus lactis*, complexed with α-D-galactose and inorganic phosphate, was reported in 2003. This bacterial GALK exhibits 24% identity and 47% similarity to its human counterpart, which contains 2 domains of nearly identical size, with the catalytic

site positioned between the N- and C-terminal domains [17].
This ATP-dependent enzyme, which differs from bacteria, first binds to ATP and then to α-D-galactose [17,24], and it can also phosphorylate 2-deoxy-D-galactose [23]. The third step of this pathway involves the enzyme GALT, which facilitates the formation of UDP–Gal. GALT catalyzes the conversion of Gal-1P and UDP-Glc to α-D-glucose 1-phosphate (Glc-1P) and UDP-Gal [19]. Human GALT consists of a homodimer, with each monomer comprising 379 amino acids. Each monomer contains an active site and a structural zinc-binding site at position 168. Although highly conserved, human GALT differs significantly from bacterial GALT in metal ligation and dimer interactions [25]. UDP-galactose 4′-epimerase (GALE) catalyzes the final step of the Leloir pathway. The enzyme GALE, consisting of 348 amino acids, mediates the interconversion between UDP-Glc and UDP-Gal [19,26].
This enzyme is classified as part of the short-chain dehydrogenase/reductase enzyme family. UDP-galactose 4-epimerase (GALE) exists as a dimer in solution that requires NAD+ for catalytic activity. Each subunit of GALE contains a substrate-binding site. The conversion of UDP-N-acetyl α-D-galactosamine (UDP-GlcNAc) can also be catalyzed by human GALE, unlike the highly specific bacterial enzyme [27-29].
The enzymatic processes of the Leloir pathway (except for GALK) can occur in both directions, although it is generally defined as the metabolism of galactose and UDP-Glc toward UDP-Gal production, depending on tissue metabolic needs and substrate availability. UDP-Gal is used as a glycosylation building block in most tissues. When there is no energy demand, UDP-Gal can be converted into UDP-Glc, which serves as a precursor for glycogen synthesis in the liver and skeletal muscle [30, 31].
Conversely, UDP-Gal plays a vital role in energy production when energy demand is high by converting to UDP-Glc, which is subsequently changed into Glc-1P by UDP-glucose pyrophosphorylase 2 (UGP2) and then into glucose-6-phosphate (Glc-6P) by phosphoglucomutase-1 (PGM1) when glycolysis begins [2, 11].
Finally, UDP-Gal is used in the mammary glands of nursing animals for both glycosylation and lactose production, which is facilitated by the lactose synthase (LS) complex. This enzyme complex, located in the GA lumen, consists of a non-catalytic regulatory component called α-lactalbumin and a catalytic subunit known as β-1,4-galactosyltransferase, also referred to as N-acetyl-lactosamine synthase. In the absence of α-lactalbumin, N-acetyl-lactosamine is produced by β-1,4-galactosyltransferase using UDP-Gal and GlcNAc [11].

5. Signs and symptoms

In the first few days of life, infants with galactosemia may show symptoms if they are fed breast milk or formula containing lactose. The symptoms could indicate a deadly blood infection caused by E. coli [10,32]. Galactosemia symptoms include spasms, irritability, fatigue or lethargy, poor nutrition; the infant refuses to drink milk-based formula, liver enlargement (hepatomegaly), jaundice, yellow skin and eye discoloration, vomiting, and poor weight gain.

6. Prevalence

The data from newborn screening programs (NBS) indicate that the incidence of classic galactosemia is 1 in 48,000 (National Newborn Screening and Genetics Resource Centre 2014). In Ireland, the incidence is approximately 1 in 16,476 [3]. Meanwhile, the prevalence of galactosemia in live births was around 1 in 39,000 in the UK in 2020 [35]. A study by Arif and colleagues surveyed 1758 Iraqi children from Baghdad between 2009 and 2012 for inborn metabolic abnormalities; 224 of these children tested positive, resulting in a detection rate of 12.7% from infancy to early adolescence. Thirty-one cases of galactosemia (1.76%) were identified [36]. The prevalence of galactosemia in Iran is roughly 1 in 24,000 [37].

7. Diagnosis

The Diagnostic methods for both classic and clinical variant galactosemia involve the following:
1. Detection of elevated galactose-1-phosphate levels in erythrocytes.
2. Detection of erythrocytes with reduced galactose-1-phosphate uridylyltransferase (GALT) enzyme activity.
3. Determination of GALT biallelic pathogenic variants [38,39].
Classic galactosemia is characterized by little or no erythrocyte GALT enzyme activity, while erythrocyte galactose-1-phosphate levels are often over 10 mg/dL [40]. In clinical variant galactosemia, the brain and intestinal tissues show significantly higher levels of erythrocyte GALT enzyme activity, although it may be absent or barely detectable, as in African Americans (e.g., 10% of control levels) [41].
In some individuals with clinical variant galactosemia, erythrocyte GALT enzyme activity may be near or above 1% of control values, but it is unlikely to exceed 10% to 15%. Newborn screening programs (NBS) that include galactosemia testing in their panel can detect nearly all cases of clinical variant galactosemia or classic galactosemia. However, neonates with clinical variation galactosemia might be missed if the program only measures blood total galactose levels rather than erythrocyte GALT [10].
Newborn screening programs are available in several countries to help with the early detection and management of galactosemia. Neonatal screening programs for galactosemia have enabled the early detection of the fatal classic and Duarte forms of the disease [42]. They also allowed for further identification of molecular abnormalities in galactosemia. The term "GG" galactosemia is derived from the fact that it made it possible to detect compound heterozygosity for one functionally severe (G) GALT mutation and a D2 allele in Duarte galactosemia, as well as to identify functionally severe (G) mutations in each of the GALT alleles in classic galactosemia [43]. According to Maverakis and his colleagues (2015), the clinical spectrum of partial GALT deficiency ranges from moderate to clinically silent, with potentially problematic developmental impairments rather than life-threatening consequences [44].

8. Establishment of the Diagnosis

A proband is diagnosed with both classic and clinical variant galactosemia through various methods. One method of molecular genetic testing is single-gene testing. If no harmful variant is detected or if none is found, the gene-targeted deletion/duplication test is performed after the GALT sequence test. First, individuals with European or African heritage can undergo targeted testing for common pathogenic mutations. This approach is most effective when analyzing large numbers of samples, such as in newborn or carrier screening [10].

9. Newborn screening:

A variety of tests conducted in the first few days of a child's life is called "newborn screening." Screening helps identify those who may have the disease from those who most likely do not. In contrast, diagnostic testing is used to confirm whether a problem exists [45]. The entire newborn screening system (NBS) includes laboratory testing, diagnosis, treatment, education, assessment,

and follow-up. The NBS system requires ongoing quality improvements, focusing on information exchange, technical support, and standardized data, to ensure its success. To confirm phenylketonuria in all newborns, Dr. Robert Guthrie developed a test in 1959 that detects high levels of phenylalanine using a microbiological bacterial inhibition test on a dried blood spot (DBS) collected on filter paper, known as the "Guthrie card" [46, 47].

For years, neonatal screening for the diagnosis of classic galactosemia in newborns has been debated without reaching a consensus. According to Clarke (2005), the criteria for newborn screening are based on the screening principles first proposed by Wilson and Jungner, then further developed by Pollitt and colleagues. For two main reasons, galactosemia has been removed from several newborn screening programs (NBS): it can be clinically detected, and even with early treatment, long-term effects may still occur.

Pollitt and his colleagues recognized that a disease could be included in newborn screening programs (NBS) without the need for an effective treatment. Nevertheless, they still did not recommend screening for galactosemia directly [49]. However, it was advised that an additional test for galactosemia be performed on all samples with elevated phenylalanine. According to a later study, parental stress was often higher in families with children diagnosed clinically, and of the children, 47% with mental disorders had it, compared to only 14% of those detected by NBS, despite equal hospitalization rates. The study compared 124 children with metabolic illnesses based on clinical symptoms (9 galactosemic) with 139 children who had metabolic disorders diagnosed via NBS (17 galactosemic) [50]. According to Khalaf et al. (2019), early newborn screening is crucial, especially in countries with high rates of consanguinity, since early detection and treatment are likely to improve neurodevelopmental outcomes and reduce death rates [51].

10. Treatment

10.1. Nutritional Therapy

Treatment for galactosemia has been based on a low-galactose diet, which has proven to be particularly effective in treating life-threatening symptoms in newborns. The importance of research in updating evidence-based practice strategies and the role of medical facilities in providing lifelong care to these patients are both emphasized by this [52,53]. The debate over the Duarte variant restriction continues; however, lifetime galactose restriction and long-term monitoring remain the accepted standard therapies, despite research raising doubts about the benefits of strict dietary restrictions. A recent study found that infants with Duarte galactosemia are not more likely to experience acute problems or developmental issues requiring care if they are fed milk or low-galactose formula throughout infancy [54].

Newborns with erythrocyte galactose-1-phosphate levels higher than 10 mg/dL and erythrocyte GALT enzyme activity at or below 10% of control values should receive immediate nutritional treatment. All milk-based products must be quickly replaced with a lactose-free formula, such as Prosobeel® or Isomi®. These soy formulas contain oligosaccharides that are insoluble in the small intestine, like sucrose, fructose, and galactose. In the past, casein hydrolysate-based elemental formulas like Nutramigen®, Pregestimil®, and Alimentum®, which contain trace amounts of galactose, have been used without noticeable adverse effects. Without causing any negative effects, Neocate®, a product that contains neither free nor bound galactose, has been used [55].

All foods containing lactose, especially all dairy products including cow's milk, must be avoided throughout life. However, after early childhood and infancy, when dairy products are no longer the primary source of energy, dietary restrictions become less critical. The strictness of the diet beyond infancy is debatable [56], since the body produces about ten times more galactose than what is found in foods other than milk. Due to the risk of calcium and vitamin D deficiencies caused by dietary restrictions, supplements should be provided as needed [2]. Over 1,000 IU/day of vitamin D and vitamin K supplements have been recommended [57].

10.2. Gene Therapy

To permanently address genetic defects, gene therapy and gene modification techniques are utilized [58,59]. This is accomplished in traditional gene therapy by delivering patients the correct coding DNA (cDNA) sequence of the defective gene, leading to normal protein production [59,60]. Vectors, either viral or non-viral, that carry the genetic instructions for proteins are used to deliver these messages [58,61]. Significant progress has been made over recent decades, and gene therapy has shown promising results in clinical trials and animal models of inherited metabolic disorders [59, 61]. Using recombinant adeno-associated virus (AAV) vectors, which demonstrate considerable potential in gene therapy [59, 62]. It is reported that viral-mediated in vivo gene therapy is currently under investigation for classic galactosemia [58]. When neonatal human GALT gene therapy using an AAV9 vector was administered into the tail vein, a recent study with a galactosemia rat model showed GALT restoration in both the liver and brain [62]. GALT activity levels of 64–595% in the liver and 2–42% in the brain were observed relative to wild-type activity, without causing noticeable negative effects. Moreover, there was a positive impact on cataracts and a reduction in galactose metabolites in the brain, liver, and blood [61].

10.3. mRNA Therapy

The effect of RNA therapy has also been studied in classical galactosemia. Nanoparticles, liposomes, viruses, and other carriers can encapsulate and deliver mRNA to the target site, where it can be translated into a functional protein [63, 64]. Immediately after delivery, a single injection of GALT mRNA reduced mortality in rats fed milk containing GALT deficiency. Moreover, using lipid nanoparticles (LNP) to deliver GALT mRNA to GALT-deficient rats resulted in a dose-dependent increase in GALT activity and expression in the liver, along with a decrease in galactose 1-P levels in the peripheral tissues, liver, and red blood cells [64, 64,65]. According to Delnoy et al. (2022), administering LNP-packaged hGALT mRNA was consistently safe and restored GALT protein levels and function in a zebrafish model of CG. Identifying the optimal dose interval, modifying LNP to target extrahepatic regions such as the brain or gonads, and assessing the immune response induced by mRNA remain significant hurdles for developing mRNA therapy as a treatment for CG. Overall, the mRNA approach holds substantial promise for treating classic galactosemia [52].

10.4. Pharmacological Chaperon Therapy

Pharmacological chaperones, which are tiny chemicals that correct misfolded proteins, are an exciting new treatment option for galactosemia [66]. To stabilize disease-associated variants, pharmacological chaperones bind selectively to their targets and preserve certain protein variants by promoting intracellular trafficking and proper folding, increasing cellular activity and stability, and/or preventing premature degradation [67,68]. This shift in the balance toward the folded form results in more protein that bypasses the quality control system, reduces abnormal trafficking, and ultimately expands the enzyme's active pool. Consequently, it has been suggested that PCs can repair folding

and trafficking defects in transporters, receptors, enzymes, and other structural proteins [70].
Pharmacological chaperones may be helpful in treating neuropathic pathologies in many rare disorders because of their (i) low synthesis cost, (ii) oral delivery with broad biodistribution, and (iii) low molecular weight, which may allow them to pass through the blood–brain barrier and reach various target tissues. Patients may find them less taxing [70,71].

10.5. Galactokinase 1 Inhibitors Therapy

Galactose-1-phosphate uridylyltransferase (GALT) loss-of-function mutations that lead to a toxic buildup of its substrate, galactose-1-phosphate (Gal-1-P), cause classic galactosemia. Inhibiting galactokinase 1 (GALK1)-catalyzed galactose-1-phosphate production is one proposed treatment [72]. Gal-1-P is believed to be a key factor in the disease mechanism of classic galactosemia, so this approach aims to reduce the accumulation of Gal-1-P in GALT deficiency [69]. Inhibiting GALK1 is a promising therapeutic target because it is a highly substrate-specific enzyme in the GHMP kinase family, and no additional undesired effects are expected [73]. High-throughput screening has identified several potential molecules. It has been shown that phenylsulfunamides decrease galactose 1-P levels in fibroblasts from CG patients [74]. Recently, non-competitive GALK1 inhibitors are being developed for potential clinical trials [72].

10.6. Aldose reductase (AR) inhibitors Therapy

Targeting the conversion of galactose to galactitol, which accumulates in cells and causes swelling and cell death in CG, aldose reductase (AR) inhibitors are enzyme inhibitors [2, 75]. Galactosemic cataracts are specifically caused by a buildup of galactitol inside the lens [75]. Neurological symptoms may also occur due to galactitol accumulation [27].AR inhibitors have been shown to reduce galactitol levels in the brain, liver, and plasma, and to prevent cataract formation in rat models with GALT deficiency [76, 76,77]. They were initially developed to treat diabetes [78]. In galactosemic rats treated with an AR inhibitor, damage to Schwann cells caused by galactitol has also been decreased [78]. Whether AR inhibitors can effectively treat other issues such as subfertility or cognitive disorders remains uncertain. Additionally, it is unclear what consequences might arise if galactose conversion to galactitol is completely blocked, such as an increase in galactonate. Overexpression of aldose reductase in the lens's epithelial cells results in galactosemic cataracts [52, 79].

11. Conclusions

Galactosemia is the most serious disease; this metabolic disorder leads to increased morbidities that threaten and impair quality of life if it remains undetected and untreated. Early detection is essential to avoid long-term complications. Neonatal screening tests are necessary to prevent severe morbidity and mortality. Pharmacological chaperones offer a new therapeutic approach for GALT protein rescue; however, unlike gene therapy or mRNA treatment, this strategy is specific to certain genetic variants.

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Conflict of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

Al-Rudaini AT: Investigation, Project administration, Resources, Roles/Writing – original draft, Supervision, and Validation, Writing–review & editing.

REFERENCES

[1] **Cerone J, Rios A.** (2019) Galactosemia. *Pediatr Rev* **40**(1):24–27. doi.org/10.1542/pir.2018-0150
[2] **Succoio M, Sacchettini R, Rossi A, Parenti G, Ruoppolo M.** (2022) Galactosemia: Biochemistry, Molecular Genetics, Newborn Screening, and Treatment. *Biomolecules* **12:** 968. doi.org/10.3390/biom12070968.
[3] **Coss KP, Doran PP, Owoeye C, Codd MB, Hamid N, et al.** (2013) Classical Galactosaemia in Ireland: incidence, complications and outcomes of treatment. *J Inherit Metab Dis* **36**(1): 21–27. doi.org/10.1007/s10545-012-9507-9
[4] **Pasquali M, Yu C, Coffee B.** (2018) Laboratory diagnosis of galactosemia: a technical standard and guideline of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* **20**:3–11. doi.org/10.1038/gim.2017.172
[5] **Druss JJ, Rudd Zhong Manis J, Potter NL, Fridovich-Keil JL.** (2023) Grip strength in patients with galactosemia and in a galactose-1-phosphate uridylyltransferase (GALT)-null rat model. *J Inherit Metab Dis* **46**(6):1131-1138. doi.org/10.1002/jimd.12684
[6] **Hermans ME, van Oers HA, Geurtsen GJ, Haverman L, Hollak CEM, et al.** (2023) The challenges of classical galactosemia: HRQoL in pediatric and adult patients. *Orphanet J Rare Dis* **18**(1):135. doi.org/10.1186/s13023-023-02749-8.
[7] **Berry GT.** (2000) Classic Galactosemia and Clinical Variant Galactosemia. In: Adam MP, Feldman J, Mirzaa GM, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1518.
[8] **Hughes J, Ryan S, Lambert D, Geoghegan O, Clark A, et al.** (2009) Outcomes of siblings with classical galactosemia. *J Pediatr* **154**: 721-726. doi.org/10.1016/j.jpeds.2008.11.052 .
[9] **Almenabawy N, Bahl S, Ostlund AL, Ghai-Jain S, Sosova I, et al.** (2024) Clinical and biochemical phenotypes, genotypes, and long-term outcomes of individuals with galactosemia type I from a single metabolic genetics center in Alberta. *Mol Genet Metab Rep* **38**:101055. doi.org/10.1016/j.ymgmr.2024.101055
[10] **Berry GT.** (2000) Classic Galactosemia and Clinical Variant Galactosemia. [Updated 2017 Mar 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2019. PMID:20301691.
[11] **Conte F, van Buuringen N, Voermans NC, Lefeber DJ.** (2021) Galactose in human metabolism, glycosylation and congenital metabolic diseases: Time for a closer look. *Biochim Biophys Acta Gen Subj* **1865**(8):129898. doi.org/10.1016/j.bbagen.2021.129898 . PMID: 33878388.
[12] **Coelho A I, Trabuco M, Silva M J, de Almeida I T, Leandro et al.** (2015) Arginine Functionally Improves Clinically Relevant Human Galactose-1-Phosphate Uridylyltransferase (GALT) Variants Expressed in a Prokaryotic Model. *JIMD reports* **23**: 1–6. https://doi.org/10.1007/8904_2015_420
[13] **Bell D.** (2012) Natural monosaccharides and oligosaccharides: their structures and occurrence. In Florkin M, editor. Comparative biochemistry: a comprehensive treatise. **3**: 287–354.
[14] **Brockway, M A I, Daniel S M, Reyes M, Granger J M, McDermid D, et al.** (2024) Human milk macronutrients and child growth and body composition in the first two years: A systematic review. *Adv Nutr* **15** (1):100149. doi.org/10.1016/j.advnut.2023.100149.
[15] **Wood IS, Trayhurn P.** (2003) Glucose transporters (GLUT and SGLT): expanded families of sugar transport proteins. *Br J Nutr* **89**:3–9. doi.org/10.1079/BJN2002763
[16] **Drozdowski L A, Thomson AB.** (2006) Intestinal sugar transport. *World J Gastroenterol* **12** (11): 1657–1670. doi.org/10.3748/wjg.v12.i11.1657
[17] **Holden HM, Rayment I, Thoden JB.** (2003) Structure and function of enzymes of the Leloir pathway for galactose metabolism. *J Biol Chem* **278** (45):43885 43888. doi.org/10.1074/jbc.r300025200
[18] **Grossiord B, Elaine E. Vaughan, Evert Luesink, Willem M. de Vos.** (1998) Genetics of galactose utilisation via the Leloir pathway in lactic acid bacteria. *Le Lait* **78** (1): 77-84.https://hal.science/hal-00929560v1
[19] **Tang M, Etokidem E, Lai K.** (2016) The Leloir pathway of Galactose

metabolism - a novel therapeutic target for hepatocellular carcinoma. *Anticancer Res* **36** (12): 6265–6271. doi.org/10.21873/anticanres.11221

[20] **Wallenfels K, Hucho F, Herrmann K.** (1965) Enzymatically catalyzed mutarotation of aldoses. Studies on aldose-1-epimerase from *E. coli*. *Biochem Z* **343** (3) :307–325.PMID: 4290293

[21] **Thoden JB, Timson D J, Reece R J, Holden HM.** (2004) Molecular structure of human galactose mutarotase. *J Biol Chem* **279** (22): 23431–23437. doi.org/10.1074/jbc.M402347200

[22] **Pai T, Chen Q, Zhang Y, Zolfaghari R, Ross AC.** (2007) Galactomutarotase and other galactose-related genes are rapidly induced by retinoic acid in human myeloid cells. *Biochemistry* **46**(51):15198-207. doi.org/10.1021/bi701891t

[23] **Walker D G, Khan H H.** (1968) Some properties of galactokinase in developing rat liver. ,*Biochem J* **108** (2):169–175. doi.org/10.1042/bj1080169

[24] **Maria E Ortiz-Soto, Makarius B, Daniela B, Malte T, Jürgen S.** (2023) Single-mutations at the galactose-binding site of enzymes GalK, GalU, and LgtC enable the efficient synthesis of UDP-6-azido-6-deoxy-D-galactose and azido-functionalized Gb3 analogs. *Glycobiology* **33** (8): 651–660. doi.org/10.1093/glycob/cwad045

[25] **McCorvie TJ, Kopec J, Pey A, Fitzpatrick L, Patel F, et al.** (2016) Molecular basis of classic galactosemia from the structure of human galactose 1-phosphate uridylyltransferase. *Hum Mol Genet* **25**: (11) 2234–2244. doi.org/10.1093/hmg/ddw091

[26] **Frey PA, Hegeman A D.** (2013) Chemical and stereochemical actions of UDP-galactose 4-epimerase. *Acc Chem Res* **46**(7):1417–1426. doi.org/10.1021/ar300246k

[27] **Timson D J.** (2006) The structural and molecular biology of type III galactosemia, *IUBMB Life* **58** (2): 83–89. doi.org/10.1080/15216540600644846

[28] **Demirbas D, Coelho A I, Rubio-Gozalbo M E, Berry G T.** (2018) Hereditary galactosemia. *Metabolism* **83**:188–196. doi.org/10.1016/j.metabol.2018.01.025

[29] **Fushinobu S.** (2021) Molecular evolution and functional divergence of UDP-hexose 4-epimerases. *Curr Opin Chem Biol* **61**: 53-62. doi.org/10.1016/j.cbpa.2020.09.007

[30] **Nolting K, Park JH, Tegtmeyer L C, Zühlsdorf A, Grüneberg M, et al.** (2017) Limitations of galactose therapy in phosphoglucomutase 1 deficiency. *Mol Genet Metab Rep* **13**:33–40. doi.org/10.1016/j.ymgmr.2017.07.010

[31] **Conte F, Ashikov A, Mijdam R, van de Ven E G P, van Scherpenzeel, M, et al.** (2023) In Vitro Skeletal Muscle Model of PGM1 Deficiency Reveals Altered Energy Homeostasis. *Int J Mol Sci* **24**(9):8247. doi.org/10.3390/ijms24098247.

[32] **Mungai L W, Mariana M, Mercy K, Hiwot N, Phoebe W, et al.** (2024) Galactosemia: A Century Later, Still, the Needed Food that Turned Toxic to the Body. *Afr J Pediatr Endocrinol Metab* **1**(2): 68-72.

[33] **Bonnardeaux A, Bichet DG.** Inherited disorders of the renal tubule. In: Skorecki K, Chertow GM, Marsden PA, Taal MW, Yu ASL (Eds.), Brenner and Rector's The Kidney. 10th ed. Philadelphia, PA: Elsevier, 2016,chap 45.

[34] **Randall JA, Sutter C, Wang S, Bailey E, Raither L, et al.** (2022) Qualitative interviews with adults with Classic Galactosemia and their caregivers: disease burden and challenges with daily living. *Orphanet J Rare Dis* **17**(1):138. doi.org/10.1186/s13023-022-02287-9

[35] **Cantley N W P, Barski R, Kemp H, Hogg SL, Wu HYT, et al.** (2024) Incidental Detection of Classical Galactosemia through Newborn Screening for Phenylketonuria: A 10-Year Retrospective Audit to Determine the Efficacy of This Approach. *Int J Neonatal Screen* **10**(2). doi.org/10.3390/ ijns10010002.

[36] **Arif H S, Thejeal RF, Farhan A.** (2016) Inborn Errors of Metabolism Status in Iraq. *IOSR J Pharm Biol Sci* **2** (2): 58-62. doi.org/10.9790/3008-1102025862

[37] **Senemar S, Ganjekarimi AH , Senemar S, Tarami B , Bazrgar M.** (2011) The Prevalence and Clinical Study of Galactosemia Disease in a Pilot Screening Program of Neonates, Southern Iran. *Iranian J Publ Health* **40** (4):99-104. https://pubmed.ncbi.nlm.nih.gov/23113108/

[38] **Wada Y, Kikuchi A, Arai-Ichinoi N, Sakamoto O, Takezawa Y, et al.** (2019). Biallelic GALM pathogenic variants cause a novel type of galactosemia. *Genet Med* **21**(6):1286-1294. doi.org/10.1038/s41436-018-0340-x

[39] **Kalay I, Gulec C, Balcı M C, Toksoy G, Gokcay G, et al.** (2023) Novel GALT variations and genetic spectrum in Turkish population with the correlation of genotype and phenotype. *Ann Hum Genet* **87**(6): 285-294. doi.org/10.1111/ahg.12523

[40] **Krasowski M D, Pelletier D.** Liver, Gastrointestinal, Pancreas, Biliary Tract. Clinical Pathology Board Review *E-Book,*2024.

[41] **Stettner N M, CutlerD J, Fridovich-Keil J L.** (2023) Racial and ethnic diversity of classic and clinical variant galactosemia in the United States. *Mol Genet Metab* **138**(4):107542. doi.org/10.1016/j.ymgme.2023.107542

[42] **Kitatani K, Idkowiak-Baldys J, Hannun YA.** (2007) The sphingolipid salvage pathway in ceramide metabolism and signaling. *Cell Signal* **20**(6):1010–1018. doi.org/10.1016/j.cellsig.2007.12.006

[43] **Turková J, Vohník S, Helusová S, Benes MJ, Tichá M.** (1992) Galactosylation as a tool for the stabilization and immobilization of proteins. *J Chromatogr* **597**(1–2):19–27. doi.org/10.1016/0021-9673(92)80093-A

[44] **Maverakis E, Kim K, Shimoda M, Gershwin M E, Patel F, et al.** (2015) Glycans in the immune system and the Altered Glycan Theory of Autoimmunity: a critical review. *J Autoimmun* **57**: 1–13. doi.org/10.1016/j.jaut.2014.12.002

[45] **Therrell BL Jr.** (2001).US newborn screening policy dilemmas for the twenty-first century. *Mol Genet Metab* **74**(1-2):64-74. doi.org/10.1006/mgme.2001.3238

[46] **Guthrie R, Susi A.** (1963) A simple phenylalanine method for detecting phenylketonuria in large populations of newborn infants. *Pediatrics* **32**(3):338-343. doi.org/10.1006/mgme.2001.3238

[47] **Taj-Aldeen F M, Abutiheen A AK, Al-Abadi M F K, Alkhafaji A F.** (2019) Assessment of Neonatal Screening Program over 5 years in Karbala Governorate. *Indian J Public Health Res Dev* **10**(2):970-974. dx.doi.org/10.5958/0976-5506.2019.00422.4

[48] **Clarke JTR.** (2005) Newborn screening. A clinical guide to inherited metabolic diseases. Cambridge University Press, Cambridge 228–240.

[49] **Coelho AI, Rubio-Gozalbo ME, Vicente JB, Rivera I.** (2017). Sweet and sour: an update on classic galactosemia. *J Inherit Metab Dis* **40**: 325–342. doi.org/10.1007/s10545-017-0029-3.

[50] **Waisbren S E, Read C Y, Ampola M, Brewster T G, Demmer L.** (2002) Newborn screening compared to clinical identification of biochemical genetic disorders. *J Inherit Metab Dis* **25**(7): 599–600. doi.org/10.1023/a:1022003726224

[51] **Khalaf S M, El-Tellawy M M, Refat N H, Abd El-Aal A M.** (2019) Detection of some metabolic disorders in suspected neonates admitted at Assiut University Children Hospital. *Egypt J Med Hum Genet* **20**:29. doi.org/10.1186/s43042-019-0030-5

[52] **Delnoy B, Coelho A, Rubio-Gozalbo M.** (2021) Current and Future Treatments for Classic Galactosemia. *J Pers Med* **11**(2):75. doi.org/10.3390/jpm11020075

[53] **Caro NAR, Cornejo V, Guevara-Morales JM, Echeverri-Peña OY.** (2022) Advances and Challenges in Classical Galactosemia. Pathophysiology and Treatment. *J Inborn Errors Metab* Screen **10**. dx.doi.org/10.1590/2326-4594-jiems-2021-0026

[54] **Fridovich-Keil JL, Walter JH,** Galactosaemia chapter 72: Valle D, Vogelstein B, Kinzler KW, Antonarakis SE, Ballabio A et al (Eds.), The Online Metabolic and Molecular Bases of Inherited Disease, OMMBID, Part 7: Carbohydrates. McGraw Hill, New York ,2008.

[55] **Zlatunich CO, Packman S.** (2005) Galactosaemia: early treatment with an elemental formula. *J Inherit Metab Dis* **28**:163–8. doi.org/10.1007/s10545-005-5516-2

[56] **Schadewaldt P.** (2004) Age dependence of endogenous galactose formation in Q188R homozygous galactosemic patients. *Mol Genet Metab* **81**:31–44. doi.org/10.1016/j.ymgme.2003.10.007

[57] **Batey L A, Welt C K, Rohr F, Wessel A, Anastasoaie V.** (2013) Skeletal health in adult patients with classic galactosemia. *Osteoporos Int* **24**(2):501–509. doi.org/10.1007/s00198-012-1983-0

[58] **Cring MR, Sheffield VC.** (2022) Gene therapy and gene correction: Targets, progress, and challenges for treating human diseases. *Gene Ther* **29**(1-2): 3–12. doi.org/10.1038/s41434-020-00197-8

[59] **Rutten MG, Rots MG, Oosterveer MH.** (2020) Exploiting epigenetics for the treatment of inborn errors of metabolism. *J Inherit Metab Dis* **43**: 63–70. doi.org/10.1002/jimd.12093

[60] **Schneller JL, Lee CM, Bao G, Venditti CP.** (2017) Genome editing for inborn errors of metabolism: Advancing towards the clinic. *BMC Med* **15**(1). doi.org/10.1186/s12916-017-0798-4

[61] **Chandler R J, Venditti CP.** (2016) Gene Therapy for Metabolic Diseases. *Transl Sci. Rare Dis* **1**:73–89. doi.org/10.3233/TRD-160007.

[62] **Yilmaz BS, Gurung S, Perocheau D, Counsell J, Baruteau J.** (2020) Gene Therapy for Inherited Metabolic Diseases. *J Mother Child* **24**(2): 53–64. doi.org/10.34763/jmotherandchild.20202402si.2004.000009.

[63] **Martini PG, Guey LT.** (2019) A New Era for Rare Genetic Diseases: mess-

enger RNA Therapy. *Hum Gene Ther* **30**: 1180–1189. doi.org/10.1089/hum.2019.090

[64] **Balakrishnan B, An D, Nguyen V, DeAntonis C, Martini PGV.** (2020) Novel mRNA-Based Therapy Reduces Toxic Galactose Metabolites and Overcomes Galactose Sensitivity in a Mouse Model of Classic Galactosemia. *Molecular* **28**: 304–312. doi.org/10.1016/j.ymthe.2019.09.018

[65] **Rasmussen SA, Daenzer JMI, Fridovich-Keil JL.** (2021) A pilot study of neonatal GALT gene replacement using AAV9 dramatically lowers galactose metabolites in blood, liver, and brain and minimizes cataracts in GALT-null rat pups. *J Inherit Metab Dis* **44**(1): 272–281. doi.org/10.1002/jimd.12311

[66] **Banford S, McCorvie TJ, Pey A L, Timson DJ.** (2021) Galactosemia: Towards Pharmacological Chaperones. *J Pers Med* **11**: 106. doi.org/10.3390/jpm 11020106.

[67] **Leidenheimer N J, Ryder KG.** (2014) Pharmacological chaperoning: A primer on mechanism and pharmacology. *Pharmacol Res* **83**: 10–19. doi.org/10.1016/j.phrs.2014.01.005

[68] **Haskovic M, Coelho A I, Bierau J, Vanoevelen JM, Steinbach LKM.** (2020) Pathophysiology and targets for treatment in hereditary galactosemia: A systematic review of animal and cellular models. *J Inherit Metab Dis* **43**(3): 392–408. doi.org/10.1002/jimd.12202.

[69] **McCorvie T J, Timson DJ.** Chapter 11—Galactosemia: Opportunities for novel therapies. In Protein Homeostasis Diseases; Pey, A.L. (Eds.), Academic Press: Cambridge, MA, USA, 2020, pp. 221–245.

[70] **TaoYn X, Conn PM.** (2018) Pharmacoperones as novel therapeutics for diverse protein conformational diseases. *Physiol Rev* **98**:697–725. doi.org/10.1152/physrev.00029.2016

[71] **Muntau AC, Leandro J, Staudigl M, Mayer F, Gersting SW.** (2014) Innovative strategies to treat protein misfolding in inborn errors of metabolism: Pharmacological chaperones and proteostasis regulators. *J Inherit Metab Dis* **37**:505–523. doi.org/10.1007/s10545-014-9701-z

[72] **Mackinnon S R, Krojer T, Foster Wi R, Diaz-Saez L, Tang M, et al.** (2021) Fragment Screening Reveals Starting Points for Rational Design of Galactokinase 1 Inhibitors to Treat Classic Galactosemia. *ACS Chem Biol* **16**(4):586-595. doi.org/10.1021/acschembio.0c00498

[73] **Odejinmi S, Rascon R, Tang M, Vankayalapati H, Lai K.** (2011) Structure-activity analysis and cell-based optimization of human galactokinase inhibitors. *ACS Med Chem Lett* **2**: 667–672. doi.org/10.1021/ml200131j

[74] **Hu X, Zhang YQ, Lee OW, Liu L, Tang M, et al.** (2019) Discovery of novel inhibitors of human galactokinase by virtual screening. *J Comput Mol Des* **33**: 405–417. doi.org/10.1007/s10822-019-00190-3

[75] **Ai Y, Zheng Z, O'Brien-Jenkins A, Bernard D J, Wynshaw-Boris T, et al.** (2000) A mouse model of galactose-induced cataracts. *Hum Mol Genet* **9**: 1821–1827. doi.org/10.1093/hmg/9.12.1821

[76] **Obrosova I, Faller A, Burgan J, Ostrow E, Williamson JR.** (1997) Glycolytic pathway, redox state of NAD(P)-couples and energy metabolism in lens in galactose-fed rats: Effect of an aldose reductase inhibitor. *Curr Eye Res* **16**: 34–43. doi.org/10.1076/ceyr.16.1.34.5113

[77] **Yabe-Nishimura C.** (1998) Aldose reductase in glucose toxicity: A potential target for the prevention of diabetic complications. *Pharmacol Rev* **50**: 21–33. PMID: 9549756

[78] **Mizisin AP, Powell HC.** (1993) Schwann Cell Injury is Attenuated by Aldose Reductase Inhibition in Galactose Intoxication. *J Neuropathol Exp Neurol* **52**:78–86. doi.org/10.1097/00005072-199301000-00010

[79] **Rubio-Gozalbo ME, Derks B, Das AM, Meyer U, Moslinger D, et al.** (2021). Galactokinase deficiency: Lessons from the GalNet registry. Genet. Med. Off. *J Am Coll Med Genet* **23**(1): 202–210. doi.org/10.1038/s41436-020-00942-9.

Author affiliation

1. Department of Biological, College of Science, University of Baghdad, Baghdad, Iraq.

ORCID:

Al-Rudaini AT: https://orcid.org/0009-0003-8289-9928