Chapter

Vitamin D and Inborn Errors of Metabolism

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Abstract

Inborn errors of metabolism are produced by an enzymatic alteration that can be fatal or leave serious neurological sequelae. Some of these conditions require specific nutritional treatment to reverse the clinical symptoms. For phenylketonuria, patients must restrict the intake of phenylalanine; for glucose transporter deficiency syndrome type 1, the treatment is a ketogenic diet; and for classic galactosemia, galactose must be eliminated from the diet. Due to nutritional restrictions, there is an increased risk of deficiency of vitamin D and calcium, which could have an effect on plasma vitamin D levels and cause alterations in bone mineral density (BMD) among children and long-term treated patients. According to scientific evidence, the risks of vitamin D deficiency among these patients are similar to those among healthy persons. While the etiology of lower BMD is not entirely clear, it is attributed to a joint effect of underlying pathology and metabolic changes generated by diet therapy. Long-term follow-up is suggested, in addition to verifying that recommendations o critical nutrients are covered. Timely evaluation of plasmatic levels of vitamin D and BMD is suggested to avoid deficiencies or excesses and to grant a better quality of life to persons with these pathologies.

Keywords: inborn errors of metabolism, phenylketonuria, glucose transporter type 1 deficiency syndrome, classical galactosemia, vitamin D, osteopenia, osteoporosis

1. Introduction

Inborn errors of metabolism (IEMs) are monogenic diseases, most of which are inherited autosomal recessive conditions. There is an enzymatic alteration that triggers biochemical alterations of each metabolic disease [1]. To date, 1450 inherited metabolic diseases or IEMs have been described [2].

These metabolic-genetic conditions can manifest at any time in life but are more frequent in the pediatric period. Clinical signs and symptoms are similar to other pathologies, which is why they should always be suspected in parallel in order to start a timely treatment and avoid irreversible sequelae that will affect the individual who suffers from it [1].

Of the total classified IEMs, approximately 15% require nutritional therapy. The main objective of therapy is to restrict the intake of the toxic metabolite precursor,

Disease	Substrate restriction	End product supplementation
Amino acid diseases		
Phenylketonuria (PKU)	Phenylalanine	L-Tyrosine
Tyrosinemia type 1-a	Tyrosine	L-Phenylalanine
Maple syrup urine disease (MSUD)	Leucine	L-Valine, L-Isoleucine
Vitamin B6 unresponsive: Classical Homocystinuria	Methionine and cysteine	Folic acid: 5 mg/day Betaine: 100 mg/kg/day(<3 years), 6 g/day (> 3 years) Pyridoxine: 100–200 mg/day B12: 1 mg (intramuscular) per month
Propionic acidemia (PA) and Methylmalonic acidemia (MMA)	Methionine, isoleucine, threonine, valine	Biotin: 5–10 mg/day (PA) B12: 1 mg (intramuscular), 10–20 mg/day(oral) (MMA) L-Carnitine: 100–300 mg/kg/day
Urea cycle disorders	High biological value protein intake	L-Arginine: 100–200 mg/kg/day (< 20 kg) and 2.5–6 g/m^2/day (> 20 kg) (CPS, OTC) 450–600 mg/kg/day(<20 kg) and 9.9–13 g/m^2/day (>20 kg) (ASS, ASL) L-Citrulline: 100–200 mg/kg/day (CPS, OTC) Sodium benzoate: 450–600 mg/kg/day (< 20 kg) and 9.9–13 g/m^2/day (> 20 kg)
Carbohydrates		
Galactosemia	Galactose (lactose)	Soy milk Elemental calcium
Glycogenosis type I-a	Sucrose, galactose, fructose, sorbitol, mannitol	Complex carbohydrates Raw starch (according to protocol) Diet fractionation Calcium, vitamin D, and vitamin C

Note: CPS: carbamoyl phosphate synthetase deficiency; OTC: ornithine transcarbamylase deficiency; ASS: argininosuccinate synthetase; and ASL: argininosuccinate lyase.

Table 1.
Examples of inborn errors of metabolism that respond to substrate restriction and supplementation of a final product.

reduce or reverse clinical advancement, prevent deficiencies or excesses of critical nutrients, and supplement with a special formula free of toxic substrate. Some IEMs require the supplementation of a vitamin as a sole or complementary treatment to nutritional therapy, and in others, the delivery of a drug that stabilizes the enzyme or prevents the synthesis of the toxic substrate is necessary (**Table 1**) [1, 3].

1.1 Vitamin D and bone health in IEMs

Vitamin D status is assessed through the 25-hydroxy-vitamin D (25OHD) metabolite, given its abundance and stability in the body. The Endocrinology Society defines severe deficiency as 25OHD values ≤12 ng/mL; deficiency as ≤20 ng/mL; insufficiency 21–29 ng/mL and sufficiency ≥30 ng/mL. Levels are evaluated by radioimmunoassay or liquid chromatography with tandem mass spectrometry in the case of clinical investigation [4].

Osteoporosis is a generalized disease of the skeletal system characterized by the loss of bone mass and by the deterioration of the microarchitecture of bone tissue. Bone resistance is compromised and, as a consequence, leads to greater bone fragility and susceptibility to fractures [5]. The World Health Organization defines osteoporosis based on bone mineral density (BMD); when values are between −1 and −2.5, adults are diagnosed with osteopenia and with osteoporosis when values are below −2.5. In all persons, the BMD z-score can be used for diagnostic purposes, except in men older than 50 years and postmenopausal women [6].

Vitamin D deficiency and bone diseases have been described in children and adults with IEMs, which is partly due to the restricted intake of vitamin D and calcium. This is possible to observe in amino acid disorders, in which the intake of proteins or a specific amino acid must be limited for life. Nutritional treatments eliminate foods of animal origin that are the main sources of these nutrients. Also, in some cases, there is low sun exposure, while in other cases, the use of medications could interact with the absorption of vitamin D and calcium. Inflammatory and genetic factors also play an important role in some patients [7].

Due to the prohibition or restriction of natural foods of the different diet therapies for IEMs, special formulas have been created according to pathology, which contains the macro and micronutrients necessary according to age and sex requirements. Formulas are fortified with vitamin D3 and, thus, contain a greater amount of this vitamin and calcium when compared with traditional infant formulas or breast milk [7]. On average, they contain 18 ug (720 IU) of vitamin D3 in 100 g (**Table 2**).

It has been reported that, among healthy children, vitamin D deficiency varies between 30 to 50% and an insufficient level between 15 and 20% of the population. Among subjects with IEMs, the prevalence is similar. A retrospective study compared the serum level of 25OHD and lumbar and femoral BMD by dual-energy X-ray absorptiometry (DEXA) between IEM patients (n = 115, mean age of 5.6 ± 4.47 years) and control subjects. Among IEM patients, 83 had amino acid disorders and received a protein-restricted diet (36 phenylketonuria, 27 organic aciduria, 10 urea cycle

Inborn errors of metabolism	Name of special formula (Company)	ug Vitamin D3 (IU) per 100 gr	Calcium (mg)per 100 gr
Phenylketonuria (PKU)	PKU anamix infant® (Nutricia)	11.2 (448)	410
	PKU start® (Vitaflo)	11.5(460)	400
	PKU express® (Yitaflo)	13.2 (528)	1192
	PKU anamix Junior® (Nutricia)	26.3 (1052)	1348
Urea cycle disorder	UCD anamix infant® (Nutricia)	11.8 (472)	670
	Dialamine® (Nutricia)	0	< 20
	Essential amino acid mix® (Nutricia)	0	0
	EAA supplement® (Vitaflo)	27 (1080)	2400
Glucose Transporter Type 1 Deficiency Syndrome (GLUT1DS)	Ketocal 3:1® (Nutricia)	17(680)	810
	Ketocal 4:1® (Nutricia)	10.5 (420)	780

Note: Information available from each company website.

Table 2.
Examples of vitamin D3 and calcium intake in special formulas for different inborn errors of metabolism.

disorders, 5 tyrosinemia, 2 alkaptonuria, and 3 homocystinuria) and 32 patients with impaired metabolism of carbohydrates (16 glycogenosis type 1 and 16 galactosemia). A mean 25OHD level of 28.1 ± 14.9 ng/mL was observed in IEM subjects, with 26.8% of patients having 25OHD deficiency and 34% having insufficient 25OHD. On the other hand, control subjects had an average 25OHD level (23.27 ± 12.1 ng/mL), with 25.4% and 35.6% with 25OHD deficiency and insufficiency, respectively. BMD was also assessed, and mean z-score was −1.1 for the low-protein diet group, −0.25 for the galactose-free diet group, and −0.75 for the control group, with no significant difference between groups. Of the patients with osteopenia (n = 18), 38% presented delayed growth. In addition, osteopenia was more frequent in patients with low 25OHD levels, which was observed in 13 of 37 patients; however, this relationship was not statistically significant. The authors concluded that it is possible to find low BMD in IEM patients, regardless of vitamin D levels [7].

A cross-sectional study compared 88 IEM patients to control subjects. IEM patients had an average age of 12.4 ± 3.5 years; 81 had amino acid disorders, and 7 with galactosemia. The authors reported a mean serum 25OHD level of 27.1 ± 10.9 ng/mL in the IEM group and 23% with 25OHD deficient levels. The control group had an average level of 27.6 ± 11.2 ng/mL of 25OHD. Only 3 of 19 patients with PKU had a low BMD assessed by DEXA (< −2 z-score): 2 of the spine and 1 of the hip. These authors observed a positive correlation between lumbar BMD and the dietary intake of calcium and the special formula. They concluded that the special formula allows for normal vitamin D and BMD values in patients with IEM and that the risk of vitamin D deficiency is similar to that of the general population [8].

The pathophysiology of a decrease in BMD is not entirely clear, although its etiology is multifactorial in nature. Determinants such as vitamin D and calcium intake, physical activity, and genetic, environmental, and endocrine factors stand out. One study has reported that a primary determinant for low BMD in patients who consume special formulas is the low intake of essential nutrients [7]. Thus, it is important to monitor that the diet reaches the recommended daily intake for calcium, magnesium, and zinc.

Next, a bibliographic review of 3 IEMs will be carried out: phenylketonuria (PKU), glucose transporter type 1 deficiency syndrome (GLUT1DS), and classic galactosemia (GALT).

2. Phenylketonuria (PKU)

2.1 Definition

Classic PKU is one of the hyperphenylalaninemia (HPA) and is the most severe form of presentation. HPAs are produced by an alteration in phenylalanine (Phe) metabolism due to the deficiency or absence of the enzyme phenylalanine hydroxylase, encoded in the 12q22-q24.1 gene (**Figure 1**) [9, 10].

2.2 Incidence and inheritance

PKU has an incidence of 1:10,000 live newborns worldwide and is an autosomal recessive condition [10]. In Chile, the incidence of PKU is 1:18,916 newborns and 1:10,198 newborns for HPA [9, 11].

2.3 Physiopathology

A high level of Phe maintained over time causes severe neurological alterations. Alterations are due to the competitive inhibition of the transport of neutral amino acids through the blood-brain barrier, which limits the synthesis of proteins, serotonin, dopamine, and catecholaminergic neurotransmitters to the brain, causing irreversible intellectual disability (**Figure 1**) [9, 10].

2.4 Diagnosis

HPA is suspected when a Phe value in blood is above 2.0 mg/dL (120 μM), and diagnosis is confirmed with a Phe to tyrosine ratio greater than 3.0 [9, 10].

2.5 Treatment

To avoid neurological sequelae, treatment should be started before 1 month of life. Treatment consists of a Phe-restricted diet, for example, a special formula without Phe and adaptation of macro and micronutrient requirements according to age and growth. The diet prohibits all foods of animal origin such as meat of all kinds, dairy products and derivatives, eggs, fish and shellfish, and legumes. In foods such as cereals, fruits, and vegetables, the Phe contribution must be calculated. Due to this nutritional restriction, the delivery of a special formula without Phe, enriched with tyrosine, vitamins, and minerals, is mandatory. The exclusion of food could cause deficiencies of some trace minerals, including vitamin B12, essential fatty acids (docosahexaenoic acid), calcium and vitamin D, which is why levels must be monitored. Nutritional treatment is for life, and a blood Phe level between 2.0 and 6.0 mg/dL (120–360 μM) must be maintained. Different alternative treatments have been proposed, such as the use of tetrahydrobiopterin (BH4), supplementation with neutral

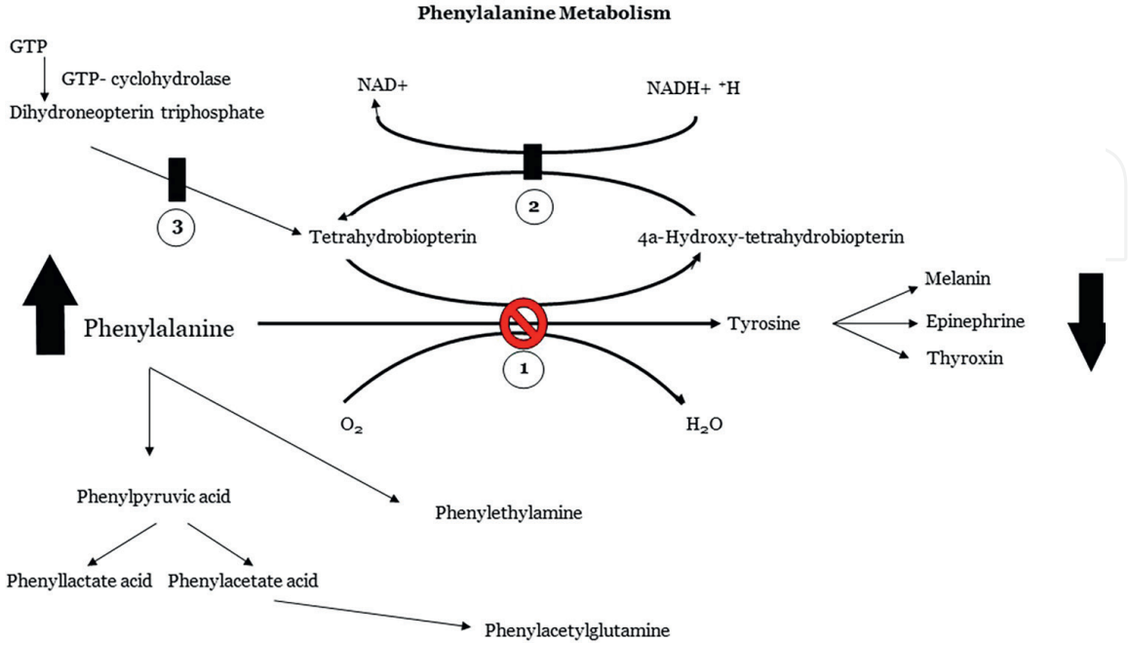

Figure 1.
Phenylalanine metabolism. 1: Phenylalanine hydroxylase, 2: Dihydropteridine reductase, and 3: 6-pyruvol-tetrahydropterin synthase and Sepiapterin reductase.

amino acids, the use of glycomacropeptide (GMP) or Pegvaliase. According to scientific evidence, there is still no treatment that can replace the Phe-restricted diet [10].

2.6 Vitamin D and bone health in PKU

A retrospective study including 90 PKU subjects (62 identified with neonatal screening and 28 with a late diagnosis) with a mean age of 29 years (50% < 30 years) evaluated 25OHD levels and BMD of the lumbar spine and/or femoral neck. The authors observed obesity, according to body mass index, in 29% of the sample and 88% had a sedentary lifestyle. In addition, 30.6% had vitamin D deficiency, 41.2% had osteopenia, and 10.3% had osteoporosis. It was observed that 38.8% and 10.4% had osteopenia and osteoporosis of the lumbar spine, respectively, while 32.3% and 3.2% had osteopenia and osteoporosis of the femoral neck, respectively. The authors propose that PKU should be considered as a secondary cause of osteoporosis and that consensus is required for a treatment algorithm by age at which treatment initiation should be optimized [12].

A systematic review that included 16 studies, of which a meta-analysis was performed with 3 studies, found that spine BMD was 0.1 g/cm^2 lower in 67 subjects with PKU compared to 161 controls. It was also observed that 20% (53 of 263) of subjects with PKU experienced clinical fractures. Only one study, which included a control group, observed a 2.6-fold higher fracture rate after 8 years in subjects with PKU. In a total of 12 studies (n = 412 subjects), the majority (75%) of the studies, representing 71% of subjects, reported no association between Phe levels and BMD. The authors concluded that further research was needed to determine the etiology and health consequences among PKU patients with lower BMD and suggested the need to improve study methodologies [13].

Another systematic review included 13 studies on BMD in PKU subjects. Of these studies, 5 were conducted with children and adolescents, 5 mixed the pediatric and adult populations, and 1 study was exclusively in adults. In 10 of the 11 studies, a lower BMD in PKU subjects compared with control subjects was found. Some analyses have evaluated differences in BMD between adherent and nondiet subjects, with lower BMD observed in the group with less adherence to specific diet therapy. Of the included cohort studies, a prevalence of osteopenia between 28 and 46% and osteoporosis between 5 and 14% was reported. In addition, 6 studies evaluated vitamin D levels, observing different results. One study did not detect differences between PKU and control subjects; in the study of adults, all PKU patients had normal vitamin D values; and another study observed lower vitamin D levels. The authors report that individual studies have reported lower BMD, which indicates a greater risk of osteoporosis; however, when BMD results of the entire group were evaluated, this finding had no clinical significance. Therefore, there is a need to use standard definitions when evaluating BMD, since this interferes with analyses and comparisons between studies [14].

It was believed that the pathophysiology of osteopenia was the result of a low intake of vitamin D and calcium; however, it was later determined that the special formulas provided for IEM patients contained amounts that often exceeded established requirements. Thus, a positive correlation between BMD, calcium, and adequate consumption of the special formula was found. Therefore, another possible etiology was raised, which relates to low adherence to nutritional treatment and increased Phe level, which could cause bone demineralization and be associated with the existence of a bone disruption. In PKU patients with poor metabolic control,

levels of parathyroid hormone and alkaline phosphatase activity are increased, and both are related to vitamin D and calcium deficiency, producing hypercalciuria. Another factor that should be mentioned is a possible inadequate intake of key nutrients such as docosahexaenoic acid (DHA), creating a deficiency that has been associated with osteopenia in PKU patients [10].

2.7 Situation in Chile

The national health survey for 2016–2017 evaluated serum levels of vitamin D in women of childbearing age, in which an average of 20 ng/mL was observed, with 52.7% of women being classified as deficient and 34.3% with insufficiency [4].

In Chile, since the 1990s, a public policy of supplementing infants with vitamin D has been implemented. The policy started with the administration of a single dose of vitamin D and now recommends 400 IU daily for the first year of life. In addition, in July 2022, a new modification to the food health regulations was published that establishes the fortification of foods with vitamin D3. Therefore, liquid milk will have to be fortified with 1 μg/100 ml, powdered milk with 10 μg/100 g, and flour with 2.25 μg/100 g. The food industry has 12 months to comply with this requirement, which is intended to improve the deficiency figures in the population as a whole [4].

The first study in the Chilean PKU population on this topic was conducted in 2014, in which PKU subjects (n = 16, mean age 14 years) were compared with subjects with HPA who did not require nutritional treatment without Phe (n = 16, mean age 12 years) and a control group (n = 16, mean age 16 years). The following were evaluated: serum levels of 25OHD, BMD of the femur, lumbar and total body were measured by DEXA. With respect to vitamin D levels (**Figure 2**), the PKU group had an average serum

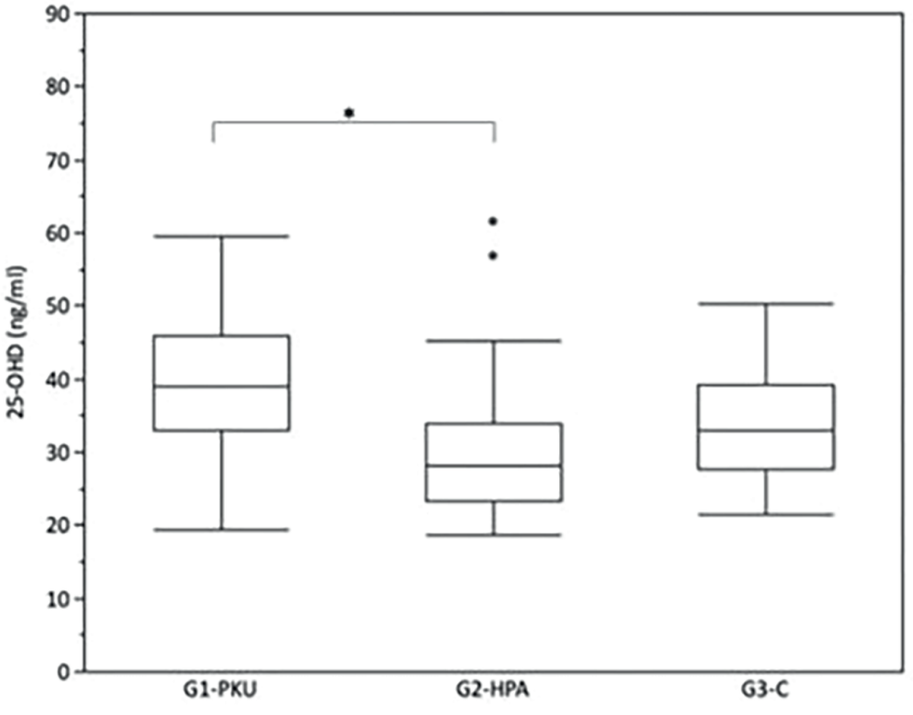

Figure 2.
Plasma 25OHD (ng/mL) concentration in each group. Plasma 25OHD concentration in three groups of patients: Group 1: PKU, Group 2: HPA, and Group 3: Control.

25OHD level of 38.9 ng/mL and 2 of the 16 had deficient values, while 10 of the 16 subjects with HPA, and 6 of the 16 controls were deficient in vitamin D. No difference was observed in the BMD z-score of the lumbar spine, femur, or total body. Therefore, it was concluded that the PKU subjects in treatment and with good adherence to diet therapy did not present 25OHD deficiency and also did not show differences in BMD [15].

Another more recent study in Chilean subjects compared 10 PKU subjects on nutritional treatment (mean age 23.6 years) with 16 PKU without treatment (mean age 22.6 years) and 26 control subjects without PKU (mean age 23.1 years). In this study, it was observed that the control group presented a higher spine BMD (1.28 ± 0.16 g/cm^2) compared to the other two groups with PKU: PKU with treatment = 1.14 ± 0.16 g/cm^2 and PKU without treatment = 1.14 ± 0.16 g/cm^2) and the PKU group without treatment had a lower femoral neck BMD (1.0 ± 0.19 g/cm^2) compared to the control group (1.15 ± 0.19 g/cm^2). Among PKU patients in treatment, vitamin D deficiency was not observed, but 30% presented insufficient values. While 33% of the PKU group without treatment had deficiency and 47% insufficiency, and in the control group, it was observed that 12% had deficiency and 46% insufficiency. In addition, a negative correlation was observed between serum vitamin D values and blood Phe levels [16].

3. Glucose transporter type 1 deficiency syndrome (GLUT1DS)

3.1 Definition

D-glucose is the primary fuel for cellular metabolism, intestinal and cellular absorption. Glucose transporter type 1 (GLUT-1) is found in erythrocytes, fibroblasts, and the blood-brain barrier, and its purpose is to deliver glucose to tissues in the absence of insulin. As this is the only transporter that delivers glucose from the blood to the brain, deficiency leads to a decrease in brain glucose. Cellular metabolism is regulated by glycoprotein systems for each tissue, specifically those that maintain glucose homeostasis in the body. In 1991, Glucose Transporter Type 1 Deficiency Syndrome (GLUT1DS) (OMIM 606777) was described in two patients who presented epileptic encephalopathy that evolved with psychomotor development delay, cranial growth arrest, microcephaly, incoordination, and spasticity. In addition, a decrease in glucose and lactate levels in cerebrospinal fluid (CSF) was detected, but hypoglycemia was not observed [17, 18]. The gene encoding the GLUT1 transporter (SLC2A1) is located on chromosome 1p34.2 [17].

3.2 Incidence and inheritance

Most patients with GLUT1DS have a new heterozygous variant in the SLC2A1 gene, and around 10% have one parent who carries the variant; it has been described as having autosomal dominant inheritance; however, there are some cases described with autosomal recessive inheritance [19]. Its general incidence has not been determined; only a prevalence based on generalized epilepsy of 1.65–4.3 per 100,000 live births has been reported [20].

3.3 Pathophysiology

GLUT1DS is a neurological disorder with broad phenotypic variability. The classic or most severe presentation involves early epileptic encephalopathy, associated with

developmental delay, acquired microcephaly, lack of motor coordination, and spasticity. Seizures appear within the first 4 months of life, usually characterized by episodes of apnea, cyanotic spasms, akinetic crisis, and characteristic eye movements. Seizures are more frequent are myoclonic or atonic or absences of early appearance. Other findings include intermittent paroxysmal ataxia, confusion, lethargy, sleep disturbances, and headaches. Many more cases with this syndrome have been described, extending the phenotype to individuals with ataxia and intellectual delay but no seizures, individuals with dystonia and choreoathetosis, and individuals without seizures and no movement disorder [21].

3.4 Diagnosis

Laboratory tests show persistent hypoglycorrhachia below 40 mg/dL in the most severe forms and between 41 and 52 mg/dL in mild forms [21]. In addition, CSF lactate may or may not be decreased (<1.4 mmol/L), and glycemia is normal. Diagnostic suspicion is established when the ratio between CSF and plasma glucose is less than 0.4. Confirmation of the diagnosis is made by determining a variant in the SLC2A1 gene. In 81–89% of patients, sequence analysis identifies heterozygous pathogenic variants (or, rarely, biallelic pathogenic variants), and in 11–14%, diagnosis is confirmed by deletion/duplication analysis. However, the absence of a variant in SLC2A1 does not exclude GLUT1DS [22].

3.5 Treatment

A ketogenic diet therapy (KDT) should be started as soon as possible, to provide the developing brain with an additional supply of metabolic fuel through ketone bodies. After beginning KDT, one study found that in 83% of cases, seizures were stopped, a reduction in 82% of movement disorders, and 59% had an improvement in their cognition [23]. KDT consists of maintaining a 3:1 fat/carbohydrate + protein ratio, with an intake of 85–87% fat, 5–10% protein, and 3–5% carbohydrate (CHO) [24]. Ketogenesis is considered when fasting ketonemia (beta-hydroxybutyrate acid) is greater than 2.0 mmol/L and should be kept below 5.0 mmol/L. It is recommended to maintain KDT throughout life due to its benefits of the KDT and because there is no evidence on effective alternative treatments nor deleterious results that would point to stopping this nutritional therapy [23]. Despite the fact that KDT is highly effective in seizure control, as it is a diet that eliminates various natural foods, there is some risk of not meeting the requirements of critical nutrients such as calcium, vitamin D, and iron, among others. Several adverse effects associated with the long-term use of KDT have been described, such as slower weight gain, osteopenia, and dyslipidemia, which is why close surveillance and long-term follow-up are recommended to prevent associated adverse effects of KDT [25, 26].

3.6 Vitamin D and bone health in GLUT1DS

Various hypotheses have been proposed as to why KDT might have a deleterious effect on bone health, but scientific evidence to support these hypotheses is scant. Findings related to changes in bone health have been mixed and performed mainly in adults with refractory epilepsy practicing KDT for short periods. Further, another variable that has a great weight on the deleterious effect on bone integrity must be considered, namely, the prolonged use of antiepileptic drugs (AEDs), which have

been shown to produce a decrease in BMD [27, 28]. A recent review of the literature indicates that various AEDs accelerate vitamin D catabolism, causing a decrease in the plasmatic level of 25OHD, inducing hypocalcemia associated with other secondary mechanisms such as: calcitonin, vitamin K, and carnitine deficiency [29, 30].

KDT is used as an alternative therapeutic intervention to control seizures among people with refractory epilepsy. However, it should be noted that KDT, by decreasing the intake of carbohydrates and proteins, and increasing the intake of lipids, increases the production of ketone bodies. This hyperketosis induces chronic ketoacidosis, increasing urinary calcium excretion, without increasing intestinal absorption of this mineral, resulting in a greater loss of bone calcium, increasing bone resorption, and decreasing renal conversion of 25OHD by 1.25-dihydroxyvitamin D3 (1,25(OH)2D3) [31, 32].

Most studies on bone health and KDT have been carried out in people with refractory epilepsy, but not in GLUT1DS, and agree that there is a close correlation between metabolic acidosis, a low calcium intake, and deficient 25OHD levels (<20 ng/mL). These factors predispose a person to bone demineralization [33]. It is important to note that demineralization is greater in patients with low mobility and those with a body mass index greater than 25. For this reason, it is recommended to perform bone densitometry annually or every 2 years, to detect bone alterations early (e.g., osteopenia and osteoporosis). It is also recommended to measure 25OHD level and determine if the KDT covers the requirements of both calcium and vitamin D. In the event that these nutrients are not in accordance with recommendations established by age and sex, pharmacological supplementation is necessary [34].

A systematic review of persons using KDT included 7 papers (6 conducted in children and 1 in adults) and evaluated levels of 25OHD pre and posttreatment, showed that the values of this vitamin at the beginning of the KDT were below what is recommended (8% had insufficient level of 25OHD). During the diet, persons were supplemented according to the doses recommended for children, and 25OHD values increased after 3 months of receiving the supplementation. Levels later stabilized or decreased. In cases where 25OHD was low, it was attributed to a decrease in 1,25(OH)2D3, suggesting that KDT interacts with hydroxylases. Regarding changes in BMD, or mineral content, only three studies indicated that there was a decrease in BMD posttreatment [35, 36].

It is important to point out that one of the complications in KDT is the risk of hypercalciuria and urolithiasis, which is why vitamin D supplementation in this diet has not been determined, since this could exacerbate this alteration. However, one study showed an inverse relationship between urinary calcium and creatinine excretion and 25OHD level, indicating that vitamin D supplementation would be useful in preventing hypercalciuria. Thus, it is recommended to maintain a 25OHD level above 40 ng/mL, which would be achieved with a vitamin D3 supplementation of 50 IU/kg/day [37].

A study carried out in adult patients with refractory epilepsy, and the Modified Atkins diet (MAD) showed that after 12 weeks of being on this diet, bone densitometry showed significant changes in bone and calcium metabolism, with a possible negative effect on bone health. The authors concluded that it is important to maintain frequent monitoring to prevent changes in bone structure [35].

It has been proposed that the chronic use of KDT in children could be associated with a decrease in bone mass and thereby increase the risk of fractures. One study showed a 0.16 standard deviation decrease in BMD for each year a child maintained the KDT [32]. Another study observed that 20% of children (over 6 years of age) in KDT and in treatment with antiepileptic drugs had a higher incidence of bone

fractures and a lower BMD. The authors proposed that this negative effect could be due to the metabolic acidosis it causes the lower intake of vitamin D, reduced physical activity, and the concomitant effect caused by AEDs [37].

Considering that KDT is the treatment for GLUT1DS, it is important to determine the state of bone health among persons with this condition [22]. However, to date, there have been very few studies that evaluate the effect of KDT on bone health and the level of 25OHD in people with GLUT1DS. In addition, most published studies have been carried out in adults. One study was conducted in three adults with GLUT1DS using KDT for more than 5 years. These adults had a normal BMD at the start of the diet and, after 5 years of the KDT, experienced no changes in BMD or bone mineral content [38]. However, it should be mentioned that these results cannot be extrapolated to children, since, in the adult stage, bone turnover is almost nothing, unlike what occurs in pediatrics, where the rate of skeletal turnover is very high due to the period of growth and the need to accumulate bone mass [24]. In another study carried out in 139 adults with refractory epilepsy who started a KDT and were followed up for a period of 5 years, osteopenia or osteoporosis was diagnosed in 8 of 11 cases. The authors noted that 6 cases had a previous history of alterations in BMD, and only 2 cases were diagnosed throughout the period of study. The authors associated these alterations with KDT and the use of AEDs [39].

In summary, we conclude that KDT adversely affects bone health and the plasmatic value of 25OHD. This is in accordance with international recommendations that state that KDT should be started as early as possible and that patients should be closely monitored to evaluate all parameters that could be altered with this nutritional treatment, for example, the prevention of nutritional deficiencies or excesses. At present, KDT is the only treatment available to eliminate or reduce seizures in more than 80% of cases of GLUT1DS [22].

4. Galactosemia

4.1 Definition

Classic galactosemia (GALT) is a deficiency of the galactose-1-phosphate-uridyltransferase (GALT) enzyme and belongs to the galactose metabolic pathway (**Figure 3**) [24].

4.2 Incidence and inheritance

GALT has an incidence of 1:30,000 to 1:60,000 live births and 1:47,000 in the Caucasian population [40]. Galactosemia has an autosomal recessive inheritance, which is classified as severe or variant depending on the phenotype, genotype, and long-term complications. GALT mortality decreased considerably since the beginning of neonatal screening; however, a large percentage of cases manifest symptoms during the first days of life, and long-term complications such as infertility and dyspraxia, among others, persist [41].

4.3 Pathophysiology

Due to the failure of this enzyme, the conversion of alpha-D-galactose-1-phosphate to alpha-D-glucose-1-phosphate does not happen, leading to an accumulation

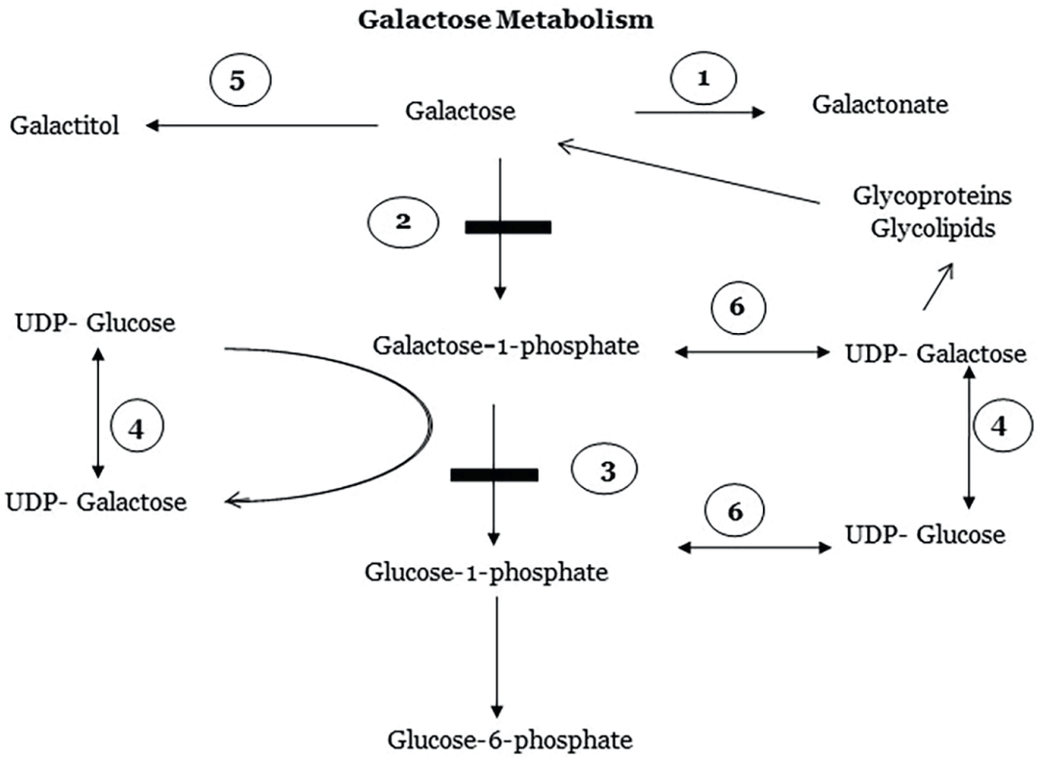

Figure 3.
Galactose Metabolism. 1: Galactose dehydrogenase, 2: Galactokinase (GALK), 3: Galactose-1-phosphate-uridyl-transferase (GALT), 4: UDP-galactose-4-epimerase (GALE), 5: Aldose reductase, and 6: UDP-glucose pyrophosphorylase and UDP-galactose pyrophosphorylase.

of galactose-1-phosphate, galactitol, and galactonate [42, 43]. Without diagnosis in the first days of life, liver failure, sepsis, and potential neonatal death can occur [44]. Despite early treatment, individuals affected by this condition may experience long-term complications, such as cognitive deficits, language problems, growth retardation, prepubertal developmental delay, low bone mineral density, persistent cataracts, and, in women, primary ovarian deficiency [42].

4.4 Diagnosis

To confirm the diagnosis is necessary to measure galactose-1-phosphate and GALT activity in red blood cells. In many countries, this condition is considered in neonatal screening, measuring both galactose and GALT activity. Also, you can request GALT gene analysis [40].

4.5 Treatment

Dietary galactose restriction has been the standard treatment since the 1950s, as it improves acute symptoms. Restriction should start from the suspicion of the pathology, even if the diagnosis is not confirmed [40]. The latest GALT guidelines recommend the elimination of galactose and lactose from all dairy products. Thus, breast milk and infant formulas should be eliminated, and nutritional recommendations should be covered with elemental or soy-based formulas [43]. In addition, the minimum contribution of galactose from other food sources such as fruits, vegetables, legumes, soybeans, mature cheeses that contain <25 mg galactose/100 gr, and foods

that contain additives such as calcium and sodium caseinate are allowed [40, 43]. Recommendations are based on various studies that have demonstrated that the intake of 200–600 mg galactose from fruits, vegetables, and cereals does not have a significant impact on urinary galactitol or galactose-1-phosphate levels (Gal-1-P), in erythrocytes, nor in physical or ophthalmological alterations [42]. Monitoring of nutritional treatment requires measurement of Gal-1-P levels at 3 and 9 months after the initiation of galactose restriction [43]. Periodic monitoring of long-term complications is relevant, such as cognitive and neurological alterations, language delay, infertility, decreased bone mineralization and cataracts [41, 43].

4.6 Vitamin D and bone health in GALT

Due to restricted galactose nutrition, foods with a higher calcium and vitamin D content are affected, such as dairy products and derivatives. Thus, treatment includes optimizing calcium and vitamin D3 intake, including supplementation and monitoring. Annual evaluation of BMD during periods of growth and every 5 years of postpuberty is recommended [40].

In different cohorts, it has been observed that BMD is affected in 26% of cases of GALT [45]. In 2006, 40 subjects (68% women) with GALT were evaluated during 2 years of intervention that included supplementation with vitamin D3, vitamin K1, and calcium and compared to a placebo group [46]. After the evaluation period, the supplemented group improved bone mineral content and osteocalcin carboxylation, a biomarker in vitamin K metabolism that also participates in improving bone structural organization and architecture [46]. In 2014, after reviewing the existing evidence, a proposal was drafted to prevent low BMD [47]. It was observed that although complications appear in the adult stage, a BMD deficiency can be observed in the prepubertal stage. One of the key points of the proposal is the measurement and control of vitamin D status, through the total serum concentration of 25OHD, which should be above 30 ng/mL. **Table 3** shows daily recommendations for calcium and vitamin D. Based on the proposal, current guidelines for the GALT population include the monitoring of vitamin D and calcium intake, in addition to measurement of serum 25OHD, to determine if supplementation is necessary and, if needed, to evaluate its effect.

Age in years	Calcium (mg/day)	Vitamin D (IU/day)
< 1	200–260*	400–1000
1–3	700	600–1000
4–8	1000	600–1000
9–13	1300	600–1000
14–18	1300	600–1000
19–70	1000 (men); 1200 (women)	1500–2000
> 70	1200	1500–2000

**Reflects adequate intake, since a daily dietary recommendation has not yet been established for this group. Adapted from Erven et al. [47].*

Table 3.
Dietary recommendations for calcium in mg/day and vitamin D in IU/day for different age groups at risk of low bone mass.

In 2016, a descriptive review regarding vitamin D status in subjects with GALT was published [48]. Six studies that measured the status of 25OHD were analyzed, and 4 of them included child cohorts [49–52]. In these cohorts, serum levels of this vitamin were in the adequate range and among adults, levels were below reference values [53, 54]. Therefore, the recommendation is to constantly monitor serum level with 25OHD, optimize dietary intake, and assess the need for supplementation with serum levels less than 30 ng/mL.

5. Conclusions

IEMs are genetic conditions that affect an enzyme of a metabolic pathway. Toxins that cause clinical manifestations accumulate, and, in some of these cases, a specific treatment should be initiated that consists of diets without the toxic metabolite, vitamin supplementation, and/or the use of detoxifying drugs.

Studies in which persons with IEMs were compared with control subjects, no differences were observed in terms of 25OHD levels or BMD. Vitamin D deficiency is similar to the healthy population, which may be due to the fact that special formulas, for the most part, are fortified in large quantities with vitamin D3.

Among persons with PKU, lower BMD has been observed but is not necessarily related to low levels of vitamin D. Therefore, the cause is likely multifactorial, possibly associated with poor adherence to diet therapy and an increase in Phe level in blood, which would produce alterations in bone metabolism.

KDT is used in the management of refractory epilepsy and GLUT1DS. This diet has been associated with greater vitamin D deficiency and lower BMD compared to control subjects or patients prior to starting KDT. This is likely due to a lower intake of vitamin D and calcium, use of AEDs, hyperketosis, and chronic metabolic acidosis that would affect bone metabolism.

In GALT, vitamin D deficiency has been reported to be related to the restrictive diet, for which bone alterations have also been detected.

For patients with IEMs who must follow these strict diets, it is important to periodically evaluate that they are meeting dietary recommendations for critical macro and micronutrients, determine vitamin D levels, and plan an early and timely check of BMD to prevent bone alterations and grant a better quality of life.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

IEM	Inborn errors of metabolism
25OHD	25-hydroxy-vitamin D
BMD	Bone mineral density
PKU	Phenylketonuria
MSUD	Maple syrup urine disease
PA	Propionic acidemia
MMA	Methylmalonic acidemia

CPS	Carbamoyl phosphate synthetase deficiency
OTC	Ornithine transcarbamylase deficiency.
ASS	Argininosuccinate synthetase
ASL	Argininosuccinate lyase
DEXA	Dual energy x-ray absorptiometry
HPA	Hyperphenylalaninemia
Phe	Phenylalanine
LNAA	Large neutral amino acids
GMP	Glycomacropeptide
DHA	Docosahexaenoic acid
GLUT1DS	Glucose transporter type 1 deficiency syndrome
CSF	Cerebrospinal fluid
KDT	Ketogenic diet therapy
CHO	Carbohydrates
AED	Antiepileptic drugs
1,25(OH)2D3	1,25-dihydroxyvitamin D3
MAD	Modified Atkins diet
GALT	Classic galactosemia
Gal-1-P	Galactose-1-phosphate

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References

[1] Raimann E, Castro G, Hamilton V, Campos K, Cornejo V. Aproximación al diagnóstico y tratamiento de los Errores innatos del metabolismo. In: Colombo M, Cornejo V, Raimann E, editors. Errores Innatos en el Metabolismo del niño. 4ª ed. actualizada. Santiago: Editorial Universitaria; 2017. pp. 77-96

[2] Ferreira CR, Rahman S, Keller M, Zschocke J, ICIMD Advisory Group. An international classification of inherited metabolic disorders (ICIMD). Journal of Inherited Metabolic Disease. 2021;**44**(1):164-177. DOI: 10.1002/jimd.12348

[3] Guillén López S, López-Mejía L, Carrillo-Nieto R, Belmont Martínez L, Ibarra González I, Fernández-Lainez C, et al. Seguimiento bioquímico y dosis de medicamentos de EIM del metabolismo intermedio. Acta Pediátrica De México. 2023;**44**(1):75-82 doi.org/10.18233/APM44No1pp75-822573

[4] Leiva C, Borzutzky A, Le Roy C, Rojas L. Deficiencia de vitamina D: Propuesta de modelo chileno para una política nacional de fortificación alimentaria. Temas de la Agenda Pública. 2020;**15**(124):1-18. Centro de Políticas Públicas UC

[5] Hermoso de Mendoza MT. Clasificación de la osteoporosis: Factores de riesgo. Clínica y diagnóstico diferencial. Anales Sis San Navarra [Internet]. 2003;**26**(Suppl. 3):29-52

[6] Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;**4**(6):368-381. DOI: 10.1007/BF01622200

[7] Olgac A, Inci A, Okur I, Ezgu F, Biberoglu G, Tumer L. Vitamin D levels and bone mineral density in inborn errors of metabolism requiring specialized diets. Journal of the College of Physicians and Surgeons–Pakistan. 2019;**29**(12):1207-1211. DOI: 10.29271/jcpsp.2019.12.1207

[8] Geiger KE, Koeller DM, Harding CO, Huntington KL, Gillingham MB. Normal vitamin D levels and bone mineral density among children with inborn errors of metabolism consuming medical food-based diets. Nutrition Research. 2016;**36**(1):101-108. DOI: 10.1016/j.nutres.2015.11.007

[9] Cornejo V, Raimann E, Pérez B, Desviat L, Arias C. Errores innatos del metabolismo de aminoácidos. In: Colombo M, Cornejo V, Raimann E, editors. Errores innatos en el metabolismo del niño. 4ª ed. actualizada. Santiago: Editorial Universitaria; 2017. pp. 97-115

[10] van Wegberg AMJ, MacDonald A, Ahring K, Bélanger-Quintana A, Blau N, Bosch AM, et al. The complete European guidelines on phenylketonuria: Diagnosis and treatment. Orphanet Journal of Rare Diseases. 2017;**12**(1):162. DOI: 10.1186/s13023-017-0685-2

[11] Cornejo V, Raimann E, Cabello JF, Valiente A, Becerra C, Opazo M, et al. Past, present and future of newborn screening in Chile. Journal of Inherited Metabolic Disease. 2010;**33**(Suppl. 3):S301-S306. DOI: 10.1007/s10545-010-9165-8

[12] Dios-Fuentes E, Gonzalo Marin M, Remón-Ruiz P, Benitez Avila R, Bueno Delgado MA, Blasco Alonso J, et al. Cardiometabolic and nutritional

morbidities of a large, adult, PKU cohort from Andalusia. Nutrients. 2022;**14**(6):1311. DOI: 10.3390/nu14061311

[13] Hansen KE, Ney D. A systematic review of bone mineral density and fractures in phenylketonuria. Journal of Inherited Metabolic Disease. 2014;**37**(6):875-880. DOI: 10.1007/s10545-014-9735-2

[14] Demirdas S, Coakley KE, Bisschop PH, Hollak CE, Bosch AM, Singh RH. Bone health in phenylketonuria: A systematic review and meta-analysis. Orphanet Journal of Rare Diseases. 2015;**10**:17. DOI: 10.1186/s13023-015-0232-y

[15] Leiva C, Bravo P, Arias C, Cabello JF, Leal-Witt MJ, Salazar F, et al. 25- Hydroxy vitamin D level, bone health, vitamin D and calcium intake in Chilean patients with phenylketonuria and Hyperphenylalaninemia. Journal of Inborn Errors of Metabolism and Screening. [Internet]. 2021;9:e20210004. DOI: 10.1590/2326-4594-JIEMS-2021-0004

[16] Rojas E, Leal-Witt MJ, Arias C, Cabello JF, Salazar MF, Peñaloza F, et al. Salud muscular y ósea en Adulto Jóvenes Chilenos con Fenilcetonuria. In: Proceedings of the XXIII Congreso de Nutrición. Valdivia, Chile; 5-8 October 2022. pp. 34

[17] Pascual JM, Wang D, Lecumberri B, Yang H, Mao X, Yang R, et al. GLUT1 deficiency and other glucose transporter diseases. European Journal of Endocrinology. 2004;**150**(5):627-633. DOI: 10.1530/eje.0.1500627

[18] De Vivo DC, Trifiletti RR, Jacobson RI, Ronen GM, Behmand RA, Harik SI. Defective glucose transport across the blood-brain barrier as a cause of persistent hypoglycorrhachia, seizures, and developmental delay. The New England Journal of Medicine. 1991;**325**:703-709

[19] Veneruzzo GM, Loos MA, Armeno M, Alonso CN, Caraballo RH. Glucose transporter type 1 deficiency syndrome: Clinical aspects, diagnosis, and treatment. Archivos Argentinos de Pediatria. 2023;**121**(1):e202202677. English, Spanish. DOI: 10.5546/aap.2022-02677.eng

[20] Symonds JD, Zuberi SM, Stewart K, McLellan A, O'Regan M, MacLeod S, et al. Incidence and phenotypes of childhood-onset genetic epilepsies: A prospective population-based national cohort. Brain. 2019;**142**(8):2303-2318. DOI: 10.1093/brain/awz195

[21] Ramm-Pettersen A, Nakken KO, Haavardsholm KC, Selmer KK. GLUT1-deficiency syndrome: Report of a four-generation Norwegian family with a mild phenotype. Epilepsy & Behavior. 2017;**70**(Pt A):1-4. DOI: 10.1016/j.yebeh.2017.02.016

[22] Klepper J, Akman C, Armeno M, Auvin S, Cervenka M, Cross HJ, et al. Glut1 deficiency syndrome (Glut1DS): State of the art in 2020 and recommendations of the international Glut1DS study group. Epilepsia Open. 2020;**5**(3):354-365. DOI: 10.1002/epi4.12414

[23] Schwantje M, Verhagen LM, van Hasselt PM, Fuchs SA. Glucose transporter type 1 deficiency syndrome and the ketogenic diet. Journal of Inherited Metabolic Disease. 2020;**43**(2):216-222. DOI: 10.1002/jimd.12175

[24] Cornejo V, Raimann E. Errores innatos del metabolismo de los hidratos

de carbono. Parte 1: Alteración del metabolismo de la galactosa. In: Colombo M, Cornejo V, Raimann E, editors. Errores innatos en el metabolismo del niño. 4ª ed. actualizada. Santiago: Editorial Universitaria; 2017. pp. 207-243

[25] Newmaster K, Zhu Z, Bolt E, Chang RJ, Day C, Mhanna A, et al. A review of the multi-systemic complications of a ketogenic diet in children and infants with epilepsy. Children. 2022;**9**:1372. DOI: 10.3390/children9091372

[26] Lyons L, Schoeler NE, Langan D, Cross JH. Use of ketogenic diet therapy in infants with epilepsy: A systematic review and meta-analysis. Epilepsia. 2020;**61**(6):1261-1281. DOI: 10.1111/epi.16543

[27] Garofalo V, Barbagallo F, Cannarella R, Calogero AE, La Vignera S, Condorelli RA. Effects of the ketogenic diet on bone health: A systematic review. Frontiers in Endocrinology (Lausanne). 2023;**14**:1042744. DOI: 10.3389/fendo.2023.1042744

[28] Simm PJ, Bicknell-Royle J, Lawrie J, Nation J, Draffin K, Stewart KG, et al. The effect of the ketogenic diet on the developing skeleton. Epilepsy Research. 2017;**136**:62-66. DOI: 10.1016/j.eplepsyres.2017.07.014

[29] Siniscalchi A, Murphy S, Cione E, Piro L, Sarro G, Gallelli L. Antiepileptic drugs and bone health: Current concepts. Psychopharmacology Bulletin. 2020;**50**(2):36-44

[30] Vestergaard P. Effects of antiepileptic drugs on bone health and growth potential in children with epilepsy. Paediatric Drugs. 2015;**17**(2):141-150. DOI: 10.1007/s40272-014-0115-z

[31] Carnauba RA, Baptistella AB, Paschoal V, Hübscher GH. Diet-induced low-grade metabolic acidosis and clinical outcomes: A review. Nutrients. 2017;**9**(6):538. DOI: 10.3390/nu9060538

[32] Husari KS, Cervenka MC. The ketogenic diet all grown up-ketogenic diet therapies for adults. Epilepsy Research. 2020;**162**:106319. DOI: 10.1016/j.eplepsyres.2020.106319

[33] Acharya P, Acharya C, Thongprayoon C, Hansrivijit P, Kanduri SR, Kovvuru K, et al. Incidence and characteristics of kidney stones in patients on ketogenic diet: A systematic review and meta-analysis. Diseases. 2021;**9**(2):39. DOI: 10.3390/diseases9020039

[34] Detopoulou P, Papadopoulou SK, Voulgaridou G, Dedes V, Tsoumana D, Gioxari A, et al. Ketogenic diet and vitamin D metabolism: A review of evidence. Metabolites. 2022;**12**(12):1288. DOI: 10.3390/metabo12121288

[35] Molteberg E, Taubøll E, Kverneland M, Iversen PO, Selmer KK, Nakken KO, et al. Substantial early changes in bone and calcium metabolism among adult pharmacoresistant epilepsy patients on a modified Atkins diet. Epilepsia. 2022;**63**(4):880-891. DOI: 10.1111/epi.17169

[36] Lee M, Lee HI, Song K, Choi HS, Suh J, Kim SH, et al. Association of hypercalciuria with vitamin D supplementation in patients undergoing ketogenic dietary therapy. Frontiers in Nutrition. 2022;**9**:970467. DOI: 10.3389/fnut.2022.970467

[37] Merlotti D, Cosso R, Eller-Vainicher C, Vescini F, Chiodini I, Gennari L, et al. Energy metabolism and ketogenic diets: What about the skeletal health? A narrative review and a prospective vision for planning clinical trials on this issue. International Journal

of Molecular Sciences. 2021;**22**(1):435. DOI: 10.3390/ijms22010435

[38] Bertoli S, Trentani C, Ferraris C, De Giorgis V, Veggiotti P, Tagliabue A. Long-term effects of a ketogenic diet on body composition and bone mineralization in GLUT-1 deficiency syndrome: A case series. Nutrition. 2014;**30**(6):726-728. DOI: 10.1016/j.nut.2014.01.005

[39] Cervenka MC, Henry BJ, Felton EA, Patton K, Kossoff EH. Establishing an adult epilepsy diet center: Experience, efficacy and challenges. Epilepsy & Behavior. 2016;**58**:61-68. DOI: 10.1016/j.yebeh.2016.02.038

[40] Welling L, Bernstein LE, Berry GT, et al. International clinical guideline for the management of classical galactosemia: Diagnosis, treatment, and follow-up. Journal of Inherited Metabolic Disease. 2017;**40**(2):171-176. DOI: 10.1007/s10545-016-9990-5

[41] Coelho AI, Rubio-Gozalbo ME, Vicente JB, Rivera I. Sweet and sour: An update on classic galactosemia. Journal of Inherited Metabolic Disease. 2017;**40**(3):325-342. DOI: 10.1007/s10545-017-0029-3

[42] Fridovich-Keil J, Berry GT. Pathophysiology of long-term complications in classic Galactosemia: What we do and do not know. Molecular Genetics and Metabolism. 2022;**137**(1-2):33-39. DOI: 10.1016/j.ymgme.2022.07.005

[43] Delnoy B, Coelho AI, Rubio-Gozalbo ME. Current and future treatments for classic Galactosemia. Journal of Personalized Medicine. 2021;**11**(2):75. DOI: 10.3390/jpm11020075

[44] Berry GT. Classic Galactosemia and Clinical Variant Galactosemia. Seattle, Seattle (WA): Book from University of Washington; 2021

[45] Rubio-Gozalbo ME, Haskovic M, Bosch AM, Burnyte B, Coelho AI, Cassiman D, et al. The natural history of classic galactosemia: Lessons from the GalNet registry. Orphanet Journal of Rare Diseases. 2019;**14**(1):86. DOI: 10.1186/s13023-019-1047-z

[46] Panis B, Vermeer C, van Kroonenburgh M, Nieman F, Menheere P, Spaapen L, et al. Effect of calcium, vitamins K1 and D3 on bone in Galactosemia. Bone. 2006;**39**(5):1123-1129

[47] Erven, Britt van, Myrna M, Römers M, Estela Rubio-Gozalbo M. Revised proposal for the prevention of low bone mass in patients with classical galactosemia. In: Johannes Z, Gibson KM, Brown G, Morava E, Peters V, editors. JIMD Reports. Berlin, Heidelberg: Springer; 2014;**17**:41-46. DOI: 10.1007/8904_2014_331

[48] van Erven B, Welling L, van Calcar S, Doulgeraki A, Eyskens F, Gribben J, et al. Bone health in classic Galactosemia: Systematic review and meta-analysis. JIMD Reports. 2016;**35**:87-96

[49] Rubio-Gozalbo ME, Hamming S, van Kroonenburgh M, Bakker J, Vermeer C, Forget P. Bone mineral density in patients with classic Galactosaemia. Archives of Disease in Childhood. 2002;**87**(1):57-60

[50] Panis B, Forget P, van Kroonenburgh M, Vermeer C, Menheere P, Nieman F, et al. Bone metabolism in Galactosemia. Bone. 2004;**35**(4):982-987

[51] Gajewska J, Ambroszkiewicz J, Radomyska B, Laskowska-Klita T. Bone turnover markers in Prepubertal children with classical Galactosemia. Indian Journal of Gastroenterology: Official Journal of the Indian Society of Gastroenterology. 2006;**25**(4):221-222

[52] Gajewska J, Ambroszkiewicz J, Radomyska B, Chełchowska M,

Ołtarzewski M, Laskowska-Klita T, et al. Serum markers of bone turnover in children and adolescents with classic Galactosemia. Advances in Medical Sciences. 2008;**53**(2):214-220

[53] Sirrs S, Bosdet T, Branov J, et al. High prevalence of vitamin D insufficiency in galactosemic adults despite compliance with supplementation. Journal of Inherited Metabolic Disease. 2010;**33**:S64

[54] Waisbren S, Potter N, Gordon C, Green R, Greenstein P, Gubbels C, et al. The adult Galactosemic phenotype. Journal of Inherited Metabolic Disease. 2012;**35**(2):279-286