B Complex Vitamins Profile in Patients with Hepatic Glycogen Storage Disease and its Possible Determinants

Journal of Inborn Errors of Metabolism & Screening
2025, Volume 13: e20240008
DOI: https://doi.org/10.1590/2326-4594-JIEMS-2024-0008

Mariana L. Scortegagna[1,8], Bibiana M. de Oliveira[2], Soraia Poloni[3], Vaneisse C. L. Monteiro[4], Bianca F. Franceschetto[1], Lilia R. Farret[3], François Maillot[5], Carolina F. M. Souza[7,8,9], Ida V. D. Schwartz[1,6,10]

Abstract

Hepatic glycogen storage diseases (GSD) are a group of rare hereditary metabolic diseases characterized by abnormalities in enzymes that regulate glycogen synthesis or degradation. Treatment is essentially dietary, with frequent administration of raw uncooked cornstarch (UCCS) to avoid hypoglycemia, in addition to the restriction of sucrose, fructose, and lactose. Nutritional deficiencies in these patients are believed to result from dietary restrictions that exclude key sources of essential vitamins. This study aimed to investigate serum levels and adequacy of dietary intake of B vitamins in patients with GSD. This is a cross-sectional study, with patients over 5 years old, diagnosed with GSD and undergoing treatment with UCCS. Clinical data were collected, in addition to the dosage of B vitamins and a 3-day food record. Fifteen patients were included, six of them reported daily use of multivitamins. Serum dosage showed that all B complex vitamins, except for vitamin B2, were within reference values. The adequacy of dietary intake of vitamins was at least 78%, except for vitamin B9. There was no correlation between dosage and vitamin intake.

Keywords

Inborn errors of metabolism, glycogen storage disease, complex B vitamins, dietary intake, supplementation, serum levels

Introduction

Glycogen storage diseases (GSD) are a group of genetic diseases that result in changes in glycogen metabolism, which can affect its synthesis (glycogenesis) or degradation (glycogenolysis) and are usually classified as hepatic and/or muscular GSD [1,2]. The global incidence is estimated at 1 case for every 20,000-43,000 live births, with types I, III, and IX representing around 80% of diagnoses [3].

The primary manifestations of hepatic GSD subtypes 0, I, III, VI, IX, and XI are fasting intolerance associated with hypoglycemia and hepatomegaly. Furthermore, patients with GSD types III and IX present, in most cases, myopathic symptoms and progressive form of cardiomyopathy [4,5] GSD I is caused by deficient glucose-6-phosphatase activity [6]; GSD III results from a deficiency of the glycogen debranching enzyme and GSD IX is caused by phosphorylase kinase deficiency [7]. Table 1 shows the classification of hepatic GSD, as well as the affected gene and inheritance pattern.

[1] Universidade Federal do Rio Grande do Sul, Programa de Pós–Graduação em Medicina: Ciências Médicas, Porto Alegre, RS, Brazil.
[2] Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre, RS, Brazil.
[3] Hospital de Clínicas de Porto Alegre, Serviço de Nutrição e Dietética, Porto Alegre, RS, Brazil.
[4] Instituto Carlos Chagas – Fiocruz, Curitiba, PR, Brazil.
[5] University of Tours, Internal Medicine Department, Imaging and Brain Unit INSERM 1253, Tours, France.
[6] Hospital de Clínicas de Porto Alegre, Serviço de Genética Médica, Porto Alegre, RS, Brazil.
[7] Hospital de Clínicas de Porto Alegre, Serviço de Pesquisa Clínica, Porto Alegre, RS, Brazil.
[8] Casa dos Raros, Porto Alegre, RS, Brazil.
[9] Universidade Federal do Rio Grande do Sul, Programa de Pós–Graduação em Saúde da Criança e do Adolescente, Porto Alegre, RS, Brazil.
[10] Instituto Nacional de Doenças Raras, Porto Alegre, RS, Brazil.

Received September 03, 2024. Accepted for publication July 19, 2025.

Associate Editor: Guilherme Baldo.

Corresponding Author:
Ida Vanessa Doederlein Schwartz, e-mail: ischwartz@hcpa.edu.br

Table 1. Classification of hepatic glycogen storage diseases.

Type (MIM)	Enzyme	Gene	Inheritance Pattern
0 (240600)	Glycogen synthase (liver)	*GYS2*	AR
Ia (232200)	Glucose-6-phosphatase	*G6PC*	AR
Ib (232220)	Glucose-6-phosphatase translocase	*SLC37A4*	AR
IIIa and IIIb (232400)	Glycogen debranching enzyme	*AGL*	AR
IV (232500)	Glycogen branching enzyme	*GBE1*	AR
VI (232700)	Glycogen phosphorylase (liver)	*PYGL*	AR
IXa (306000)	Phosphorylase kinase (alpha subunit)	*PHKA2*	XLR
IXb (261750)	Phosphorylase kinase (beta subunit)	*PHKB*	AR
IXc (613027)	Phosphorylase kinase (gamma subunit)	*PHKG2*	AR
XI (227810)	Glucose transporter 2	*GLUT2*	AR

Abbreviations: GSD: glycogen storage disease; AR: autosomal recessive; XLR: X-linked recessive
Adapted from: dos Santos et al. [8]

Treatment for GSD is basically nutritional, with recommendations for restricting simple carbohydrates and frequent and individualized use of uncooked cornstarch (UCCS) in order to maintain normoglycemia and avoid glycogen accumulation [9,10]. In GSD I, restriction of sucrose, fructose, and lactose is widely used. Unlike the diet used to treat patients with GSD I, the diet used to treat GSD III and IX is high-protein and the intake of fructose and galactose is allowed [6,11,12].

B complex vitamins participate in the production of energy and biosynthesis of vital molecules for cells. As these vitamins are classified as water-soluble, they are not stored in the body, so intake must be daily [13].

The dietary restrictions imposed by the treatment, as well as the large consumption of UCCS, can lead to nutritional deficiencies in these patients. Due to their wide distribution in foods, deficiency of most of these vitamins is uncommon. Little is known regarding the profile of B complex vitamins presented by these patients, however case reports indicate that individuals with this group of diseases may be associated with vitamin deficiencies, especially in complex B [14,15]. In the study by Hinkel et al. [16], however, it was observed that patients with GSD had increased serum vitamin B12 values when compared to healthy patients.

This study aims to evaluate the levels of B vitamins presented by patients with hepatic GSD and their association with clinical and treatment variables.

Methods

A cross-sectional study was carried out with the following inclusion criteria: patients over 5 years old due to the difficulty in performing blood collection in children younger than that age; confirmed diagnosis of GSD (type Ia, Ib, III, IXa, IXb, and IXc) by enzymatic assay or genotyping. Additionally, participants were required to have undergone treatment with UCCS for a minimum of one year while under the clinical supervision of the Medical Genetics Service at Hospital de Clínicas do HCPA (SGM-HCPA).

The present study obtained approval from the Ethics and Research Committee of the Hospital de Clínicas de Porto Alegre (Approval Number: 2019-0256; CAAE: 13353419100005327). The sample was selected using convenience sampling, comprising patients or their legal guardians who voluntarily agreed to participate in the research and formalized their consent by signing the Informed Consent Form.

Vitamin Dosage

B complex vitamins, including B1, B2, B3, and B6, were quantified using the High-performance Liquid Chromatography (HPLC) method, while B7 was assessed via Enzyme Linked Immunosorbent Assay (ELISA), B9 through chemiluminescence, and B12 via gas chromatography. Specifically, vitamins B1, B2, B6,

and B9 were analyzed in red blood cells and B3 and B7 in serum. These specific vitamins were selected due to their widespread determination capabilities in specialized laboratories and their representation of various food source classes. No fasting time was stipulated prior to blood collection. Subsequently, the samples were sent to a specialized laboratory for analysis, with the reference values established by the laboratory itself.

Collection of Clinical and Treatment Data

Data regarding clinical variables (type of GSD, age, anthropometric data, presence of hypoglycemia, signs, and symptoms related to possible nutritional deficiencies) and nutritional variables (use of alternative feeding route, amount of UCCS) were obtained through review of the medical and food records. The data collected referred to the last twelve months prior to the date of blood collection.

Body mass index (BMI) was calculated as weight (kg) divided by height in meter square (m^2) and classified as underweight, normal weight, overweight, or obese, per the World Health Organization (WHO) criteria [17,18]. In patients aged <19 years, nutritional status was calculated using BMI for age Z-scores calculated in WHO Anthroplus version 1.0.4 [19]. It is important to note that BMI may not accurately reflect nutritional status in pediatric patients, particularly those with short stature. To address this limitation, BMI-for-age Z-scores were calculated to better account for age- and height-related variations.

Nutrient Intake

Dietary intake of macronutrients and micronutrients, including consumption of vitamin B1 (thiamine), B2 (riboflavin), B3 (niacin), B6 (pyridoxine), B9 (folic acid), and B12 (cobalamin), was assessed through was assessed using 3-day food records 1 weekend day and 2 working days, these being the same week as the blood collection. Vitamin B7 (biotin) was not calculated because the software used did not measure this vitamin in question.

The calculation of total daily nutrient intake was performed using Nutribase™ software (NB16Cloud, CyberSoft, Inc., Phoenix, AZ, USA). Adequacy of dietary intake was classified according to the Recommended Dietary Allowances (RDA) established by the Dietary References Intakes (DRIs) [20]. When RDA values were not available, Adequate Intake (AI) cutoff points were used. The intake of nutrients from supplements used by patients were also considered.

Statistical Analysis

Categorical variables will be presented as frequencies and percentages and continuous variables as means and/or medians and standard deviation. Continuous variables were compared using the Wilcoxon test, and the association between variables was assessed using Spearman correlation.

Statistical analysis was performed using version 29.0 Statistical Package for Social Sciences (SPSS Inc. Chicago, IL). *P* value <0.05 was considered statistically significant.

Results

Fifteen patients were included, ten of whom were male, with a mean age of 16.4±7.9 years, diagnosed with the following types of GSD: Ia: 8, Ib: 4, IXa: 1, IXb: 1, IXc: 1. The characterization of the included patients is shown in Table 2.

Seven patients were classified with body mass index (BMI) as eutrophic, four as overweight and four as obese (Figure 1). BMI-for-age Z-scores findings were consistent with those derived from the standard BMI classification.

All patients were being treated with UCCS, in accordance with the recommendations established for the type of GSD (recommendation range: I=1.6 g/kg/dose; IX=0.6 to 2.5 g/kg/dose) [8]. Median UCCS intake was 315 grams per day (g/day) (IQR: 233-396 g/day). Eight patients (Ia: 4; Ib: 3 and IXc: 1) reported at least 1 episode of hypoglycemia due to forgetting the UCCS dose (n=7) or after physical activity (n=1) in the last month. Four patients (Ia: 4 and IXc: 1) had previously used gastrostomy, with 2 (Ia and IXc) patients requiring the alternative route due to reports of food aversion. At the time of data collection, all patients had an exclusive oral route. Episodes of hematochezia (n=1), diarrhea (n=2), vomiting (n=1), itching (n=1) were reported in outpatient consultations. No signs or symptoms have been reported that are related to B vitamin deficiencies.

Ten patients use vitamin supplements daily and regularly (calcium, vitamin A, C, and D), of which 6 use multivitamins that include vitamins from the B complex, which were included in the calculation of dietary intake. Data regarding serum food intake levels are described in Table 3.

One patient (8) had low dietary intake for all vitamins; six (1, 2, 4, 11, 12, 13) had adequate intake of all vitamins, except for vitamin B9 and two patients (5, 6) achieved adequate dietary intake equal to or greater than 80% of recommendations. Patient 3 had low intake of vitamins B1, B6, B9, and B12; patient 7 for vitamins B2, B6 and B9; patient 9 for vitamins B1 and B9; patient 10 for vitamin B6 and finally, patient 15 for vitamins B1, B2, B9, and B12.

Nine patients had low serum levels of vitamin B2 (Ia: 5, Ib: 1, IXa: 1, IXb: 1, IXc 1), six patients did not have low levels of B vitamins (Ia: 3, Ib: 3). Only one patient presented more than one possible vitamin deficiency, with values below the established reference for vitamin B2 and vitamin B12 (IXa). In general, vitamins B1, B7, B9, and B12 were within the reference value and vitamins B3 and B6 were slightly above the upper level.

There was a moderate correlation between UCCS consumption and BMI (r_s -0.625; *P* 0.013) and there was no correlation with age. There was a correlation between the dosage of vitamin B9 and the amount per g/kg/day of UCCS (r_s -0.652; *P* 0.011). Correlation data are presented in Table 4.

Table 2. Summary of the patients included in the study.

ID	Sex	GSD Type	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m^2)	W/A*	H/A*	BMI/I*	UCCS (g/day)	UCCS (g/kg/day)	Supplementation
1	F	Ia	10	53.5	151.0	23.4	NA	0.76	1.91	262	0.8	Yes (Vitamins A, B1, B2, B3, B5, B12, C, D)
2	F	Ia	13	70.0	148.0	31.9	NA	-1.57	2.73	390	0.9	Yes (Vitamins A, B3, B6, B7, B12, C, D, E
3	M	Ia	13	37.8	143.0	18.5	NA	-2.13	-0.03	315	1.3	Yes (Vitamin D, Ca)
4	F	Ia	14	51.5	148.0	23.6	NA	-1.74	1.18	386	1.2	No
5	M	Ia	16	90.7	167.7	32.9	NA	-0.51	2.73	406	0.6	Yes (Vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, E)
6	F	Ia	19	78.1	162.3	29.6	NA	NA	NA	282	0.6	Yes (Vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, E)
7	M	Ia	25	76.5	174.4	25.1	NA	NA	NA	473	1.0	No
8	M	Ia	30	72.8	169.0	25.4	NA	NA	NA	432	0.9	No
9	M	Ib	8	27.0	124.5	17.4	0,10	-0.89	0.89	246	1.5	No
10	M	Ib	11	40.5	144.0	19.5	NA	-0.09	1.06	348	1.4	Yes (Ca)
11	M	Ib	12	61.7	138.0	32.3	NA	-1.86	3.27	220	0.5	Yes (Vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, E)
12	M	Ib	16	60.4	164.5	22.3	NA	-1.25	0.53	402	1.1	Yes (Vitamins A, B1, B2, B3, B5, B6, B9, B12, C, D, E)
13	M	IXa	35	59.0	168.0	20.9	NA	NA	NA	160	0.6	Yes (Ca)
14	M	IXb	17	61.0	174.0	20.1	NA	-0.09	-0.33	160	0.6	Yes (Vitamin B12)
15	F	IXc	7	32.3	122.5	21.5	2.14	0.31	2.54	200	1.5	No

Abbreviations: GSD: glycogen storage disease; Y: year; F: female; M: male; BMI: body mass index; W: weight; A: age; H: height; UCCS: uncooked cornstarch; g: gram; kg: kilogram; Ca: calcium
*Z-score

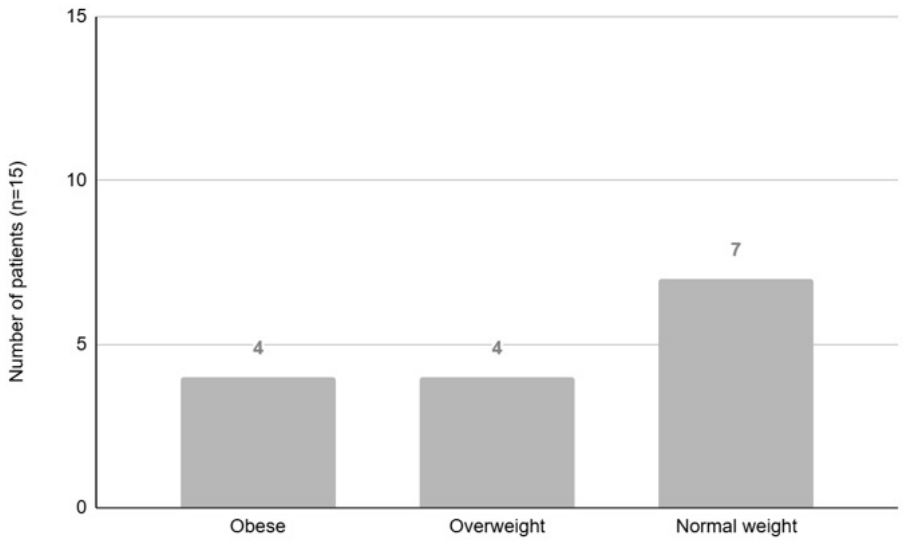

Figure 1. Classification of the nutritional status of patients with hepatic glycogen storage disease, according to body mass index [17,18].

Table 3. Serum levels, daily intake and adequacy in percentage of dietary intake of B vitamins.

	Daily Intake	Adequacy (%)*	Serum Levels	Reference Values†
	Median (IQR)			
Energy (kcal)	2544.0 (2235.7 – 2811.5)	NA	NA	NA
Protein (g)	109.5 (79.3 – 115.7)	NA	NA	NA
Carbohydrate (g)	39.8 (331.8 – 466.1)	NA	NA	NA
Lipids (g)	40.6 (33.6 – 68.5)	NA	NA	NA
B1	0.8 mg (0.4 – 1.4)	78.8 (49.9 – 138.5)	54 (33.5 – 90.2)	28 – 85 µg/L
B2	0.8 mg (0.4 – 1.2)	90.0 (58.5 – 135.9)	121 (1.7 – 317.9)	137 – 370 µg/L
B3	18.3 mg (11.6 – 24.7)	128.1 (88.0 – 197.5)	36.7 (11.3 – 80)	9 – 30 µg/L
B6	0.8 mg (0.3 – 1.4)	76.6 (43.4 – 108.4)	23.5 (10.2 – 58.1)	8.7 – 27.2 µg/L
B7	NA	NA	233 (110 – 984)	100 – 250 ng/dL
B9	64.6 µg (27.4 – 114.3)	26.0 (7.9 – 41.8)	285.5 (216 – 497)	≥ 151 ng/dL
B12	1.4 µg (0.8 – 2.2)	96.1 (66.1 – 166.6)	529 (158 – 2000)	187 – 883 pg/mL

Abbreviations: B1: thiamine; B2: riboflavin; B3: niacin; B6: pyridoxine; B7: biotin; B9: folic acid; B12: cobalamin; IQR: interquartile range; kcal: kilocalories; *g*: gram; kg: kilogram; mg: milligram; µg: microgram; NA: not applicable.
*Recommended Dietary Allowances (RDA) established by Dietary References Intakes (DRIs) [16].
†For serum levels.

Table 4. Correlation between study variables.

	Correlation (r_s)	p Value
Vitamin intake and dosage		
B1	-0.164	
B2	0.066	
B3	-0.025	
B6	-0.019	
B9	-0.011	
B12	-0.239	
UCCS and BMI		
g/kg/day	-0.625*	0.013
g/kg/dose	-0.654*	0.008
Total/day	0.441	
UCCS and age		
g/kg/day	-0.254	
g/kg/dose	-0.483	
Total/day	0.294	
UCCS (g/kg) and vitamin dosage		
B1	-0.378	
B2	-0.125	
B3	0.249	
B6	-0.152	
B9	-0.652*	0.011
B12	-0.143	

Table 4. Cont.

	Correlation (r_s)	p Value
UCCS (g/kg) and vitamin intake		
B1	0.056	
B2	0.060	
B3	0.318	
B6	-0.061	
B9	0.035	
B12	-0.060	

Spearman's correlation test.
Abbreviations: B1: thiamine; B2: riboflavin; B3: niacin; B6: pyridoxine; B9: folic acid; B12: cobalamin; BMI: body max index; UCCS: uncooked cornstarch; g: gram; kg: kilogram.
P<0.05 was considered statistically significant.
*Correlation was significant (0,05).

Discussion

A diet rich in carbohydrates and with several dietary restrictions, as in the case of patients with hepatic GSD, may be deficient in some B vitamins [13,21]. It is known that vitamin deficiencies manifest after many months of vitamin deprivation [21], however, when reviewing the clinical data and medical history of the study patients, no related signs or symptoms were reported.

The status of vitamin B1, thiamine, can be assessed by determining the activity of erythrocyte transketolase, through blood or serum concentrations of thiamine and also by urinary excretion of thiamine. Whole grains are the most important source of vitamin B1, and it is also found in foods of animal origin, such as pork [22]. In the present study, the serum B1 level was within the reference value, while consumption represented 78.8% of adequacy, showing no correlation between them. In the study by Idris et al. [15], the case of a 16-year-old patient with type Ia GSD, with symptoms related to Wernicke's encephalopathy, is described. The diagnosis of thiamine deficiency was based on symptoms and laboratory tests, with no data provided regarding dietary intake.

In the present study, patients had low serum vitamin B2 levels. This vitamin is abundant in foods with yellow pigments (vegetables and fruits), as well as milk and dairy products [23], and these foods are restricted for patients with hepatic GSD, especially patients with subtypes Ia and Ib. Cereal processing significantly decreases riboflavin levels in the food, around 38-73% in wheat flour is lost when compared to whole meal flour and around 33-57% in rice when compared to brown rice [24]. Analysis of diet records showed that the majority of patients do not consume whole foods, nor milk and dairy products, making the availability of this vitamin low. However, if the patient takes supplementation as prescribed, the levels reach the recommended recommendations. Riboflavin plays an important role in converting macronutrients into energy usable by the body, and therefore, patients with vitamin B2 deficiencies may experience feelings of fatigue and weakness. After analyzing the medical records, no patient included in the study complained about any characteristic sign and/or symptoms of vitamin B2 deficiency. Regarding the assessment of vitamin B2 status, the meta-analysis by Hoey et al. [23] — which aimed to identify the most reliable biomarkers of riboflavin — indicated that erythrocyte glutathione reductase activity coefficient (EGRac) is an effective biomarker for evaluating vitamin B2 intake. In contrast, plasma or erythrocyte riboflavin concentrations, which were the methods used in the present study, were found to be inconsistent.

Vitamin B9 intake was low in most patients (13/15), with an adequacy of dietary intake of 26%. This vitamin is widely present in dark green leafy vegetables (spinach, asparagus, broccoli), as well as beans and peas. The body absorbs about 100% of folic acid from supplements and fortified foods, but only two-thirds of folate is naturally present in foods [25]. Additionally, there is a loss of 50 to 90% of folate during storage, cooking or processing at high temperatures [22]. In Brazil, the National Agency for Food Surveillance and Safety (ANVISA) regulated the addition of folic acid to wheat and corn flour (0.15 mg/100g) in 2004, citing the difficulty in ingesting this vitamin only with a normal, balanced diet [26]. Although regulations exist, patients with GSD rarely consume flour products (breads, cookies, pasta), mainly because some products contain added sugar. Another explanation for the low adequacy of dietary intake is due to the complexity of analyzing food sources of folate, in addition to the fact that the values of this vitamin in food composition tables are generally very low [22]. Even though there was no correlation between dosage and intake, serum folic acid values were in line with reference values (≥151 ng/dL), thus ruling out the possibility of nutritional deficiency.

Unlike the study sample by Hinkel et al. [16], in which patients with GSD (n=44) had high levels of B12, only 2 patients

(Ib and IXc) in the present study had serum vitamin B12 levels above the reference value, the other patients maintained the dosage within the established range (187-883 pg/mL). Although previous studies correlate vitamin B12 intake with plasma concentration in healthy patients [27,28], both Hinkel's study [16] and ours, this finding was not correlated. In the study by Jacoby et al. [29], the use of vitamin supplements impacts the adequacy of dietary intake in patients with hepatic GSD. After supplementation, vitamin B6 reached >100% and vitamin B12 >150% of intake adequacy. In our study, these same vitamins had an adequacy of 76 and 96% respectively, even with the inclusion of supplements in the food record calculation. Therefore, B vitamin supplementation is important for these patients, as otherwise the intake of these vitamins could be insufficient, causing a possible nutritional deficiency.

It is noteworthy that the majority of patients in the studied sample regularly use multivitamins, which may have been an analysis bias, but demonstrates the importance of supplementation in this genetic condition of restrictive diet. For both GSD and other types of inborn errors of metabolism (IEM), poor adherence ends up being a significant factor that interferes with treatment success [30]. Daly et al. [31] considers it essential that in the long term nutritional supplements, such as glucose polymers, fat emulsions and other products, are enriched with vitamins and minerals in order to improve nutritional quality as well as adherence. In phenylketonuria (PKU), there is evidence to suggest that long-term adherence is better when vitamins and minerals are already added to protein replacement products.

The nutritional status has been extensively studied in the literature. A correlation has been suggested between the consumption of uncooked cornstarch (UCCS) and increased fat mass in these individuals. UCCS has an energy value of around 361 calories in 100g of food [32]. The patients' average UCCS intake was 1137.15 kilocalories/day, representing 44.7% of the total daily calories, that is, almost half of the daily caloric intake is due to the imposed treatment. In the present study, half of the patients included are classified as overweight or obese. This data corroborates previous studies by our research group, in which patients with GSD have a tendency to be overweight or obese [8,29,33,34,35].

Another important point to highlight is in relation to the food selectivity that children with IEM have. Eating difficulties are often considered inherent to metabolic disease, but there is little evidence describing their frequency or severity [36]. In patients with PKU, whose treatment is a diet free of the amino acid phenylalanine, Tonon et al. [37], observed that food phobia is common in this group due to the dietary restrictions imposed from the first days of life. In patients with hepatic GSD, in the study conducted by Martinez et al. [38], the prevalence of feeding difficulties in patients was 72.2% (n=32), being related to the use of alternative feeding (tube or gastrostomy), food selectivity and prolonged meals and lack of meals with the family. These findings were also found in studies by Venema et al. [39] and Bérat et al. [40]

Conclusion

Multidisciplinary care in patients with hepatic GSD is essential for successful treatment. Because the treatment is based on UCCS and this is correlated with an increase in BMI, patients are advised to ingest sufficient amounts of UCCS to maintain adequate metabolic control, avoiding excessive carbohydrate overload. Furthermore, requesting periodic tests to biochemically assess nutritional status becomes important, considering that clinical manifestations of vitamin deficiency can take months for symptoms to appear.

The study corroborates previous data in the literature on the need to indicate vitamin replacement in patients with different forms of GSD due to the nutritional restriction imposed by the treatment. It can be seen from the food record that just consuming food is not enough to meet established needs. Therefore, we recommend the practice of evaluating food intake and the use of multivitamins for patients.

More studies from our group are under development to evaluate the dietary intake profile of patients with GSD, including the fatty acid profile and its possible correlations with lipid intake and UCCS.

Acknowledgments

The authors acknowledge the Coordination for the Improvement of Higher Education Personnel (CAPES), the Postgraduate Program in Medicine: Medical Sciences at the Federal University of Rio Grande do Sul (UFRGS) and the patients for their time and willingness to participate in this study.

Funding

Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) and *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq).

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data Availability

The manuscript has data included as electronic supplemental material; Additional data will be available on reasonable request.

References

1. Wolfsdorf JI, Weinstein DA. Glycogen storage diseases. *Rev Endocr Metab Disord*. 2003;4(1):95-102. doi: 10.1023/a:1021831621210
2. Hannah WB, Derks TGJ, Drumm ML, Grünert SC, Kishnani PS, Vissing J. Glycogen storage diseases. *Nat Rev Dis Primers*. 2023;9(1):46. doi: 10.1038/s41572–023–00456–z
3. Ozen H. Glycogen storage diseases: New perspectives. *World J Gastroenterol*. 2007;13(18):2541-2553. doi: 10.3748/wjg.v13.i18.2541
4. Bhattacharya K. Dietary dilemmas in the management of glycogen storage disease type I. *J Inherit Metab Dis*. 2011;34(3):621-629. doi: 10.1007/s10545–011–9322–8
5. Weinstein DA, Wolfsdorf JI, Smit PA, Schoser B. Glycogen Storage Diseases. In: Sarafoglou K, Hoffmann GF, Roth KS, eds. *Pediatric Endocrinology and Inborn Errors of Metabolism*. 2nd ed. New York, NY: McGraw-Hill Education; 2017. pp. 4826-5868.
6. Kishnani PS, Austin SL, Abdenur JE, et al. Diagnosis and management of glycogen storage disease type I: a practice guideline of the American College of Medical Genetics and Genomics. *Genet Med*. 2014;16(11):e1. doi: 10.1038/gim.2014.128
7. Derks TG, van Rijn M. Lipids in hepatic glycogen storage diseases: Pathophysiology, monitoring of dietary management and future directions. *J Inherit Metab Dis*. 2015;38(3):537-43. doi: 10.1007/s10545–015–9811–2
8. Dos Santos, Nalin T, Grokoski KC, et al. Nutritional status and body composition in patients with hepatic glycogen storage diseases treated with uncooked cornstarch – A controlled study. *J Inborn Errors Metab Screen*. 2017;5:1-7. doi: 10.1177/232640981773301
9. Steunenberg TAH, Peeks F, Hoogeveen IJ, et al. Safety issues associated with dietary management in patients with hepatic glycogen storage disease. *Mol Genet Metab*. 2018;125(1-2):79-85. doi: 10.1016/j.ymgme.2018.07.004
10. Derks TGJ, Rodriguez-Buritica DF, Ahmad A, et al. Glycogen Storage Disease Type Ia: Current Management Options, Burden and Unmet Needs. *Nutrients*. 2021;13(11):3828. doi: 10.3390/nu13113828
11. Kishnani PS, Austin SL, Arn P, et al. Glycogen storage disease type III diagnosis and management guidelines. *Genet Med*. 2010;12(7):446-463. doi: 10.1097/GIM.0b013e3181e655b6
12. Kishnani PS, Goldstein J, Austin SL, et al. Diagnosis and management of glycogen storage diseases type VI and IX: A clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2019;21(4):772-789. doi: 10.1038/s41436–018–0364–2
13. Schellack G, Harirari P, Schellack N. B-complex vitamin deficiency and supplementation. *S Afr Pharm J*. 2016;83(4):14-19. https://journals.co.za/doi/pdf/10.10520/EJC190765
14. Ihara K, Abe K, Hayakawa K, Makimura M, Kojima-Ishii K, Hara T. Biotin deficiency in a glycogen storage disease type 1b girl fed only with glycogen storage disease-related formula. *Pediatr Dermatol*. 2011;28(3):339-341. doi: 10.1111/j.1525–1470.2011.01238.x
15. Idris S, Ahmed AA, Ali R, Alsharari H, Ahmed EN, Deeba F. Wernicke's Encephalopathy: A Precipitation of Glycogen Storage Disease. *Cureus*. 2022;14(11):e31471. doi: 10.7759/cureus.31471
16. Hinkel J, Schmitt J, Wurm M, et al. Elevated Plasma Vitamin B_{12} in Patients with Hepatic Glycogen Storage Diseases. *J Clin Med*. 2020;9(8):2326. doi: 10.3390/jcm9082326
17. World Health Organization. Physical status: The Use and interpretation of anthropometry. Report of a WHO Expert Committee. Geneva: WHO; 1995.
18. World Health Organization. WHO Child growth standards: Methods and Development: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. Geneva, WHO; 2006.
19. World Health Organizations. WHO Anthro for Personal computers manual: Software for assessing growth and development of the world's children. Geneva: WHO; 2010.
20. Padovani RM, Amaya-Farfán J, Colugnati FAB, Domene SMÁ. Dietary reference intakes: Application of tables in nutritional studies. *Rev Nutri*. 2006;19: 741-760. doi: 10.1590/S1415–52732006000600010
21. Fogelholm M, Tikkanen H, Näveri H, Härkönen M. High-carbohydrate diet for long distance runners--a practical view-point. *Br J Sports Med*. 1989;23(2):94-6. doi: 10.1136/bjsm.23.2.94
22. Gallagher ML. Ingestão: os nutrientes e seu metabolismo. In: Mahan LK, Escott-Stump S, Raymond JL, eds. *Krause – Alimentos, Nutrição e Dietoterapia*. 13th ed. Rio de Janeiro: Elsevier, 2012: 32-128.
23. Hoey L, McNulty H, Strain JJ. Studies of biomarker responses to intervention with riboflavin: A systematic review. *Am J Clin Nutr*. 2009;89(6):1960S-1980S. doi: 10.3945/ajcn.2009.27230B
24. Hrubša M, Siatka T, Nejmanová I, et al. Biological properties of vitamins of the B-Complex, part 1: vitamins B1, B2, B3, and B5. *Nutrients*. 2022;14(3):484. doi: 10.3390/nu14030484
25. Rubert A, Engel B, Rohlfes ALB, Marquardt L, Baccar NM. B complex vitamins: A brief review. *Rev Jovens Pesquisadores*. 2017;7(1):30-45. foi: 10.17058/rjp.v7i1.9332

26. Santos LM, Pereira MZ. The effect of folic acid fortification on the reduction of neural tube defects. *Cad Saude Publica*. 2007;23(1):17-24. doi: 10.1590/s0102–311x2007000100003

27. Tucker KL, Rich S, Rosenberg I, Jacques P, Dallal G, Wilson PW, Selhub J. Plasma vitamin B-12 concentrations relate to intake source in the Framingham Offspring study. *Am J Clin Nutr*. 2000;71(2):514-522. doi: 10.1093/ajcn/71.2.514

28. Lederer AK, Hannibal L, Hettich M, et al. Vitamin B12 status upon short-term intervention with a vegan diet-a randomized controlled trial in healthy participants. *Nutrients*. 2019;11(11):2815. doi: 10.3390/nu11112815

29. Jacoby JT, Bento dos Santos B, Nalin T, et al. Bone mineral density in patients with hepatic glycogen storage diseases. *Nutrients*. 2021;13(9):2987. doi: 10.3390/nu13092987

30. Kishnani PS, Boney A, Chen YT. Nutritional deficiencies in a patient with glycogen storage disease type Ib. *J Inherit Metab Dis*. 1999;22(7):795-801. doi: 10.1023/a:1005549823146

31. Daly A, Evans S, Chahal S, Surplice I, Vijay S, Santra S, MacDonald A. The challenges of vitamin and mineral supplementation in children with inherited metabolic disorders: A prospective trial. *J Hum Nutr Diet*. 2016;29(4):434-440. doi: 10.1111/jhn.12354

32. Núcleo de Estudos e Pesquisas em Alimentação – NEPA, Universidade Estadual de Campinas – UNICAMP. Tabela Brasileira de composição de alimentos. 4. ed. Campinas, São Paulo: NEPA/UNICAMP, 2011.

33. Santos BL, Souza CF, Schuler-Faccini L, et al. Glycogen storage disease type I: Clinical and laboratory profile. *J Pediatr (Rio J)*. 2014;90(6):572-579. doi: 10.1016/j.jped.2014.02.005

34. Monteiro VCL, de Oliveira BM, Dos Santos BB, et al. A triple-blinded crossover study to evaluate the short-term safety of sweet manioc starch for the treatment of glycogen storage disease type Ia. *Orphanet J Rare Dis*. 2021;16(1):254. doi: 10.1186/s13023–021–01877–3

35. Dos Santos BB, Colonetti K, Nalin T, et al. Body composition in patients with hepatic glycogen storage diseases. *Nutrition*. 2022;103-104:111763. doi: 10.1016/j.nut.2022.111763

36. Evans S, Alroqaiba N, Daly A, Neville C, Davies P, Macdonald A. Feeding difficulties in children with inherited metabolic disorders: A pilot study. *J Hum Nutr Diet*. 2012;25(3):209-216. doi: 10.1111/j.1365–277X.2012.01229.x

37. Tonon T, Martinez CC, Poloni S, et al. Food neophobia in patients with phenylketonuria. *J Endocrinol Metab*. 2019;9(4): 108-112. doi: 10.14740/jem581

38. Martinez CC, Tonon T, Nalin T, Refosco LF, de Souza CFM, Schwartz IVD. Feeding Difficulties and orofacial myofunctional disorder in patients with hepatic glycogen storage diseases. *JIMD Rep*. 2019;45:21-27. doi: 10.1007/8904_2018_131

39. Venema A, Peeks F, de Bruijn-van der Veen M, et al. A retrospective study of eating and psychosocial problems in patients with hepatic glycogen storage diseases and idiopathic ketotic hypoglycemia: Towards a standard set of patient-reported outcome measures. *JIMD Rep*. 2021;63(1):29-40. doi: 10.1002/jmd2.12253

40. Bérat CM, Roda C, Brassier A, et al. Enteral tube feeding in patients receiving dietary treatment for metabolic diseases: A retrospective analysis in a large French cohort. *Mol Genet Metab Rep*. 2021;26:100655. doi: 10.1016/j.ymgmr.2020.100655