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Nutritional Status of Patients with Glycogen Storage Diseases – Polish Experience

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Abstract

Background: Glycogen Storage Diseases (GSDs), known as glycogenoses, belong to inborn metabolic defects in the glycogen metabolism pathway. Several types of GSDs are distinguished, including Ia, Ib, III, VI, and IX. GSDs manifest as excessive glycogen deposition in the liver and muscles, resulting in the dysfunction of these organs. Therefore, the treatment of choice is multitherapy that, due to dietary restrictions, may lead to nutritional deficiencies and organ complications. This study aims to assess anthropometric, body composition, skeletal status, results of selected laboratory tests, dietary, lifestyle and physical capacity analyses in patients with glycogenoses and compare the results between GSD I and GSD III-VI-IX groups. Results: The results indicate that GSD patients were overweight or obese (44% of patients had BMI +1SD or +2SD) with high percentage of fat tissue (50% of patients had above 30% of body fat) and inadequate bone mineralization (total body less head: median z-score -0.9, L2-L4 segment: median z-score -1.65). GSD I patients had the highest risk of developing obesity (67% of them had above 30% of body fat) and osteoporosis (total body less head: median z-score -1.0, L2-L4 segment: median -1.7). Conclusions: Special attention should be paid to appropriate diet and supplementation in patients with glycogenoses.

Keywords: Glycogen storage diseases; Glycogenoses; Body composition; Obesity; Fat tissue; Bone mineral density

Introduction

Glycogen Storage Diseases (GSDs), or glycogenoses, are rare diseases. The incidence is 1 per 65,000-85,000, from 1 per 100,000 to as many as 1 per 1 million cases. GSDs belong to inborn defects of metabolism in the glycogen metabolism pathway – glycogenogenogenesis and glycogenolysis. There are several types of GSDs, each associated with a different enzyme disorder – this paper describes patients with types Ia, Ib, III, VI, and IX (Table 1). The diagnosis is based on clinical symptoms and laboratory findings; genetic tests must be performed to confirm the diagnosis (Table 1) [1-5].

Glycogenoses I, III, VI and IX show a predominant hepatic manifestation. Patients, depending on the type of GSD, are found to have hypoglycaemia, hypertransaminasemia, hyperlipidaemia including hypertriglyceridaemia, hypercalcaemia, hyperuricaemia, neutropenia, ketosis, hepatomegaly, liver failure, high creatine kinase levels, myopathies and cardiomyopathies, inflammatory bowel diseases, hypertension,osteopenia and osteoporosis, obesity, mainly abdominal obesity and short stature [1–14].

The treatment of glycogenoses is based on dietary recommendations. The essential nutritional recommendation is to eat regularly, sometimes at night, and avoid prolonged starvation [1-3,15]. In addition, the protein and carbohydrate content of the diet is modified. Daily protein intake depends on the type of GSD, and it is recommended to consume:

- Up to 2 g of protein per kg of body weight in GSD I,
- 3-4 g protein/kg body weight in GSD III (20-30% of dietary energy),
- 2-3 g protein/kg body weight in GSD VI and IX (20-25% of dietary energy).

Protein can be of animal and plant origin. Therefore, the intake of a protein supplement may be suggested [2,4,7,8,11,15].

The diet should limit carbohydrate intake (35-55% of dietary energy). Complex carbohydrates should be offered at 15-30g per meal, including sugars up to 2.5-5g per meal. Moreover, patients are not allowed to eat fruit (fructose), sugar, sweets, and drink sweetened beverages (sucrose) and, in GSD I, milk and dairy products (galactose restriction) [1-5,8,13,15]. Uncooked Cornstarch (UCCS) is introduced in place of carbohydrates, mainly in GSD I, while proteins are also introduced in GSD III-

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Table 1: Types of glycogenoses, corresponding enzyme defects and gene mutations.

Glycogenosis type	Enzyme disorders	Gene mutation
Ia	glucose-6-phosphatase alpha-subunit deficiency	*G6PC*
Ib	glucose-6-phosphate translocase deficiency	*SLC37A4*
III	glycogen-debranching enzyme deficiency	*AGL*
VI	hepatic glycogen phosphorylase deficiency	*PYGL*
IXa	subunit alpha 2-related hepatic phosphorylase kinase deficiency	*PHKA2*

VI-IX. Starch is a long-digested source of glucose. Patients drink UCCS as a suspension in water or an approved beverage (for GSD III-VI-IX: in cow's milk or milk mixture, for GSD I: in a soy beverage without added sugar or a milk formula without lactose and fructose). The starch dose is calculated according to the patient's body weight given in kilograms. It rarely started before the age of one year, and its administration starts with small doses (from 1 g/serving) according to the regimen below:

- In GSD I: 6-8 servings/day (regular administration, every 3-4 hours during the day and every 4-6 hours at night),
- In GSD III: 6-8 servings/day in young children, 1-3 servings/day in older children, always one dose before bedtime,
- In GSD VI: 1-4 servings/day, always one dose before bedtime,
- In GSD IX: 1-3 servings/day, always one dose before bedtime.

In some patients, a modified starch preparation containing more amylopectins (Glycosade®) works well [1-3,5,7,8,15-17].

Due to nutritional deficiencies that may occur with the diet, as mentioned earlier, and due to GSD-related complications, vitamin D_3 and calcium supplementation should be introduced [1,2,4,5,7,8,13,15].

This nutritional management should maintain stable glycaemia, ensure normal development, and avoid long-term sequelae of glycogenoses [17-19].

This study aims to assess anthropometric, body composition, skeletal status, results of selected laboratory tests, dietary, lifestyle and physical capacity analyses in patients with glycogenoses and compare the results between GSD I and GSD III-VI-IX groups.

Materials and Methods

Study Design

The study was prospective. It was conducted at the Children's Memorial Health Institute in Warsaw (Poland) in 2020-2021. The study included 18 patients with different types of GSDs, and they were divided on two groups. The division of the groups was determined by dietary recommendations based on the type of glycogenosis. The groups differed in their intake of milk and dairy products, daily protein intake and UCCS and/or Glycosade® intake. GSD I patients are assumed to be calcium deficient due to non-consumption of milk and dairy products (galactose), consume less protein than GSD III-VI-IX patients and drink more UCCS and/or Glycosade®, which may have a worse effect on their body composition and bone mineralisation. The groups were equivalent in size.

Assessments

Data analysis was performed using anthropometric measurements, densitometry, biochemical blood tests, dietary assessment, lifestyle and physical capacity.

Anthropometric Assessments: Anthropometric studies included weight and height measurements were used to calculate the body mass index (BMI). BMI was calculated from the formula: the quotient of body weight expressed in kilograms to the square of height expressed in metres: BMI = body mass (kg)/body height $(m)^2$

BMI was related to the OLA and OLAF centile grids (3-18 years of age) [20].

Assessment of bone mineral density and body composition: Bone mineral density as well as body composition measurements were done using the Dual-energy X-ray Absorptiometry method (DXA). A Prodigy Advance densitometer (GE Healthcare, USA) with software v. 14.0 was used. Scan modes were automatically selected by the software based on body dimensions. Total body less head (TBLH) and lumbar spine (L2-L4) measurements were done, according to the International Society for Clinical Densitometry recommendation (ISCD). Z-scores were calculated by the apparatus software based on combined NHANES (National Health and Nutrition Examination Survey)/Lunar reference data. Total body soft tissue was divided into 2 compartments: fat and fat-free (which is a surrogate of the muscle mass) [21-23]. For the calibration of the densitometer, a daily quality control procedure and anthropomorphic spine phantom (Hologic, USA) scans were performed [24].

Biochemical Measures: Blood tests included total protein, albumin, vitamin D3, calcium, phosphorus, lactate and glucose. Total protein, albumin and calcium levels were analysed by colorimetric method, phosphorus levels by photometric method, vitamin D3 (25-hydroxycholecalciferol, 25(OH)D3) levels by chemiluminescence, lactate and glucose levels by enzymatic method. The results were related to age-dependent laboratory standards. Blood for testing was taken in the morning on an empty stomach.

Dietary Assessment: The patients' diets were analysed by the software Diet_6.0 v. 3 [25]. Based on a 3-day running record of the menus, daily mean values were calculated for dietary energy, dietary protein content, including protein from dietary supplements, and dietary carbohydrate content, including carbohydrates from UCCS and/or Glycosade®, calcium and vitamin D3, including dietary supplements.

The daily energy content of the diet was related to the energy expenditure measured by indirect calorimetry. The basis of the method is the assumption that the energy used by the body is obtained through the oxidation of nutrients. In these reactions, oxygen is consumed, and carbon dioxide is released, and their amounts are proportional to the energy expended. Measurement of energy expenditure involves determining the exchange of respiratory gases (volume of oxygen consumed and carbon dioxide released) per unit of time [26]. Cosmed Quark RMR equipment was used for the study. In patients, a calorimetric test was performed before lunch after approximately 3 hours since the last meal (breakfast). Patients were instructed not to snack after breakfast, although they could drink non-energetic beverages (water, tea without sugar). The test was per-

formed in the supine position. The protein and carbohydrates intake were related to individual dietary recommendations. The calcium was compared to standards at the Recommended Dietary Allowance (RDA) and vitamin D3 intake was compared to standards at the Adequate Intake (AI) [27].

Lifestyle and Physical Capacity Assessment: Lifestyle was assessed using a questionnaire on planned and unplanned activities, time spent passively in front of the TV and computer, and sleep duration. Physical capacity testing included mechanically assessing patients' muscular fitness using the Leonardo diagnostics platform. The test consisted of a single two-foot jump (performed three times). The power put into the jump was considered, and the percentage of it was checked. Values for the highest jump were taken. A test involving standing up from a sitting position (sit-to-stand test) using a diagnostic bench was also performed. For technical reasons, patients over 140 cm could not participate in the test. The repetition time of sit-to-stand was counted in seconds; 2 seconds were taken as the limit of the norm. Finally, a dynamometer test (Jamar company) was used to assess the grip strength of the non-dominant hand. The grip strength was measured in Kilograms (kg).

Ethical Permission

The study was conducted in full conformance with the principles of the "Declaration of Helsinki" (52nd WMA General Assembly, Edinburgh, Scotland, 3–7 October 2000) and Good Clinical Practice guidelines.

Approval was obtained from the Bioethics Committee of the "Children's Memorial Health Institute" in Warsaw (43/KBE/2018). Written consent was obtained for all subjects from at least one caregiver with parental responsibility, and written consent was obtained from the subject if appropriate for their age and level of understanding.

Statistical Analysis

Statistical analysis was performed with Statistica 7.1 (StatSoft Incorporation) using non-parametric tests because the distribution of variables did not correspond to a normal distribution: the Wilcoxon rank-sum test for related variables, the Mann-Whitney U test for independent variables, Spearman's rank correlation - a measure of statistical dependence between random variables. Therefore, $p < 0.05$ was deemed to be statistically significant.

Preprint Information

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Results

Characteristics of the Group

The study included 18 patients (four girls, 22% and fourteen boys, 78%) with glycogenoses genetycally confirmed, including n=4 GSD Ia patients, n=5 GSD Ib patients (GSD I group) and n=4 GSD III patients, n=1 GSD VI patients, n=4 GSD IX patients (GSD III-VI-IX group). Patients with GSD Ia and Ib were diagnosed before 1 year of age (range 4 month to 8 month), patients with GSD III-VI-IX were diagnosed from 2 to 5 years old (median 3). Patients' ages ranged from 6 to 18 years (median 11 years).

Patients have complications of glycogenoses: inflammatory bowel disease (n=4 GSD Ib), hypertention (n=3 GSD Ia, n=1 GSD Ib), neutropenia (n=5 GSD Ib), anemia (n=2 GSD Ib, n=1 GSD III), hyperuricemia (n=1 GSD Ia, n=1 GSD 1b), hepatosplenomegaly (n=1 GSD 1b), kidney stones (n=1 GSD Ia), cardiomyopathy (n=1 GSD III). In addition they had: hearing loss (n=2 GSD Ia, n=2 GSD Ib), hypothyroidism (n=1 GSD Ia, n=1 GSD III), epilepsy (n=2 GSD III), inhalant allergy (n=2 GSD IX), Crohn's Disease (n=1 GSD IX), cholecystolithiasis (n=1 GSD Ib), anxiety disorders (n=1 GSD Ia). Only 1 patient (with GSD VI) had a broken leg and this happened before the diagnosis of GSD. Bone pain was reported by 56% patients with GSD I and 33% patients with GSD III-VI-IX.

Anthropometric Results

The weight, height and BMI of the patients are shown in Table 2. The vast majority of patients (66%) had short stature. The BMI of 3 patients (16.7%) with GSD Ia and III indicated obesity (+2 SD), five patients (27.8%) with GSD Ia, Ib, and IX were overweight (+1 SD), nine patients (50%) had normal BMI and one patient with GSD III was underweight (-1 SD). Overweight and obese patients predominated in the GSD I group ($p<0.05$).

Body Composition

Half of patients with GSDs had above 30% of body fat, including 67% of GSD I and 33% of GSD III-VI-IX. The patient with the highest percentage of fat tissue (55%) had GSD III. Lean body mass (or muscle mass) was higher in patients with GSD III-VI-IX (median 71,7%) than GSD I (median 58,6%). The median values of percentage of body fat and lean body mass was significally different between groups GSD I and GSD III-VI-IX ($p<0.05$). All measurement are shown in Table 2.

Mineral Bone Density

The Mineral Density (DXA) of the Total Body Less Head (TBLH) of patients with glycogenoses was most often within the normal range but negative (Table 2). In most cases, the lumbar spine (L2-L4) showed values within the wide normal range but negative. There were no statistically significant differences between the groups. However, the z-score value of the mineral density of the headless skeleton correlated positively with the mineral density of the lumbar spine. No correlation was found between patients' BMI values and bone mineral density of the lumbar spine and the TBLH.

Blood Results

The serum total protein concentration of most patients indicated a normal level. The results were above normal in 2 children (11%); one had GSD Ib, the other GSD VI. The serum albumin concentration of the patients indicated a normal level; in 1 child (5.6%) with GSD Ib the result was below normal. The median serum 25(OH)D3 indicated suboptimal concentration. In 2 children (11%) with GSD Ib, the results were above the optimal concentration (> 50 ng/ml); in 2 children (11%) with GSD Ia and VI, they were within the optimal concentration range (30-50 ng/ml) and in the rest (78.8%) they were below this norm (< 30 ng/ml). The serum calcium concentration of the majority of subjects indicated a normal level. In 1 child (5.6%) with GSD Ia, the result was above normal, in 2 children (11%) with GSD Ib - below normal. The phosphorus serum concentration of a large group of patients indicated a normal level; in 2 children (11%) with GSD IX, the results were above normal. The serum lactates concentration of most patients (78%) indicated a normal range. The results were above in 2 patients (22%) with GSD Ia, 1 patients (11%) with GSD Ib and 1 patient (11%) with GSD VI. The serum glucose concentration of most patients indicated a normal level. The results were above normal in 3 children (17%);

one had GSD Ib, the other GSD III and GSD VI. Blood test results between groups did not indicate statistically significant differences. The results of blood tests are shown in Table 2.

Diet Results

The dietary energy of most patients (83%) was excessive, with the difference between intake and requirement ranging from 145 kcal to 1422 kcal (median 481 kcal). The energy per kg of body weight was: median 45.4 kcal/ kg, First Quartile (Q1) 41.35 kcal/kg, third quartile (Q3) 72 kcal/kg. Values between

Table 2: Anthropometric mesurement, body composition, bone mineral density, blood test results, diet analysis, lifestyle results, physical capacity of patients with glycogenoses by group.

		N	Groups	Median	Q1	Q3
Anthropometric mesurement	Body weight (kg)	18	GSD	34.25	29.08	58.88
		9	GSD I	55.5	29.8	67
		9	GSD III-VI-IX	31	29	40
	Body height (m)	18	GSD	1.36	1.27	1.6
		9	GSD I	1.46	1.23	1.66
		9	GSD III-VI-IX	1.36	1.29	1.47
	BMI (kg/m2)	18	GSD	19.14	16.52	23.25
		9	GSD I	21.8	20.02	26.04
		9	GSD III-VI-IX	16.5	16.1	18.3
Body composition	Body fat tissue (%)	18	GSD	30.5	25.38	39.98
		9	GSD I	39.9	27.8	40.2
		9	GSD III-VI-IX	29.2	19.5	39.2
	Lean body mass (%)	18	GSD	63.65	57.25	71.51
		9	GSD I	58.58	57.13	66.05
		9	GSD III-VI-IX	71.68	61.14	73.62
Bone mineral density	Mineral density of the TBLH [z-score]	18	GSD	-0.9	-1.1	0.18
		9	GSD I	-1	-1.1	0.1
		9	GSD III-VI-IX	-0.8	-1.1	0.2
	Mineral density of the L2-L4 segment [z-score]	18	GSD	-1.65	-2.45	-0.83
		9	GSD I	-1.7	-3	-1.6
		9	GSD III-VI-IX	-1.1	-1.8	-0.8
Blood tests results	Total protein (g/l)	18	GSD	73.4	70.1	77
		9	GSD I	77	73.4	77.9
		9	GSD III-VI-IX	70.75	69.1	73.6
	Albumins (g/l)	18	GSD	45.4	42.9	48
		9	GSD I	46.4	43.7	48
		9	GSD III-VI-IX	43.1	42.8	47.4
	Vitamin D3 (ng/ml)	18	GSD	22.6	21.1	29.2
		9	GSD I	26.9	25.4	32.4
		9	GSD III-VI-IX	21.25	20.9	21.8
	Calcium (mmol/l)	18	GSD	2.4	2.34	2.5
		9	GSD I	2.43	2.35	2.46
		9	GSD III-VI-IX	2.37	2.34	2.45
	Phosphorus (mmol/l)	18	GSD	1.56	1.35	1.75
		9	GSD I	1.37	1.18	1.61
		9	GSD III-VI-IX	1.7	1.51	1.77
	Lactates (mg/dl)	18	GSD	16.35	10.93	19.3
		9	GSD I	19	17.7	23.3
		9	GSD III-VI-IX	11.8	9.9	16
	Glucose (mg/dl)	18	GSD	87.05	80.15	94.93
		9	GSD I	90.1	83.1	92.9
		9	GSD III-VI-IX	86.9	72.2	95.6
Diet analysis	Protein (g/kg)	18	GSD	2.2	1.3	3.3
		9	GSD I	1.3	1.2	1.6
		9	GSD III-VI-IX	3.3	2.8	3.9
	Protein (%)	18	GSD	17.8	12.6	23.7
		9	GSD I	12.6	9.5	13.2
		9	GSD III-VI-IX	24.1	19.7	25.8
	Carbohydrates (%)	18	GSD	53	41	65
		9	GSD I	65	59	67
		9	GSD III-VI-IX	41	38	49
	UCCS/GlycosadeÒ (g/d)	18	GSD	110	30	231
		9	GSD I	235	212	275
		9	GSD III-VI-IX	30	30	40
	Calcium Diet + supplement (mg/d)	18	GSD	491.5	227	638
		9	GSD I	211	167	295
		9	GSD III-VI-IX	622	501	643
	Vitamin D3 Diet + supplement (µg/d)	18	GSD	26	14.06	32.31
		9	GSD I	33.49	25.86	38.9
		9	GSD III-VI-IX	14.08	13.99	26.03

Lifestyle analysis	Sleep (hrs/d)	18	GSD	9	8	10
		9	GSD I	9	8	10
		9	GSD III-VI-IX	9	8	10
	Time spent passively (hrs/d)	18	GSD	4	3.25	4.75
		9	GSD I	4.5	4	7.25
		9	GSD III-VI-IX	4	1.5	4
	Activity (hrs/week)	18	GSD	9.5	7	16.5
		9	GSD I	7.5	2.25	25.5
		9	GSD III-VI-IX	9.5	8	16
Physical capacity	Two-foot jump (kW)	17	GSD	72	63	82.75
		9	GSD I	63.5	58.25	77.75
		8	GSD III-VI-IX	79	66	85.25
	Two-foot jump (% power)	17	GSD	79	74	88.5
		9	GSD I	73.5	63.25	74.75
		8	GSD III-VI-IX	87.5	80.5	111.5
	Repetition time (sec.)	6	GSD	1.92	1.65	2.23
		5	GSD I	2	1.84	2.3
		1	GSD III-VI-IX	1.59	1.59	1.59
	Handgrip strength (z-score)	18	GSD	-1.9	-2.77	-0.8
		9	GSD I	-1.8	-3.3	-1.4
		9	GSD III-VI-IX	-1.97	-2.26	-0.78

groups were not statistically significant (GSD I: median 42.5 kcal/ kg, Q1 40.4 kcal/kg, Q3 69,8 kcal/kg; GSD III-VI-IX: median 45.6 kcal/ kg, Q1 45.2 kcal/kg, Q3 76,7 kcal/kg). Median values for protein intake (per kg of body weight and percentage of dietary energy) were within the normal range for the patients and the groups. Protein intake in the GSD I group was lower than in the GSD III-VI-IX group, which aligned with dietary recommendations. Almost one-third of the patients were taking a protein supplement. In 55% of subjects, carbohydrate intake was within normal limits; these were mainly children with GSD III-VI-IX. GSD I patients consumed too many carbohydrates in 78% of cases. The patients followed the recommendations for UCCS and/or Glycosade® intake. The GSD I group took it regularly throughout the 24 hours in doses calculated per kg of body weight. In the GSD III-VI-IX group, the intake was only at night, and one subject with GSD IX did not take it. The amount of dietary protein and carbohydrates and UCCS and/or Glycosade® was statistically significant between groups ($p<0.05$). Most of the patients (94%) did not meet the standard for calcium intake (RDA 1000 mg/d for children aged 7 to 9 and RDA 1300 mg/d for children aged 10 to 18). One child with GSD Ib supplemented calcium regularly. Intake was higher among patients with GSD III-VI-IX ($p<0.05$). The intake of vitamin D3 was in line with Polish national recommendation for 67% of patients (AI 15 µg/d). All of the children had vitamin D3 supplement (doses from 12,5 µg/d to 50 µg/d), but for 33% of them daily dose was inadequate (in 1 child with GSD Ia and 56% children with GSD III-VI-IX) (Table 2).

Positive correlation was found between energy intake (kcal/d), BMI (kg/m2) and fat tissue (%). No correlation was found between dietary energy (kcal/d) and bone mineral density of the lumbar spine and the TBLH. In contrast, protein intake (g/kg) correlated positively with lumbar spine mineral density. Intake of UCCS and/or Glycosade® did not correlate with BMI, body fat and bone mineral density.

Lifestyle Results

The results of the lifestyle assessment questionnaire - length of sleep, time spent passively in front of the TV and/or computer (measured daily) and time spent on physical activity (counted weekly) are shown in Table 2. Patients spent more time passively than actively.

Physical Capacity Results

All patients' median value for jump power was below the norm for age. In the GSD I group, the jump power of 1 patient (11%) was within the normal range for age, and the remaining values were below it. In the GSD III-VI-IX group, the jump power of 4 patients (44%) was within the normal range for age. The further four patients were below normal, and one patient could not jump and was not taken into account in the statistics. The utilisation of the jump power of 7 patients (39%) was within the normal range, including one patient with GSD I and six patients with GSD III-VI-IX. More than half of the patients (61%, including 44% in GSD I and 78% in GSD III-VI-IX) were too short of performing the repetition sit-to-stand test. In the GSD I group, two patients (22%) did not finish the repetitions within the allotted time, and the other two completed the task within the time standard. In the GSD III-VI-IX group, one patient (11%) could not complete the task (stand up), and the other met the criteria for normal. The handgrip strength results corresponded in most cases (83% of patients) to negative z-score values below normal for age and sex. Patients with GSD I had a negative z-score for handgrip strength in every case, and subjects with GSD III-VI-IX had a positive z-score in 3 cases (33%). The results between groups were statistically significant for the utilisation of power in the two-foot jump and the z-score of the handgrip strength (Table 2).

Discussion

The literature indicates that patients with glycogenoses, mainly with GSD Ia, are obese [8]. In Derks et al. (2015), the body weight of 25% of patients with GSD Ia and 33% of those with GSD Ib was above the 90th centile on centile grids for age and sex [28]. 44% of the Polish patients were overweight (BMI +1SD or +2SD), and most were GSD I patients. Their fat tissue exceeded 30% and their lean body mass was below 60%. Patients with higher BMI had more body fat and less lean body mass.

Dietary analysis of the GSD patients' diets revealed that they provided more energy than their requirements, ranging from 5% to 53%. Only four patients (22%) ate less or as much as their energy requirements. Overconsumption was reflected in excessive body weight. In many cases of patients with type I glycogenosis, this was influenced by an excessive carbohydrate intake. As many as 78% of patients with GSD I provided more than 55% of their dietary energy in carbohydrates. Part of this

carbohydrate intake was the UCCS intake; however, in type I glycogenosis, starch must be consumed regularly throughout the 24 hours; hence limiting the carbohydrate intake from food is very important [15]. Thanks to the night supply of UCCS, most of patients had fasting normoglycemia, none of whom had hypoglycemia.

A study from the 1990s by Talente et al. (1994) showed the multitude of complications observed among patients with glycogenoses, including those involving fractures and/or osteopenia, which affected 27% of individuals [29]. Patients with GSD types I, III, VI and IX are at increased risk of developing osteoporosis [1,5,8,9,30,31]. The cause is multifactorial. Dietary deficiencies (calcium in the case of GSD I and vitamin D3 in all patients) or the inability to achieve metabolic control, in which the presence of chronic metabolic acidosis will manifest, are essential. In ketotic types (mainly GSD III), the problem may be exacerbated by muscle weakness associated with insufficient exercise [4,5,7,8,31]. Cabrera-Abreu et al. (2004) found low and very low bone mineralisation in patients with GSD I and III [30]. Kishnani et al. (2014) mention a delayed bone age in children [5]. In 2016, Sentner et al. published the results of the ISGDSIII study of 175 patients with GSD III. They found that osteoporosis can develop in these patients from childhood, which they confirmed with bone density test results [9]. Only one polish patient had a fracture, and 44% of patients complained of bone pain, mainly in the limb and spine (56% with GSD I and 33% with GSD III-VI-IX).

Consequently, patients are advised to have regular densitometric examinations [1]. The bone density of the patients in our study was within a wide normal range for age but was inadequate in many cases. As many as 90% of the patients had a reduced mineral density of lumbar spine (negative z-score in all quartile) and 86% of them of total body less head (negative z-score in Q1 and Q2). The lowest values were found in patients with GSD I. Nevertheless, this group included two patients with positive z-scores for all measurements. These patients also exhibited the best activity, and one showed perfect physical capacity.

Protein intake in the GSD I group needed to be increased, and 44% of patients did not reach even 10% of the energy content of the diet. In the case of GSD III-VI-IX patients, 33% had too low protein intake (less than 20% of the dietary energy). Calcium intake were inadequate, and supplementation was used only by one patient. Patients consumed from 6% to 66% (median 48%, Q1 17%, Q3 51%) daily RDA, and one child with GSD Ib 108% RDA. GSD III-VI-IX patients consumed more calcium than in GSD I group (median 49% vs 16%, $p<0,05$), mainly with dairy products, forbidden in case of GSD I. These facts may have influenced the patients' reduced bone mineralisation.

Blood tests were normal, including total protein, albumin, calcium and phosphorus concentrations in most subjects (90%) with GSD. Median lactate was in normal range in 78% subjects (33% patients with GSD I and 11% with GSD III-VI-IX had higher results), so most of children didn't have metabolic acidosis. Unfortunately, a large group, 78%, had vitamin D3 concentration below the optimal 30 ng/dl. As a result, despite medical advice, patients did not take or only occasionally took dietary supplements containing this vitamin, which may have negatively affected their bone mineralisation [28,31]. Participation in sports by patients with glycogenoses is not contraindicated. However, they should monitor their glycaemia and/or ketonuria (GSD III-VI-IX), and eat a snack or drink UCCS before exercise to avoid hypoglycaemia. The study patients often spent time passively in front of a computer or TV, almost 4 hours a day, and up to a maximum of 10 hours. Several patients did not exercise, and the time allocated to planned or spontaneous activity (e.g. playing in the yard) of the remaining study subjects was about 7.5 hours per week. That may have been reflected in poor physical fitness, as evidenced by mechanography or handgrip strength results. Physical activity, as part of the prevention of obesity and osteoporosis, should be recommended [8,10].

Conclusions

Polish patients with GSDs had fasting normoglycemia (median 87 mg/dl), normal range of lactates (median 16.25 mg/dl), albumin (median 45.4 g/l), calcium (median 2.4 mmol/l) and phosphorus (median 1.56 mmol/l). Unfortunately, many patients were overweight or obese (44%) with hight percentage of fat tissue (50% of patients had above 30% of body fat). They had inadequate bone mineralisation (TBLH: median z-score -0.9, L2-L4: median z-score -1.65). These results could be caused by non-compliance with dietary recommendations (higher caloric intake than requirements, high carbohydrates intake, low protein intake, lack of or insufficient vitamin D3 or calcium supplementation - when following a galactose-free diet like GSD I patients) and low physical activity. Inadequate bone mineralisation and thus increase the risk of osteoporosis in patients with GSD types Ia, Ib, III, VI, IX. The z-score values of the bone mineral density of Polish patients with glycogenoses were mainly reduced but still within a wide normal range. Therefore, close attention should be paid to dietary analysis, and patients should constantly be reminded of adequate protein consumption (if necessary, supplementation) and intake of calcium and vitamin D3 supplements.

Author Statements

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