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Resting energy expenditure and substrate oxidation in malnourished patients with type 1 glycogenosis.

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Context. Type 1a and 1b glycogenosis (GSD1a, GSD1b) are rare diseases generally associated with malnutrition. Although abnormal substrate oxidation rates and/or elevated energy expenditures might contribute to malnutrition, this issue has not been investigated.
Objective. To investigate whether abnormal resting energy expenditure and substrate oxidation rate characterize patients with GSD1.
Design. Cross-sectional study.
Setting. Outpatient referral center for rare diseases and laboratory of clinical nutrition at the university hospital of Palermo (Italy).
Patients. Five consecutive patients with GSD1 (4 type a, 1 type b), 3 males/2 females, age range 19-49 years.
Main Outcome Measures. In the context of usual clinical procedures for patients with malnutrition, resting energy expenditure (REE, indirect calorimetry), basal substrate oxidation rate (indirect calorimetry), body composition (bioimpedance method), muscle strength (hand-grip test) and usual laboratory tests were performed.
Results. Malnutrition was clearly diagnosed in 2 patients (1 GSD1a and 1 GSD1b), and REE was elevated in all 5 patients but in particular in the 2 malnourished patients (+124% and +32.1% versus predictive values according to Harris-Benedict equations). The 2 malnourished patients also exhibited lower basal protein oxidation rates (7.7% and 6.6%) than the non-malnourished patients (range: 12.1-24.7%), with higher carbohydrate or lipid oxidation rates. Additionally, the 2 patients with malnutrition exhibited higher blood concentrations of lactic acid than the non-malnourished patients.
Conclusions. According to data obtained in this small sample of patients with GSD1, an elevated REE seems to be a common characteristic that may contribute to malnutrition. A low basal protein oxidation rate and elevated blood lactic acid concentrations appear to be associated with malnutrition.

Type 1 glycogenosis are rare diseases associated with malnutrition. The measured resting energy expenditure was elevated in 5 patients and contributed to explain the occurrence of malnutrition. .

Abbreviations:

BMI, body mass index; GSD, glycogen storage disorders; FFM, fat-free mass; FM, fat mass;

NPRQ, nonprotein respiratory quotient; REE, resting energy expenditure; RQ, respiratory quotient

INTRODUCTION

Glycogen storage disorders (GSDs) are a heterogeneous group of inborn errors of carbohydrate metabolism due to variants in genes encoding individual enzymes in the glycogen metabolic pathway (1). In the spectrum of GSD, GSD type 1 is the most frequently observed rare disease and is characterized by both defective glycogenolysis and gluconeogenesis with liver, kidney and intestinal involvement. Two subtypes of this GSD are distinguished, namely, type 1a (GSD1a) or Von Gierke disease, which is characterized by glucose-6-phosphatase deficiency, and type 1b (GSD1b), which is due to a deficit of glucose-6-phosphate translocase, a protein that transports glucose-6-phosphate across the microsomal membrane from the cytosol to the endoplasmic reticulum. As a result of insufficient hepatic conversion of glucose-6-phosphate into glucose through glycogenolysis and gluconeogenesis, hypoglycemia and increased blood lactate levels occur after a short period of fasting. Although almost all patients with GSD1 are malnourished and lean, there is a lack of studies that have evaluated energy expenditure in this clinical condition. Resting energy expenditure (REE) is the main component of total daily energy expenditure (approximately 70% in adult sedentary people) (2). The REE represents the amount of energy expended by a person at rest, in post-absorptive fasting and in thermoneutral conditions, it differs from the basal metabolic rate in that the latter is measured just after awakening in the morning; in practice, the REE and the basal metabolic rate differ by less than 10%. Only one short study (3) measured energy expenditure in 7 patients with GSD1, and although a high REE was reported, no data were obtained about energy substrate oxidation and the possible nutritional effects.

In this study, we measured REE and basal substrate oxidation rates in a small sample of patients with GSD1a to investigate the possible influences of their nutritional state.

MATERIALS and METHODS

Patients

Between 2017 and 2018, 1 patient (patient #1) with GSD1b and 4 patients (patients #2, #3, #4, #5) with GSD1a were referred by the outpatient "Regional Center of Metabolic Rare Diseases" to the "Laboratory of Metabolism and Clinical Nutrition" for nutritional evaluation. Both facilities are located in the University Hospital Policlinico "P. Giaccone" (Palermo, Italy). All measurements were obtained in the morning between 8:00 and 8:30 a.m. after the last intake of corn flour (1 g/kg-body weight) at 6:00 a.m. (measurements taken over more prolonged periods of fasting are not possible due to hypoglycemia). The characteristics of the habitual diet were as follows: 60–70% calories were from carbohydrates, 10–15% calories from protein (to provide the daily recommended intake) and the remaining calories from fat; in particular, patients consumed 1.7-2.5g of cornstarch per kilogram of body weight (ideal body weight) every 4–5 hours and one dose at bedtime. Patients periodically used iron supplements, folate, vitamin D and B12. All patients included in the study had normal thyroid hormone concentrations. The presence of hepatic lesions possibly related to adenomas or hepatocellular carcinoma were excluded on the basis of ultrasound examination.

The study was conducted according to the Declaration of Helsinki guidelines, and the protocol was approved by the Institutional Review Board at the Dipartimento Biomedico di

Medicina Interna e Specialistica (DIBIMIS) of the University of Palermo (now, Dipartimento di Promozione della Salute, Materno-Infantile, Medicina Interna e Specialistica di Eccellenza (PROMISE). All exams and procedures performed were part of the regular clinical procedures of the center for patients with nutritional diseases. All participants provided written informed consent before their inclusion in the study.

Anthropometric and clinical measurements

Height and body weight were measured with participants lightly dressed and without shoes (SECA; Hamburg, Germany); the body mass index (BMI) was calculated as body weight (kg)/height^2 (m^2). Fat mass (FM, % body weight) and fat-free mass (FFM, kg) were estimated by means of bioelectrical impedance as previously described (4), using an 800 mA, 50 kHz, tetrapolar impedance plethysmograph (BIA; BIA-101 Anniversary, Akern; Florence, Italy) to obtain body resistance (R, Ohm), reactance (Xc, Ohm) and phase angle (PA degrees = arctan (Xc/R)·(180/p). The use of crude BIA measures, such as the phase angle (PA), has received increasing attention as a plausible indicator of intra/extracellular hydration and nutritional status (5). Also, skinfolds (subscapular, suprailiacal, tricipital, bicipital) were measured using the Holtain caliper (Holtain Ltd; Ceosswell, UK) and skinfold-derived fat mass was calculated according to the equations of Womersley and Durnin (6). Body circumference was measured at the umbilicus (waist circumference) and at the most prominent buttock level (hip circumference); the waist-to-hip ratio (WHR) was used as an indirect index of body fat distribution. Grip strength was measured using a hydraulic hand dynamometer (JAMAR SH5001, Saehan, Republic of Korea). Patients performed the test while sitting with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position. Patients were instructed to perform a maximal isometric contraction. The test was repeated within 15-20 s with each hand, and the average value (kg) of the three tests was used for the analysis (7). Systolic and diastolic arterial blood pressure were measured at 5-min intervals in the seated position and performed twice using standardized procedures (Omron M6; Omron Healthcare Co., Matsusaka, Mie, Japan).

Indirect calorimetry

Resting energy expenditure, respiratory quotient (RQ; VCO_2/VO_2), an indirect measure of the mixture of carbohydrate and lipid oxidation, and nonprotein RQ (NPRQ), which included the measurement of urinary nitrogen excretion over the last 12 hours for calculating the protein, carbohydrate and lipid oxidation rates (g/h or % of energy expenditure), were obtained by means of the indirect calorimetry method, as described elsewhere (8, 9), using a ventilated hood system (Quark RMR; Cosmed, Roma, Italy). The device was equipped with an infrared analyzer for carbon dioxide measurement (VCO_2) and a zirconium cell analyzer for oxygen measurement (VO_2). Analyzers were calibrated before each test using gases with known percentages of O_2 and CO_2. Briefly, respiratory gas exchanges were continuously measured for approximately 1 h; data were obtained from at least 30 min of stable measurements, and the average intrasubject variability was 3.9% for REE. The REE was calculated using the equation of Weir (10) and was expressed both in absolute terms (kcal/24 h) and was normalized for FFM size (kcal/kg-FFM·24 h). Concerning the substrate oxidation measurement (11), the urea nitrogen excreted in the urine over the last 12 hours is assumed to be derived from protein oxidation; the grams of oxidized proteins are obtained by multiplying the amount (g) of ureic nitrogen by 6.25. Since the quantity of O_2 necessary to oxidize one gram of protein and the amount of CO_2 produced are known, the QRNP is obtained by subtracting these estimated volumes from the measured volumes, and this value exclusively reflects the relative proportions of lipid and carbohydrate oxidation. An RQ value of <0.70 may indicate that significant neoglucogenic and ketogenic activity take place; an RQ value of >1 is indicative of lipogenesis starting from carbohydrates. A particular case is when an

increased production of lactate occurs, which produces CO_2 displacement from bicarbonates of the alkaline reserve to the exhaled component with a consequent increase in the RQ value.

For each patient, the value of the measured REE was compared with the individual predicted values according to the equations of Mifflin-St Jeor (12), Schofield (13) and Grande and Keys (14).

Laboratory analysis

Fasting plasma glucose (FPG), total cholesterol, HDL-cholesterol, triglyceride, uric acid and creatinine concentrations were measured using standard clinical chemistry methods (Glucosio HK UV; Colesterolo tot. Mod P/D; Colesterolo HDL gen 3 mod P/917; Trigliceridi; Acido urico MOD P/917; Creatinina enzimatica; Roche Diagnostics, Monza, Italy). Basal insulin concentrations (Elecsys insulina; Roche Diagnostics; Monza, Italy) and HbA_1c (B-analyst HbA1c; Menarini diagnostics; Florence, Italy) were also measured. The low-density lipoprotein (LDL) cholesterol serum concentration was calculated with Friedewald's formula, and eGFR was estimated based on the CKD-EPI equation. Insulin resistance was estimated according to the HOMA-IR formula: fasting plasma insulin (mUI/l) x fasting plasma glucose (mmol/l)/22.5.

Measurements of blood bicarbonate and lactate concentrations were obtained from venous samples using an amperometric method (ABL 800 FLEX; Radiometer Copenhagen, Denmark).

RESULTS

The physical, clinical and laboratory characteristics of patients are presented in Tables 1 and 2. In particular, body size based on the BMI was within the normal range, with the exception of patients #1 and #5 who were underweight. The FFM was normal in all 5 patients; however, reduced muscle strength (Table 3) was observed in patients #1, 3 and 5. Patients #1 and 5 also exhibited low blood concentrations of hemoglobin, high lactic acid concentrations and low bicarbonate concentrations. Therefore, a condition of malnutrition was evident, especially in patients #1 and #5. High REE values were observed in all 5 patients (Table 4), particularly in patients #1 and #5 (Table 5). The basal rates of substrate oxidation are presented in Table 4. Patient #1 exhibited a high lipid oxidation rate, patient #5 exhibited a high carbohydrate oxidation rate, and both patients had a low protein oxidation rate.

DISCUSSION

The incidence of GSD1 is approximately one in every 100,000 births; in particular, type 1b has an estimated incidence of one case per million births (1, 15). Therefore, due to the rarity of the disease we could include only a small group of 5 patients and this is a clear but almost inevitable limitation of the study. The data presented in this study suggest that malnutrition is a condition that may be present in patients with GSD1 (16; 17). In fact, although only patients #1 and #5 were clearly underweight, patient #3, whose BMI and FFM were within the normal range, exhibited reduced muscle strength indicative of malnutrition. Bioelectrical PA is known to be inversely correlated with the ratio of extra/intracellular water, and low PA values are generally found in malnourished and/or clinically compromised patients (5, 18). Contrary to what was expected, we found normal/high PA values in the two patients (patients #1 and #5) with advanced malnutrition. A possible explanation is that, as is known, each molecule of glycogen needs six molecules of water in depots (19); therefore, the high glycogen depots in FFM require more glycogen-associated intracellular water, which may have contributed to the high values of both FFM and PA that we found. The high REE observed in all patients may contribute to the development of malnutrition. Interestingly, the highest REE values were observed in those patients (patients #1 and #5) with severe

malnutrition. Our results agree with the unique study by Feillet and coll. (3) that investigated the REE in 7 adult patients with GSD1a demonstrating values that were on average +116±11% of the predictive value. A clear explanation for the high REE observed in all the patients included in our study is not evident. As known, the FFM, and above all its metabolically active cellular fraction without the extracellular water component, namely, the body cell mass, is the main determinant of REE (20). However, our patients did not exhibit any increase in FFM; furthermore, even when normalized for the amount of FFM, the REE still remained high. On speculative grounds, it is necessary to observe that the FFM has different components with potentially different contributions to the REE. In fact, different organs constitutive of FFM, including the heart, liver and kidney, although representing an average of 5-6% of body weight, contribute approximately 60% to the REE; in contrast, muscles that provide approximately 40% of body weight contribute approximately 22% to the REE (21). As the contribution of visceromegaly to the FFM is expected to be high in patients with glycogenosis (1), it cannot be excluded that the hypermetabolic status suggested by the elevated REE is a consequence of the high contribution from these organs. In particular, hepatomegaly characterizes patients with GSDI (16) and it has been calculated that the contribution of this organ may range 200-400 kcal according to its size (22, 23). Alternatively, neoglucogenic activity is increased in patients with GSD1, although it does not extend beyond glucose-6-phosphate production (1). In our patients, this metabolic tendency was suggested by the high serum lactate concentrations. It is well known (9) that neoglucogenesis from alanine takes place with an energy cost and possibly contributes to the high value of REE observed. Although, to our knowledge, no study addressed this issue in patients with GSD1, there is indirect evidence to support this hypothesis. In fact, very high concentrations of alanine were found in post-absorptive fasting conditions in patients with GSD1 compared to normal control individuals; furthermore, the concentrations of alanine significantly reduced following glucose intake (24). This behavior may suggest that there is a fasting gluconeogenesis attempt starting from alanine which, clearly, cannot be completed due to the lack of the G6P-ase enzyme, however in the previous intermediate steps there is consumption of ATP. In mouse model of GSD1a it was proved an increased production and mitochondrial accumulation of pyruvate also from alanine and other tricarboxylic acid cycle intermediates (25). On the other hand, pyruvate may flow into other energy-consuming processes. In fact, another potential regulatory mechanism may be the increased activity of the ATP consuming futile cycle pyruvate → oxaloacetate → phosphoenolpyruvate → pyruvate that contributes to attenuate the gluconeogenic flux (26). Jones demonstrated in GSD1a patients an increased fraction of acetyl-CoA from pyruvate and increased pyruvate recycling fluxes, all ATP consuming pathways. Finally, even a minimal contribution to neoglucogenesis would seem to be possible at the muscular level (where a glucose-6-phosphatase-β would act) although strongly insufficient to guarantee an adequate endogenous glucose production (27). Both the RQ and the NPRQ of the patients included in this study are intermediate and comparable to those found in the healthy population (28). It is likely that two metabolic phenomena occur concomitantly with an opposite effect on the RQ value, thus canceling out any global influence on the RQ value. In fact, on the one hand, neoglucogenic activity would produce low RQ values; on the other hand, the consumption of bicarbonates (as documented by low blood concentrations in the patients included in this study) due to increased lactate production would lead to an increased elimination of CO_2 with breathing, thus increasing the RQ value. Although the evaluation of the RQ would not allow us to identify metabolic abnormalities in our GSD1 patients, the calculation of protein oxidation suggested low metabolic rates in the patients with advanced malnutrition (patients #1 and #5) that were compensated for by higher lipid or carbohydrate oxidation. Furthermore, in stable body weight conditions the mixture of substrates oxidized is influenced by diet composition

and by the size of body fat stores (the more the fat mass the more the lipid oxidation), if in negative energy balance the body oxidizes more fats (and vice versa) (29). Our patients were in stable body weight (therefore in energy balance) and had limited fat stores, therefore they oxidized an intermediate mixture of substrates or had a high carbohydrate oxidation rate as a result of their habitual diet composition.

The laboratory values obtained in our GSDI patients were largely expected (16) due to metabolic derangements (triglycerides in particular), liver complications (γ-GT in particular) and malnutrition (hemoglobin, low creatinine values, urinary nitrogen). Also the low HOMA-I values were largely expected since GSDI patients tend to low glycemic values with consequently low insulin production. An exception was patient #3 that was the oldest one out of 5 and had higher glycemic (with comparable HbA1c) and HOMA-I values than the other patients; we do not have a clear explanation for these values, however it has been reported that overtreatment with cornstarch can result in insulin resistance (16, 30).

An important limitation of our study is the use of bioimpedance analysis for determining body composition as no specific body composition equations are available for patients with GSD. This method in fact is based on the prediction of FFM from body water (4) and in our patients total body water might be altered by GSD thus reducing the accuracy of BIA. Unfortunately, patients with GSD are usually very suffering and poorly tolerate investigations that are not strictly necessary for their treatment; therefore, only investigations that are part of the usual clinical practice at our center were carried out and a more accurate evaluation of body composition was not performed. Another important limitation of our study is the inadequate procedure of normalizing the REE simply dividing its value by the kg of FFM. In fact, more correctly, we should have considered the value of the positive intercept usually observed in the linear regression between the REE and FFM (31). Unfortunately, our study included only 5 patients so that it was inappropriate to evaluate the correlation between REE and FFM. However, we are confident that despite this limitation the results of our study may well support the hypothesis that patients with GSDI have a high REE since also the individual measured absolute values of REE measured resulted well above the predicted values obtained with different predictive equations (Table 5). Although REE is generally a high percentage of total energy expenditure (60-70%), this issue is completely unknown in GSDI patients therefore, we cannot exclude that TEE may not be elevated in GSDI and it need to be investigated using more sophisticated methods as the doubly labeled water (32).

In conclusion, the metabolic and nutritional aspects of GSD1 are extremely complex and require careful evaluation. As a result of hepatomegaly and hypoglycemia, patients with GSD1 may be characterized by high REE, normal RQ, low/normal BMI, normal FFM with low muscle strength, high lactate and low bicarbonate blood concentrations. Malnutrition may be associated with this clinical condition and contribute to limiting patients' quality of life and life expectancy. To date, pharmacological therapeutic aids are almost nonexistent, and dietetic aids appear inadequate to guarantee a satisfactory outcome. A commitment by both the pharmaceutical and the food industries is desirable to ensure real progress in the treatment of this clinical condition.

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DISCLOSURE STATEMENT:

The authors have nothing to disclose.

DATA AVAILABILITY:

Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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Table 1. Physical and clinical characteristics of patients

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	25	32	49	19	27
Sex (m/f)	m	f	f	m	m
Cigarette smoking	no	no	no	yes	yes
Body weight (kg)	49.4	62	53.9	64.7	44.1
Body mass index (kg/m^2)	17.3	25.2	24.9	23.9	17.2
Blood pressure (mmHg):					

systolic	110	110	125	125	120
diastolic	65	60	70	80	70
Heart rate (beats/min)	68	75	68	86	82
Waist circumference (cm)	76	92	84	91	72
Hip circumference (cm)	85	103	97	92	84
Waist-to-hip ratio	0.89	0.89	0.87	0.99	0.86
Bioimpedance analysis:					
resistance (Ω)	725	807	681	598	666
reactance (Ω)	91	66	58	66	71
phase angle (°)	7.2	4.6	4.8	6.2	6.1
fat mass (%)	10.3	27.4	24.4	26.5	10.9
fat-free mass (kg)	44.3	45.0	40.7	47.6	39.3
Body skinfolds (mm):					
subscapular	4	18	14	9	6
suprailiacal	3	13	7	9.5	3
tricipital	6.5	10.5	4	8.5	7
bicipital	7	5	4.5	7	5
fat mass (%)	4.3	27.4	24.4	14.6	8.5

Table 2. Laboratory measurements of patient s

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**	**Patient 5**
Blood concentrations of:					
glucose (mg/dl)	50	71	126	76	63
cholesterol (mg/dl)	104	208	244	195	112
HDL-cholesterol (mg/dl)	20	17	5	31	21
triglycerides (mg/dl)	284	452	551	387	198
LDL-cholesterol (mg/dl)	27	101	129	87	51
uric acid (mg/dl)	6	4.3	2.8	7.9	9.1
insulin (μUI/ml)	0.2	2.03	28.8	5.15	1.2
AST (U/l)	25	38	18	48	16
ALT (U/l)	38	35	13	58	23
γ-GT (U/l)	62	122	19	62	27
creatinine (mg/dl)	0.49	0.45	0.62	0.50	0.98
hemoglobin (g/dl)	10.7	11.4	10.6	11.5	8.3
lactic acid (mmol/l)	8.8	3.4	6.3	5.6	7.6
$HCO3^-$ (mmol/l)	16.1	21.7	21.3	21.3	18.0
HbA1c (%)	4.5	4.5	4.1	4.5	4.6
HOMA-I	0.02	0.36	8.96	0.97	0.20
Urinary ketone bodies (mg/dl)	0	0	0	0	0
Urinary ureic nitrogen (g/24 h)	9.1	9.7	14.2	9.3	4.5

ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c, glycated hemoglobin; γ-GT, gamma-glutamyl transferase; HDL, high density lipoproteins; LDL, low-density lipoproteins; HOMA-I, homeostatic model assessment for insulin resistance

Table 3. Hand-grip test of patients

Patient #	Right hand (kg)	Normal values for right hand (media ± sd)	Left hand (kg)	Normal values for left hand (media ± sd)
1	17	54.79 ± 10.43	18	50.12 ± 7.35
2	30	35.70 ± 8.71	28	30.84 ± 8.03
3	18	28.21 ± 6.85	14	25.40 ± 5.76
4	38	49 ± 11.1	32	42.18 ± 12.6
5	22	49 ± 11.1	22	42.18 ± 12.6

Table 4. Resting energy expenditure and substrates oxidation of patients.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
REE:					
kcal/24 h	3192	1600	1578	2116	1710
kcal/kg-FFM·24 h	72	35.6	38.8	44.4	43.5
RQ	0.81	0.94	0.81	0.89	0.96
NPRQ	0.81	0.97	0.80	0.90	0.97
Basal oxidation of:					
carbohydrates, g/h	12.7	13.7	4.3	14.0	14.7
%	35.7	78.0	25.9	58.8	82.7
lipids, g/h	8.3	0.4	3.6	2.6	0.9
%	56.6	7.0	49.2	29.0	10.7
proteins, g/h	2.5	2.5	4.1	2.4	1.2
%	7.7	15.0	24.7	12.1	6.6

FFM, fat-free mass; REE, resting energy expenditure; RQ, respiratory quotient; NPRQ, nonprotein respiratory quotient.

Table 5. Differences between measured and predicted resting energy expenditure of patients.

	REE (kcal/24 h)						
Patient #	Measured	Mifflin-St Jeor[12]	Δ%	Schofield[13]	Δ%	Grande & Keys[14]	Δ%
1	3192	1432	+122.9	1436	+122.3	1382	+131.0
2	1600	1282	+24.8	1349	+18.6	1404	+14.0
3	1578	1055	+49.6	1284	+22.9	1270	+24.3
4	2116	1583	+33.7	1666	+27.0	1485	+42.5
5	1710	1313	+30.2	1356	+26.1	1226	+39.5

Δ, percentage difference of measured REE vs predicted value
REE, resting energy expenditure