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Impact of hematopoietic stem cell transplantation in glycogen storage disease type Ib: A single-subject research design using ^{13}C-glucose breath test

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ABSTRACT

Background: Glycogen storage disease type Ib (GSD Ib) is an autosomal recessively inherited deficiency of the glucose-6-phosphate translocase (G6PT). Clinical features include a combination of a metabolic phenotype (fasting hypoglycemia, lactic acidosis, hepatomegaly) and a hematologic phenotype with neutropenia and neutrophil dysfunction. Dietary treatment involves provision of starches such as uncooked cornstarch (UCCS) and *Glycosade*® to provide prolonged enteral supply of glucose. Granulocyte colony-stimulating factor (G-CSF) is the treatment of choice for neutropenia. Because long-term stimulation of hematopoiesis with G-CSF causes serious complications such as splenomegaly, hypersplenism, and osteopenia; hematopoietic stem cell transplantation (HSCT) has been considered in some patients with GSD Ib to correct neutropenia and avoid G-CSF related adverse effects. Whether HSCT also has an effect on the metabolic phenotype and utilization of carbohydrate sources has not been determined.

Objective: Our objective was to measure the utilization of starch in a patient with GSD Ib before and after HSCT using the minimally invasive ^{13}C-glucose breath test (^{13}C-GBT).

Design: A case of GSD Ib (18y; female) underwent ^{13}C-GBT four times: UCCS (pre-HSCT), UCCS (3, 5 months post-HSCT) and *Glycosade*® (6 months post-HSCT) with a dose of 80 g administered via nasogastric tube after a 4 h fast according to our patient's fasting tolerance. Breath samples were collected at baseline and every 30 min for 240 min. Rate of CO_2 production was measured at 120 min using indirect calorimetry. Finger-prick blood glucose was measured using a glucometer hourly to test hypoglycemia (glucose <4 mmol/L). Biochemical and clinical data were obtained from the medical records as a post-hoc chart review.

Results: UCCS utilization was significantly higher in GSD Ib pre-HSCT, which reduced and stabilized 5 months post-HSCT. UCCS and *Glycosade*® utilizations were low and not different at 5 and 6 months post-HSCT. Blood glucose concentrations were not significantly different at any time point.

Abbreviations: ^{13}C-GBT, ^{13}C-glucose breath test; ALT, alanine aminotransferase; AML, acute myeloid leukemia; ANOVA, analysis of variance; AST, aspartate aminotransferase; AUC, area under the curve; BIA, bioelectrical impedance analysis; BMI, body mass index; CF-IRMS, continuous flow isotope ratio mass spectrometer; C_{max}, maximum peak enrichment in $^{13}CO_2$ oxidation; CGM, continuous glucose monitor; CRP, C-reactive protein; ER, endoplasmic reticulum; FFM, fat free mass; FM, fat mass; G-CSF, granulocyte colony-stimulating factor; G6P, glucose-6-phosphate; G6Pase-α, glucose-6-phosphatase-α; G6Pase-ß, glucose-6-phosphatase-β; G6PT, glucose-6-phosphate translocase; GGT, gamma glutamyltransferase; GSD I, glycogen storage disease type I; GSD Ia, glycogen storage disease type Ia; GSD Ib, glycogen storage disease type Ib; GSD III, glycogen storage disease type III; HSCT/BMT, hematopoietic stem cell transplantation / bone marrow transplantation; IBD, inflammatory bowel disease; IM, intramuscular; NG, nasogastric; TBW, total body water; t_{max}, time to reach maximum $^{13}CO_2$ oxidation; UCCS, uncooked cornstarch; VCO_2, rate of carbon dioxide production..

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Conclusions: Findings show that HSCT stabilized UCCS utilization, as reflected by lower and stable glucose oxidation. The results also illustrate the application of ^{13}C-GBT to examine glucose metabolism in response to various carbohydrate sources after other treatment modalities like HSCT in GSD Ib.

1. Introduction

Glycogen storage disease type Ib (GSD Ib, OMIM 232220) is an autosomal recessively inherited deficiency of the glucose-6-phosphate translocase (G6PT) that arises from *SLC37A4* gene mutation [1–3]. The major role of G6PT is to translocate glucose-6-phosphate (G6P) from the cytoplasm across the membrane of the endoplasmic reticulum (ER) where the liver/ kidney/ intestine-restricted glucose-6-phosphatase-α (G6Pase-α) enzyme or the ubiquitously expressed enzyme glucose-6-phosphatase-ß (G6Pase-ß) can hydrolyze G6P into glucose and phosphate [4–6]. A deficient activity of G6Pase-α (GSD Ia) results in glycogenosis type Ia which is characterized by severe fasting hypoglycemia, lactic acidosis and hepatomegaly, whereas disruption in G6Pase-β causes severe congenital neutropenia syndrome resulting in recurrent infections and inflammatory bowel disease (IBD) [7,8]. G6PT (GSD Ib) leads to impaired G6P availability to both enzymes and thus causes a combination of the metabolic phenotype seen in G6Pase-α deficiency (GSD Ia) and the hematologic phenotype seen in G6Pase-β deficiency [5,7]. The insufficiency to meet increased glucose demands in non-gluconeogenic cells like neutrophils results in enhanced ER stress and apoptosis of neutrophils [9,10].

Dietary treatment of the metabolic phenotype involves provision of starches to provide prolonged enteral supply of glucose whereas treatment neutropenia includes granulocyte colony-stimulating factor (G-CSF). Treatment of GSD Ib includes management both of the hematologic phenotype using G-CSF and of the metabolic phenotype. The latter involves the avoidance of fasting, the restriction of fructose and galactose, and the provision of uncooked cornstarch (UCCS) to prevent hypoglycemia and other metabolic sequelae [3]. Whereas UCCS has to be provided in 3–5 hourly intervals around the clock, a novel modified cornstarch (*Glycosade*®) has been shown to maintain normoglycemia over a longer period of time in GSD I [11–13]. To date, clinical trials have primarily studied overnight periods of use, with few and limited data on daytime use [13,14].

There is a lack of consensus on the optimal carbohydrate sources in GSD Ib [14], as concomitant IBD leads to intolerance and inefficiency of starches to maintain blood glucose levels. In addition, energy demands are higher during the daytime and may not be sufficiently covered with a slower release starch like *Glycosade*® [14]. Treatment of neutropenia in GSD Ib also has major limitations, because long-term stimulation of hematopoiesis with G-CSF causes serious complications such as splenomegaly, hypersplenism, and osteopenia and long term risk of acute myeloid leukemia (AML) [15–17]. Although novel medications like inhibitors of the sodium-glucose transporter type 2 (SGLT2) can improve neutropenia in some patients with GSD Ib [18–20], these are not always successful and were not yet available for this indication when this patient was being assessed. Hematopoietic stem cell transplantation / bone marrow transplantation (HSCT/BMT) is still considered in some patients with GSD Ib to correct neutropenia and avoid G-CSF related adverse effects. Whether HSCT also has an effect on the metabolic phenotype e.g., via improved and better intestinal utilization of carbohydrate sources, has not been determined.

We recently developed a minimally invasive ^{13}C-glucose breath test (^{13}C-GBT) to examine the oxidative utilization of different exogenous carbohydrate sources (UCCS and *Glycosade*®) in patients with GSD Ia [21].

The objective of the current study was to measure the utilization of starch using our minimally invasive ^{13}C-GBT, in a patient with GSD Ib before and after HSCT/BMT. We hypothesized that $^{13}CO_2$ oxidation from starch would differ before and after HSCT/BMT in a patient with GSD Ib.

2. Material and methods

2.1. Subject

We studied a single-subject with GSD Ib (18-year-old; female) who was followed by the Biochemical Diseases Clinic at British Columbia Children's Hospital, Vancouver, Canada. The patient is the third child of Pakistani consanguineous parents, and was diagnosed with GSD Ib at the age of 5 months when she presented with organomegaly and hypoglycemia. The diagnosis was confirmed with molecular testing showing she was homozygous for c.936dupA variant (p.Val313SerfsX13) in *SLC37A4* gene (Table 1). From the age of 4 years, she developed persistent neutropenia, for which she was treated with G-CSF, upon which she developed marked hypersplenism leading to pancytopenia and thrombocytopenia. Numerous complications related to her disease include hepatomegaly, splenomegaly, hepatic adenomas, osteoporosis, vertebral compression fractures, hyperuricemia, dyslipidemia, and restrictive lung disease secondary to obesity and organomegaly. She has had at least two episodes of pneumonia. The decision was made to proceed with HSCT from her matched sibling donor, for treatment of neutropenia, to potentially reduce the risk of recurrent infections.

At the time of the study, the participant was ensured to be free of cold or flu-like symptoms on all study days. The patient underwent the ^{13}C-GBT test four times: UCCS (pre-HSCT), UCCS (3, 5 months post-HSCT), and *Glycosade*® (6 months post-HSCT) at BC Children's Hospital Research Institute within our Clinical Research and Evaluation Unit. We chose 3, 5, and 6 months following HSCT based on patient availability. The interval of 3 months post-HSCT was during readmission and recovery due to shingles, which was a complication of HSCT; however, the participant was symptom free from shingles on the study day. The 5, 6 months post-HSCT was during routine clinical visits. All procedures were reviewed and approved by the Research Ethics Board involving Human Subjects at the University of British Columbia and British Columbia Children's Hospital (CW16–0377 / H16–03050). The written informed consent was provided to the patient's parents; and adolescent assent (14–18 y) was obtained. The purpose and potential risks of the

Table 1
Characteristics of the GSD Ib participant.

Subject	Age (y)	Gender	Mutation	Pre-dose fast (hr)	Weight (kg)	Height (cm)	BMI percentile (%)	Fat free mass[a] (kg)	Fat mass (%)
BTGSD01	18	F	c.936dupA (p. Val313SerfsX13)	4	72.8	155.6	> 97[b]	35.1	51.73

BMI, body mass index; GSD Ib, glycogen storage disease type Ib.
[a] Fat free mass measured using bioelectrical impedance analysis (BIA).
[b] The BMI is 30.1, placing the BMI-for-age > 97th percentile for girls aged 18 years. This child has obesity [31].

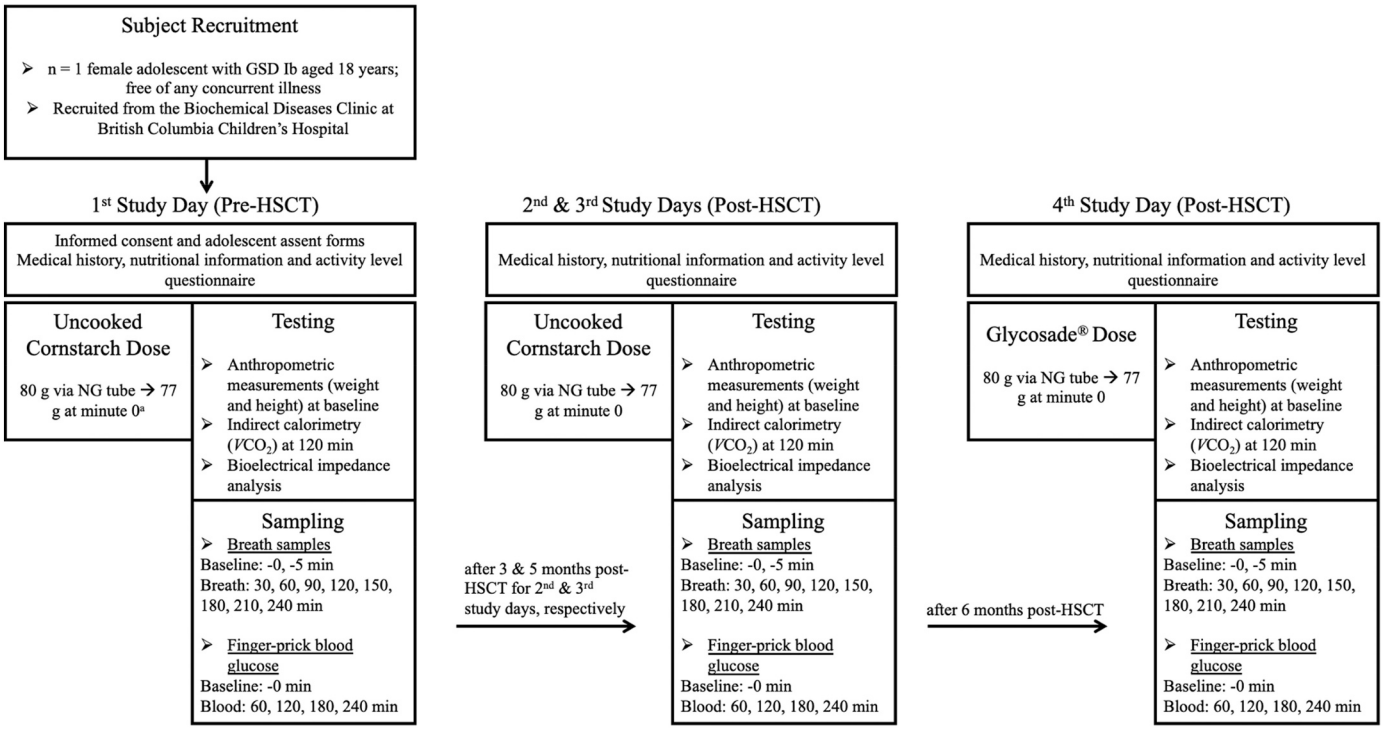

Fig. 1. Experimental design for the ^{13}C-glucose breath test (^{13}C-GBT) in the adolescent with glycogen storage disease type Ib (GSD Ib).
[a]Nasogastric (NG) tube was weighted prior to feeding = 10 g; and then was weighted after feeding = 13 g. There was some residual amounts ~3 g of UCCS or *Glycosade*® at each study day. Therefore, the actual dose that the subject received of UCCS or *Glycosade*® was 77 g.

study were explained to the patient and her parents before their participation in the study. Compensation was provided in the form of an honorarium for each completed study day.

2.2. Experimental design (^{13}C-glucose breath test)

The experimental design of the ^{13}C-GBT has been described in detail in [21]. In brief the test is based on the natural ^{13}C enrichment of UCCS and *Glycosade*® and its utilization measured in breath $^{13}CO_2$.

The test was performed after a 4-h fast based on our clinical assessment of patient's fasting tolerance (maintain normoglycemia, glucose >4 mmol/L) in GSD I [22] and was standardized across all study days [22]. Our goal was to establish daytime carbohydrate management in this patient. On each study day, the patient consumed standardized 65 g carbohydrate meal at 8:00 am and arrived at Clinical Research Evaluation Unit at 12:00 pm. Basic anthropometric measurements (body weight and height) were recorded, and a brief study day questionnaire was administered to collect information on medical, diet, and physical activity history. Two baseline breath samples were collected to determine natural background ^{13}C abundance. The participant received UCCS Fleischmann's®, the standard starch preparation used in Canada (ACH Food Companies, Inc. Mississauga, ON) in the pre-HSCT, 3 and 5 months post-HSCT; she received the modified cornstarch *Glycosade*® (Vitaflo International Ltd., Liverpool, UK) at 6 months post-HSCT. For each study day, the test starch dose of 80 g dissolved in 150 mL water was administered via nasogastric (NG) tube (based on patient's prescribed dose and the route of administration from the dietitian at British Columbia Children's Hospital). The NG tube was weighed using an electronic scale prior to and after feeding to measure residual amounts of test starch, which was ~3 g (actual intake of UCCS or *Glycosade*® 77 g).

On the first study day she was in the luteal phase of her cycle, and for the remaining study days she was on leuprolide acetate (Lupron®, AbbVie Inc., North Chicago, IL) intramuscular (IM) monthly for menstrual suppression prescribed from the pediatric gynecology team. This would continue for the duration of the patient's immunosuppressant treatment and help prevent any regular cyclical blood losses.

The participant remained fasting and resting in the unit for the entire period of the study to eliminate variability in CO_2 production. Breath samples in triplicates were collected at 30, 60, 90, 120, 150, 180, 210, and 240 min after administration of the test starch (Fig. 1).

During each study visit, the rate of carbon dioxide production (VCO_2) was measured for 20 min, two hours after the test starch dose, using an indirect calorimeter (Vmax Encore, Viasys Healthcare Inc. Yorba Linda, CA). Assessment of body composition was performed using bioelectrical impedance analysis (BIA-Quantum IV, RJL Systems, MI). The prediction of total body water (TBW) from BIA in obese adolescents was described previously [23]. Fat free mass (FFM) and fat mass (FM) were calculated from measured TBW using the equations described by Wabitsch et al., 1996 [23].

Finger-prick blood glucose was measured hourly using a glucometer (OneTouch® Ultra®2 LifeScan, Canada Ltd) as a screening tool to monitor blood glucose and identify hypoglycemia (glucose <4 mmol/L).

2.3. Sample collection and analysis

Breath samples were collected and stored in disposable vacuum glass Exetainer® tubes as described earlier [21,24]. Expired $^{13}CO_2$ enrichment was measured using a continuous flow isotope ratio mass spectrometer (CF-IRMS IsoPrime100, Cheadle, UK) and expressed as δ per mil (δ ‰) when compared against a reference standard of compressed CO_2.

The oxidation of glucose from UCCS and *Glycosade*® (UCCS and *Glycosade*® utilization) was calculated from the ^{13}C enrichment in expired CO_2 with the formula calculating glucose oxidation as a measure of expired $^{13}CO_2$ over time (240 min) after taking baseline $^{13}CO_2$ into account and expressed in mg glucose/kg/min [21].

Finger-prick blood glucose measurements were performed at 60 min intervals, mainly to prevent hypoglycemia in GSD Ib patient using a glucometer (OneTouch® Ultra®2 LifeScan, Canada Ltd). Self-monitoring using finger-prick blood glucose has been part of our

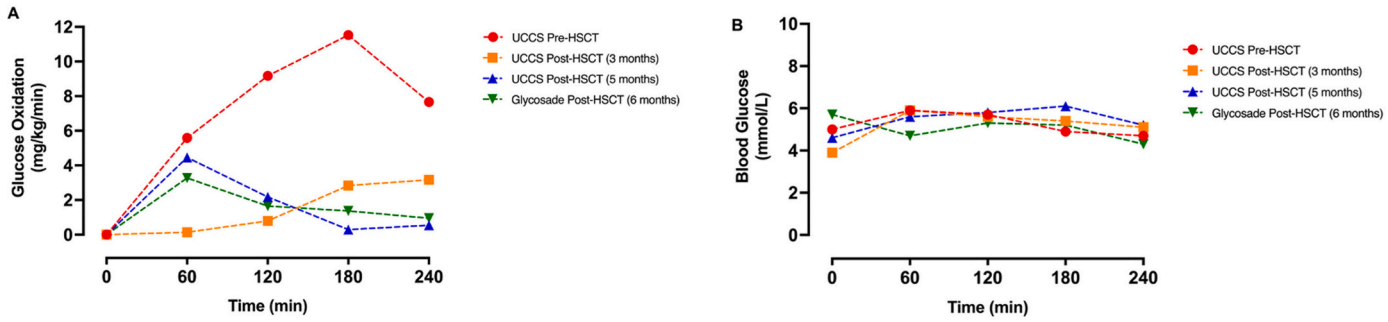

Fig. 2. ^{13}C-glucose breath test (^{13}C-GBT) and finger-prick blood glucose concentrations in the adolescent with GSD Ib.
A. Glucose oxidation in GSD Ib (18 y, F) from UCCS (pre-HSCT), UCCS (3 & 5 months post-HSCT), and *Glycosade*® (6 months post-HSCT) during the minimally invasive 4-h study protocol. Data are presented every 60 min instead of every 30 min due to the variability in the patient responses that might be related to hepatomegaly and splenomegaly.
B. Finger-prick blood glucose concentrations in GSD Ib measured hourly using glucometer.

center's protocol to ensure safety before physical activity or meals. Therefore, we decided to follow the same protocol, rather than continuous glucose monitor (CGM) to reduce burden for study participation.

2.4. Biochemical, hospital admissions frequency, and medical nutrition therapy data before and after transplantation

Biochemical, hospital admissions frequency, and medical nutrition therapy data were obtained from the medical records as a post-hoc chart review. Biochemical data, specifically for complete blood count, general chemistry, and insulin were totalled over 12 months prior to transplant and approximately 20 months post-HSCT (Table 3). The post-HSCT was separated into three time-periods as follows:

1) hospitalization and postoperative care (lasting 2 months), 2) readmission period for shingles as a complication of HSCT (lasting 1 month); during this time the patient received intravenous acyclovir, and 3) hospital discharge period, which represents the patient's full recovery (lasting 17 months). Number of hospital admissions was collected over 16 months pre-HSCT and 16 months post-HSCT. Medical nutrition therapy including feeding regimen, starch treatment / NG doses, and carbohydrate requirements based on the prescribed nutrition plan from the dietitian were retrieved before and after transplantation (Table 4).

2.5. Statistical analysis

Subject characteristics are presented for the individual subject. All statistical analyses were performed using GraphPad Prism 9.1.0 (GraphPad Software Inc., CA). Categorical variables are expressed as frequencies and continuous variables as means ± standard deviations or medians (interquartile range) based on data distribution. Normality of data was assessed by Shapiro-Wilk test. UCCS and *Glycosade*® utilization represented as glucose oxidation (mg/kg/min) was the primary outcome measure. Area under the curve (AUC) for the subject's $^{13}CO_2$ oxidation from t_0 to t_{240}, the time to reach maximum $^{13}CO_2$ oxidation (t_{max}), and the maximum peak enrichment in $^{13}CO_2$ oxidation (C_{max}) were calculated. Repeated measures of analysis of variance (ANOVA) were used to compare glucose oxidation pre-HSCT, 3, 5, and 6 months post-HSCT. A follow up test to compare the mean of each study day with the mean of a control (UCCS pre-HSCT) was performed using Dunnett's test, which is a multiple comparison adjustment test. Each *P* value is adjusted to account for multiple comparisons. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Subject characteristics

The study took place over a 7-month period from February 2018 to September 2018 with a total of 4 study days. The patient was treated with G-CSF (dose 150 μg/day, ~ 2 μg/kg/day) prior to transplantation. She was prescribed Allopurinol for hyperuricemia, Acyclovir (antiviral medication) mainly when she was readmitted for shingles, Penicillin (antibiotics), and Leuprolide Acetate for menstrual suppression. The demographic and anthropometric characteristics are presented in (Table 1). BMI-for-age was within the obese category; among the body composition measures, FM was high when compared with reference values [25].

Table 2
Glucose oxidation by measurement of exhaled $^{13}CO_2$ pre-HSCT and post-HSCT in the GSD Ib participant.

Study days	$^{13}CO_2$ exhaled			
	AUC_{240}[a] (mg/kg/min)	t_{max}[b] (min)	C_{max}[c] (mg/kg/min)	*P* value[d]
1st Study day: UCCS pre-HSCT	1807	180	11.53	
2nd Study day: UCCS post-HSCT (3 months)	321.6	240	3.17	0.06
3rd Study day: UCCS post-HSCT (5 months)	431.9	60	4.46	0.14
4th Study day: *Glycosade*® post-HSCT (6 months)	405.4	60	3.27	0.10

AUC, area under the curve; GSD Ib, glycogen storage disease type Ib; HSCT, hematopoietic stem cell transplantation; UCCS, uncooked cornstarch.
[a] Area under the curve for $^{13}CO_2$ oxidation from t_0 to t_{240}.
[b] Time to reach maximum $^{13}CO_2$ oxidation.
[c] Maximum peak enrichment in $^{13}CO_2$ oxidation.
[d] Each *P* value is adjusted to account for multiple comparisons. Compare the mean of each study day with the mean of the subject's baseline value of UCCS pre-HSCT.

3.2. Glucose oxidation (UCCS/Glycosade® utilization)

The glucose oxidation derived from UCCS or *Glycosade*® would reflect UCCS/*Glycosade*® utilization. Breath test is presented every 60 min instead of every 30 min due to the variability in the patient responses that is likely related to her medical history, including restrictive lung disease secondary to obesity and organomegaly (Fig. 2A). Glucose oxidation from UCCS prior to HSCT was significantly higher ($P = 0.036$) with peak enrichment (C_{max}) at t_{180} of 11.53 mg/kg/min, potentially reflecting inflammation induced glucose uptake and glycolysis in the liver (Fig. 2A, Table 2). Three months following transplantation, glucose oxidation from UCCS declined (C_{max} of 3.17 mg/kg/min at t_{240}), likely representing lower glucose uptake and oxidation in the liver (Table 2). Five and six months following HSCT glucose oxidation from UCCS and *Glycosade*® (C_{max} of 4.46 mg/kg/min from UCCS, and 3.27 mg/kg/min

Table 3
Biochemical data in the adolescent with GSD Ib before and after HSCT[a].

	Pre-HSCT	Post-HSCT (separated into three time-periods)			
		Hospitalization, pre and postoperative care	Readmission[b]	Hospital discharge	Reference values
Observation date range	Feb 2017 – Jan 2018	Feb 2018 – May 2018	Jun 2018	Jul 2018 – Nov 2019	
White blood cells	1.97 ± 1.2 (n = 21)[c]	1.75 (0.20–4.33)[d] (*n* = 86)	2.20 (1.70–2.78) (*n* = 10)	4.97 ± 0.8[e] (*n* = 14)	3.9–10.2 × 10^9/L
Platelet count	103.62 ± 29.3 (*n* = 21)	83.5 (36.75–110.25) (n = 86)	96.5 (87.75–117.75) (n = 10)	135.31 ± 19.6 (*n* = 13)	165–397 × 10^9/L
Neutrophil count	0.79 ± 0.9 (n = 21)	3.56 (1.67–3.95) (*n* = 56)	1.55 (1.23–2.04) (n = 10)	3.45 ± 0.5 (n = 14)	1.8–6.8 × 10^9/L
Glucose (random)	5.51 ± 2.5 (n = 10)	6.32 ± 1.1 (*n* = 83)	5.11 ± 1.0 (*n* = 12)	5.33 ± 0.5 (*n* = 9)	3.3–7 mmol/L
Lactate	1.23 ± 0.6 (n = 8)	0.75 ± 0.3 (*n* = 84)	1.17 ± 0.5 (n = 10)	0.88 ± 0.2 (*n* = 4)	0.5–2.2 mmol/L
Urate	256.25 ± 76.5 (n = 8)	228.00 (163.00–273.00) (*n* = 19)	185.22 ± 19.2 (n = 9)	207.25 ± 22.8 (n = 8)	180–345 μmol/L
ALT	36.88 ± 15.7 (n = 8)	26.51 ± 9.2 (*n* = 57)	39.25 ± 18.9 (n = 4)	36.54 ± 15.1 (n = 13)	5–35 U/L
AST	36.57 ± 16.7 (*n* = 7)	28.91 ± 9.8 (n = 57)	45.00 ± 14.0 (n = 4)	39.92 ± 12.5 (n = 12)	5–30 U/L
Alkaline phosphatase	79.14 ± 11.2 (n = 7)	97.19 ± 49.0 (*n* = 26)	124.25 ± 40.3 (n = 4)	95.17 ± 20.1 (n = 12)	50–130 U/L
GGT	59.71 ± 22.9 (n = 7)	78.57 ± 70.6 (n = 56)	143.50 ± 66.8 (n = 4)	91.85 ± 29.0 (n = 13)	11–28 U/L
CRP	<5.00, <5.00 (n = 2)	9.00 (6.50–16.50) (n = 5)	–	12.00 (8.00–44.50) (n = 5)	<10 mg/L
Albumin	32.67 ± 4.7 (*n* = 3)	36.00 (35.00–37.00) (*n* = 80)	–	40.25 ± 1.5 (n = 4)	37–56 g/L
Pre-albumin	118.00 (n = 1)	117.00 (n = 1)	–	196.00 (137.25–199.25) (n = 4)	205–419 mg/L
Ferritin	896.00, 107.00 (n = 2)	132.60 ± 54.0 (n = 5)	–	124.00 ± 33.4 (*n* = 6)	9–49 μg/L
Triglycerides	1.24 ± 0.2 (n = 6)	1.91 ± 0.7 (*n* = 77)	1.89 ± 0.3 (n = 4)	1.67 ± 0.3 (n = 5)	0.4–1.5 mmol/L
Cholesterol	3.41 ± 0.4 (n = 4)	3.88 (n = 1)	2.96, 3.21 (n = 2)	3.92, 4.53 (n = 2)	2.6–5.2 mmol/L
Hemoglobin A1C	5.1 (n = 1)	–	–	5.0, 5.0 (n = 2)	Therapeutic goal = 7%
Insulin	205.17 ± 130.4 (n = 6)	279.40 ± 143.7 (*n* = 15)	233.00 ± 103.6 (*n* = 3)	239.00 (165.50–369.50) (n = 9)	13–129 pmol/L

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma glutamyltransferase; GSD Ib, glycogen storage disease type Ib; HSCT, hematopoietic stem cell transplantation.

[a] A normality test (Shapiro-Wilk test) was used to evaluate normality. When data were normally distributed, they presented as mean ± standard deviation. When data were not normally distributed, they are presented as median (interquartile range). If the number of observations was 1 or 2 then they are presented as numerical values; '-'denotes no available data.

[b] Readmission for shingles – a complication of HSCT transplant and patient was placed on acyclovir.

[c] Number of observations.

[d] Median (interquartile range).

[e] Mean ± standard deviation.

from *Glycosade*®, which was non-significant) remained low; both values suggesting HSCT stabilized UCCS / *Glycosade*® utilization as reflected by lower and stable glucose oxidation (Fig. 2A, Table 2). The time to reach maximum enrichment (t_{max}) changed from t_{180} pre-HSCT to t_{60} at 5 and 6 months post-HSCT. The diminished *Glycosade*® curve compared to UCCS curve and could likely represent delayed gastric emptying.

3.3. Finger-prick blood glucose concentrations

Finger-prick blood glucose measurements were performed at 60 min intervals until the test end as a screening tool to assess hypoglycemia (glucose <4 mmol/L). There were no statistically significant differences ($P < 0.58$) noted in the blood glucose concentrations at any time point prior to and after transplantation (Fig. 2B), with no incidence of hypoglycemia. These findings could be that the traditional blood glucose concentrations rely on the accumulation of substrate in the circulation, unlike ^{13}C-GBT which represents the metabolic end point of glucose metabolism.

3.4. Biochemical, hospital admissions frequency, and medical nutrition therapy data before and after transplantation

After successful transplantation there was a notable improvement in the patient's state of health. In addition to a lower and stable glucose oxidation in the ^{13}C-GBT following transplantation, there was an improvement of neutrophil count levels in response to HSCT compared to pre-HSCT. Neutropenia was corrected at all the three time-frames post-HSCT (Table 3) with no G-CSF treatment. Metabolic control was relatively stabilized, reflected by maintenance of blood glucose, lactate, and urate within reference ranges after HSCT, while a few biochemical changes were observed. Triglycerides and insulin were high 12 months pre-HSCT and ~ 20 months post-HSCT (Table 3). Mild thrombocytopenia continued with no further bleeding complications.

The patient had 6 hospital admissions during the 16 months pre-HSCT with issues related to GSD Ib such as fever, neutropenia and hypersplenism, feeding intolerance, nausea, and vomiting. The number of hospital admissions was reduced by 67% in the 16 months after transplantation (6 visits pre-HSCT vs. 2 visits post-HSCT). The 2 hospital admissions post-HSCT were related to shingles, and mild fever,

Table 4
Medical nutrition therapy data in adolescent with GSD Ib before and after HSCT.

	Pre-HSCT	Post-HSCT	% Reduction from pre-HSCT[c]
Feeding regimen[a]	3.5–4 hourly daytime feeds with UCCS and overnight feeds with Tolerex using NG tube	Daytime feeds with UCCS every 1.5–4 h and overnight feeds with UCCS followed by *Glycosade*® via NG 3 h later	
Starch treatment and NG doses	Daytime feeds (8:00 am – 6:30 pm): 144 g UCCS Overnight feeds (8:00 pm – 8:00 am): Tolerex at 52 ml/h × 12 h	Daytime feeds (8:00 am – 7:30 pm): 117 g UCCS Overnight feeds: (10:00 pm) 31 g UCCS (1:00 am) 107 g *Glycosade*®	19%
Carbohydrate requirements[b]	Daytime average (8:00 am – 6:30 pm): 202.8 g carb, 16.9 g carb/h × 12 h, 4 mg/kg/min Nighttime average using Tolerex (8:00 pm – 8:00 am): 141 g carb, 11.8 g carb/h × 12 h, 2.8 mg/kg/min 24 h total average intake: 344 g carb, 14.3 g carb/h, 3.4 mg/kg/min	Daytime average (8:00 am – 7:30 pm): 182.1 g carb, 13 g carb/h × 12 h, 3.1 mg/kg/min Nighttime average using UCCS & *Glycosade*® (10:00 pm & 1:00 am): 122 g carb, 12.23 g carb/h × 10 h, 2.9 mg/kg/min 24 h total average intake: 304 g carb, 12.7 g carb/h, 3.0 mg/kg/min	10% 13% 12%

GSD Ib, glycogen storage disease type Ib; HSCT, hematopoietic stem cell transplantation; NG, nasogastric; UCCS, uncooked cornstarch.

[a] Feeding regimen refers to UCCS intervals during the daytime and Tolerex or starches intervals at night.

[b] Carbohydrate requirements based on the nutrition plan from the dietitian (2 days food records were analyzed using the Genetic Metabolic Dietitians International (GMDI) MetabolicPro™ food database) including starch treatment with food carbohydrate during daytime and starch treatment/NG during nighttime feeding.

[c] % Reduction in daytime feeds starch treatment, daytime average carbohydrate intake, nighttime average carbohydrate intake, and 24 h total average carbohydrate intake from pre-HSCT.

respectively.

Diet history from the dietitians' records reveals that pre-HSCT the patient was on UCCS doses during the day (every 3.5–4 h) and used Tolerex feeds overnight (Table 4). Post-HSCT daytime UCCS treatment dose to maintain blood glucose concentrations was decreased by 19% (144 g pre-HSCT vs. 117 g post-HSCT). There was a change of UCCS dose post-HSCT, as reflected by the patient receiving overnight UCCS doses followed by *Glycosade*® via NG tube 3 h later which held her blood glucose for 7 h, instead of using Tolerex feeds overnight. The 24-h total average carbohydrate intake was reduced by 12% (344 g carbohydrate pre-HSCT vs. 304 g carbohydrate post-HSCT) (Table 4). Whether these short-term diet changes would improve long-term management post-HSCT is unknown.

4. Discussion

The objective of the current study was to measure the utilization of UCCS and *Glycosade*® in a case with GSD Ib, using a minimally invasive and sensitive test. We examined glucose metabolism in vivo, based on the natural enrichment of ^{13}C from both starches, and oxidation to $^{13}CO_2$ [21]. To the best of our knowledge, this is the first time that ^{13}C-breath test has been used to determine glucose oxidation as a non-invasive marker of in vivo glucose metabolism before and after HSCT in a GSD Ib patient.

The most outstanding finding in our study was that glucose oxidation from UCCS was significantly higher prior to HSCT compared to 3 and 5 months after with the peak enrichment (C_{max}) being approximately 7 to 8 times lower in the post-transplant experiments. Chronic inflammation associated with the neutropenia in GSD Ib and supported by very high plasma ferritin levels, might be an explanation. As shown in arthritic rats [26,27], chronic inflammation affects the hepatic glucose metabolism by enhancing hepatic glucose uptake and glycolysis. Furthermore, the early rise in blood glucose and its downward trend during rising glucose oxidation likely reflects insulin secretion.

There was also a substantial difference in the time the maximal oxidation rate (t_{max}) was reached. While in the pre-transplant experiment t_{max} was reached at 180 min after UCCS ingestion, t_{max} was reached as early as 60 min after UCCS ingestion 5 months after HSCT.

Interestingly there was no major difference in the extent (AUC) and pattern (t_{max}) of UCCS and *Glycosade*® oxidation rates measured 5 and 6 months after HSCT respectively. *Glycosade*® has different physical properties compared to UCCS as the amylopectin content gives *Glycosade*® a delayed digestibility profile and reduced glucose oxidation. At the end of the experiment (240 min after ingestion) the oxidation rates were similar. An extension of the observation period beyond the 240 min mark might have shown whether the availability of *Glycosade*® derived glucose lasts longer than the UCCS derived glucose. The lower blood glucose levels observed after *Glycosade*® ingestion compared to higher levels observed during UCCS ingestion are an indication of delayed glucose release from *Glycosade*®.

The glucose oxidation of UCCS observed 3 months post-HSCT show a different pattern with slowly increasing oxidations rates towards the 240 min mark. Delayed intestinal digestion of UCCS might be a reason. However, the patient had an uncomplicated course post-HSCT and there was no evidence of graft vs. host reaction which could have affected the gut. Another reason could be related to a possible block in the NG tube through which the UCCS was given, however this was unlikely since the pre and post weighing of NG tube on all study days were comparable. It has also been reported that GSD Ib patients have frequent bacterial infections and IBD [28], which would have an influence in the metabolism of carbohydrates and glucose oxidation. In this study there were no reports of gastrointestinal pain, discomfort concurrent with study days, and there were no formal diagnosis of IBD in the patient. Furthermore, the ^{13}C-GBT test we use involves the collection of baseline breath samples prior to the carbohydrate dose, and the ^{13}C enrichment values are deducted from all subsequent time point breath samples. This would reduce the influence on the study ^{13}C-GBT values.

Our case study adds to the experience of HSCT in GSD Ib. The first case, published in Birmingham, UK, reported improved neutrophil counts and metabolic control, reduced infections and hospitalizations post-HSCT, and discontinuing G-CSF [29]. HSCT from a matched unrelated donor has been reported in a GSD Ib patient from the USA for the reasons of poor quality of life related to frequent hospital admissions and emergency visits [30]. After transplantation, the GSD Ib subject showed resolved neutropenia and decreased infections. Two other cases showed signs of enhanced GSD Ib-related issues with normalized neutrophil counts after HSCT [16]. Our patient underwent HSCT from her sibling to reduce the risk of recurrent infections and her post-HSCT course was notable for corrected neutropenia, decreased hospital admissions, and maintained metabolic control (mainly for glucose, lactate, and urate). However, other elements related to the patient's underlying disorder, including hepatic adenomas, persist and may require alternative treatment. Further studies are needed to understand the glucose metabolism in GSD Ib after other treatment modalities such as liver transplantation.

More studies are also required to validate the ^{13}C-GBT in response to different starch doses within the same participant, which will help in further refining dietary management along with the use of CGM for aiding in glucose follow up. We are currently in the process of defining the repeatability of the ^{13}C-GBT in healthy participants, and preliminary results suggest that the ^{13}C-GBT values have very less CV% within the same individual. We hope to expand this to GSD patients in the future.

One limitation of the ^{13}C-GBT is the availability of instrumentation to measure the ^{13}C enrichment from breath reliably. Our study used an Isotope Ratio Mass Spectrometer (IRMS), which is sensitive to the 5th decimal in expired air ^{13}C enrichment, and has a very short turnaround time for analysis; although not easily available/accessible to all clinics. The cost of the breath analysis while prohibitive to have wider applications of the method, breath samples are relatively easy to obtain, store (room temperature) and ship. Thus, a multi-center collaborative effort can be undertaken in future with a centralized institute/site providing the sample analysis.

Overall, our study shows that matched related donor HSCT in GSD Ib resolved neutropenia, reduced the number of hospital admissions, and stabilized UCCS utilization.

The glucose utilization in the current study relates to the rate and extent of starch digestion, absorption, and glucose disposal through oxidation. The breath test offers more dynamic and patient-specific details of in vivo disposal of glucose, compared to measuring blood glucose concentrations, and could provide important value to tailor GSD Ib management according to individual needs.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

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AT, RE, SS, SS contributed to the study design and development; AT collected and analyzed the data; KD, GH contributed to patient recruitment; AT contributed to clinical data retrieval; AT, SS, SS, and RE contributed to writing the manuscript; RE had primary responsibility for final content. All authors read and approved the final manuscript.

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