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Clinical Research Article

A Prospective Study on Continuous Glucose Monitoring in Glycogen Storage Disease Type Ia: Toward Glycemic Targets

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Abstract

Context: Although previous research has shown the benefit of continuous glucose monitoring (CGM) for hepatic glycogen storage diseases (GSDs), current lack of prospectively collected CGM metrics and glycemic targets for CGM-derived outcomes in the hepatic GSD population limits its use.

Objective: To assess CGM metrics for glycemic variation and glycemic control in adult patients with GSDIa as compared to matched healthy volunteers.

Design: Prospective CGM data were collected during the ENGLUPRO GSDIa trial (NCT04311307) in which a Dexcom G6 device was used. Ten adult patients with GSDIa and 10 age-, sex- and body mass index–matched healthy volunteers were enrolled. Capillary blood glucose was concurrently measured during 2 standardized 2-hour time intervals. Descriptive [eg, glycemic variability (GV), time below range, time in range (TIR), time above range (TAR)] and advanced (ie, first- and second-order derivatives, Fourier analysis) CGM outcomes were calculated. For each descriptive CGM outcome measure, 95% CIs were computed in patients with GSDIa and healthy volunteers, respectively.

Results: CGM overestimation was higher under preprandial and level 1 hypoglycemia (ie, capillary glucose values ≥ 3.0 mmol/L and < 3.9 mmol/L) conditions. GV and TAR were higher while TIR was lower in patients with GSDIa compared to healthy volunteers ($P < 0.05$). Three patients with GSDIa showed descriptive CGM outcomes outside the calculated 95% CI in GSDIa patients. Advanced CGM analysis revealed a distinct pattern (ie, first- and second-order derivatives and glucose curve amplitude) in each of these 3 patients within the patients group.

Conclusions: This is the first study to prospectively compare CGM outcomes between adult patients with GSDIa and matched healthy volunteers. The generation of a set of CGM metrics will provide guidance in using and interpreting CGM data in GSDIa and will be useful for the definition of glycemic targets for CGM in patients with GSDIa. Future studies should investigate the prognostic value of CGM outcomes and their major determinants in patients with GSDIa.

Key Words: glycogen storage disease type Ia, continuous glucose monitoring, precision medicine, diet, monitoring, management

Abbreviations: CBG, capillary blood glucose; CGM, continuous glucose monitoring; CNGDF, continuous nocturnal gastric drip-feeding; GSDIa, Glycogen storage disease type Ia; GV, glycemic variability; TAR, time above range; TBR, time below range; TIR, time in range; UCCS, uncooked corn starch.

Glycogen storage disease type Ia (GSDIa; MIM #232200) is an inherited disorder of glycogen metabolism due to mutations in the *G6PC1* gene, encoding the glucose 6-phosphatase-α enzyme. Impaired glycogenolysis and gluconeogenesis results in fasting intolerance with hypoglycemia, elevated lactate, metabolic acidosis, and secondary metabolic derangements, including hypertriglyceridemia, hypercholesterolemia, and hyperuricemia (1). A strict, personalized diet, including frequent feedings, uncooked corn starch (UCCS) and/or continuous nocturnal gastric drip-feeding (CNGDF) constitutes the cornerstone of the treatment for patients with GSDIa and has improved their prognosis in the past decades. Yet, patients with GSDIa are still at a risk of developing acute hypoglycemia and long-term complications (2).

Dietary compliance and the patients' overall "metabolic control" are currently assessed by a combination of clinical (eg, height, weight, liver size) and biochemical (blood glucose, lactate, triglycerides, cholesterol, uric acid) markers (3). Although such biomedical parameters can reflect the degree of the disease (de)compensation, they do not capture the swift changes in the GSDIa patients' glucose levels. Hepatic GSD clinical evaluation requires regular (expensive

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and invasive) in-hospital and/or outpatient investigations, and there is considerable phenotypical heterogeneity among patients (eg, blood triglycerides levels vary largely even between treated siblings carrying the same G6PC1 genotype) (4). Finally, it is unknown whether the traditional biomedical parameters are sufficiently reliable to assess the dynamic effects of emerging treatment strategies for GSDIa, such as gene therapy (NCT03517085; NCT05139316) or messenger RNA therapy (NCT05095727).

Over the past years, continuous glucose monitoring (CGM) has developed into a valuable monitoring modality (5). For patients with diabetes mellitus (DM), glycemic targets for CGM-parameters [eg, time in range (TIR) and time above range (TAR)] have been defined (6), and the percentage of TIR has been included in the standard set of person-centered outcomes (7). As CGM has previously been shown valuable to detect unrecognized hypoglycemia and to monitor individual glycemic variability (GV) (8, 9), its potential benefit for patients with hepatic GSD is high. However, the current lack of documented CGM data on glycemic variation and glycemic control complicates the comparison of CGM outcomes between patients and limits the use of this technology in both day-to-day care and clinical trials.

We have recently proposed indications for CGM monitoring and CGM outcome parameters in patients with hepatic GSDs (10). As a follow-up, the aim of the present study was to prospectively assess CGM metrics in patients with GSDIa as compared to matched healthy volunteers.

Subjects and Methods

Study Approval

CGM data were collected during the Endogenous Glucose Production in Patients With Glycogen Storage Disease Type Ia (ENGLUPRO GSDIa; NCT04311307) study. The study protocol was approved by the Medical Ethical Committee of the University Medical Center Groningen, Groningen, The Netherlands (reference no. METc 2020/342). The study was conducted according to the principles of the Helsinki Declaration of 1975 as revised in 2013. All participants provided written informed consent prior to inclusion in the study.

Study Design

The ENGLUPRO GSDIa study was a single-center, prospective, observational clinical trial conducted at the University Medical Center Groningen between October 2020 and July 2021. Data on CGM were collected and stored as exploratory endpoints. On study day 1, a Dexcom G6 (Dexcom, San Diego, CA, USA) CGM sensor was placed on either the upper arm (n = 18) or the abdomen (n = 2; participants 014 and 015). Instructions on the appropriate use of the CGM device were provided by experienced research nurses. Participants were asked to keep the CGM device for 10 days while performing their everyday activities and following their usual diet. At the end of the study, the CGM device was removed by each participant, and the material was sent back to the study site. CGM data of each study participant were collected for further analysis during the entire course of the study.

Study Participants

Participant flow chart is presented in Supplementary Figure 1 (11). Ten patients with GSDIa and an equal number of age-, sex- and body mass index (BMI)-matched healthy volunteers healthy volunteers were included in the study. Inclusion criteria were (1) age > 16 years, (2) stable medical condition before the start of the test procedures and for patients with GSDIa, (3) confirmation of GSDIa with enzyme assay and/or *G6PC1* variant analysis. *G6PC1* mutations were reported according to ClinVar or based on published literature in case a mutation was not deposited on ClinVar. Exclusion criteria included (1) pregnancy, (2) recent (<1 month) history of hospitalization due to hypoglycemia, (3) intercurrent illness [defined as (a combination of) decreased dietary intake, vomiting, diarrhea and fever (>38.5°C) in the week prior to the study visit]. For healthy volunteers, exclusion criteria also included (1) confirmed diagnosis or history suggestive of DM, (2) first-degree family member with a confirmed diagnosis associated with fasting intolerance, and (3) symptoms or signs suggestive of fasting intolerance, metabolic instability, fever, or gastrointestinal complaints. No patient with GSDIa had either a first-degree family member with a confirmed diagnosis or a history suggestive of DM or ultrasound signs of liver cirrhosis.

Continuous Glucose Monitoring System

In this study, a Dexcom G6 (Dexcom, San Diego, CA, USA) device was used. Dexcom G6 exhibits a relatively high accuracy in the hypoglycemic range and sensitivity for detecting hypoglycemia in patients with DM (12). The CGM device consists of a wireless receiver, a transmitter, and a sensor. The sensor is inserted in the subcutaneous tissue in the interstitial space. The sensor coated with glucose oxidase reacts with glucose, producing an electrical current every 5 minutes, resulting in 288 measurements per day. The glucose concentration is derived from the interstitial glucose concentration using a computer-driven algorithm, and sensor glucose measurements are transmitted to the wireless receiver. As the Dexcom G6 is factory calibrated, calibration by the user is not required.

Capillary Blood Glucose Measurements

Capillary blood glucose (CBG) measurements were performed at the study site under supervision of a research nurse and a physician using a Freestyle Freedom Lite device (Abbott, Chicago, IL, USA). CBG values were collected during two 2-hour time frames (occurring on the same day) in which CBG and CGM levels were concurrently measured (every 10 minutes during the first hour and subsequently at +75, +90, and +120 minutes after starting the synchronized measurements) in a preprandial/fasted (ie, before breakfast) and fed (ie, after lunch) state, respectively. As a result, 20 paired CGM and CBG measurements (ie, 10 paired measurements in a preprandial/fasted state and 10 paired measurements in a fed state) were generated for each study participant.

Outcome Parameters and Data Analysis

Data on participants' demographic, genotype, diet, and CBG were collected and stored as exploratory outcome parameters during the ENGLUPRO GSDIa study. The raw CGM data files were retrieved from the Dexcom CLARITY Clinical Portal (https://clarity.dexcom.eu/professional/patients) and stored anonymously as CSV files prior to the

analysis (https://www.dexcom.com/g6-cgm-system). The Dexcom CGM System has been validated for glucose concentrations > 2.2 mmol/L (>40 mg/dL). In case the CGM sensor indicated a low value, the lowest possible CGM value of 2.2 mmol/L was used, as omitting these values would introduce bias in the descriptive statistical analyses.

CGM-derived outcome parameters were defined as previously described (10) and included the following descriptive CGM outcomes: (1) median, minimum, maximum, and range; (2) outcomes of GV [SD, variance, coefficient of variation (CV; calculated as SD divided by the mean)]; and outcomes of glycemic control (6) [time below range (TBR), defined as glucose values either ≥3.0 mmol/L and <3.9 mmol/L (ie, level 1 hypoglycemia) or <3.0 mmol/L (ie, level 2 hypoglycemia)]; TIR (defined as glucose values either ≥3.9 and ≤7.8 mmol/L or ≥ 3.9 and ≤10.0 mmol/L), and TAR (TAR defined as glucose values either >7.8 mmol/L or >10.0 mmol/L). The occurrence of level 3 hypoglycemia (ie, low glucose levels associated with mental or physical functioning impairment) was also recorded.

To minimize the effect of diurnal variations in dietary intake and physical activity on glucose values, descriptive CGM outcomes were calculated on 24-hour CGM data as well as on CGM data collected between 1:00 and 5:00 AM (ie, overnight). Advanced CGM outcomes included (1) the first-order derivative (change over time) calculated as $glucose' = \frac{dglucose}{dt}$ and the second-order derivative (speed of change overtime) calculated as $glucose'' = \frac{d^2glucose}{dt^2}$; and (2) Fourier analysis, performed as described previously (13) by mathematically transforming the CGM data with a fast Fourier transformation and converting the data in 1 or more sinusoidal curves. Two major parameters define a sinusoidal curve (1) amplitude (ie, the peak deviation of the curve from 0) and (2) frequency [ie, the number of oscillations (cycles) that occur within the time unit (a cycle is a complete wave oscillation)].

Three parameters were considered in this study: the frequency (ie, the number of cycles in the glucose curve during the overnight interval), the number of frequencies in the overnight glucose curve (a glucose pattern can consist of 1 frequency or multiple patterns), and the amplitude of each overnight glucose curve. Adequate glucose control is characterized by a low frequency, a low number of frequencies, and a small amplitude.

Statistical Analysis

Statistical analysis for descriptive CGM outcomes was performed using Prism 9.2 software (GraphPad Software, Inc. La Jolla, CA, USA). Agreement between the paired CBG and CGM measurements was assessed using the Bland-Altman analysis. Difference between CGM values and CBG was expressed both as absolute and fractional (ie, percentage difference between CGM values and CBG) change. 95% CIs were calculated as $95\%CI = x \pm z_{\alpha/2}\left(\frac{\sigma}{\sqrt{n}}\right)$, where x is the sample mean; α equals 0.95, σ is the standard deviation, n is the sample size, and z is calculated at the 95% confidence level. For each descriptive CGM parameter, 95% CI of 24-hour and overnight CGM-derived outcomes were compared between patients with GSDIa and healthy volunteers. In case the 95% CI of patients and healthy volunteers did not overlap, the difference was considered statistically significant ($P < 0.05$).

Results

Study Participants

General characteristics of the study participants are presented in Table 1. Ten patients with GSDIa (5 females, 5 males) with a median age of 22.2 years (range: 17.8-53.1) and a median BMI of 26.1 kg/m^2 (range 22.4-29.8) were enrolled. Nine patients were using frequent feedings and UCCS, of whom 2 patients (participants 007 and 017) also received CNGDF. One patient (participant 009) was on frequent feedings without UCCS but with CNGDF. Ten age-, sex- and BMI-matched healthy volunteers were also enrolled.

Comparison between CBG vs CGM

Bland-Altman analysis showed a nonsignificant overestimation of interstitial CGM glucose concentrations as compared to CBG values (mean glucose difference: −0.85 ± 0.87 mmol/L, with 95% limits of agreement from −2.6 mmol/L to 0.9 mmol/L) (Fig. 1A). Although a significant trend for larger differences between CBG and CGM values at higher glucose concentrations was observed, a similar trend was not observed when fractional changes in CBG and CGM values were compared (mean difference: −14.5 ± 14.7%, with 95% limits of agreement, from −43.2% to 14.2%) (Fig. 1B). Analysis of preprandial (Fig. 1C and 1D) and post-prandial (Fig. 1E and 1F) values resulted in consistent observations. Yet, mean difference was higher in preprandial than postprandial conditions. Although agreement between CBG and CGM was also found when analyzing values corresponding to level 1 hypoglycemia (ie, capillary glucose values ≥ 3.0 mmol/L and < 3.9 mmol/L), CGM overestimation was higher in this condition (mean glucose difference: −1.08 ± 0.79 mmol/L with 95% limits of agreement from −2.6 mmol/L to 0.5 mmol/L). A similar trend was observed when considering fractional changes in CBG and CGM values (mean difference: −24.2 ± 18.1%, with 95% limits of agreement from −59.7% to 11.3%) (Fig. 1G and 1H). CGM overestimation was higher in patients with GSD Ia than healthy volunteers (Fig. 1I and 1L).

Descriptive Measures

Descriptive outcomes are presented in Table 2. Mean 24-hour CGM values for patients with GSDIa and healthy volunteers were 6.1 mmol/L (95% CI: 5.2-7.1; n = 25 504) and 5.9 mmol/L (95% CI: 5.2-6.6; n = 27 153), respectively. Mean 24-hour glucose SD, glucose variance, and glucose CV were significantly higher in patients with GSDIa compared to healthy volunteers. Between 1:00 and 05:00 AM (ie, overnight), mean values for maximum CGM values, glucose SD, and glucose CV were significantly higher in patients with GSDIa compared to healthy volunteers.

TBR, TIR, and TAR are presented in Table 3. Level 3 hypoglycemia was not observed, while level 2 hypoglycemia (ie, glucose values < 3.0 mmol/L) occurred in 6/10 patients with GSDIa (of whom 5/6 patients for <1% of the recorded time) during the 24-hour period and in 1/10 patients with GSDIa during the overnight time frame. Mean 24-hour TBR (glucose values ≥ 3.0 mmol/L and < 3.9 mmol/L) and 24-hour TAR (glucose values > 10.0 mmol/L) were higher while the mean 24-hour TIR (glucose values ≥ 3.9 and ≤ 10.0 mmol/L) was lower in patients with GSDIa compared to healthy volunteers.

Table 1. Clinical and molecular characteristics of the study participants

Participant	Age, years	Sex	BMI, kg/m²	Genotype, *G6PC1* variants		Dietary regimen	UCCS/Glycosade intake, g/kg/day
				Nucleotide change	Protein change		
001	44.1	F	25.3	c.809G > T c.1039C > T	p.Gly270Val p.Gln347Ter	Frequent feedings Glycosade	3.2
002	21.6	M	29.8	c.189G > A c.189G > A	p.Trp63Ter p.Trp63Ter	Frequent feedings Glycosade	2.2
004	17.8	F	22.4	c.1039C > T c.1039C > T	p.Gln347Ter p.Gln347Ter	Frequent feedings Glycosade	1.6
006	53.1	F	27.3	c.1039C > T c.247C > T	p.Gln347Ter p.Arg83Cys	Frequent feedings Glycosade	2.4
007	22.7	M	29.5	c.1039C > T c.247C > T	p.Gln347Ter P.Arg83Cys	Frequent feedings Glycosade[a] CNGDF[b]	2.1
009	18.0	F	24.5	c.562G > A c.508C > T	p.Gly188Arg p.Arg170Ter	Frequent feedings CNGDF	-
014	26.9	F	25.6	c.247C > T c.187T > C	p.Arg83Cys p.Trp63Arg	Frequent feedings Glycosade	3.2
015	19.3	M	23.0	c.247C > T c.187T > C	p.Arg83Cys p.Trp63Arg	Frequent feedings Glycosade	3.1
017	18.3	M	26.6	c.247C > T c.866G > A	p.Arg83Cys p.Ser289Asn	Frequent feedings UCCS CNGDF	1.9
020	48.3	M	26.9	c.809G > T c.1039C > T	p.Gly270Val p.Gln347Ter	Frequent feedings UCCS Glycosade	2.3
Healthy volunteers	22.4 (17.1-50.8)[c]	5 M/5 F	23.2 (19.8-28.9)[c]	—	—	—	—

Abbreviations: CNGDF, continuous nocturnal gastric drip-feeding; F, female; M, male; UCCS, uncooked corn starch; N.A., not available.
[a]Glycosade during the day.
[b]CNGDF overnight.
[c]Data are given as median (range).

Overnight TIR (glucose values ≥ 3.9 and ≤ 10.0 mmol/L) was lower, and TAR (glucose values > 10.0 mmol/L) was higher in patients with GSDIa compared to healthy volunteers. No substantial difference in GV, TIR, and TAR was noted when stratifying patients based on their nocturnal dietary regimen [Supplementary Figure 2 (11)].

CGM Glucose Course

Overnight (1.00-5.00 AM) CGM time courses are shown in Figure 2. During 2 nighttime intervals (ie, 2:15-3:00 AM and 4.00-4:30 AM), CGM values were significantly higher in patients with GSDIa compared to healthy volunteers.

Single-Patient Analysis

After comparing the CGM parameters between patients with GSDIa and healthy volunteers, we questioned whether extreme, individual GSDIa patients' CGM outcomes would be associated with extremes in the traditional biomedical markers of metabolic control. As compared with current glycemic goals defined for patients with DM [ie, %CV < 36%, TAR (>10.0 mmol/L) < 25%, TIR (3.9-10.0 mmol/L) > 70%, TBR (<3.9 mmol/L) < 4%, TBR (<3.0 mmol/L)] (6), all GSDIa patients met these targets, except patients 002, 014, and 015 who showed higher TBRs (Table 3). Based on the individual descriptive measures and outcomes of glycemic control, 3 patients with GSDIa were identified who remarkably deviated within the patient cohort (Tables 2 and 3). Participant 007 (compound heterozygote for the c.1039C > T and c.247C > T variants) showed higher median and minimum glucose levels, lower TIR, and higher TAR. Participant 015 (compound heterozygote for the c.247C > T and c.187T > C variants) showed higher GV and TBR and lower TIR. Participant 020 (compound heterozygote for the c.809G > T and c.1039C > T variants) showed lower GV, TBR, and TAR and higher TIR. However, the targets for traditional biomedical markers and diet characteristics were met in these 3 patients [Table 4; also see Supplementary Table 1 (11)]. Comparison of the overnight CGM curves and advanced CGM outcome parameters with those from the other patients with GSDIa revealed a remarkable divergence of participant 007 from the 95% CI of the other patients with GSDIa (Fig. 3), while the CGM curves from participant 015 and participant 020 showed a large overlap with those from the other patients with GSDIa (data not shown).

Assessment of the first- and second-order derivatives curves showed that the fluctuations in CGM values (first-order derivative) and the speed of such fluctuations (second-order derivative) were higher in participants 007 and 015, compared to their matched healthy volunteers. Conversely, both curves

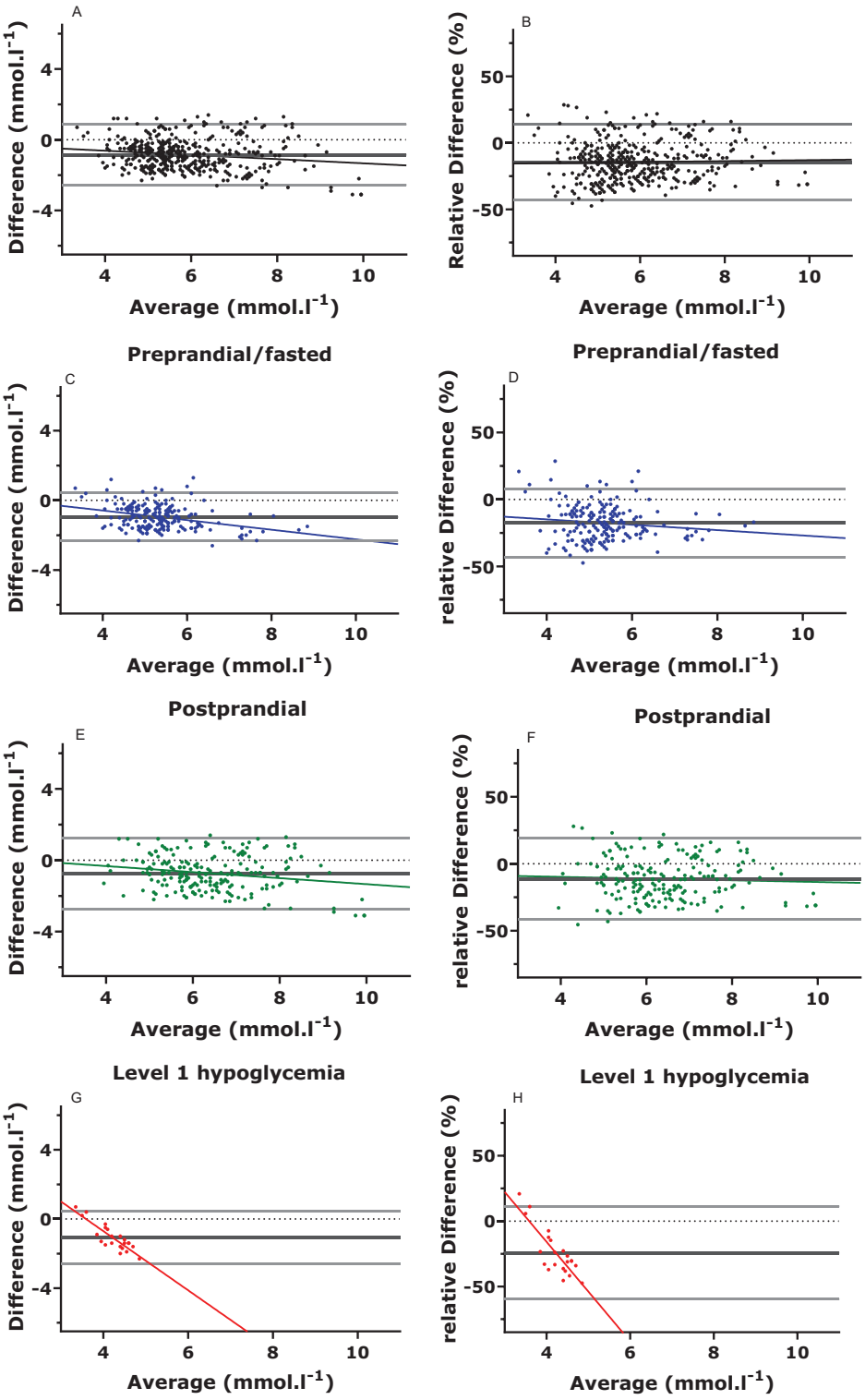

Figure 1. Bland-Altman plots. Difference between continuous glucose monitoring (CGM) values and capillary blood glucose (CBG) measured by the Freestyle Freedom Lite (Abbott, Chicago, IL, USA) device, expressed as absolute (A, C, E, G, I, and K, in mmol/L) and relative (B, D, F, H, J, and L, in %) values. Y-axis shows the absolute (A, C, E, G, I, and K) or relative (B, D, F, H, J, and L) difference between CBG and CGM values at each study time point. X-axis shows the average glucose value at each study time point. Bias (black thick line), 95% CI (grey thin lines), and regression line (diagonal line, various colors) are shown. (A and B) Data were collected under preprandial/fasted [n = 200 (ie, 10 time points × 20 participants)] and fed [n = 200 (ie, 10 time points × 20 participants)] conditions. (C and D) Data were collected under preprandial/fasted conditions [n = 200 (ie, 10 times points × 20 participants)]. (E and F). Data were collected under postprandial conditions [n = 200 (ie, 10 times points × 20 participants). (G and H) Data were collected under level 1 hypoglycemia (ie, capillary glucose values ≥ 3.0 mmol/L and < 3.9 mmol/L; n = 22. (I and J) Data were collected in patients with glycogen storage disease type Ia (n = 200). (K and L) Data were collected in healthy volunteers (n = 200). (A) Bias: −0.85 ± 0.87; Slope: −0.119 ± 0.037 ($P < 0.01$). (B) Bias: −14.50 ± 14.70; Slope: −0.363 ± 0.629 ($P > 0.05$). (C) Bias: −0.96 ± 0.70; Slope: −0.28 ± 0.06 ($P < 0.001$). (D) Bias: −17.6 ± 13.1; Slope: −2.0 ± 1.1 ($P = 0.06$). (E) Bias: −0.74 ± 1.01; Slope: −0.17 ± 0.06 ($P < 0.01$). (F) Bias: −11.4 ± 15.5; Slope: −0.6 ± 0.9 ($P = 0.50$). (G) Bias: −1.08 ± 0.79; Slope: −1.71 ± 0.22 ($P < 0.001$). (H) Bias: −24.2 ± 18.1; Slope: −38.1 ± 5.6 ($P < 0.001$). (I) Bias: −0.16 ± 0.05; Slope: −0.83 ± 0.97 ($P < 0.01$). (J) Bias: −0.19 ± 0.86; Slope: −13.82 ± 16.82 ($P = 0.82$). (K) Bias: −0.03 ± 0.06; Slope: −0.87 ± 0.74 ($P = 0.60$). (L) Bias: −1.56 ± 0.95; Slope: −15.07 ± 12.10 ($P = 0.10$).

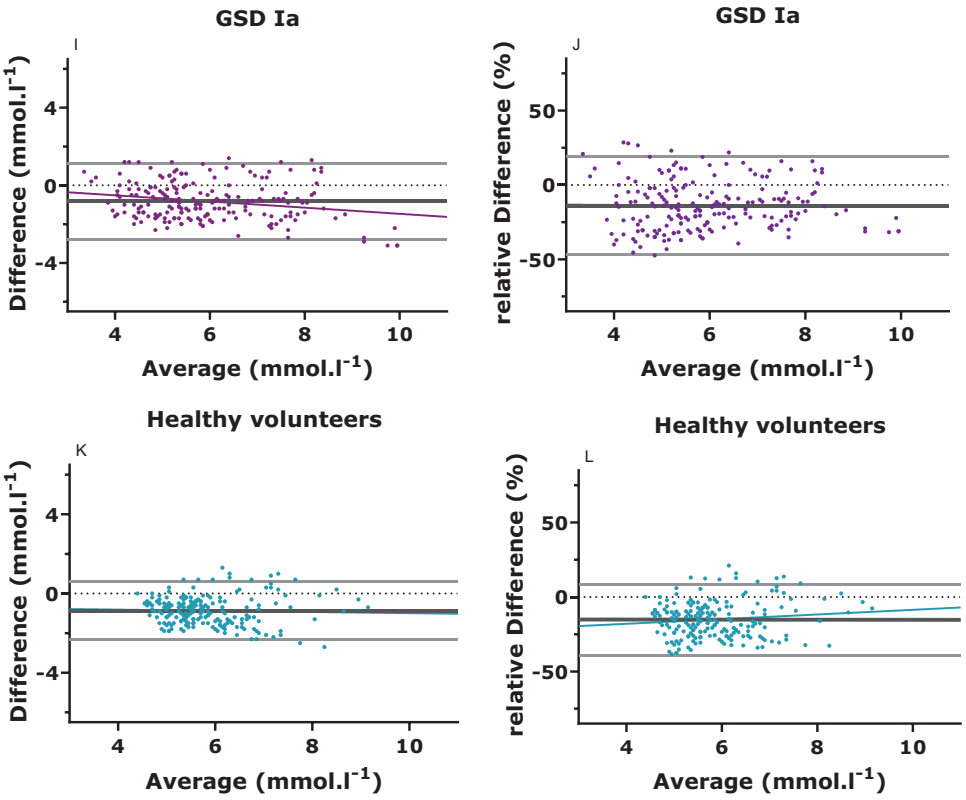

Figure 1. Continued.

showed overlapping trends when comparing participants 020 (patient with GSDIa) and 018 (matched healthy volunteer) [Supplementary Figure 3 (11)]. The Fourier analysis showed higher amplitude in all 3 patients with GSDIa compared to their respective matched healthy volunteer. Remarkably deviant patterns on specific days (compared to the other days) were noted in healthy volunteers, while figures appeared more consistent in each single patient. Still, wide differences between patients could be noted. A pattern with limited number of frequencies (indicating more stable glucose concentrations) was noted on 5/10 days in participant 020, 3/10 days in participant 015, and 1/8 days in participant 007 [Supplementary Figure 4 (11)].

Discussion

Despite the benefit of CGM in patients with hepatic GSDs has previously shown (8, 9), glycemic targets for CGM-derived outcomes have not yet been defined in patients with GSDIa. This is the first prospective study to compare CGM outcomes between adult patients with GSDIa and matched healthy volunteers. Compared to healthy volunteers, the 24-hour CGM profiles of patients with GSDIa revealed significantly more time spent in level 1 hypoglycemia, more time spent in "above-range" glucose (>10.0 mmol/L) and less time "in range" (glucose values ≥ 3.9 and ≤ 10.0 mmol/L), whereas GV was increased. No level 3 hypoglycemia was observed. In contrast to the 24-hour measurement, where 6/10 patients with GSDIa displayed level 2 hypoglycemia, only 1/10 patients with GSDIa demonstrated level 2 hypoglycemia between 1.00 and 5.00 AM. These data show that dietary management can be effective for preventing level 3 hypoglycemia (ie, low glucose levels associated with mental or physical functioning impairment) and (most of) level 2 hypoglycemia. Interestingly, patients with GSDIa displayed higher overnight maximum glucose, GV, and TAR (>10.0 mmol/L) and lower TIR (glucose values ≥ 3.9 and ≤ 10.0 mmol/L) than healthy volunteers.

CGM-derived outcome parameters are increasingly recognized to assess the efficacy of (novel) dietary and/or pharmacological treatments in patients with DM (15-17). Previous studies demonstrated the feasibility of CGM in patients with hepatic GSDs, and evidence on the benefit of CGM use in patients with hepatic GSDs is accumulating (8, 9, 18, 19). Monitoring glucose levels at home, alarming tools, and real-time CGM data sharing with caregivers and healthcare professionals significantly improves hypoglycemia awareness and allows for treatment optimization (9, 18, 19). However, the definition of CGM outcome parameters (such as the time spent in the low range), the type of devices used, the duration of monitoring, and the study population characteristics varied among the previous studies in patients with hepatic GSDs. Those studies showed that historical CGM results can be used as a reference for monitoring individual patients with hepatic GSD before and after therapeutic interventions (9, 10, 18, 19).

In the current study, CGM metrics were prospectively generated in a GSDIa population and compared to a group of matched healthy volunteers. As a result, these data will provide guidance in interpreting CGM data in individual patients with GSDIa and will be useful for the definition of glycemic targets for this patient cohort. Results on healthy volunteers herein presented are comparable to reference values which

Table 2. Continuous glucose monitoring median, minimum, maximum glucose values, and outcomes of glycemic variability in the study participants

Participant	Time points, n	Days/ nights, n	Descriptive outcomes, mmol/L			Glycemic variability		
			Median, mmol/L	Min, mmol/L	Max, mmol/L	SD, mmol/L	Variance, $mmol^2/L^2$	CV, %
001								
24 hours	2845	10	6.2	2.8	11.0	1.4	1.9	21.3
1:00-5:00 AM	480	10	7.2	4.9	11.0	1.1	1.3	15.7
002								
24 hours	1206	4	5.4	2.2	9.3	1.2	1.4	21.5
1:00-5:00 AM	192	4	5.0	3.3	7.7	0.8	0.7	16.6
004								
24 hours	2802	10	5.4	2.4	9.2	1.0	1.0	17.9
1:00-5:00 AM	480	10	5.4	3.7	8.2	0.7	0.5	13.1
006								
24 hours	2612	9	6.7	2.8	17.0	1.7	2.8	24.7
1:00-5:00 AM	437	9	6.8	3.7	10.0	1.2	1.3	16.8
007[a]								
24 housr	2207	8	7.6	3.7	13.0	1.5	2.2	19.2
1:00-5:00 AM	384	8	8.0	4.6	12.4	1.7	2.8	20.6
009[a]								
24 hours	2851	10	5.4	3.0	10.4	1.3	1.6	22.2
1:00-5:00 AM	480	10	5.1	3.7	7.0	0.6	0.3	11.5
014								
24 hours	2480	9	5.6	2.7	13.8	1.7	2.9	28.5
1:00-5:00 AM	432	9	5.0	3.2	10.0	1.4	1.9	25.3
015								
24 hours	2856	10	5.7	2.2	13.9	1.9	3.5	32.0
1:00-5:00 AM	490	10	4.9	2.4	8.9	1.6	2.6	30.6
017[a]								
24 hours	2713	10	5.7	2.2	10.0	1.1	1.2	19.0
1:00-5:00 AM	480	10	5.9	3.2	8.3	0.9	0.8	15.0
020								
24 hours	2932	10	5.7	3.2	9.7	1.0	0.9	16.7
1:00-5:00 AM	461	10	5.9	3.4	8.2	0.8	0.7	14.0
GSDIa[b]								
24 hours	25 504	90	5.9 (5.5-6.4)	2.7 (2.4-3.0)	11.7 (10.1-13.3)	1.4 (1.2-1.6)[c]	1.9 (1.4-2.5)[c]	22.3 (20.0-24.6)[c]
1:00-5:00 AM	4264	90	5.9 (5.3-6.6)	3.6 (3.2-4.1)	9.2 (8.1-10.3)[c]	1.1 (0.8-1.3)[c]	1.3 (0.7-1.9)	17.9 (14.2-21.6)[c]
Healthy volunteers[b]								
24 hours	27 153	96	5.7 (5.4-6.0)	2.8 (2.4-3.2)	10.4 (9.9-10.9)	1.0 (0.9-1.1)	1.0 (0.8-1.1)	16.5 (15.8-17.2)
1:00-5:00 AM	4616	96	5.6 (5.3-6.0)	3.7 (3.1-4.3)	7.3 (6.6-8.0)	0.6 (0.4-0.8)	0.5 (0.1-0.8)	10.7 (8.2-13.2)

Abbreviation: CV, coefficient of variation; GSDIa, glycogen storage disease type Ia.
[a]GSDIa patients receiving continuous nocturnal gastric drip-feeding.
[b]For descriptive and glycemic variability measures mean (95% CI) are shown.
[c]Significant difference between GSDIa patients and healthy volunteers.

have been recently generated for various CGM outcomes in healthy individuals (age ≥ 7 years) (20), except lower 24-hour TBR and higher 24-hour TAR and lower overnight TBR and TAR found in the present study [Supplementary Table 2 (11)].

GV is an independent risk factor for macro- and microvascular complications in DM (21). A wide GV correlates with the risk of developing cardiovascular and microvascular complications (22). The latter includes DM-related kidney disease (23), which shares a common pathogenesis with GSDIa-related kidney disease (24). Circulating glucose concentrations are important biomarkers to monitor the hepatic GSD disease course and (over)treatment of GSDIa (25). By

Table 3. Outcomes of glycemic control in the study participants

Participant	Time points, n	Days/nights, n	TBR, %		TIR, %		TAR, %	
			<3.0 mmol/L	≥ 3.0 to <3.9 mmol/L	≥ 3.9 to ≤7.8 mmol/L	≥3.9 to ≤10.0 mmol/L	>7.8 mmol/L	>10.0 mmol/L
001								
24 hours	2845	10	0.1	1.1	82.1	97.9	16.7	1.0
1:00-5:00 AM	480	10	0.0	0.0	76.9	96.9	23.1	3.1
002								
24 hours	1206	4	0.6	5.1	89.6	94.3	4.7	0.0
1:00-5:00 AM	192	4	0.0	4.2	94.8	94.8	0.0	0.0
004								
24 hours	2802	10	0.4	2.1	95.8	97.5	1.7	0.0
1:00-5:00 AM	480	10	0.0	0.4	98.1	98.8	0.6	0.0
006								
24 hours	2612	9	0.0	1.0	80.9	95.6	17.8	3.2
1:00-5:00 AM	437	9	0.0	0.5	83.1	98.2	15.1	0.0
007[c]								
24 hours	2207	8	0.0	0.1	56.8	92.5	42.7	7.1
1:00-5:00 AM	384	8	0.0	0.0	44.3	86.2	53.6	11.7
009[c]								
24 hours	2851	10	0.0	3.8	89.3	95.7	6.6	0.2
1:00-5:00 AM	480	10	0.0	1.0	96.9	96.9	0.0	0.0
014								
24 hours	2480	9	0.2	4.4	79.9	92.3	15.0	2.6
1:00-5:00 AM	432	9	0.0	2.8	88.4	94.4	6.0	0.0
015								
24 hours	2856	10	1.8	10.7	73.6	84.1	13.3	2.8
1:00-5:00 AM	490	10	8.8	12.2	72.9	76.1	3.3	0.0
017[c]								
24 hours	2713	10	0.9	1.9	92.8	96.6	3.9	0.0
1:00-5:00 AM	480	10	0.0	1.0	93.8	95.6	1.9	0.0
020								
24 hours	2932	10	0.0	1.0	96.1	99.0	2.9	0.0
1:00-5:00 AM	461	10	0.0	0.4	98.3	99.6	1.3	0.0
GSD Ia[a]								
24 hours	25 504	90	0.5 (0.0-0.8)	3.4 (1.2-5.0)[b]	82.6 (76.3-91.1)	94.2 (91.8-97.2)[b]	13.5 (4.5-20.1)	1.9 (0.3-3.1)[b]
1:00-5:00 AM	4264	90	1.0 (0.0-2.6)	2.2 (0.0-4.7)	86.1 (74.4-95.2)	95.4 (89.3-98.3)[b]	10.7 (0.0-21.0)	1.4 (0.9-6.1)[b]

Table 3. Continued

Participant	Time points, n	Days/nights, n	TBR, %		TIR, %		TAR, %	
			<3.0 mmol/L	≥ 3.0 to <3.9 mmol/L	≥ 3.9 to ≤7.8 mmol/L	≥3.9 to ≤10.0 mmol/L	>7.8 mmol/L	>10.0 mmol/L
Healthy volunteers[a]								
24 hours	27 153	96	0.2 (0.0-0.2)	0.7 (0.3-1.1)	92.6 (89.4-96.6)	98.8 (98.6-99.4)	6.4 (2.2-10.2)	0.2 (0.1-0.3)
1:00-5:00 AM	4616	96	0.1 (0.0-0.1)	0.6 (0.0-1.4)	95.9 (90.5-100)	99.3 (98.5-100)	3.3 (0.0-8.8)	0.0 (0.0-0.0)

For each glycogen storage disease type Ia (GSDIa) patient and cumulatively in the GSDIa study population and healthy volunteers TBR, TIR, and TAR represent the percentage of time calculated either on all time points (24 hours) or on time points within the interval 1:00-5:00 AM.
Abbreviations: TBR, time below range; TIR, time in range; TAR, time above range.
[a]For TBR, TIR and TAR mean and 95% CI (in brackets) are shown.
[b]Significant difference between GSDIa patients and healthy volunteers.
[c]GSDIa patients receiving continuous nocturnal gastric drip-feeding.

means of CGM, Kasapkara et al demonstrated that the decreased number of hypoglycemic events following a dietary intervention in patients with GSDI was associated with a reduction in liver size and improvement of multiple disease biomarkers, such as blood lactate and triglyceride levels (9). In a cohort of 14 patients with GSDI monitored by CGM, Kaiser et al showed that an increased TBR (defined as glucose < 4.0 mmol/L) and more daily hypoglycemic events were associated with the presence of liver adenomas or microalbuminuria in patients with GSDI (26).

Besides GV, parameters of glycemic control (ie, TBR, TIR, and TAR) are established prognostic markers in DM (6, 27, 28). In the present study, patients with GSDIa demonstrated lower TIR and higher TAR compared to healthy volunteers. This may be explained by the combination of (1) higher GV and (2) differences between CGM curves during the day and night. Multiple factors may influence glucose homeostasis and CGM parameters, such as dietary intake, exercise, medication, and time frame duration. The relationship between CGM results and dietary intake was not an objective of present study, but the dietary regimen may cause (counter)regulatory responses of glucose homeostasis due to disproportionate (ie, excessive or insufficient) carbohydrate intake and/or imbalanced meal/UCCS schedules. In this respect, dietary overtreatment may account for the higher overnight TAR observed in patients with GSDIa in the present study. CNGDF likely results in fluctuating CGM curves possibly showing in-range TIR and TAR but associated with higher glucose variability due to the combination of intermittent gastric emptying, intestinal glucose absorption, and hormonal reactions (10). Future studies are warranted to assess the prognostic role of CGM-derived parameters as well as their value in forecasting acute hypoglycemia in patients with GSDIa.

Analysis of descriptive CGM outcome parameters allowed us to identify 3 patients with GSDIa who differed remarkably from the patient and healthy volunteer reference populations in the present study. The Fourier analysis also revealed clearly different patterns when comparing each of the 3 participants with their matched healthy volunteer. To assess the reliability of novel CGM-derived parameters, information on the traditional biochemical and dietary targets was collected. In this small sample size study, most of the traditional biomedical targets were met in these 3 patients with GSDIa, not allowing any major differentiation among them. Whether longer duration of CGM would enable further assessment of the correlation between CGM outcome parameters and traditional biomedical outcomes remains to be established.

The present study showed an overall agreement between CBG and CGM values. Yet, a mean glucose difference of −1.08 ± 0.79 mmol/L (ie, CGM overestimation) was observed during level 1 hypoglycemia. Previous work has shown satisfactory agreement between CBG and CGM values in patients with hepatic GSDs, in whom MiniMed (Medtronic) and Dexcom G4 Platinum (Dexcom) devices were used, respectively (9, 19). However, smaller mean differences between CBG and CGM values were found in those previous studies compared to the present study (0.20-0.23 mmol/L vs 0.85 mmol/L). We hypothesize that the larger differences in CBG and CGM may be related to the postprandial sampling in the current study. The higher difference between CBG and

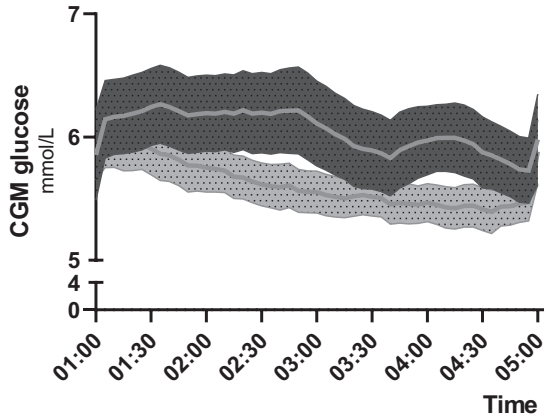

Figure 2. Overnight continuous glucose monitoring (CGM) values in all glycogen storage disease type Ia patients (dark grey) and healthy volunteers (light grey). Mean (thick line) and 95%CI (shaded area) are shown. X-axis shows the time period (ie, 1:00-5:00 AM). Y-axis shows the CGM values.

CGM observed during level 1 hypoglycemia may be due to the swift changes in glucose levels occurring in this situation.

Several limitations of this study need to be addressed. First, a relatively small number of patients with GSDIa was studied. Therefore, it is unclear whether the current sample size adequately reflects the large clinical and biochemical heterogeneity present in patients with GSDIa (4). No apparent correlation between the severity of hypoglycemia and the genotype (ie, predicted residual glucose 6-phosphatase-α activity based on the *G6PC1* variant) was noted. Second, the number of measurements that are minimally required to obtain a reliable CGM profile in patients with GSDIa remains to be established. In patients with DM, 14-day data collection is recommended to adequately predict GV over a 3-month period (29). The setup of the current study did not allow us to establish a similar time frame for patients with GSDIa. Third, a 6-hour interval (ie, 12:00-6:00 AM) is usually considered for the overnight period in patients with DM (6). As patients with GSDIa usually receive UCCS every 4 to 6 hours (3), a 4-hour overnight interval (ie, 1:00-5:00 AM) was considered in the present study. Third, additional factors (eg, dietary intake, physical activity, emotional stress) known to affect glucose concentrations were not systematically recorded in the present study. Fourth, per manufacturer instructions, the Dexcom G6 does not require calibration (30). Yet, it is possible that the instrument's accuracy varies within the initial days after sensor insertion. Fifth, although participants with a BMI > 30 kg/m^2 were excluded from the present study, subcutaneous fat may impact on the equilibrium between interstitial glucose concentrations and the blood compartment, affecting the CGM accuracy in participants with relatively large subcutaneous fat depots (31). In this respect, sensor location (ie, upper arm vs abdomen) may impact accuracy. Finally, to date, not all CGM parameters can be directly derived from the Dexcom CLARITY Clinical Portal but require additional data processing, potentially limiting their immediate use.

Clinical studies in patients with hepatic GSD have traditionally employed multiple outcome parameters to assess clinical efficacy, such as glycemic responses during invasive in vivo starch load tests (NCT02318966) or controlled fasting challenges (NCT03517085, NCT05139316). The

Table 4. Traditional biomarkers and dietary information for participants 007, 015, and 020

Participant	Preprandial capillary glucose, mmol/L	BMI, SDS	TG, mmol/L	UA, mmol/L (Ref 0.20-0.45)	UCCS, g/kg/6 hours	Interval between UCCS doses/24 hours, hours	CNGDF, % daily TEI
Reference target							
Rake et al 2002 (14)	>3.5-4.0	0.0/+2.0	<6.0	High normal range	1.5-2.0		25-30
Kishnani et al. 2014 (3)	>4.0				1.7-2.5	4-6	
007	3.7-6.3	+1.5	3.4	0.52	1.0 Glycosade	3-4 during the day	33 (CH: 25 g/hour = 4 mg/kg/min)
015	3.6-5.7	+0.1	3.3	0.37	1.0 Glycosade	6-7 during the day and night	n.a.
020	3.8-4.7	+1.0	4.2	0.18	1.1 UCCS Glycosade	3 hours during the day 7 hours in the night	n.a.

Abbreviations: CH, carbohydrates; CNGDF, continuous nocturnal gastric drip feeding; n.a., not applicable; SDS, SD score, TEI, total energy intake; TG, triglycerides, UA, uric acid, UCCS, uncooked corn starch.

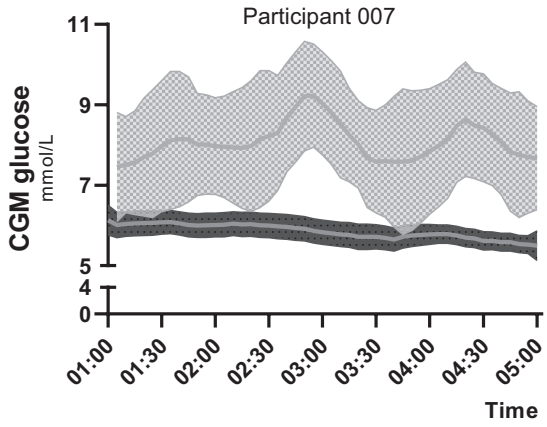

Figure 3. Overnight continuous glucose monitoring (CGM) course in participant 007 (light grey), compared to the average CGM values of the remaining 9 glycogen storage disease type Ia patients (dark grey). Mean (thick line) and 95%CI (shaded area) are shown. X-axis shows the time period (ie, 1:00-5:00 AM). Y-axis shows the CGM values.

development of CGM-derived outcome parameters is particularly relevant as clinical trials with novel medical (32) (NCT03517085, NCT05139316, NCT05095727) and dietary (NCT02318966) treatments are currently being performed. The results of this study further support the application of CGM as a (additional) monitoring tool in both regular healthcare and clinical research. Future work may address the application of CGM as an educational tool to detect hypoglycemia unawareness, for example, by integrating the CGM data with a diary on disease symptoms. This appears particularly relevant as hypoglycemia unawareness contributes to disease burden in GSDIa (33). CGM-derived algorithms allow for hypoglycemia prediction, detection, and prevention of (medical/dietary) under- or overtreatment and unrecognized hypoglycemia in patients with DM (34). The development of GSD-specific algorithms through machine learning approaches offers opportunities to increase GSDIa patients' safety by early warning and further improvement of (self-) management.

In summary, this study has generated the first prospectively collected CGM metrics in patients with GSDIa, which can be used to improve monitoring of individual patients with GSDIa (both in regular healthcare and clinical research) and to support precision medicine in this group of patients. Particularly, these data will be useful for the definition of glycemic targets for CGM in patients with GSDIa. Ideally, individual GSDIa patients' CGM parameters could be compared with the patient's historical CGM data as well as CGM data from both a matched patients' cohort and matched healthy volunteers. To ensure proper interpretation of CGM results, we advise that CGM data collected should be separately analyzed and compared during day- and nighttime intervals.

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Author Contributions

A.R., G.P., M.H.O., and T.G.J.D. designed research. A.R., P.H., M.H.O., and T.G.J.D. conducted research. A.R., A.V., P.H., L.F., R.B., D.R.B., G.P., and M.H.O., analyzed data. A.R., A.V., M.H.O., and T.G.J.D. wrote the first version of the manuscript. P.H., L.F., R.B., C.D., D.R.B., G.P., M.H.O., and T.G.J.D. critically reviewed the manuscript. T.G.J.D. is responsible for design, writing, and final content. All authors have read and approved the final manuscript.

Clinical Trial Information

Clinical Trial Registry number: NCT04311307.

Disclosures

The authors have nothing to disclose.

Data Availability

Data analyzed during the current study are available from the corresponding author on reasonable request.

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