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Published in:
Molecular Genetics and Metabolism

DOI:
10.1016/j.ymgme.2024.108573

Molecular Genetics and Metabolism 143 (2024) 108573

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Continuous glucose monitoring metrics in people with liver glycogen storage disease and idiopathic ketotic hypoglycemia: A single-center, retrospective, observational study

Ruben J. Overduin [a,1], Annieke Venema [a,1], Charlotte M.A. Lubout [a], Marieke J. Fokkert-Wilts [a], Foekje De Boer [a], Andrea B. Schreuder [a], Alessandro Rossi [a,b], Terry G.J. Derks [a,*]

[a] Department of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands
[b] Department of Translational Medicine, Section of Pediatrics, University of Naples "Federico II", Naples, Italy

ARTICLE INFO

Keywords:
Continuous glucose monitoring
Glycogen storage disease
Idiopathic ketotic hypoglycemia
Person-centered outcomes
Monitoring

ABSTRACT

Background: Cohort data on continuous glucose monitoring (CGM) metrics are scarce for liver glycogen storage diseases (GSDs) and idiopathic ketotic hypoglycemia (IKH). The aim of this study was to retrospectively describe CGM metrics for people with liver GSDs and IKH.

Patients and methods: CGM metrics (descriptive, glycemic variation and glycemic control parameters) were calculated for 47 liver GSD and 14 IKH patients, categorized in cohorts by disease subtype, age and treatment status, and compared to published age-matched CGM metrics from healthy individuals. Glycemic control was assessed as time-in-range (TIR; ≥3.9 - ≤7.8 and ≥3.9 - ≤10.0 mmol/L), time-below-range (TBR; <3.0 mmol/L and ≥3.0 - ≤3.9 mmol/L), and time-above-range (TAR; >7.8 and >10.0 mmol/L).

Results: Despite all patients receiving dietary treatment, GSD cohorts displayed significantly different CGM metrics compared to healthy individuals. Decreased TIR together with increased TAR were noted in GSD I, GSD III, and GSD XI (Fanconi-Bickel syndrome) cohorts (all $p < 0.05$). In addition, all GSD I cohorts showed increased TBR (all $p < 0.05$). In GSD IV an increased TBR ($p < 0.05$) and decreased TAR were noted ($p < 0.05$). In GSD IX only increased TAR was observed ($p < 0.05$). IKH patient cohorts, both with and without treatment, presented CGM metrics similar to healthy individuals.

Conclusion: Despite dietary treatment, most liver GSD cohorts do not achieve CGM metrics comparable to healthy individuals. International recommendations on the use of CGM and clinical targets for CGM metrics in liver GSD patients are warranted, both for patient care and clinical trials.

1. Introduction

Liver glycogen storage diseases (GSDs) are a group of inherited metabolic diseases due to a defect in either an enzyme or a transporter protein involved in glycogen metabolism, resulting in fasting hypoglycemia. Liver GSDs include GSD types 0, I, III, IV, VI, IX, and XI (Fanconi-Bickel syndrome; FBS). The cornerstone of treatment is a personalized and medically prescribed diet including frequent meals, uncooked cornstarch (UCCS) or Glycosade® and/or tube feeding; diet enrichments (protein) or restrictions (fructose, saccharose and galactose) may also be indicated. Metabolic control is monitored by combinations of clinical and biochemical markers [1–7]. Despite current management and monitoring options, people with liver GSD may still develop both acute and long-term complications including hypoglycemia, growth retardation, delayed puberty, liver adenomas, nephropathy and (cardio) myopathy [8]. For some long-term complications, an increased risk has been described to be associated with poorer metabolic control, such as liver adenomas and chronic kidney disease in GSD Ia [9,10].

Abbreviations: CGM, continuous glucose monitoring; CV, coefficient of variation; GSD, glycogen storage disease; IKH, idiopathic ketotic hypoglycemia; IQR, interquartile range; SD, standard deviation; TAR, time-above-range; TBR, time-below-range; TIR, time-in-range; UCCS, uncooked cornstarch.

* Corresponding author at: Department of Metabolic Diseases, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, PO Box 30 01, 9700 RB Groningen, the Netherlands.
E-mail address: t.g.j.derks@umcg.nl (T.G.J. Derks).

[1] Shared first authors

https://doi.org/10.1016/j.ymgme.2024.108573
Received 28 June 2024; Received in revised form 20 August 2024; Accepted 29 August 2024
Available online 30 August 2024

Idiopathic ketotic hypoglycemia (IKH) is considered the most frequent cause of hypoglycemia in childhood [11]. Since the etiology of IKH is unknown, it remains a diagnosis of exclusion. The IKH population is heterogenous, ranging from children with occasional mild ketotic hypoglycemia (termed 'physiological IKH') to people with severe fasting intolerance (termed 'pathological IKH') [12]. Remission of IKH occurs mostly around the age of 6–7 years, but sometimes symptoms persist into adulthood. Treatment is started depending on the severity of symptoms and the preferences of patients, families and their treating healthcare providers. IKH treatment may consist of avoidance of prolonged fasting, frequent meals, UCCS and close monitoring of the dietary intake. To date, no guidelines are available for the diagnosis and management of IKH patients.

Monitoring of blood glucose levels is considered important in both liver GSDs and IKH. This is traditionally done by means of finger stick capillary blood glucose measurements using a portable glucose meter. Several studies have shown the potential of continuous glucose monitoring (CGM) for people with liver GSDs, reducing the duration of hypoglycemic episodes and unveiling unrecognized/asymptomatic hypoglycemia [13,14]. However, it is difficult to compare studies of CGM in people with liver GSDs as studies differ with respect to (a) study design, (b) different (generations of) CGM devices used, (c) different indications for CGM use, and (d) the reported CGM metrics (Table 1) [13–22]. The development of new methods for patient monitoring, such as CGM, has recently been identified as a top research priority for liver GSDs [23]. Subsequently, we have recommended a minimal set of CGM metrics for liver GSDs [19], and we have proposed glycemic targets for GSD Ia [20].

The aim of this study was to retrospectively study CGM metrics in a large cohort of people with liver GSDs and IKH. We questioned if people with liver GSDs or IKH, either with or without dietary treatment, may achieve CGM metrics comparable to healthy individuals.

2. Subjects and Method

2.1. Ethical approval

The Medical Ethical Committee of the University Medical Center Groningen (UMCG) stated that the Medical Research Involving Human Subjects Act was not applicable and that further study approval by the Medical Ethical Committee was not required for retrospective, non-interventional studies (METc 2019/119).

2.2. Study design, CGM system and subjects

This is a single-center, retrospective, observational study performed at the UMCG, Groningen, the Netherlands. In this study a Dexcom G6 (Dexcom, San Diego, California) CGM device was used, as described previously [19]. Individuals were included in the study if they used a Dexcom G6 as part of routine clinical care and either had (i) an enzymatically or genetically confirmed diagnosis of liver GSD, or (ii) a clinical diagnosis of IKH [12]. For each subject the following information was collected from the electronic patient records: disease (sub)type, genotype, sex, age (in years), weight, dietary treatment, medication use, comorbidities, inpatient and outpatient healthcare provider visits, and indication for CGM use.

2.3. Data analysis

CGM metrics (descriptive, glycemic variation, glycemic control) were defined as previously described [19]. Raw CGM data recorded from the 1st of December 2018 onwards were retrieved from the Dexcom CLARITY Clinical Portal (https://clarity.dexcom.eu/professional) and exported on the 28th of April 2022. Data were removed if collected during acute hospitalizations or when other conditions or therapies (except empagliflozin) were present that could significantly affect CGM results and/or glucose homeostasis (e.g., diabetes mellitus, pregnancy, and prednisolone use). CGM 'low' readings were replaced by the lowest possible CGM value of 2.2 mmol/L, as removing these values would introduce bias in descriptive statistical analysis. Individuals' CGM data were used for analysis when at least five consecutive days of monitoring were present.

For each individual patient, CGM data were analyzed both in their entirety (pooled data) and in separate intervals. Separate CGM intervals were generated when each data series contained at least five days of CGM data, and based on one of the following conditions: a substantial change in prescribed diet (e.g., >20 % dose-adjustment of UCCS or Glycosade, switching to or from continuous gastric drip feeding), change in medication (e.g., start or change in empagliflozin dose), six months of continuous CGM use, or a period of at least 30 days with no CGM use.

Patient cohorts were formed based on disease (sub)type, treatment status, and age categories (<1, 1–6 and >6 years), as previously described in CGM studies with healthy individuals [24,25]. When applicable, CGM data of an individual was divided into multiple age categories.

2.4. Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics 28. CGM metrics of each individual patient were first calculated using the pooled data. Subsequently, for each cohort, CGM metrics were reported as medians with interquartile ranges (IQR). To minimize the effect of diurnal variations in dietary intake and physical activity on glucose values, CGM metrics were calculated in a 24-h fashion as well as between 1:00 and 5:00 am ("night") [20].

For comparison, raw CGM data of healthy individuals aged >6 years and 1–6 years captured with a Dexcom G6 CGM device, were retrieved from the studies of Shah et al. [24] and DuBose et al. [25], respectively. These data were analyzed similarly to those of the patients with GSD and IKH. For each variable the normality of the distribution was assessed by the Kolmogorov-Smirnov test. As data were not normally distributed, non-parametric tests (Mann-Whitney U) with a significance level of 0.05 were used to assess for differences between patient cohorts and healthy individuals.

After statistical analysis, case studies of individuals with CGM intervals of particular interest were conducted.

3. Results

3.1. General

In total, CGM data from 61 patients were included and analyzed. All 47 liver GSD patients (18 GSD Ia, 8 GSD Ib, 8 GSD III, 3 GSD IV, 9 GSD IX, and 1 FBS) received dietary treatment during CGM. Of the 14 IKH patients, CGM intervals were obtained in 7 patients who did not receive any (dietary) treatment, and in 9 patients with dietary treatment (note, two patients used CGM both with and without dietary treatment). The pooled CGM metrics per individual patient are presented in Supplementary Table S1.

3.2. Cohort study

Figs. 1 and 2, and Table 2 present the median (IQR) for CGM metrics in GSD and IKH cohorts compared to published, age-matched reference values from healthy individuals.

GSD Ia and Ib cohorts were the only cohorts presenting significantly decreased time-in-range (TIR), which was accompanied by both significantly increased time-below-range (TBR) and time-above-range (TAR), compared to healthy individuals. Additionally, the GSD Ia and Ib cohorts aged >6 years displayed significantly increased mean glucose values and glycemic variation.

Both the GSD III and Fanconi-Bickel cohorts aged >6 years displayed

Table 1
Characteristics of cohort studies describing CGM metrics in liver GSD patients.

Reference	Device	Area	Patients, n	Age, range in years	GSD subtype	CGM use, range in days	CGM metrics	Clinical outcomes
Hershkovitz ea. J Inherit Metab Dis. 2001.	MiniMed (Medtronic)	Israel	4	2–15	Ia	3	Glucose (mean ± SD; range) TBR < 4 mmol/L; TBR < 2.8 mmol/L	Symptomatic hypoglycemia
Maran ea. Diabetes MetabRes Rev. 2004.	Glucoday® (Menarini)	Italy	4 1 1	14–47 22 10	Ia Ib III	2	Hypoglycaemia <60 mg/dL min/day	Clinically relevant hypoglycemia
White ea. J Inherit Metab Dis. 2011.	iPro™ (Medtronic)	UK	1 6 2 7 4 2	6 0–13 0–3 4–20 5–16 2–24	0 Ia Ib III IX FBS	2–6	Glucose curves in individual management	Biochemical metabolic parameters (e.g. lactate, ketones, triglycerides)
Kasapkara ea. Eur J Clin Nutr. 2014.	MiniMed (Medtronic)	Turkey	15 1	2–18	Ia Ib	3	Correlations between CBG and CGM Biomedical outcomes before/after	Liver size, biochemical metabolic parameters (e.g. lactate, triglycerides, aminotransferases)
Herbert ea. J Inherit Metab Dis. 2018.	Dexcom G4 Platinum	USA	7 2 6 5	2–56 9–17 6–44 7–17	Ia Ib III IX	3–32	TBR < 70 / 60 / 50 mg/dL TIR 70–150 mg/dL TAR >150 mg/dL Correlation between CBG and CGM	Biochemical metabolic parameters (triglycerides, cholesterol, uric acid)
Kaiser ea. Mol Gen Metab. 2019.	iPRO2® (Medtronic) Guardian® (Medtronic) FreeStyle Libre® (Abbott)	Switzerland	12 2	11–49	Ia Ib	9.4 ± 5.2 (mean ± SD)	Mean, minimum, maximum AUC and TBR <4.0 mmol/L AUC and TAR >8.0 mmol/L	HCA, (micro)albuminuria, low bone density, quality of life (SF-12 questionnaire)
Peeks ea. J Inherit Metab Dis. 2021.	Dexcom G6 Dexcom G4 Dexcom G6	Netherlands	1 12 3	9 2–22 2–11	Ia Ia, III, IX Ib	1–238	Median, minimum, maximum, range, SD, variance, coefficient of variation TBR <3.0 mmol/L; ≥3.0 mmol/L and < 3.9 mmol/L TIR ≥3.9 and ≤ 7.8 mmol/L; ≥ 3.9 and ≤ 10.0 mmol/L TAR >7.8 mmol/L; >10.0 mmol/L	Anthropometrics, liver size, biochemical control parameters (triglyceride, cholesterol)
Rossi ea. J Clin Endocrinol Metab. 2022	Dexcom G6	Netherlands	10	17–53	Ia	4–10	Median, minimum, maximum, range, SD, variance, CV TBR <3.0 mmol/L; ≥3.0 mmol/L and < 3.9 mmol/L TIR ≥3.9 and ≤ 7.8 mmol/L; ≥ 3.9 and ≤ 10.0 mmol/L TAR >7.8 mmol/L; >10.0 mmol/L	Biochemical metabolic parameters (triglycerides, uric acid)
Hsu ea. Mol Genet Genomic Med. 2023	MiniMed (Medtronic)	Taiwan	9	9–33	Ia	7	Mean nighttime and morning glucose levels Low glucose alarm <70 mg/dL	Biochemical profile (e.g. lactate, triglycerides, aminotransferases), sleep quality (PSQI) and quality of life (SF-36 questionnaire)
Fukuda ea. J Inherit Metab Dis. 2023	Dexcom G4	Japan	30	3–52	Ia	14	Mean, minumum, maximum, SD, CV TBR, AUC and frequency < 3.5 mmol/L; <4.0 mmol/L TBR <3.0 mmol/L; <3.9 mmol/L TAR, AUC and frequency > 8.0 mmol/L TAR >7.8 mmol/L	Hyperuricemia, metabolic acidosis, renal disorder, hypertension, hyperlipidemia, hypertriglyceridemia, short stature, symptomatic hypoglycemia

Abbreviations: AUC: area under the curve; CBG: capillary blood glucose; FBS: Fanconi-Bickel syndrome; HCA: hepatocellular adenoma; PSQI: Pittsburgh Sleep Quality Index; TAR: time-above-range; TBR: time-below-range; TIR: time-in-range; SD: standard deviation. Updated and adapted from Rossi et al. [27]

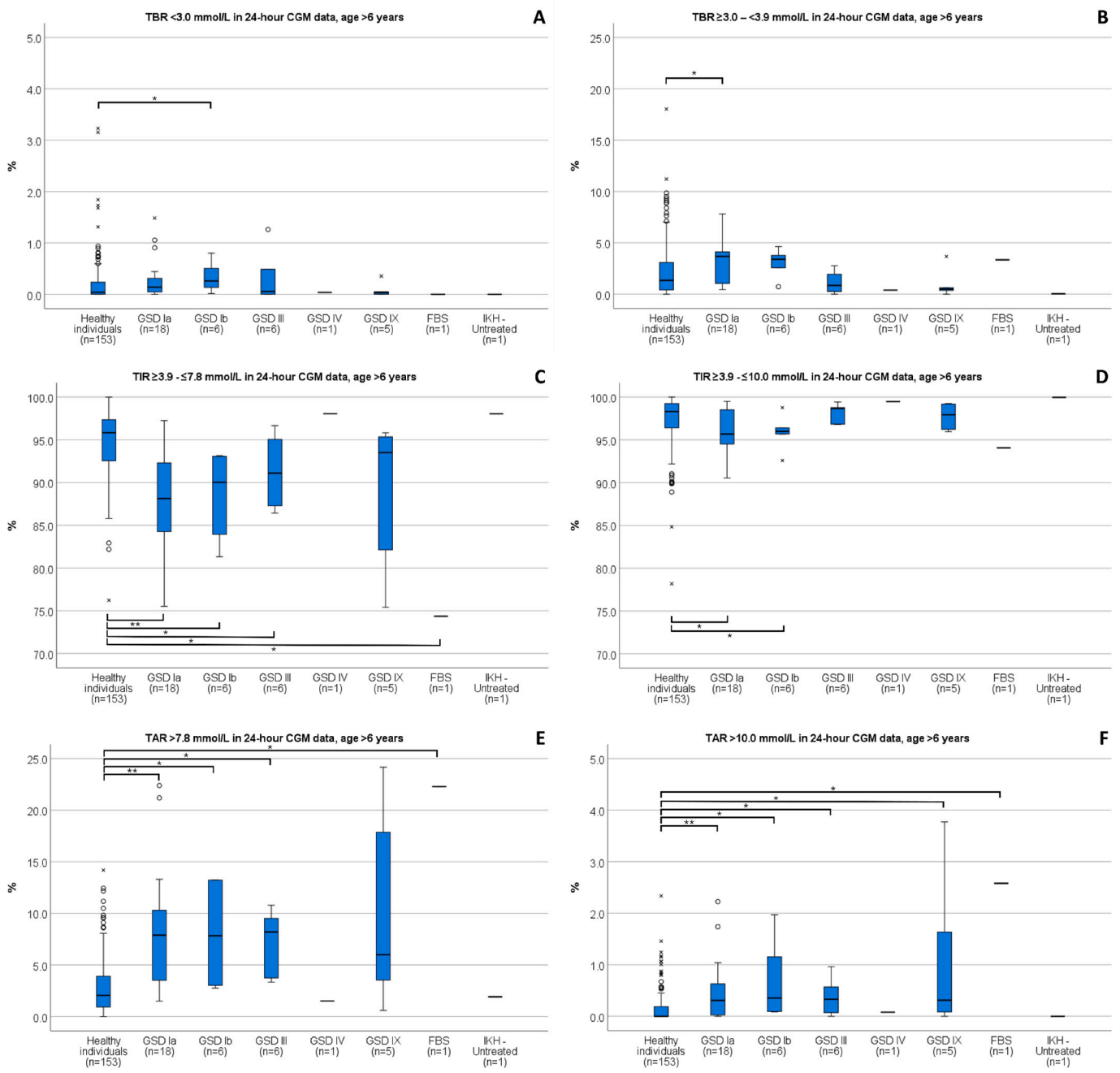

Fig. 1. Boxplots of percentages of time-below-range (A-B), time-in-range (C—D) and time-above-range (*E*-F) of 24-h CGM metrics in people with liver glycogen storage disease and idiopathic ketotic hypoglycemia aged >6 years, compared to healthy individuals from Shah et al. [24]
Box represents p25, p50 and p75 values, and the whiskers represent minimum and maximum values that are not outliers. ○ represents mild outliers, i.e., values that are more than 1.5 times the IQR below p25 or above p75; x represents extreme outliers, i.e., values that are more than 3.0 times the IQR below p25 or above p75. *indicates p-value <0.05. **indicates p-value <0.001.

combinations of significantly decreased TIR, increased TAR, and higher mean glucose values. In the GSD IV cohort aged 1–6 years, significantly increased TBR together with a decreased TAR and lower mean glucose values were observed. The GSD IX cohort aged >6 years had significantly increased TAR.

The IKH cohorts with and without dietary treatment showed CGM metrics comparable to healthy individuals in 24-h data. When only the night-time data were analyzed, the IKH cohort with dietary treatment showed significantly increased glycemic variation.

3.3. Case studies

Table 3 presents the CGM metrics of specific patient intervals used in the case studies (of note, Subject IDs correspond with Supplementary Table S1, in which the pooled CGM metrics from all individual patient intervals are presented per patient).

3.3.1. GSD III

Subject 29, diagnosed with GSD IIIa (homozygous c.4529dupA variants in the *AGL* gene), presented in our center at the age of 8 months with failure to thrive and hepatomegaly. A ketotic GSD type was suspected based on increased transaminases, hyperlipidemia, and

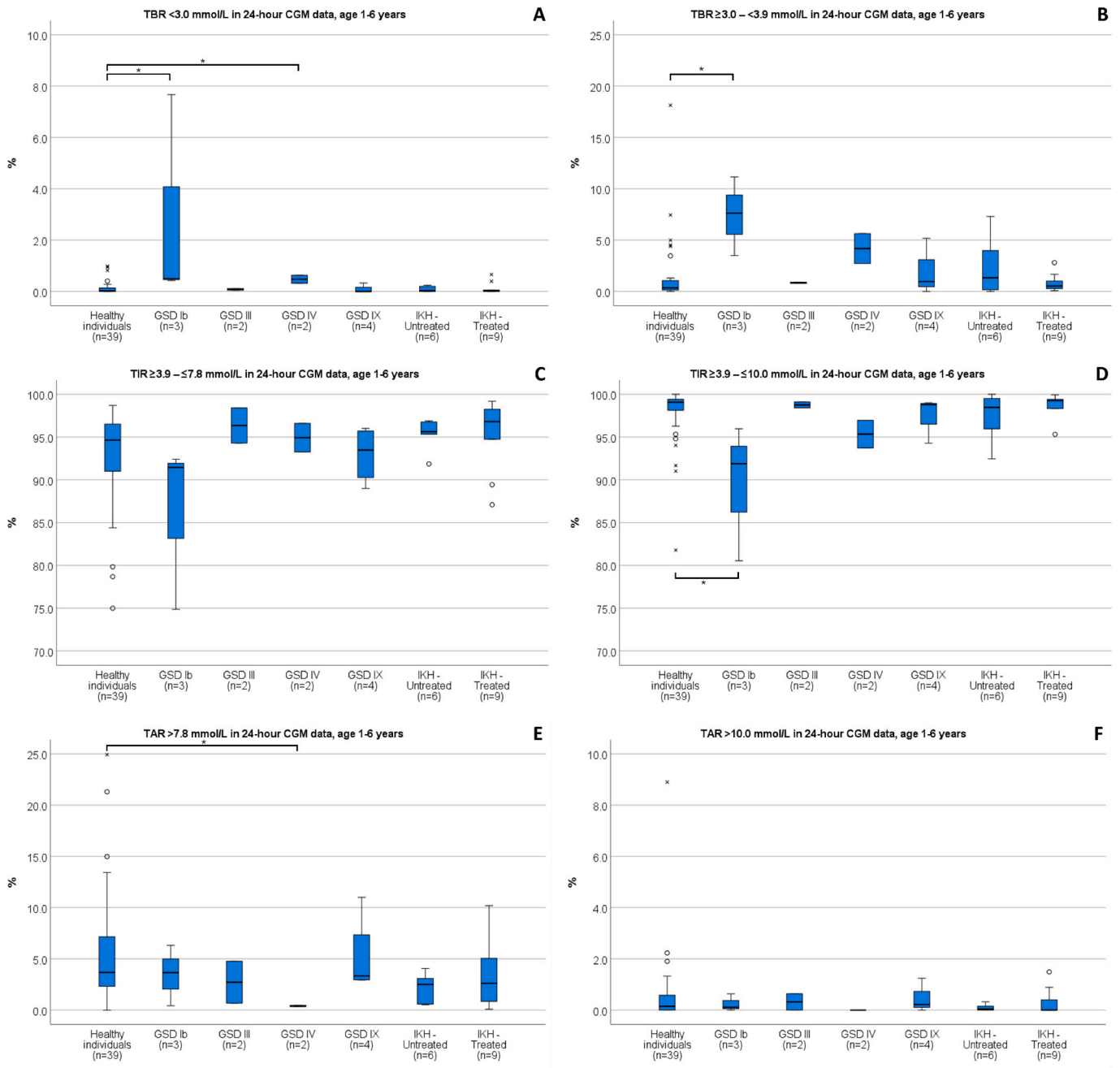

Fig. 2. Boxplots of percentages of time-below-range (A-B), time-in-range (C—D) and time-above-range (E-F) of 24-h CGM metrics in people with liver glycogen storage disease and idiopathic ketotic hypoglycemia aged 1–6 years, compared to healthy individuals from DuBose et al. [25]
Box represents p25, p50 and p75 values, and the whiskers represent minimum and maximum values that are not outliers. ○ represents mild outliers, i.e., values that are more than 1.5 times the IQR below p25 or above p75; x represents extreme outliers, i.e., values that are more than 3.0 times the IQR below p25 or above p75. *indicates p-value <0.05. **indicates p-value <0.001.

preprandial hyperketosis. The patient was hospitalized to introduce dietary management under CGM (interval 29-A). Initially, TBR <3.0 mmol/L and ≥3.0 - <3.9 mmol/L were 4.4 % and 10.8 %, respectively. At 10 months of age, after the diet was fully implemented, CGM was performed in an outpatient setting (interval 29-B), revealing a marked decrease in TBR together with an increased TAR.

In subject 31, diagnosed with GSD IIIa (homozygous c.4529dupA variants in the *AGL* gene), CGM was used to evaluate dietary treatment (interval 31-A). CGM showed markedly higher TAR >7.8 mmol/L (10.8 %), especially during night-time (21.1 %), as compared to the GSD III >6 years patient group and healthy individuals (Table 2). Based on the first four days of CGM data the night-time Glycosade dose was tapered stepwise from 60 to 40 g during the interval, which improved glycemic control. Post-hoc analysis of first two days of CGM data (i.e., before change in diet) revealed TAR >7.8 mmol/L of 22.6 % (24-h) and 50.0 % (night-time), while the final two days of CGM data (i.e., after change in diet) showed TAR >7.8 mmol/L of 2.6 % (24-h) and 0.0 % (night-time).

3.3.2. *Fanconi-Bickel syndrome*

In subject 47, diagnosed with FBS (homozygous c.IVS4-2A>G variants in the *SLC2A2* gene), continuous nocturnal gastric drip-feeding (CNGDF; 0.34 g/kg/h carbohydrate and 0.15 g/kg/h protein content) was initiated during interval 47-A. Fifteen months later (interval 47-B), an evening dose of 60 g of Glycosade and 30 g of protein was prescribed

Table 2
Median (IQR) of CGM metrics in cohorts of people with liver GSD and IKH, and compared to CGM metrics of healthy individuals from Shah et al. [24] (>6y) and DuBose et al. [25] (1-6y) that were analyzed and presented similarly.

Cohort	Age	Time-frame[1]	N	Descriptives		Glycemic variation		Glycemic control					
								TBR		TIR		TAR	
			Participants	CGM records	Mean	SD	CV	<3.0 mmol/L	≥3.0 - <3.9 mmol/L	≥3.9 - ≤7.8 mmol/L	≥3.9 - ≤10.0 mmol/L	>7.8 mmol/L	>10.0 mmol/L
				n	mmol/L	mmol/L	%	%	%	%	%	%	%
GSD Ia	>6y	24h	18	7,008 (2,862-63,365)**	5.9 (5.6-6.2)**	1.2 (1.1-1.4)**	20.3 (18.8-23.4)**	0.14 (0.05-0.35)	3.69 (0.99-4.39)*	88.13 (84.15-92.41)**	95.68 (94.49-98.57)*	7.89 (3.51-10.58)**	0.31 (0.02-0.64)**
		Night	18	1,727 (480-10,572)**	6.2 (5.6-6.8)**	1.1 (0.9-1.3)**	17.4 (14.8-19.2)**	0.04 (0.00-0.51)*	0.76 (0.42-3.09)	91.98 (83.39-95.35)**	98.42 (95.91-99.25)*	4.97 (1.89-16.42)**	0.03 (0.00-0.31)**
GSD Ib	<1y	24h	1	40,543	5.0	1.3	25.6	6.14	13.14	79.16	80.71	1.56	0.01
		Night	1	6,834	4.9	1.2	23.6	6.26	12.45	80.89	81.28	0.40	0.00
	1-6y	24h	3	48,045 (22,003-230,436)**	5.3 (5.0-5.7)	1.1 (0.9-1.6)	19.8 (17.7-30.3)	0.49 (0.43-7.38)*	7.62 (3.49-11.01)*	91.45 (74.86-92.38)	91.88 (80.55-95.81)*	3.66 (0.43-6.21)	0.11 (0.00-0.62)
		Night	3	8,001 (3,705-38,356)**	5.0 (4.8-5.5)	1.1 (0.9-1.2)*	19.9 (18.0-25.1)*	0.77 (0.51-5.07)*	10.44 (4.56-13.33)*	88.48 (79.27-91.71)*	88.79 (81.21-94.68)*	2.04 (0.32-3.04)*	0.00 (0.00-0.08)
	>6y	24h	6	21,068 (13,303-151,708)**	6.0 (5.5-6.2)*	1.2 (1.1-1.5)**	20.5 (20.2-23.3)**	0.26 (0.11-0.58)*	3.41 (2.12-4.00)	90.04 (83.29-93.09)*	96.00 (94.92-96.99)*	7.83 (2.95-13.23)*	0.35 (0.09-1.36)*
		Night	6	3,458 (2,556-25,469)**	6.3 (5.6-6.7)*	1.2 (1.1-1.3)**	19.2 (18.4-21.1)**	0.15 (0.02-0.66)**	1.13 (0.83-2.78)	89.34 (80.17-93.88)**	97.43 (95.70-98.24)	9.43 (2.86-18.41)**	0.76 (0.03-2.00)**
GSD III	<1y	24h	1	6,915	5.2	1.2	23.3	3.09	9.65	85.05	87.16	2.21	0.10
		Night	1	1,152	5.4	1.2	23.3	2.00	7.47	86.02	90.28	4.51	0.26
	1-6y	24h	2	1,899	5.8	1.0	16.6	0.08	0.84	96.35	98.76	2.73	0.32
		Night	2	312	6.1	0.7	11.1	0.00	0.15	98.81	99.85	1.04	0.00
	>6y	24h	6	2,360 (1,045-9,351)	6.1 (6.0-6.2)**	1.1 (1.0-1.3)*	18.4 (16.5-22.0)*	0.06 (0.00-0.68)	0.86 (0.20-2.15)	91.11 (87.07-95.46)*	98.67 (96.83-98.93)	8.20 (3.65-9.83)*	0.33 (0.05-0.67)*
		Night	6	384 (171-1,581)	6.3 (6.1-6.7)**	0.8 (0.6-1.0)	12.0 (9.6-14.8)	0.00 (0.00-0.46)	0.00 (0.00-0.65)	97.42 (89.11-100)	99.55 (98.89-100)	2.13 (0.00-9.60)*	0.00 (0.00-0.22)
GSD IV	1-6y	24h	2	2,666	5.0*	0.8	16.2	0.48*	4.18	94.93	95.35	0.42*	0.00
		Night	2	456	5.0	0.7	14.0	0.35	2.95	96.70	96.70	0.00	0.00
	>6y	24h	1	2,518	5.8	0.7	12.8	0.04	0.40	98.05	99.48	1.51	0.08
		Night	1	432	5.7	0.5	9.3	0.00	0.00	100	100	0.00	0.00
GSD IX	1-6y	24h	4	1,625 (1,406-1,964)*	5.6 (5.4-6.3)	1.1 (1.0-1.2)	19.2 (17.3-21.0)	0.00 (0.00-0.25)	0.96 (0.23-4.13)	93.48 (89.63-95.86)	98.81 (95.40-98.97)	3.34 (2.95-9.18)	0.22 (0.05-0.99)
		Night	4	279 (240-332)*	5.2 (4.8-5.7)	0.7 (0.6-0.8)	13.3 (11.7-17.1)*	0.00 (0.00-1.42)	1.46 (0.00-8.75)	97.05 (89.82-99.27)	98.54 (89.84-100)	0.00 (0.00-2.23)	0.00 (0.00-0.00)
	>6y	24h	5	1,895 (1,465-62,388)	6.0 (5.4-6.9)	1.2 (0.9-1.4)*	19.2 (16.7-19.7)	0.03 (0.00-0.20)	0.50 (0.18-2.15)	93.51 (78.77-95.59)	97.94 (96.10-99.23)	5.99 (2.07-21.02)	0.31 (0.04-2.70)*
		Night	5	336 (264-10,504)	6.0 (5.5-6.6)*	0.9 (0.5-1.1)	15.3 (9.2-17.3)	0.00 (0.00-0.00)	0.00 (0.00-0.42)	98.61 (90.70-99.79)	99.58 (98.28-100)	1.39 (0.00-9.08)	0.00 (0.00-1.50)**
FBS	>6y	24h	1	3,994*	6.7*	1.6*	23.2	0.00	3.36	74.36*	94.07	22.28*	2.58*
		Night	1	672*	6.8*	1.6*	23.2*	0.00	7.29	63.24*	92.26	29.46*	0.45
IKH - Untreated	1-6y	24h	6	1,992 (1,609-2,547)	5.5 (5.0-5.9)	0.9 (0.8-1.0)	17.2 (16.0-17.5)	0.03 (0.00-0.21)	1.32 (0.12-4.81)	95.62 (94.48-96.80)	98.47 (95.10-99.64)	2.52 (0.58-3.34)	0.04 (0.00-0.19)
		Night	6	336 (276-372)*	5.2 (4.7-5.4)	0.5 (0.5-0.6)	10.8 (8.7-16.3)	0.00 (0.00-0.00)	0.42 (0.00-5.72)	98.99 (94.28-100)	99.58 (94.28-100)	0.00 (0.00-0.30)	0.00 (0.00-0.00)
	>6y	24h	1	2,657	5.7	0.8	13.6	0.00	0.04	98.04	99.96	1.92	0.00
		Night	1	432	5.4	0.6	10.7	0.00	0.00	100	100	0.00	0.00
IKH - Treated	1-6y	24h	9	3,942 (1,603-4,933)	5.7 (5.5-5.9)	0.9 (0.8-1.2)	15.5 (14.6-19.8)	0.02 (0.00-0.22)	0.53 (0.25-1.34)	96.80 (92.09-98.38)	99.26 (98.33-99.55)	2.61 (0.69-7.38)	0.00 (0.00-0.65)
		Night	9	632 (264-837)	5.5 (5.2-5.7)	0.7 (0.6-0.9)*	12.6 (10.6-16.3)*	0.00 (0.00-0.00)	0.45 (0.00-1.19)	98.33 (96.71-99.83)	99.55 (98.81-100)	0.35 (0.00-1.95)	0.00 (0.00-0.00)
Healthy controls	1-6y	24h	39	2,474 (2,016-3,746)	5.8 (5.5-6.1)	1.0 (0.9-1.1)	16.2 (15.6-18.8)	0.02 (0.00-0.14)	0.35 (0.10-1.08)	94.65 (90.95-96.65)	99.07 (98.01-99.41)	3.68 (2.20-7.67)	0.15 (0.00-0.66)
		Night	39	432 (336-624)	5.3 (5.1-5.6)	0.5 (0.4-0.7)	9.8 (8.5-13.0)	0.00 (0.00-0.00)	0.42 (0.00-1.49)	99.07 (95.38-100)	99.37 (97.14-100)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
	>6y	24h	153	2,395 (2,164-2,561)	5.5 (5.3-5.8)	0.9 (0.8-1.0)	16.0 (14.4-18.3)	0.04 (0.00-0.24)	1.35 (0.41-3.11)	95.84 (92.44-97.37)	98.32 (96.37-99.26)	2.06 (0.93-4.01)	0.00 (0.00-0.20)
		Night	153	421 (374-444)	5.4 (5.1-5.7)	0.6 (0.5-0.7)	11.0 (9.2-13.8)	0.00 (0.00-0.00)	0.46 (0.00-2.58)	98.79 (95.21-100)	99.51 (96.80-100)	0.00 (0.00-0.43)	0.00 (0.00-0.00)

CGM metrics with statistical significant differences compared to healthy individuals are color-coded: blue when p-value <0.05 and median is lower than median value of healthy individuals, red when p-value <0.05 and median is higher than median value of healthy individuals. Grey cells: no comparison could be made as no data from healthy controls aged <1 year were available; the reference cohorts of healthy controls are also grey-colored.
*indicates *p*-value <0.05. **indicates p-value <0.001.
[1]Night is defined as: 01:00 am till 05:00 am.
Abbreviations: CV: Coefficient of Variation; TAR: time-above-range; TBR: time-below-range; TIR: time-in-range; SD: Standard Deviation; y: year.

to bridge 8 hours of sleep as an alternative to CNGDF. A clear shift towards higher glucose values was observed in the second interval.

3.3.3. IKH

In subject 48, CGM was used for outpatient glucose evaluation (interval 48-A). CGM metrics showed high TBR ≥3.0 - <3.9 mmol/L in both 24-h data (7.3 %) and night-time (5.9 %) compared to the healthy population. This CGM data, combined with measurements of early-morning capillary blood glucose (range 3.5–4.3 mmol/L) and ketones (range 0.1–0.6 mmol/L) over 7 days, led to the initiation of dietary management. After fasting duration was restricted to 10.5 hours and night-time UCCS (20 g) was introduced, parents reported their son to be

Table 3
CGM metrics of individual intervals in GSD and IKH subjects, compared to interquartile ranges of healthy individuals [24,25] and patient cohorts.

Subject ID – CGM Interval	Patient characteristics				CGM use			Descriptives	Glycemic variation		Glycemic control					
											TBR		TIR		TAR	
	Patient cohort	Sex	Age	Summary of Diet/treatment	CGM Indication	Days of CGM	Time frame[1]	Mean	SD	CV	<3.0 mmol/L	≥3.0 - <3.9 mmol/L	≥3.9 - ≤7.8 mmol/L	≥3.9 - ≤10.0 mmol/L	>7.8 mmol/L	>10.0 mmol/L
			y			n		mmol/L	mmol/L	%	%	%	%	%	%	%
29-A	GSD III <1y	M	8mo	**UCCS: 0.1-0.5 g/kg every 4 hours** (0.1 g/kg/dose increase every 3 days) **Pro: 1.5-3.0 g/kg/day** (1.5 g/kg/day increase after 6 days)	Inpatient, diagnostic	17	24h	5.0	1.1	22.2	**4.35**	**10.78**	84.25	84.86	0.62	0.00
							Night	5.1	1.0	20.5	**2.82**	**9.80**	86.15	87.38	1.23	0.00
29-B			10mo	**UCCS: 0.45 g/kg** every 4 hours **Pro: 4 g/kg/day**	Outpatient, diet evaluation	7	24h	5.7	1.3	23.2	**0.10**	**6.94**	86.95	92.62	**6.01**	0.34
							Night	6.0	1.5	24.7	**0.00**	**1.79**	85.71	97.32	**12.50**	0.89
31-A	GSD III >6y	F	39	**UCCS: night: 0.7 g/kg before sleep; after 4 days decreased to 0.5 g/kg before sleep** Pro: night: 0.9 g/kg before sleep;	Outpatient, diet evaluation	7	24h	6.1 [=]	1.4 [↑]	22.2 [↑]	0.00 [=]	2.78 [↑]	86.43 [↓]	96.84 [=]	10.79 [↑]	0.38 [=]
							Night	7.2 [↑]	1.0 [=]	14.6 [=]	0.00 [=]	0.00 [=]	78.87 [↓]	99.11 [=]	**21.13 [↑]**	0.89 [↑]
47-A	FBS >6y	M	11	UCCS: day: 0.4 g/kg every 4 hours **CNGDF: night: CHO 0.34 g/kg/h**	Inpatient, diet evaluation	4	24h	5.8	1.7	29.0	0.00	11.76	77.52	85.69	10.71	2.55
							Night	4.9	1.3	25.7	0.00	**25.52**	74.48	74.48	**0.00**	**0.00**
47-B			13	UCCS: day: 0.5 g/kg every 4 hours **night: 1.8 g/kg before sleep** Pro: 1.8 g/kg/day	Inpatient and outpatient diet evaluation	10	24h	7.1	1.3	19.0	0.00	0.00	73.10	97.41	26.90	2.59
							Night	7.6	0.9	12.5	0.00	**0.00**	58.75	99.38	**41.25**	**0.63**
48-A	IKH – Untreated 1-6y	M	2	No diet	Outpatient glucose evaluation	6	24h	5.1 [=]	0.9 [=]	17.3 [=]	0.24 [↑]	**7.30 [↑]**	91.87 [↓]	92.46 [↓]	0.60 [=]	0.00 [=]
							Night	4.7 [=]	0.5 [=]	19.4 [↑]	0.00 [=]	**5.90 [↑]**	94.10 [↓]	94.10 [↓]	0.00 [=]	0.00 [=]
48-B	IKH – Treated 1-6y		3	**UCCS: night: 1.1 g/kg before sleep**	Outpatient diet evaluation	7	24h	5.7 [=]	0.8 [=]	14.1 [↓]	0.00 [=]	**0.29 [=]**	99.19 [↑]	99.71 [↑]	0.52 [↓]	0.00 [=]
							Night	5.6 [=]	0.8 [=]	14.7 [=]	0.00 [=]	**0.00 [=]**	99.65 [=]	100 [=]	0.35 [=]	0.00 [=]

CGM metrics are compared to the interquartile ranges of healthy individuals using color-coding: blue cells indicate values below 25th percentile, white cells indicate values between 25th and 75th percentile, red cells indicate values above 75th percentile; grey cells: no comparison could be made as no data from healthy controls aged <1 year were available. CGM metrics were also compared to the interquartile ranges of the respective patient cohorts (when available in Table 2), using markings between square brackets: [↓] indicate values below 25th percentile, [=] indicate values between 25th and 75th percentile, [↑] indicate values above 75th percentile. Values in **bold** indicate values that are specified in text.
Abbreviations: CHO: Carbohydrate intake; CNGDF: continuous nocturnal gastric drip feeding; CV: coefficient of variation; n dd: n daily doses; Mo: months; Pro: protein suppletion; SD: standard deviation; TAR: Time-above-range; TBR: Time-below-range; TIR: Time-in-range; UCCS: uncooked cornstarch.
[1]Night is defined as: 01:00 am till 05:00 am.

much more awake and energetic in the morning. During an outpatient evaluation (interval 48-B), CGM metrics showed improved TBR ≥3.0 - <3.9 mmol/L in both 24-h data (0.3 %) and night-time (0.0 %). Measurements of early-morning capillary blood glucose (range 4.4–4.7 mmol/L) and ketones (range 0.1–0.2 mmol/L) over 6 days also improved.

4. Discussion

This is the first detailed study of CGM metrics (descriptive, glycemic variation, glycemic control) in a relatively large cohort of people with liver GSD and IKH. In principle, CGM metrics of an individual patient can be compared to (1) published reference values from age-matched healthy volunteers, (2) reference values from age-matched people with the same condition, and (3) historical data from the same patient (e.g., before and after an intervention). By using the CGM metrics as previously proposed [19], we demonstrated that despite dietary treatment, people with liver GSD do not always achieve CGM results comparable to healthy individuals. While in IKH patients CGM metrics are comparable to healthy individuals, CGM may help to identify hypoglycemic episodes and to initiate or adjust dietary treatment.

In this study, especially the cohorts of patients with GSD Ia and Ib displayed abnormal CGM metrics compared to healthy individuals. Among all analyzed patient cohorts they were the only to display significantly decreased TIR together with both significantly increased TBR and TAR. These results were in line with our recent prospective study in GSD Ia patients [20]. Previous studies have also demonstrated how CGM can help detect (subclinical) hypoglycemia and hyperglycemia in these patient groups and guide dietary optimization [13,14,17,18]. People with GSD Ia and Ib display severe fasting intolerance and the burdensome dietary management aims to compensate for the impaired endogenous glucose production [7]. The CGM metrics may reflect the narrow therapeutic window between undertreatment (e.g., aiming to prevent TBR) and overtreatment (e.g., aiming to maintain a normal TIR and to prevent increased TAR and hence, glycogen storage in the liver).

Among the ketotic GSD subtypes, our study demonstrates the most abnormal CGM metrics in the GSD III cohort. Under dietary treatment, the GSD III cohort presented increased TAR and decreased TIR, in comparison to healthy individuals. As also described in the case studies of subject 29 and 31, these observations may reflect that dietary treatment is effective to prevent hypoglycemias but it can easily increase

TAR. Overtreatment in GSD III can contribute to various complications like obesity and (cardio)myopathy. Consequently, detecting increased TAR and preventing dietary overtreatment are important and CGM can play an important role in this [5,26]. In addition, in adult GSD III patients with increased TAR, a diagnosis of diabetes mellitus type 2 (DM2) should be considered next to overtreatment. Sentner et al. reported a higher percentage of DM2 among adult GSD III patients (8/91 (9 %) patients) than in the general population (6 %) [5]. Whether overtreatment and increased TAR play any causal role in the development of DM2 in these patients is an important topic for future research.

In people with (suspected) IKH, 'critical' serum samples during times of hypoglycemia are often not available. CGM – together with point-of-care capillary blood glucose and ketone (beta-hydroxybutyrate) measurements – may provide a low-invasive technique to assess fasting (in) tolerance at home [27]. As demonstrated in the case study of subject 48, CGM may aid clinical decision making and guide (initiation of) dietary treatment. To date, very limited data on CGM metrics in IKH exists. One retrospective study by Worth et al. [28] – while aiming to quantify the timing of CGM-recorded hypoglycemia in patients with hyperinsulinism – also reported on a limited amount of CGM data (i.e., number, duration and time of day of hypoglycemic events) in IKH patients. Worth et al. included a group of 24 people with IKH with a mean (SD) age of 82 (43) months, and concluded that in IKH there was no particular period of day with increased hypoglycemia risk. In line with their observations, we observed no important differences between 24-h or night-time CGM metrics in IKH patients, both in the treated and untreated cohorts. Our study provides a first comprehensive overview of real-world CGM metrics in a selected cohort of people with IKH to which individual and cohort data can be compared to. This may help in identifying people with a more severe IKH phenotype who may benefit from advanced monitoring and dietary treatment [12].

Data herein presented highlight that guidelines and recommendations on the use of CGM in liver GSD are strongly warranted. While guidelines and care pathways have been published for the most common liver GSD subtypes (such as the European guidelines for GSDs Ia [4] and GSD Ib [6] in 2002, and the American College of Medical Genetics and Genomics guidelines for GSD III [2], GSD I [1], and GSD VI and IX [3], in 2010, 2014 and 2019, respectively), CGM has been barely mentioned in these guidelines. Simultaneously since 2001, the number of published articles describing CGM usage in liver GSD has remained low, and comparison of these studies is complicated (Table 1) [13–22]. In diabetes there are agreed international recommendations on the use of CGM, both for patient care and for use in clinical trials [29,30]. However, it is questionable whether these recommendations in diabetes can be directly applied to GSD patients. Diabetes is a disorder in which the pharmacological treatment of the condition is associated with a risk of hypoglycemia, as opposed to the disorder itself. Moreover, the CGM target ranges set in diabetes (i.e., TBR <3.9 mmol/L; TIR 3.9–10.0 mmol/L; TAR >10.0 mmol/L) may not adequately appreciate the pathophysiology of liver GSD, as insulin and glycogen are already produced at blood glucose values within the diabetes target range of 3.9–10.0 mmol/L. For example, in our study, the additional metrics of TIR 3.9–7.8 mmol/L and TAR >7.8 mmol/L take more account of glycogen storage, as an important part of the pathophysiology.

Some limitations of this study need to be addressed. First, accuracy of CGM point measurements are a matter of concern, especially in patients with non-diabetes hypoglycemia [31], and may have influenced our results. In this study, the Dexcom G6 device was used, which is well studied in diabetes mellitus, with relatively high sensitivity to detect hypoglycemia [32]. This sensor is factory calibrated which partly explains why capillary glucose values were not routinely recorded and corroboration between CGM and capillary glucose values could not be studied. Second, the retrospective nature of our study in a center of expertise may have introduced selection bias. Third, due to technical difficulties and the associated burden for (families of) GSD patients, it is almost impossible to acquire reliable data on both the prescribed and the used diets. Similarly, potential episodes of hypoglycemia or infections that were treated at home and did not lead to hospitalization, were not routinely captured in electronic health records and could not be included in the data analysis. Last, expressing TBR as a percentage of time does not consider frequency and duration of hypoglycemias [33].

To conclude, most liver GSD cohorts do not achieve CGM metrics comparable to healthy individuals, despite dietary treatment. Although individuals with IKH display CGM metrics comparable to healthy individuals, CGM can be used to guide (initiation of) dietary treatment in this population. Prospective CGM studies and data collections for patients with rare diseases are highly necessary but seriously complicated by (a) the rarity of the diseases themselves, (b) the limited possibilities for reimbursement and availability of CGM, and (c) the poor connection and integration of different digital data systems, between home and the hospital, and between hospitals. To the authors' opinions, based on existing expertise international consensus guidelines and recommendations are warranted on the use of CGM and CGM metrics in liver GSD, both for patient care and clinical trials.

Ethics approval and patient consent statement

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Funding

The MD-PhD scholarship of A.V. (MD-PhD 21–65) is funded by the Junior Scientific Masterclass from the University of Groningen, University Medical Center Groningen (granted to A.V. and T.G.J.D.). A.R. is funded by: Associazione Italiana Glicogenosi, Grant/Award Number: 01/2020 (granted to A.R. and T.G.J.D.).

CRediT authorship contribution statement

Ruben J. Overduin: Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Annieke Venema:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Charlotte M.A. Lubout:** Writing – review & editing, Data curation. **Marieke J. Fokkert-Wilts:** Writing – review & editing, Data curation. **Foekje De Boer:** Writing – review & editing, Data curation. **Andrea B. Schreuder:** Writing – review & editing, Data curation. **Alessandro Rossi:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization. **Terry G.J. Derks:** Writing – review & editing, Supervision, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

All authors declare that they have no conflicts of interest related to the content of this manuscript.

R.J.O.: There are confidentiality agreements with third parties. There is a consultation agreement (with Ultragenyx Pharmaceutical Inc). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG.

A.V., C.M.A.L.: No conflicts of interest.

M.J.F.W., F.D.B., A.B.S.: There are confidentiality agreements with third parties. For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG.

A.R.: There are confidentiality agreements with third parties. In the past 36 months there have been consultation agreements or honoraria for lectures or presentations with Nestlé, Danone and Ultragenyx Pharmaceutical Inc.

T.G.J.D.: There are confidentiality agreements with third parties. In the past 36 months, there have been consultation agreements (with Danone, Ultragenyx Pharmaceutical Inc, ModernaTX Inc., and Beam Therapeutics), contracts for financial research support for investigator-initiated research (NCT04311307) and sponsor-initiated research (NCT03517085, NCT03970278, NCT05139316, and NCT05196165), honoraria for lectures or presentations (by MEDTalks, Prelum, and Danone), and participations in a Data Safety Monitoring Board (NCT05095727) and Advisory Boards (Ultragenyx Pharmaceutical Inc, ModernaTX Inc., and Beam Therapeutics). For all private-public relationships, all contracts are via UMCG Contract Research Desk and all payments are to UMCG.

Data availability

Supplementary Table S1 includes CGM metrics on the pooled CGM data of all individual patients, and was used for statistical analysis that support the findings of this study. Additional anonymized data are available on reasonable request to the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2024.108573.

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