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Use of waxy maize heat modified starch in the treatment of children between 2 and 5 years with glycogen storage disease type I: A retrospective study

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ABSTRACT

Background: Glycogen storage disease type I (GSDI) is caused by deficiency of the enzyme glucose-6-phosphatase or glucose-6-phosphate transporter. Mainstay of treatment is provision of uncooked cornstarch (and/or continuous nocturnal pump feed (CNPF) to maintain normoglycemia). Waxy maize heat modified starch (WMHMS) is another treatment option to maintain normoglycemia overnight. Our objective was to describe our experience treating children 2–5 years of age with GSDI using WMHMS overnight.

Method: This is a retrospective case series review ($n = 5$) comparing the overnight feeding regimen and biochemical control one year before and after nocturnal WMHMS therapy. The WMHMS trial, in which blood glucose and lactate levels were monitored hourly, is reported in detail.

Results: Most patients successfully transitioned to nocturnal WMHMS feeds. These patients had stable glucose and lactate throughout the overnight period, permitting a fasting period of 6.5–8 h overnight. Within the time period studied, WMHMS appeared to have improved overnight control of blood glucose levels with fewer reported episodes of hypoglycemia compared to CNPF.

Conclusion: WMHMS can be an effective substitute treatment to achieve stable nocturnal glucose control in children younger than five years of age. A larger multicenter prospective study is recommended to establish stronger evidence of the efficacy and safety of using WMHMS in treatment of young children with GSDI.

1. Background

Glycogen storage disease type I (GSDI/von Gierke disease), is the most common glycogen storage disease. It is an autosomal recessive genetic condition caused by the deficiency of the glucose-6-phosphatase enzyme or its mediating transporter. This deficiency leads to excessive accumulation of glycogen and fat in the liver, kidneys, and the intestinal mucosa. Researchers have classified GSDI into two phenotypes that differ in their symptoms and genetic causes: GSDIa (OMIM 232200) and GSDIb (OMIM 232220). Statistically, the disease afflicts approximately 1 in 100,000, with about 80% diagnosed with GSDIa [1].

Patients with GSDI usually do not present with symptoms within the first 3 months of life. After 3 months of age, when feeding is less frequent, symptoms caused by hypoglycemia begin to manifest such as irritability, excessive crying, and episodes of tachypnea. The clinical manifestations observed in patients with GSDI are numerous and may include hepatomegaly, nephromegaly, fasting hypoglycemia, lactic acidemia, hyperlipidemia, hyperuricemia, and growth retardation. The disease spectrum varies depending on age of onset, disease progression, and severity. Patients diagnosed with GSDIb will also present with neutropenia, impaired neutrophil function, and inflammatory bowel disease along with the common GSDI symptoms displayed [2].

The main goal of treatment is to maintain normoglycemia and normalize the metabolic abnormalities as much as possible while

Abbreviations: GSD, Glycogen storage disease; UCCS, uncooked cornstarch; WMHMS, waxy maize heat modified starch; CNPF, continuous nocturnal pump feed; TGs, triglycerides; abdominal US, abdominal ultrasound; ALT, alanine aminotransferase; AST, aspartate aminotransferase; kg, kilogram; cm, centimeter; BMI, body mass index; GI, gastrointestinal; hrs, hours

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avoiding and treating complications that may arise [1]. GSDI therapy is based mainly on diet modifications [2,3]. A consistent intake of carbohydrates is needed to prevent hypoglycemia and to control metabolic parameters efficiently. Overnight, continuous glucose feeding has been the mainstay of therapy since 1970 [4]. Using uncooked cornstarch as a treatment was first introduced in the early 1980s, and it has continued to be the treatment of choice in North America to date [5].

Using uncooked cornstarch (UCCS) for the management of patients with GSDI has significantly improved outcomes and improved the quality of life for these patients. The recommended dose of cornstarch is 1–1.6 g per kg every 3–4 h in young children and 1.7–2.5 g per kg every 4–5 h subsequently [1]. The main drawback of uncooked cornstarch is the short duration of action requiring sleep to be interrupted in the overnight period. In addition, UCCS is only partially metabolized and has been associated with malabsorption in GSD1 [6]. As such, a very gradual introduction is required in patients < 1 year of age. GI intolerance (bloating, flatulence, diarrhea) and undesirable taste is reported by many patients taking UCCS.

The search for a form of starch with better digestibility by intestinal enzymes while retaining the ability to achieve normoglycemia led to the study of waxy maize heat modified starch (WMHMS) as an alternative to UCCS in recent years. WMHMS is a source of slow-release starch. The use of WMHMS has shown clinical improvement in the duration of normoglycemia in the overnight period in patients with GSD Ia and Ib compared to UCCS [6]. Additionally, observations in test subjects indicate that WMHMS is a better alternative to continuous overnight feeding, resulting in better blood sugar control [4].

The use of WMHMS in a treatment plan for GSDI patients has been permitted for patients over 2 years of age in Canada and for patients over 5 years old in the United States. To date, the literature available on the administration of WMHMS to patients between the ages of 2 to 5 years of age is limited. This is a retrospective descriptive case series reporting outcomes of patients with GSDI who started on overnight WMHMS treatment between 2 and 5 years of age. It describes the effects of WMHMS on blood glucose, lactate and other disease burden parameters.

2. Methods

2.1. Subjects

Eligibility criteria included patients diagnosed with GSDI who were started on WMHMS between 2 and 5 years of age. The diagnosis of GSDI in all subjects was established using:

a) Clinical diagnosis based on clinical manifestations consistent with GSDI: hypoglycemia with hyperlactatemia, hypertriglyceridemia, hyperuricemia, hepatomegaly, and failure to thrive.
b) Molecular diagnosis: GSDI was confirmed by the presence of two pathogenic mutations in the *G6PC* gene for patients with GSD Ia or in the *SLC37A*3 gene for patients with GSD Ib.

Data from a total of 5 patients were retrieved and analyzed. All five patients had GSD Ia. This analysis was approved by the Ethics Committee at The Hospital for Sick Children, Toronto, ON, Canada. Parental informed consent and when applicable assent from capable minors under the age of 18, was obtained prior to enrollment in this case series.

2.2. Study design

This study was a retrospective chart review with a cross-sectional analysis of the variables of interest. The medical charts for each participant were reviewed. The variables of interest were sex, current age, age at diagnosis, age at introduction of WMHMS, and mutation type. We have documented the overnight feeding record including feeding regimen, doses of cornstarch and WMHMS, fasting interval during night, nutrition supplements, and the frequency and timing of hypoglycemic events. Doses of both daytime and overnight cornstarch preparations and the continuous nocturnal pump feeding were titrated based on close monitoring at home and in outpatient clinic visits.

We have recorded clinical disease parameters, including anthropometric measurements, developmental assessment, and signs of GI intolerance such as abdominal discomfort, bloating, diarrhea, emesis etc. Data collection also included biochemical disease markers including blood glucose, lactate, urine lactate/creatinine ratio, urate, triglycerides, cholesterol, ALT, AST and imaging studies (abdominal US). All parameters were collected during a time period of one year before and after introduction of WMHMS.

Anthropometric assessment consisted of weight (kg) and height (cm) measurements. Body weight was measured using Tronix Pediatric scale 4802 with a maximum limit of 400 kg and a resolution of 0.5 kg, certified by the department of medical engineering. Patients were weighed while wearing light clothes and barefoot. Height was measured with a wall-mounted stadiometer with a 1 mm precision.

2.3. The waxy maize heat modified starch (WMHMS) trial

Four out of five patients underwent WMHMS trial at our center. The overnight challenge was performed using a protocol established at our center. WMHMS dose was calculated based on estimated glucose needs ($Y = 0.0014 \times {}^{3}–0.214 \times {}^{2} + 10.411 \times - 9.084$, *where* $Y = mg/\min^{5}$ [7].) or glucose provision on previous overnight regimen. WMHMS was administered in hospital orally or via gastrostomy tube as the last feed before sleep, with soy formula or unsweetened soymilk and/or water. An in-dwelling intravenous catheter was placed, and baseline blood glucose, lactate, ALT, AST, triglycerides, cholesterol, and urate were measured. Hourly monitoring of glucose and lactate was performed until glucose concentration fell to 4.2 mmol/L or patients fasted for a maximum of 8 h. Following completion of the WMHMS trial, patients with acceptable responses were discharged home permitted to use WMHMS overnight. Generally, patients remained on their baseline cornstarch doses throughout the day. However, in some cases, daytime feeds of UCCS were adjusted to permit a convenient period of fasting overnight for patients.

3. Results

3.1. Patients' characteristics

Five patients with GSDI fulfilled the inclusion criteria for our study (two males, three females). The mean age of patients was 3.4 ± 0.8 years at the time of the WMHMS trial and the age range was between 2.1 and 4.1 years. All patients had GSD type Ia. We did not have patients diagnosed with GSD1b that met the inclusion criteria for age of treatment. All patients were initiated on WMHMS for clinical management of GSDIa. Reasons for trialing the patient on WMHMS included nocturnal hypoglycemia due to CNPF malfunction or missed doses of UCCS, sibling use of WMHMS overnight and poor tolerance of CNPF. Growth parameters, including height, weight, and BMI for each patient in the time period used for data collection were within the same z score, so the mean ± SD was used. The time period of study for patient 1 was only 6 months before and after WMHMS administration. The characteristics of the patients are summarized in Table 1.

3.2. Waxy maize heat modified starch (WMHMS) trial

All patients underwent the WMHMS trial before 5 years of age. The trial was successful in 4 out of 5 patients with steady levels of blood glucose and blood lactate within our treatment goal (≥ 4.2 mmol/L and < 3 mmol/L, respectively) as shown in Figs. 1 and 2. Mean fasting period was 8.2 ± 0.4 h. Mean blood glucose and lactate levels at the end of the WHMHS trial were 4.9 ± 0.9 mmol/L (goal ≥ 4.2 mmol/L)

Table 1
Patient characteristics.

	Sex	Age at diagnosis (months)	Age at introduction of WMHMS (years & months)	Mutation	Weight (Z score) [mean ± SD]	Height (Z score) [mean ± SD]	BMI (Z score) [mean ± SD]
1	M	20	2 yrs. 2 mos	G6PC c.323C > T, Homozygous	0.9 ± 0.2	- 0.3 ± 0.2	1.5 ± 0.1
2	F	12	3 yrs. 1 mo	G6PC c.247C > T, Homozygous	2.2 ± 0.2	0.9 ± 0.1	2.1 ± 0.2
3	M	11	4 yrs[a]	G6PC c.648G > T, c.356A > T	0.4 ± 0.1	- 0.5 ± 0.1	1.1 ± 0.2
4	F	10	3 yrs. 8 mos	G6PC c.34G > C, c.137 T > C	2.3 ± 0.0	0.3 ± 0.3	2.7 ± 0.2
5	F	Prenatal[b]	4 yrs2 mos	G6PC c.1022 T > A, c.727G > T	0.0 ± 0.2	- 0.1 ± 0.1	0.3 ± 0.2

[a] Patient 3 has another WMHMS trial at the age of 5 years and 1 month.
[b] Prenatal diagnosis based on positive family history.

and 2.7 ± 1.2 mmol/L (goal < 3 mmol/L) respectively.

Patient 3 underwent two admissions one year apart (the trial was done twice in each admission, Figs. 3 and 4). In Figs. 1 and 2, his data is presented as a mean of these 2 trials. The WMHMS treatment was discontinued at home in patient 3 after his first trial due to high lactate level during the in-patient trial and frequent early morning vomiting at home during the first week of using WMHMS. The second trial for patient 3 ended with the decision to not permit the use of WMHMS at home due to high lactate levels during the in-hospital trial (6.2 mmol/L and 6.9 mmol/L after 8 h of WMHMS dose) and the patient was re-initiated on CNPF regimen.

3.3. Overnight feeding regimen one year before and after nocturnal WMHMS therapy

Table 2 shows the overnight feeding regimens of patients one year before and after WMHMS.

3.4. Overnight feeding regimen one year before nocturnal WMHMS therapy

Three out of five patients were on overnight CNPF: patient 1 was started on UCCS overnight regimen upon diagnosis but switched to CNPF due to GI intolerance with recurrent overnight vomiting, while patient 3 and 4 were treated with overnight CNPF from time of diagnosis. Two out of the five patients were on overnight UCCS, with a fasting interval of 4 h. Regarding hypoglycemic events, low blood glucose readings (< 4.2 mmol/L, lowest of 3.2 mmol/L) in early morning hours were reported in patient 1. In patient 3, there was a history of one hypoglycemic episode due to malfunctioning of feeding pump. Many episodes (> 6) of nocturnal hypoglycemia were reported in patient 4, most unexplained but one of which was attributed to the disconnection of feeding pump. There was no history of hypoglycemic episodes in patient 5.

3.5. Overnight feeding regimen one year after nocturnal WMHMS therapy

Four of the five patients considered in our study were able to include WMHMS in their daily treatment regimen successfully. Efficacy for extending fasting for a 6.5–7.5-h period beyond baseline was demonstrated for two of four patients and for 4 h beyond baseline for the other two patients. Patient number 1 was initially able to fast 7.5 h during the WMHMS trial. However, this was shortened to 6.5 h during the 6 months after initiation of WMHMS therapy. There was no evidence of nucturnal hypoglycemia in all 4 patients while on WMHMS therapy. Anthropometric measurements were taken during the whole period of the study (one year before and after WMHMS). There was no significant change in the parameters for all patients before and after WMHMS introduction.

3.6. Biochemical markers one year before and after nocturnal WMHMS therapy

There was no statistically significant difference in biochemical markers levels before and after nocturnal WMHMS therapy. All biochemical markers of metabolic control remained stable in our patients (Table 3).

4. Discussion

The objective of this study was to describe the effects of nocturnal WMHMS administration on the control of blood glucose and other disease parameters in children with GSD1a < 5 years. This is the first published study to date to report outcomes of using WMHMS in young children under 5 years of age. The youngest patient included in this retrospective study was 26 months old when first trialed on WMHMS.

WMHMS was successfully integrated into treatment regimens of 4 out of the 5 patients with GSDI included in this case series. Symptoms of

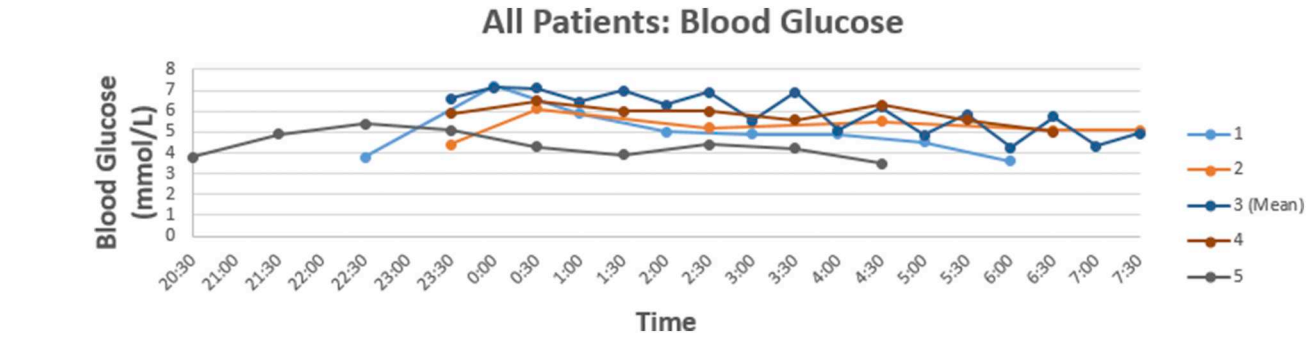

Fig. 1. Overnight blood glucose on WMHMS.

intolerance such as vomiting, abdominal pain, abdominal distension, or change in bowel habits were not usually reported. However, some patients had challenges with taking the required dosage of WMHMS orally due to the large volume and required feeding through G-tube. Furthermore, elevated lactate levels and early morning vomiting was reported in one patient with the initiation of WMHMS. This patient was maintained on previous treatment regimen with overnight CNPF. This study showed no correlation to growth parameters related to the WMHMS therapy.

The frequency of nocturnal hypoglycemia and borderline blood glucose in patients on CNPF was higher than UCCS therapy. This was related to unexpected discontinuation of feeding as a result of pump failure which has been previously reported by Santos et al. [8]. The WMHMS improved the control of overnight blood glucose in patients on CNFP; follow up showed acceptable glucose levels (> 4.2 mmol/L). There was no difference between the UCCS therapy and the WMHMS regarding reported overnight hypoglycemic episodes in patients on both regimens.

This case series describes the extension of the overnight fasting period with WMHMS compared to UCCS and CNFP. Four of five patients were able to fast for 6.5–8 h with blood glucose and lactate levels within treatment goal. Two patients previously on CNPF lasted 6.5 to 7.5 h and two patients previously on UCCS lasted an additional four hours to a total fasting period of 8 h overnight. Similar findings were reported in Rousseau-Nepton et al. [9], Ross et al. [5], Correia et al. [10] and Bhattacharya et al. [11] in adults. These studies also speak to the improvement of quality of life with less disruption of overnight sleep due to longer fasting period with WMHMS therapy. Another potential benefit of WMHMS compared to CNFP is that it requires less equipment for feeding and potentially reduces the need for a nighttime nurse/ worker to help with feeding, monitoring and maintaining equipment.

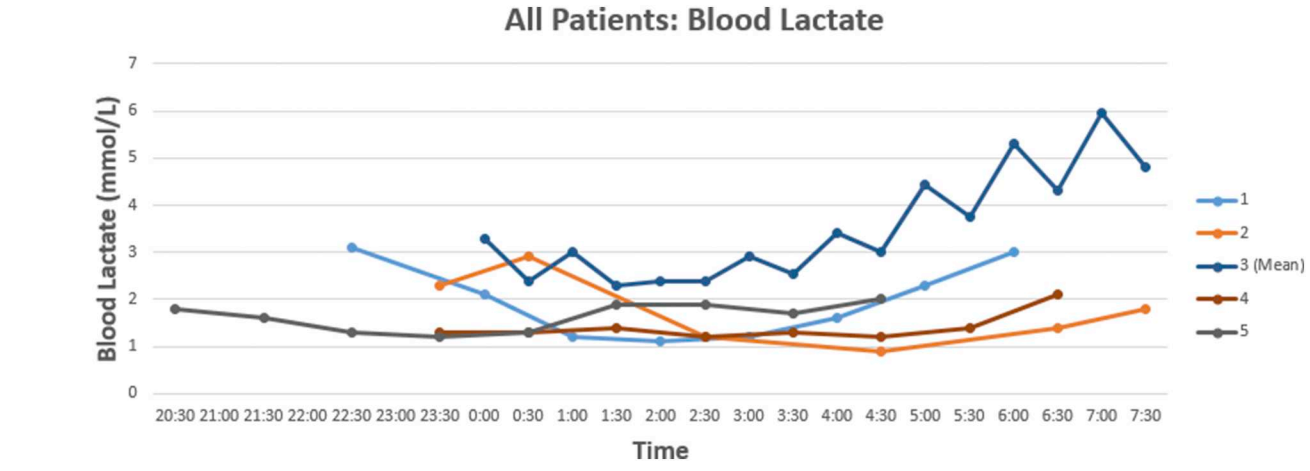

Fig. 2. Overnight blood lactate on WMHMS.

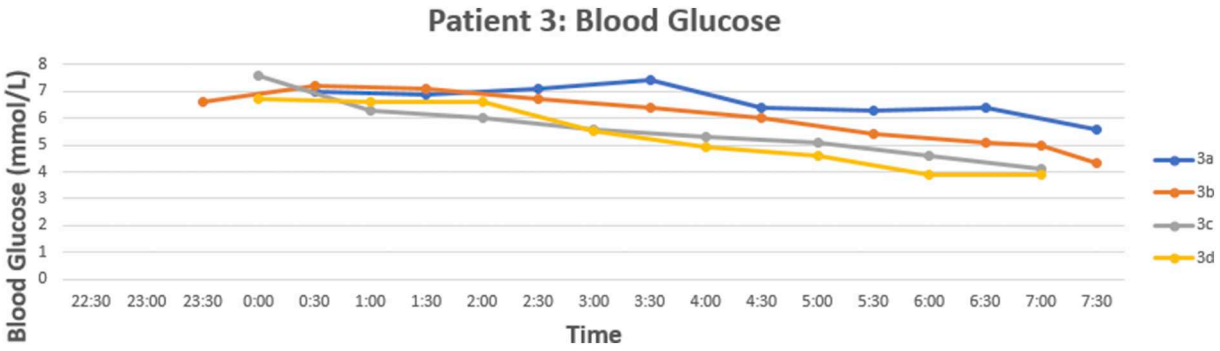

Fig. 3. Patient 3: overnight blood glucose on WMHMS.

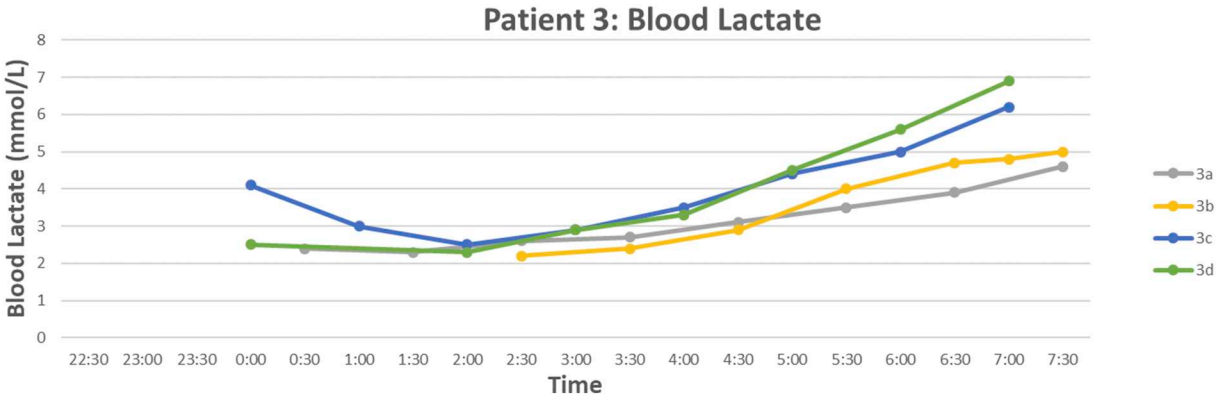

Fig. 4. Patient 3: overnight blood lactate on WMHMS.

Table 2
Overnight Feeding Regimen One Year before and after nocturnal Waxy Maize Heat Modified Starch therapy.

	Pre- WMHMS therapy				Post- WMHMS therapy		
	Overnight feeding regimen[a]	Fasting interval/ night (hrs)	Nocturnal hypoglycemia	Overnight feeding regimen	Fasting Interval /night (hrs)	Nocturnal hypoglycemia	WMHMS dose in grams/dose
1	CNPF	N/A	0	WMHMS	6.5	0	60 g
2	UCCS	4	0	WMHMS	8	0	70 g
3	CNPF	N/A	1	CNPF	0	0	95 g/100 g[b]
4	CNPF	N/A	> 6	WMHMS	7.5	0	90 g
5	UCCS	4	0	WMHMS	8	0	90 g

[a] CNPF continuous nocturnal pump feed, UCCS Uncooked Cornstarch.
[b] Doses used during the first and second trial.

While WMHMS appears to be an alternative for UCCS to maintain blood glucose and lactate levels within treatment goals during the overnight period, the administration and close monitoring of the therapy regime is critical. Ross et al. [5] reported a 13-year old patient who died after a single missed overnight dosage. The patient experienced severe hypoglycemia the next morning, causing a seizure that was fatal. Thus, the study suggests that the risk of increased duration of fasting while on nocturnal WMHMS can be severe in comparison with the traditional therapy. It is important to note that WMHMS treatment in young children may require closer monitoring to adjust doses appropriately during rapid growth periods of early childhood.

Although WMHMS appears effective in maintaining adequate

Table 3
Glycogen storage disease type Ia biochemical markers one year before and after nocturnal waxy maize heat modified starch therapy.

	Pre-therapy [mean ± SD] (n = 5)	Pre-therapy median	Pre-therapy range	Post-therapy [mean ± SD] (n = 4)	Post-therapy median	Post-therapy range
Glucose (mmol/L)	5.4 ± 0.9	5.6	2.2–6.4	5.5 ± 0.4	5.5	4.8–6.2
Lactate (mmol/L)	3.2 ± 1.8	2.9	1.5–8.2	1.8 ± 0.3	1.9	1.1–2.2
Urine lactate/creatinine ratio (mol/mol)	0.04 ± 0.03	0.03	0.003–0.152	0.017 ± 0.008	0.01	0.01–0.03
Triglycerides (mmol/L)	3.4 ± 1.7	3.3	0.67–6.9	2.02 ± 0.7	1.99	1.15–2.9
Cholesterol (mmol/L)	4.6 ± 0.9	4.6	2.7–6.7	4.1 ± 0.9	4.4	2.75–4.97
AST (U/L)	61.2 ± 48.1	40.5	23–208	33.2 ± 6.5	34.5	22–40
ALT (U/L)	51.2 ± 44.7	35	15–188	25.6 ± 4.5	26	19–31
Urates (umol/L)	283.1 ± 48	278	142–386	241.4 ± 58.3	234.5	154–321

glucose control, no significant difference was found in lactate levels and other disease parameters such as: urate, liver function tests, cholesterol, TGs, or abdominal US findings. However, these parameters also depend on other variables like daytime glucose control and feeding regimen. The small sample size of this study makes it difficult to form strong evidence and conclusions about the efficacy and safety of WMHMS in young children.

5. Conclusion

In conclusion, this case series demonstrates that children < 5 years with GSDIa can achieve stable nocturnal glucose control using an appropriate amount of WMHMS as dietary therapy. The introduction of WMHMS enabled longer overnight fasting period in comparison with UCCS and permitted a fasting period for patients on CNPF. However, this was not possible for all patients. A limitation of this study includes the short time period of analysis of outcomes which may not capture long-term complications and effects on disease parameters which are important in treatment decision-making. For instance, patient 1 currently receives WMHMS in two divided doses overnight at parent's discretion due to reported early morning GI intolerance (gagging, emesis) when full WMHMS dose given in one dose. Another limitation is the small sample size and the lack of patients with GSDIb. As such, no conclusions can be made for possible effects of WMHMS therapy in patients with GSDIb. A larger multicenter prospective study is needed for stronger evidence regarding the efficacy and safety of WMHMS in treatment of young children with GSDI. This study highlights a possible way to reduce the risks associated with CNPF including hypoglycemia secondary to failure of pump or pump disconnection using WMHMS. The improvement of quality of life with WMHMS regimen in this study was largely based on anecdotal parental reports of less disruption of overnight sleep. A more formal approach with a validated questionnaire may highlight other aspects of quality of life that was not examined in this case series.

Declaration section

1. Ethics approval and consent to participate – Approved REB# 1000061800; This study was approved by the Ethics Committee at The Hospital for Sick Children, Toronto, ON, Canada. When applicable assent from capable minors under the age of 18, was obtained prior to enrollment in this case series. Written informed consent was obtained from participants' legal guardians.
2. Consent for publication – This paper contains de-identified information
3. Availability of data and material- The datasets generated and/or analyzed during the current study are not publicly available due to individual privacy of the 5 cases reported but some non-identified information required are available from the corresponding author on reasonable request.
4. Competing Interests and Disclosure – The authors declare that there is no conflict of interest or competing interest
5. Funding - not applicable, no funds required
6. Authors' contributions - you have this section I sent it to you before we submitted this paper.
7. Acknowledgements - not applicable
8. Authors' information (optional) - not applicable

Author contributions

GH: analysis and interpretation of the data, drafting and revising the manuscript for intellectual content. NP: analysis and interpretation of the data, revising the manuscript for intellectual content. LN: analysis and interpretation of the data, revising the manuscript for intellectual content. SH: analysis and interpretation of the data, revising the manuscript for intellectual content. JD: analysis and interpretation of the data, revising the manuscript for intellectual content. MR: analysis and interpretation of the data, revising the manuscript for intellectual content. MIF: design and conceptualization of the study, analysis and interpretation of the data, revising the manuscript for intellectual content. All authors have read and approved the manuscript.

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