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ORIGINAL ARTICLE

Alternative nighttime nutrition regimens in glycogen storage disease type I: a controlled crossover study

Michel Hochuli[1,5] · Emanuel Christ[3] · Fabian Meienberg[4] · Roger Lehmann[1] ·
Jan Krützfeldt[1] · Matthias R. Baumgartner[2,5]

Abstract
Background Traditional approaches for nighttime glycemic
control in glycogen storage disease type I (GSDI) include
continuous tube feeding, or ingestion of uncooked corn starch
(CS) at bedtime. A modified corn starch (MCS) has been
shown to prolong euglycemia in some patients. The aim of
this study was to evaluate whether stable nighttime glucose
control can be achieved with other types of slowly digested
carbohydrates in adult GSDI patients.
Methods In this cross-over study, nocturnal glucose control
and fasting times were assessed with three different nocturnal
nutrition regimens in five patients, using continuous glucose
monitoring (CGMS) in an outpatient everyday life setting. For
each patient, continuous glucose profiles were measured after
ingestion of (1) CS, (2) MCS or (3) a pasta meal at bedtime,
during 5 to 6 consecutive nights for each regimen.
Results Stable nocturnal glucose control was achieved for all
patients with a pasta meal, with a mean duration of glycemia

>3.5 mmol/l of 7.6 h (range 5.7-10.8), and >4 mmol/l of 7 h
(5.2-9.2), similar to CS and MCS. Fasting glucose before
breakfast on workdays (after 7.1 ± 0.8 h) was not significantly
different between the three interventions (CS 4.1 ± 0.5 mmol/l,
MCS 4.6 ± 0.7 mmol/l, pasta 4.3 ± 0.9 mmol/l). During
prolonged fasting on weekends, longer duration of
normoglycemia was achieved with CS or MCS than with pasta.
Conclusion Consumption of cooked pasta is a suitable and
more palatable alternative to uncooked corn starch to achieve
nighttime glucose control in adult patients with GSDI.

Introduction

Glycogen storage disease type I (GSDI, van Gierke's disease
OMIM 232200) is an autosomal recessive disorder with an
incidence of approximately 1:100,000. There are two types
of GSDI, resulting from deficiencies of either glucose-6-
phosphatase (type GSDIa, about 80 % of affected patients)
or the glucose-6-phosphate transporter (type GSDIb) (Chou
et al 2010; Chen et al 2013). The primary metabolic abnor-
mality of all GSDI patients is fasting hypoglycemia, because
glucose-6-phosphate produced either via gluconeogenesis or
glycogenolysis can not be converted to glucose. Other associ-
ated metabolic abnormalities are lactic acidosis, marked
hypertriglyceridemia, hypercholesterolemia, and hyperurice-
mia, depending on the quality of metabolic control. Despite
optimal treatment, many patients with GSDI will develop
complications such as liver adenomas, chronic kidney disease,
urolithiasis, low bone density/osteoporosis, and anemia. Poor
metabolic control is a risk factor for the development of these
complications. Neutropenia and inflammatory bowel disease
(IBD) are characteristic features or complications of GSDIb.

Dietary treatment is the cornerstone of GSDI therapy (Rake
et al 2002; Bhattacharya 2011; Kishnani et al 2014). A regular

✉ Michel Hochuli
michel.hochuli@usz.ch

[1] Division of Endocrinology, Diabetes, and Clinical Nutrition,
University Hospital Zurich, Rämistrasse 100,
CH-8091 Zurich, Switzerland

[2] Division of Metabolism and Children's Research Center, University
Children's Hospital, Zurich, Switzerland

[3] Division of Endocrinology, Diabetology and Clinical Nutrition,
University Hospital of Bern, Inselspital, Bern, Switzerland

[4] Endocrinology, Diabetes, and Metabolism, University Hospital
Basel, Basel, Switzerland

[5] Radiz – Rare Disease Initiative Zurich, Clinical Research Priority
Program for Rare Diseases, University of Zurich, Zurich, Switzerland

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carbohydrate intake is necessary to avoid hypoglycemia and to achieve good metabolic control. Traditional approaches to maintain normoglycemia during nighttime are continuous tube feeding (especially in children), or ingestion of slowly digested carbohydrates at bedtime, usually uncooked corn starch (CS) (Wolfsdorf and Crigler 1997; Weinstein and Wolfsdorf 2002; Shah and O'Dell 2013). A modified form of corn starch (Glycosade®, MCS) with a different content of amylopectin and resistant starch can prolong euglycemia during nighttime in some patients (Bhattacharya et al 2007; Correia et al 2008). Glucose requirements generally decrease with age, and adults typically have a longer fasting tolerance compared to children, which facilitates overnight glucose control.

However, studies addressing dietary issues specifically in adults are scarce. Although standard therapy with uncooked corn starch (CS), or modified corn starch (Glycosade®, MCS) generally is well tolerated, some gastrointestinal discomfort sporadically occurs with bloating, diarrhoea, or in certain cases abdominal cramps. Given the longer fasting tolerance, adults may prefer other more palatable or convenient types of slowly digested carbohydrates before bedtime in certain situations. However, nutrition regimens other than CS or MCS have not been formally tested in adults.

Most controlled studies comparing the effects of different dietary treatments on metabolic control were performed in standardized inpatient settings, but studies evaluating glucose homeostasis in everyday life settings are rare. Continuous glucose monitoring systems (CGMS) are now routinely used in outpatient clinics to evaluate and improve glucose control in patients with type 1 diabetes mellitus. CGMS is also sporadically being used by some metabolic centers to assess the quality of glucose control (White and Jones 2011; Kasapkara et al 2014), but has not been used in controlled studies in patients with GSDI.

In the present controlled crossover study, nocturnal glycemic control of adult patients with GSDI is evaluated under three different nighttime nutrition regimens, including the two standard treatments with CS or MCS, and a pasta meal (P) as an alternative regimen. The study was performed in an outpatient everyday life setting, using current CGMS technology and capillary glucose measurements.

Materials and methods

Study design

This single centre study consisted of three different nighttime oral nutrition regimens in a crossover design. For each patient, continuous glucose profiles (CGMS) were measured in an outpatient everyday life setting after bedtime ingestion of (1) uncooked corn starch (CS, Maizena®), (2) modified corn starch (MCS, Glycosade®) or (3) a freshly cooked pasta meal (P). Each type of nutrition regimen was prescribed for 6 consecutive days, which corresponds to the maximum time of uninterrupted sensor (CGMS) data recording. For the CGMS measurement period with the pasta meal, patients took their usual diet with corn starch for the first night to ensure stable sensor function, and pasta was taken for the following 5 consecutive nights. Patients returned to their usual nutrition plan between the interventions (range 3-8 weeks).

Patients

Male or female patients>18 yrs with GSDIa or GSDIb were eligible for this study. Inclusion criteria were stable nighttime glucose control under the current dietary treatment with CS or MCS, and willingness to adhere to the proposed protocol. Exclusion criteria were unstable nighttime glucose control with frequent or severe hypoglycemia, the need for gastric tube feeding, or comorbidities which could adversely affect the safe participation in the study. Patients were recruited from the adult metabolic clinics of the University Hospitals in Zurich, Bern and Basel (Switzerland), on the occasion of a regular consultation. Eligible patients were screened at the University Hospital Zurich. Informed consent was obtained from all patients included in the study. The first patient started the study in December 2013, the last patient completed the study in November 2014.

Dietary therapy

For all interventions, patients received detailed oral and written dietary instructions by a specialist dietician. Patients were asked to write a food diary with the exact time of ingested meals during the CGMS measurement period. For the first measurement period patients continued the established treatment with the usual type and amount of cornstarch (CS or MCS, Table 1). For the following two dietary interventions the prescribed quantity of MCS, CS, or pasta corresponded to an equivalent amount of carbohydrates (in grams) provided by the usual dietary treatment (90 g carbohydrates per 100 g CS), with the option for a dose increase by ~10 g after 2-3 nights. A conversion factor of 1.1 was used to calculate the amount (in grams) of MCS from CS, according to the specifications of the manufacturer. The dry weighed amount of CS or MCS was dissolved in 120 ml of cold water per 60 g of cornstarch, and consumed immediately after mixing in a shaker. No carbohydrates other than cornstarch were allowed at bedtime. For the pasta meal, patients received prepacked weighed portions of dried, commercially available italian pasta ("Penne rigate", Barilla®, containing 72 g of carbohydrates per 100 g dry pasta). Pasta was freshly cooked in boiling water by the patients before bedtime, with a standardized cooking time of 11 min to obtain a consistency which can be described as 'firm to the

Table 1 Patient characteristics

Patient, sex	Age [y]	GSD type	Mutation	Glc-6-Pase activity (liver) [E/g][1]	Weight [kg]	BMI [kg/m²]	Triglycerides [mmol/l][2]	Usual nocturnal dietary treatment[3]	Average minimal fasting time (daytime)[4]
1, M	21	1b	G6PT1 c.250 T>A,homozygous		70	23.4	7.1	MCS 1.7 g/kg	3 – 4.5 h
2, F	35	1b	G6PT1 c.1211delCT/c.1348G>A		78	33.8	1.5	CS 1.7 g/kg	2.5 – 3.5 h
3, M	30	1a	G6PC c.407G>A/c.675A>G	0.5	87	28.7	5.4	CS 1.4 g/kg	3 – 4 h
4, M	35	1a	n.a.	0.4	59	19	3.4	CS 1.0 g/kg	3 – 4 h
5, F	19	1a	n.a.	n.a.	62	24.2	6.0	CS 1.3 g/kg	3.5 – 4 h

[1] Glucose-6-phosphatase activity in liver (normal 3.7-9.7 U/g)

[2] Average of measurements during regular medical visits during the last 2 years prior to inclusion to the study (normal<1.7 mmol/l)

[3] CS uncooked corn starch, MCS modified corn starch (Glycosade®). Corn starch is taken as a single dose before bedtime in the given amount. Patient 4 is undertreated, because he does not tolerate higher amounts of CS

[4] Approximate average minimal fasting times during the day (without CS, MCS or P), according to CGMS curves and capillary glucose measurements. All patients participating in the study need regular carbohydrate intake every 3-4 h during the day to maintain normoglycemia. Patients 2 and 3 had one episode of severe hypoglycemia (requiring assistance) during the day in recent years.

n.a. not available

bite' ('al dente'). Patients were allowed to use a small amount of commercial tomato sauce (Sauce Napoletana, Barilla®) or oil for the meal.

On workdays, the first meal in the morning was taken at the usual time outside the study, unless low blood glucose would necessitate earlier intake of carbohydrates. On weekends, breakfast was delayed to assess the glucose curve with prolonged fasting under the given dietary regimen. Participants were advised that the latest time to eat breakfast is when hypoglycemia occurs. There is no uniformly accepted definition of hypoglycemia. In patients without diabetes probably the best definition is neuroglycopenia (Wiesli et al 2002). In this study hypoglycemia was defined as a glucose concentration of ≤2.5 mmol/l without symptoms of hypoglycemia, or symptoms of hypoglycemia and a capillary blood glucose <3.1 mmol/l. Average fasting times on weekends were assessed for glucose cut-off values of >3.5 mmol/l and >4 mmol/l, in accordance with recommended preprandial blood glucose targets in European (>3.5-4.0 mmol/l) and American guidelines (>3.8 mmol/l, 70 mg/dl) (Rake et al 2002; Kishnani et al 2014).

Continous glucose measurements

An unblinded continuous glucose monitoring system (CGMS) was used during the dietary interventions (Enlite® glucose sensors combined with the Minilink® Real Time Transmitter, MedTronic®). A Minimed Paradigm Veo® insulin pump (void of insulin) was used to store and display sensor results. Patients were instructed to use the CGMS system by specialist diabetes nurses or the investigator. The sensor was placed on the abdomen, and used according to the manufacturers' specifications. Patients regularly performed capillary glucose measurements (device: Contour Next Link USB, Bayer®) to calibrate the glucose sensor (at least 3 times/day) and to check for accurate sensor function. All patients made a capillary glucose measurement before the first meal in the morning in addition to the sensor readings. An alarm was set to warn patients in case of nocturnal hypoglycemia (threshold <2.5 mmol/l). Confirmation of hypoglycemia by a capillary glucose measurement was mandatory in case of an alarm prior to carbohydrate intake. CGMS data were downloaded with the Carelink Professional® Software (MedTronic®) for statistical analysis, and discussed with the patients.

Data analysis and statistics

Data are presented as arithmetic means with standard deviation or ranges. Nine nights of CGMS data with unstable technical sensor function and a clear discrepancy of the sensor reading to the capillary glucose measurements were omitted from the analysis. Statistical analysis was performed using the statistical package SPSS 22 (IBM SPSS Statistics). A two-sided value of $P<0.05$ was considered significant. Post-hoc sequential Bonferroni correction was applied to account for multiple comparisons. The effect of the interventions on fasting glucose and the fasting time was examined using multiple linear regression (Senn 2002), always controlling for between-patient differences. For comparison of capillary and sensor fasting glucose measurements, a paired samples t-test was applied. The rate of decline of the glucose concentration during nighttime was assessed by linear regression (curve fit) of the glucose sensor curves, using Graph Pad Prism® Version 6.

Results

Five patients with GSDI fulfilled the inclusion criteria (three GSDIa, two GSDIb). All patients had stable overnight glucose control under their established dietary treatment with a single intake of cornstarch before bedtime. Uncooked corn starch (CS) was the usual treatment for four patients included in this study, one patient used modified cornstarch (MCS, Glycosade®). The characteristics of the patients are summarized in Table 1. All patients had confirmed diagnosis of GSDI by molecular genetics or enzyme testing in a liver biopsy sample.

During the CGMS measurement periods, the actual average amounts of cornstarch (as a single dose) ingested before bedtime were 100±28 g of CS, or 109±29 g of MCS respectively. The actual average amount of pasta (dry weight) consumed before bedtime was 136±33 g. These quantities correspond to 90 g of carbohydrates for CS and MCS, and a slightly higher amount of 98 g for the pasta meal (P). Glucose sensor function was reliable for an average number of 4.7 nights per intervention and patient (range 3-6), according to capillary glucose measurements.

All patients achieved stable glucose control during each night with a pasta meal at bedtime, with a mean duration of glycemia >3.5 mmol/l of 7.6 h (range 5.7-10.8), and >4 mmol/l of 7 h (5.2-9.2), similar to the results obtained for CS and MCS (Fig. 1). Nocturnal hypoglycemia was not observed with any of the three dietary regimens. The first meal in the morning was taken on average 8.0±1.6 h after bedtime intake of carbohydrates for all nutrition regimens. The shape and characteristics of the nocturnal sensor glucose curves were similar for all three nutrition regimens, although the linear rate of decline of glucose concentration after reaching the plateau was somewhat slower for MCS (MCS 0.21±0.01 mmol/l*h, as compared to CS and P 0.29±0.01 mmol/l*h, p<0.001). Glucose concentrations at bedtime were comparable between the regimens (CS 5.3±1.3 mmol/l, MCS 5.1±0.8 mmol/l, pasta 4.7±0.9 mmol/l, differences ns), and the time to peak glucose after the bedtime meal was between 1 h and 1.5 h for all interventions (peak at 5.9 mmol/l after 1 h for CS, 6.1 mmol/l after 1.5 h for MCS, 6.2 mmol/l after 1.1 h for pasta, ns). On workdays, when the first meal in the morning was taken at the usual time outside the study, capillary fasting glucose concentrations before breakfast were not significantly different between the three regimens, although there was a trend for slightly higher values with modified cornstarch (CS 4.1±0.5 mmol/l, MCS 4.6±0.7 mmol/l, pasta 4.3±0.9 mmol/l, ns) (Fig. 2). Sensor readings of fasting glucose were similar to capillary values, with no statistically significant differences. Average fasting times from bedtime to breakfast on workdays were 7.1 h (5.5-8.5) for CS, 7.1 h (5.6-7.7) for MCS, and 6.9 h (5.7-8.2) for P (ns). During the weekend, patients were asked to delay breakfast to assess the kinetics of glucose concentration with prolonged fasting. While stable nocturnal glucose
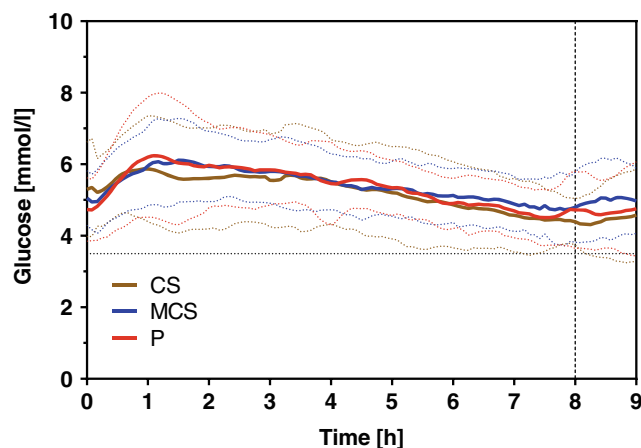

Fig. 1 Nocturnal glucose curves for three different nutrition regimens at bedtime. Brown line: uncooked corn starch (CS). Blue line: modified corn starch (MCS). Red line: pasta meal (P). The solid lines represent the mean glucose concentration, with the standard deviation indicated by the dotted lines. Curves were recorded by subcutaneous continous glucose measurement (CGMS). All patients achieved stable nighttime glucose control with a pasta meal at bedtime, similar to the results obtained for CS and MCS. Number of measurements per intervention: CS n=24, MCS n=23, pasta n=24. The vertical line indicates the average time until ingestion of the first meal in the morning. The bedtime meal is ingested at time-point zero

control was achieved for all patients with a pasta meal when the breakfast was taken at the usual time, longer duration of normoglycemia could be achieved for some patients with CS and MCS than with pasta during the prolonged fasting on weekends (Fig. 3). The average fasting times with stable glucose >4 mmol/l during weekends were 8.3 h (5.3-10) for CS, 8.9 h (6.8-10.5) for MCS, and 7.2 h (6.2-8.2) for P. The average times with stable glucose >3.5 mmol/l were 9.2 h (6.9-11) for CS, 9.3 h (7.4-11.2) for MCS, and 8.7 h (7.8-10.3) for P (Fig. 3). Although the fasting times were not significantly longer with MCS for the whole group of patients, two patients (Nr. 4 and 5, Table 1) achieved relevantly longer fasting times (1.5-2 h) with glucose>4 mmol/l using MCS as compared to CS (p<0.01 MCS vs CS).

Discussion

This study demonstrates that in adult patients with GSDI alternative sources of carbohydrates such as a pasta meal before bedtime can maintain normoglycemia during the night to the same extent as uncooked corn starch. To the best of our knowledge, this is the first controlled interventional study in patients with GSDI using current CGMS technology to monitor glucose control in an outpatient setting resembling everyday life. The primary goal of dietary therapy in GSDI is stable normoglycemia. For adults, uncooked corn starch is the standard dietary regimen to achieve nighttime glucose control, and most adults will achieve good nocturnal glucose control with a
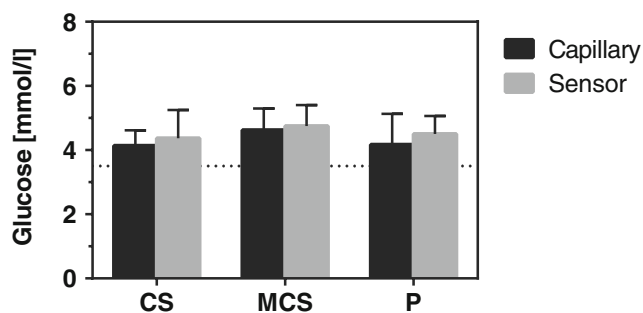
Fig. 2 Fasting glucose from capillary and sensor measurements. Bars represent arithmetic means of glucose concentration with standard deviation, measured on workdays when the first meal was taken at the usual time, on average 7.1 h (range 5.5-8.5) after bedtime. Fasting glucose concentrations were not significantly different between the three regimens. The dotted horizontal line indicates a glucose limit >3.5 mmol/l. (CS) uncooked corn starch, (MCS) modified corn starch, (P) pasta meal

single ingestion of corn starch at bedtime. Most patients are habituated to the use of cornstarch since childhood and are not adversely affected by this treatment. Although we do not advocate a permanent replacement of the established treatment with corn starch by cooked pasta, cooked pasta can be a more palatable alternative to corn starch to achieve nighttime glucose control in certain situations, and to allow for variety in
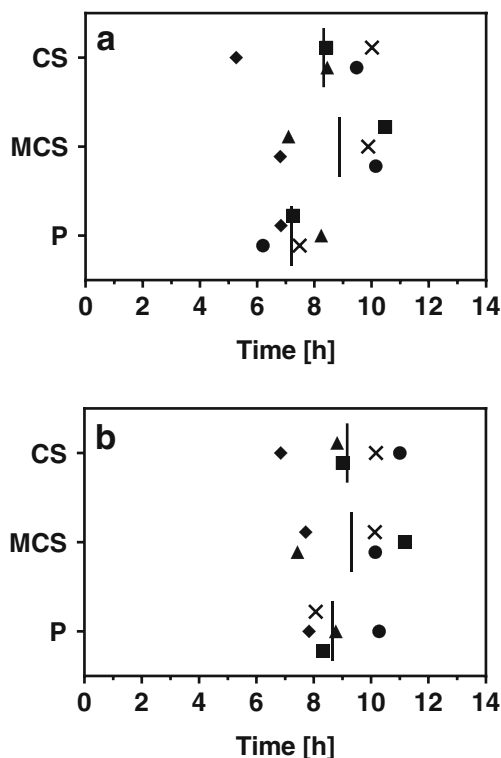

Fig. 3 Average fasting times when breakfast is delayed at weekends. (**a**) Stable glucose >4 mmol/l. (**b**) Stable glucose >3.5 mmol/l. The vertical line indicates the arithmetic mean, the points represent average fasting times of individual patients, identified by different symbol shapes (● patient 1, ▲ patient 2, ✖ patient 3, ◆ patient 4, ■ patient 5). (CS) uncooked corn starch, (MCS) modified corn starch, (P) pasta meal

choice. For an equivalent amount of carbohydrates, more calories are delivered with a pasta meal than with corn starch dissolved in water (e.g. +70-100 kcal for 126 g dry pasta compared to 100 g cornstarch, +70 kcal for a small serving of tomato sauce). Care has to be taken to avoid excessive calorie intake and overtreatment, considering that overweight is a frequent problem for patients with GSDI. Pasta is a slowly digested form of carbohydrate, since the compact structure created during the extrusion process in production of dry pasta leads to a dense protein network that reduces the availability of starch granules and their rate of breakdown by amylases (Fardet et al 1999; Aravind et al 2013). In this study, pasta was cooked just before the meal in order to guarantee good standardization. However, cooked pasta stored in the refrigerator (e.g. as pasta salad) is assumed to be at least equivalent to freshly cooked pasta, and may even have a more favourable glycemic profile with slower glucose release, due to retrogradation of starch (i.e. formation of microcrystalline structures of resistant starch from gelatinized starch (Riva et al 2000). We postulate that dry industrial pasta freshly cooked 'al dente' can substitute CS. Cooking should be firm to the bite ('al dente') to achieve adequate fasting times, and overcooking should be avoided. Different glycemic responses and fasting times may be obtained with other types of pasta. "Penne" were chosen for this study because of ease of standardization of the cooking procedure. Spaghetti may also be suitable due to a higher product density with compact structure, depending on the fabrication process (Wolever et al 1986; Bjorck et al 1994). Indeed, before this study was initiated, one of our patients who does not tolerate CS or MCS, but normally relies on overnight gastric tube feeding, consumed spaghetti meals instead of tube feeding at several occasions when using continuous glucose monitoring, and achieved good and stable glucose control (this patient was not included in the study).

The present study did not demonstrate a significant benefit of MCS compared to CS with respect to fasting time in the overall study population, although two of five patients achieved relevantly longer glucose control with MCS. However, the present study was designed to demonstrate stable nocturnal glucose control with alternative carbohydrates such as a pasta meal, and may not be powered to delimit differences between the two preparations of cornstarch. In an inpatient controlled trial, MCS has been shown to prolong fasting in some patients by 1-2 h compared to CS, however most of the benefit was noted after glucose values fell below 3.9 mmol/l (Correia et al 2008). In general, children and young adults have shorter fasting tolerance and possibly may profit to a greater degree from therapy with MCS, although this has not been proven in controlled studies.

The present study confirms that CGMS is a reliable tool to monitor glycemic control in patients with GSDI in an outpatient setting. This study has several limitations. (1) An

unblinded real time CGMS was used to protect patients from potential nocturnal hypoglycemia. Because of stable glucose control, carbohydrate intake was not necessary during night-time. We therefore assume that usage of this unblinded system did not affect the results of our study. (2) This study focuses on nocturnal glucose control, and the outpatient study design precluded measurements of lactate and triglyceride concentrations under the different nutrition regimens. However, the concentrations of these metabolite also depend on daytime glucose control and the amount of ingested sucrose/fructose or fat during the day, which have not been controlled in this study. Several dietetic studies with GSDI were performed with inpatients in a strictly controlled environment. Although this approach is helpful to reveal small differences between various nutrition regimens, it does not reproduce normal daily life and usual patient activity levels in an outpatient setting.

In conclusion, the present study clearly demonstrates that adult patients with GSDI achieve stable nocturnal glucose control with alternative slowly digested carbohydrates such as a pasta meal, and modified cornstarch may prolong fasting times compared to uncooked corn starch in some patients. In practice, large intra- and interindividual differences in glucose response to diet are common, and the optimal mode to deliver carbohydrates remains to be tailored to the individual patient. More prospective studies are needed to assess effects of different dietary treatment options on long-term outcome and quality of life in GSDI.

Conflict of interest Michel Hochuli, Emanuel Christ, Fabian Meienberg, Roger Lehmann, Jan Krützfeldt and Matthias Baumgartner declare that they have no conflict of interest.

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