

Hypoglycemia during treatment with the ketogenic diet in a child with refractory epilepsy- results of continuous glucose monitoring

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Abstract

The ketogenic diet (KD) is an effective treatment for intractable epilepsy in children. Hypoglycemia can be one of its side-effects, which is considered to be present mainly during the introductory phase of KD. Continuous glucose monitoring in a 6-year old non-diabetic child treated with KD for more than 8 months revealed long periods of asymptomatic hypoglycemia (8.9% of the total time under 2.5 mmol/l, 10.6% of the total time in the range between 2.5-3.0, 29.1% in the range of 3.0-3.6 mmol/l). The episodes of serious hypoglycemia were associated with a fasting state. The amount of sacharides in KD was increased with substantial glycemic profile improvement.

Abbreviations:

CGM	- continuous glucose monitoring
GAM	- generalized Additive Model
GT	- gastrostomy tube
KD	- ketogenic diet
MRI	- magnetic Resonance Imaging
kcal	- kilocalorie
kcal/kg	- kilocalorie per kilogram
mmol/l	- milimol per litre

INTRODUCTION

The ketogenic diet (KD) is an effective treatment for intractable epilepsy in children. It is based on a high proportion of fat, a low proportion of carbohydrate and an amount of protein adequate to the needs of the patient (deCampo & Kossoff, 2019). Although the mechanisms of its action are not fully understood, it has been shown that KD induces a small reduction in glycolysis, concomitant with an increase in non-glucose sources of fuel through the oxidation of fatty acids and ketone bodies. Thus, glycolytic restriction,

among other factors, may be an important mechanism mediating the anti-seizure properties of the KD (Rho, 2017).

Common side-effects of KD include nausea and vomiting, acidosis, hypoglycemia, and dehydration (deCampo & Kossoff, 2019).

In clinical practice, a glucose value of <3.6 mmol/l has been most often accepted as the level for defining hypoglycemia (Ly et al. 2014).

It has been documented in type 1 diabetes patients that severe as well as chronic subclinical hypoglycemia might cause alterations in normal brain and cognitive development (Cato & Hershey, 2016; Rovet & Ehrlich, 1999).

Transient hypoglycemia during the introduction of the KD is well documented (Schwartz et al. 1989). Hypoglycemic episodes in the latter phases of a stabilized diet are generally considered as not common and mild (>2.5 mmol/l), although a recently published case report showed a not inconsiderable number of hypoglycemic episodes revealed by random flash glucose monitoring also in this period of KD treatment, including those under 2.5 mmol/l (Cai QY et al. 2017; Korta et al. 2019). Regular glucose concentration monitoring is recommended during the diet initiation phase, but not in the latter phase; thus, a detailed knowledge of blood glucose excursions during the long-term treatment with KD is lacking (Kossoff et al. 2018).

Furthermore, an effect of hypoglycemia, especially serious ones (< 2.5 mmol/l) on the brain in patients on long term KD treatment, has not been investigated in detail.

Continuous glucose monitoring (CGM) is a method of tracking glucose levels in subcutaneous tissue throughout the day and night. CGM systems take glucose measurements at regular intervals of 5 minutes. These systems are used by diabetes patients treated with insulin in a „real time mode“ to improve their glycemic values but can be also used in a „blinded mode“, thus patients cannot see the values and these are retrospectively analysed in a device software (Mian et al. 2019).

We present here the results of almost 7 days of CGM in a non-diabetic patient suffering from intractable epilepsy who had been treated with KD for more than 8 months. To the best of our knowledge, this is the first use of CGM in a non-diabetes patient treated with KD.

CASE PRESENTATION

This 6-year-old girl with severe psychomotor retardation of unknown origin (metabolic screening and genetic testing were negative, brain MRI was normal), minimal motor activity, who had been fed with a gastrostomy tube (GT) since her third year, had a history of atypical absences and generalized tonic clonic seizures (GTCS), beginning at 8 months of age. She repeatedly suffered from super-refractory status epilepticus provoked by febrile illness.

Because of the refractory seizures, which occurred despite the use of multiple antiepileptic drugs, a KD (3:1, feeding 6 times a day via GT) was initiated in October 2018, while the anticonvulsants were continued without changes. KD was well tolerated. During the first 7 months, she gained 4 kg (she reached her optimal weight for her height and age); later, her weight remained stable. As for the patient, the total intake of calories per day was recently controlled at 1045 kcal (80 kcal/kg/day).

The KD led to a more than 50% reduction of seizures, and parents observed a mild improvement of behavioral functioning and activity.

The amount of ketone bodies was measured at 4.21 to 6.06 mmol/l, and the concentration of plasma glucose was measured at 4.1 to 8.0 mmol/l during the regular check-ups.

In June 2019 she was admitted for a surgical GT replacement. CGM was used to observe any glucose concentration changes during the prolonged fasting period connected to this minor surgery, and then to compare them with those during non-fasting days. During the whole period of admittance, the patient's mother was present.

Materials and Methods

For CGM the Dexcom™ G4 Platinum CGM System® (Dexcom, Inc, San Diego, CA), which measures glucose concentrations from interstitial fluid in the range of 2.2 to 22.0 mmol/l every 5 minutes, was used. The system was „blinded“, thus parents or staff were not able to see glycemic values during the monitoring period.

Data analysis

We analyze and summarize the data obtained from the CGM monitor. Because of occasional internal device problems, some glycemic values are missing during the period of interest (about 5.35% both as isolated, missing occurrences and short periods of several missing values in a row) precluding straightforward analysis. Therefore, we had to complete the data first to get unbalanced characteristics over time (means, percentages of time spent in a predefined glycemic interval, etc.). To this end, we fit a penalized spline Generalized Additive Model (GAM) using quadratic smoothness penalty and generalized cross-validation. The fitted GAM model is then used to evaluate the best prediction for the missing data points. All computations were done in the R environment (R Core Team, 2014). We considered mild hypoglycemia to be between the values 3.5-3.1 mmol/l, moderate hypoglycemia 3.0-2.6, and serious hypoglycemia ≤ 2.5 mmol/l. The completed dataset is then analyzed and summarized by various summary statistics.

Results

CGM was continuously applied for a total of 6 days 8 hours and 16 minutes with mean glycemic value

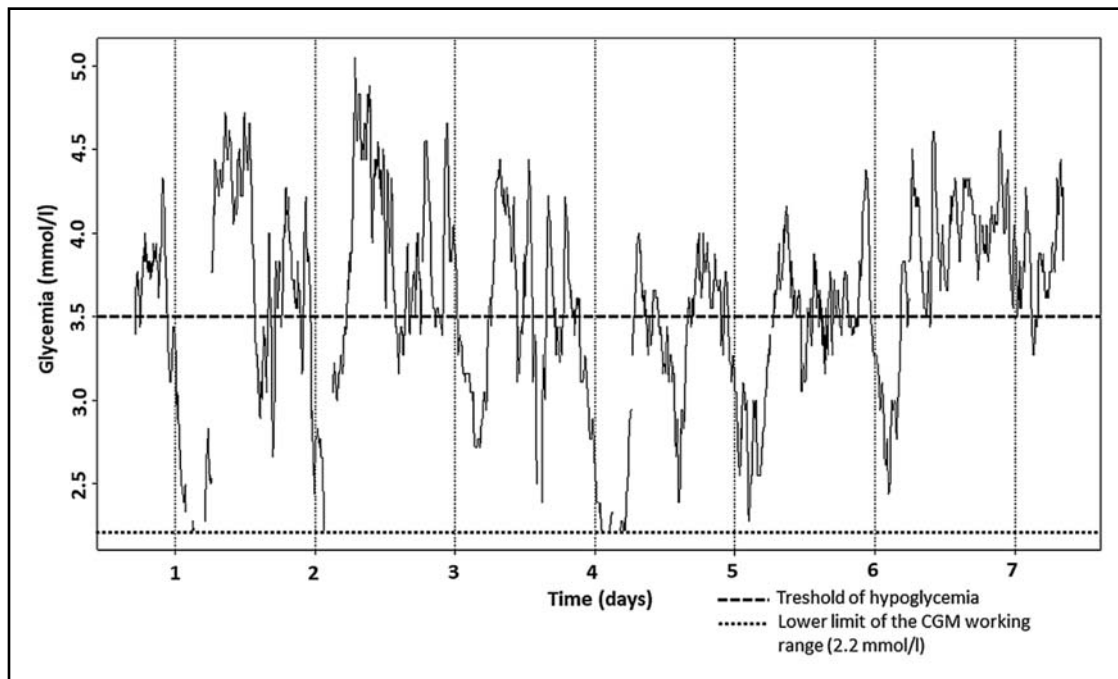


Fig. 1. Glycemic excursions during monitoring

3.6 ± 0.55 mmol/l (range, 2.2-5.1). CGM values were calibrated according to the device recommendations with the capillary glucose levels at 6:00 and 18:00. Glycemic excursions during the monitoring are shown in Figure 1.

The mean value of glycemia during fasting (defined as the period from the point of 2 hours after the last meal of the day to the point of the first meal of the following day, total time of 54 hours and 27 minutes) was 3.3 ± 0.57 mmol/l, (range, 2.2 - 4.66). The mean value of glycemia during feeding (defined as the period since the first daily meal to the point of 2 hours after the last meal of the day, total time 97 hours and 49 minutes) was 3.8 ± 0.43 mmol/l (range, 2.39-5.1). The difference was statistically significant ($p < 0.0001$, t-test). The percentage of time spent in the glycemic range ≤ 2.5 mmol/l was 8.9%; in the range between 2.6-3.0 mmol/l 10.6 %; in the range of 3.1-3.5 mmol/l 29.1%, and above 3.5 mmol/l it was 51.4% (Figure 2).

The GT replacement took 30 mins, the period of fasting was prolonged for 232 min compared with a usual day (no infusions with glucose were administered during the procedure), and glycemic values during this period were in the range 3.5-4.3 mmol/l.

The capillary glycemia was obtained regularly at 6.00 in the morning (fasting state) with a mean value 3.6 ± 0.29 , and at 18.00 with a mean value 3.7 ± 0.29 mmol/l. The levels of ketone bodies remained within the recommended range between 4.9 and 6.1 mmol/l.

During CGM, no symptoms of hypoglycemia occurred, no worsening in terms of atypical absences frequency, and no GTCS occurred.

Therapeutic intervention

An increase in carbohydrate intake was performed by the the diet ratio change to 2:1 (from previous 3:1) and also the last daily feeding was shifted to 23.00 (from previous 22.00). Subsequent systematic glucose monitoring with portable glucometer showed the mean glycemic value 4.1 ± 0.57 mmol/l, (range, 3.1 - 6.2 mmol/l). The levels of ketone bodies remained within the recommended range between 4.1 and 5.6 mmol/l. No change in the seizure frequency and types was found after the intervention.

DISCUSSION

This 6-year-old girl with severe psychomotor retardation was successfully treated with KD for refractory epilepsy for 8 months with no symptomatic or documented hypoglycemia in her history and who underwent „blinded“ CGM. For several hours of prolonged fasting during minor surgery, no significant changes of ketone levels, or hypoglycemic episodes, occurred. However, during the whole monitoring period, we could observe long episodes of hypoglycemia, in which glucose concentrations even lower than 2.5 mmol/l were recorded, especially during periods of fasting. All these hypoglycemic events, including those during waking, were asymptomatic. Additionally, during the whole period of hospitalization, no GTCS occurred, and only a few minor seizures (atypical absences) happened.

The majority of hypoglycemic episodes occurred during the period of fasting. Mean glycemia during fasting periods was significantly lower than that compared with feeding periods. Thus, we can conclude

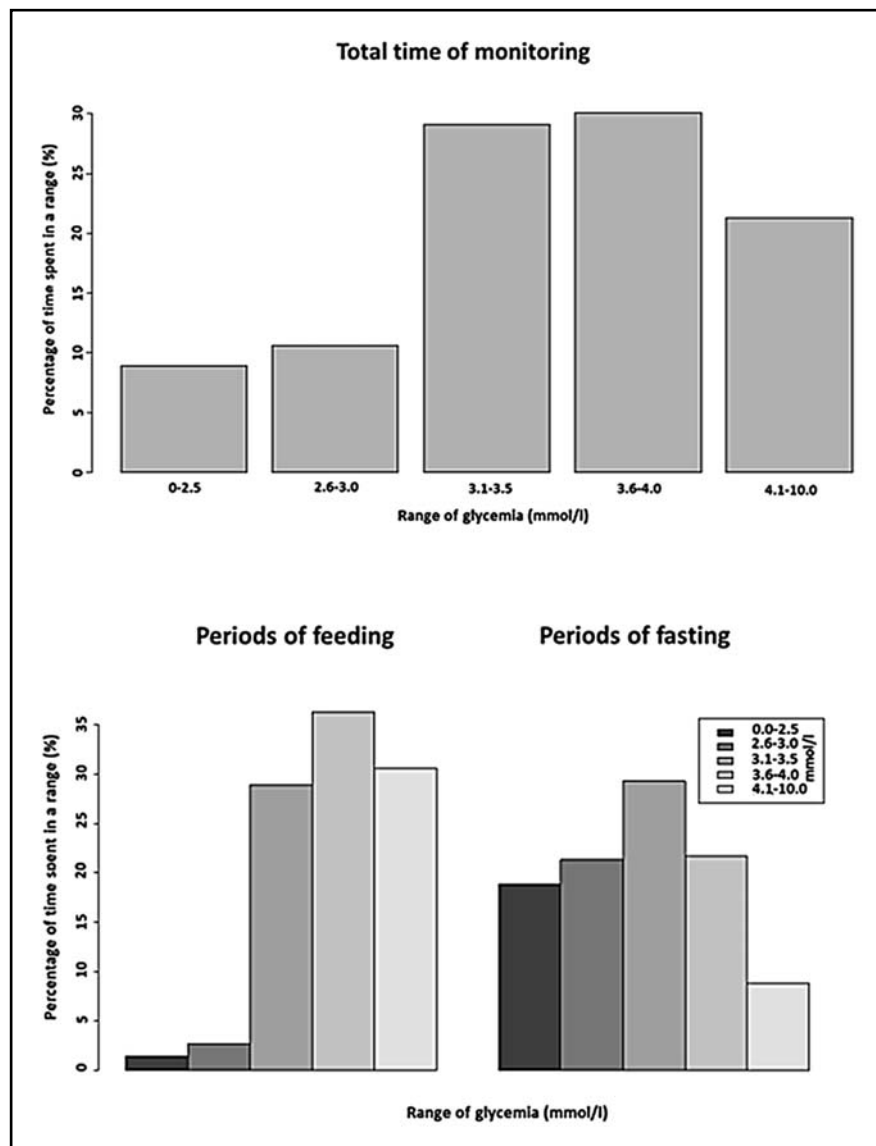


Fig. 2. Percentage of time spent in the different glycemic ranges. The upper part of the picture shows the glycemia distribution during the whole monitoring period. The lower part shows the same separately for periods of feeding (left) and periods of fasting (right)

that in this patient with minimal physical activity glucose concentration was related to feeding and serious hypoglycemias occurred mainly during fasting periods.

A limitation of our study method was the well described time-lag of the CGM (glycemic difference between capillary blood and interstitial tissue), which is mainly connected to the periods of rapid blood glucose concentrations changes (such as meals and physical activity) and may alter the accuracy of the measurement (Cengiz & Tamborlane, 2009). However, as serious hypoglycemia were found most frequently during fasting periods, we do not expect such an effect in our patient who has minimal motor activity.

CONCLUSION

In conclusion, our main finding is that periods of serious hypoglycemia can often be present during the established KD phase and may not be revealed by

random glycemia examination. The levels of glucose concentration may be asymptomatic, or overlooked in severely disabled bed-ridden patients, and are associated mainly with the time of fasting. Thus, they may be easily overlooked and constitute a source of potential danger. Further investigation in the other patients treated with KD is needed to confirm our findings. CGM may be an important tool for such an investigation.

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DISCLOSURE

None of the authors has any conflict of interest to disclose.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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