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Continuous Glucose Monitoring in Children and Adolescents with Congenital Adrenal Hyperplasia

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What is already known on this topic?

Patients with congenital adrenal hyperplasia (CAH) receive lifelong therapy with steroids. It is known that hypoglycaemia can occur in infancy and early childhood, even at night. This is a life-threatening complication. In adolescence, visceral obesity, hypertension, hyperinsulinism and insulin resistance may occur in these patients. Insulin resistance is a known risk factor for cardiovascular diseases. To date, systematic studies of glucose profiles using continuous glucose monitoring (CGM) technology in patients with CAH are lacking.

What this study adds?

Until now, there has been no systematic study of glucose profiles by CGM in patients with CAH. In this study, we examined children and adolescents with different therapy regimens using a last-generation CGM device in a home-based, blinded setting. We found morning fasting hyperglycaemia, elevated calculated glycosylated haemoglobin and overall elevated average glucose values. In particular, adolescents with reverse circadian therapy showed significantly higher values at night. These results suggest that routine and easily implementable monitoring of even subtle changes in glucose metabolism in patients with CAH should be considered. Thus, it may be possible to detect metabolic complications of the disease and also of the therapy at a very early stage.

Abstract

Objective: Patients with congenital adrenal hyperplasia (CAH) require lifelong therapy with glucocorticoids to suppress androgen excess and substitute for deficient cortisol. An important aspect of care is the prevention of metabolic sequelae. In infants, potentially lethal nocturnal hypoglycaemia has been described. In adolescence, visceral obesity, hypertension, hyperinsulinism and insulin resistance are reported. To date, systematic studies of glucose profiles in this age group with CAH are lacking.

Methods: This was a monocentric, prospective, observational study to determine the glucose profiles under different treatment regimens in a cohort of young patients with CAH. The continuous glucose monitoring device used was the latest generation FreeStyle Libre 3® sensor in blinded mode. Therapeutic and auxological data were obtained.

Results: The cohort consisted of 10 children/adolescents with a mean age of 11 years. Three patients exhibited morning fasting hyperglycaemia. Overall, 6 out of 10 patients had unacceptably few total values in the desired range of 70-120 mg/dL. Tissue glucose values above 140-180 mg/dL were found in 5 of 10 patients. The mean value for glycosylated haemoglobin for the cohort was of 5.8%. All pubertal adolescents with reverse circadian regimens had significantly higher glucose levels at night. Two adolescents showed asymptomatic nocturnal hypoglycaemia.

Conclusion: Most of the patients exhibited abnormalities in glucose metabolism. Two-thirds had elevated total 24h glucose values outside the age-appropriate reference values. Thus, this aspect may need to be addressed early in life by adjusting the doses, treatment regimen or dietary measures. Consequently, reverse circadian therapy regimens should be critically indicated and closely monitored due to the potential metabolic risk.

Keywords: Congenital adrenal hyperplasia, continuous glucose monitoring, hypoglycaemia, hydrocortisone

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Introduction

Patients with classical congenital adrenal hyperplasia (CAH) have a genetically impaired steroid biosynthesis, which in most cases is due to a reduction or lack of function of the enzyme 21-hydroxylase. Impaired steroid synthesis affects glucocorticoids and, in some cases, mineralocorticoids (1,2,3). A distinction is made between two forms, the simple virilizing (SV) and the salt wasting (SW) form (4). If left untreated, CAH can lead to life-threatening SW crises in both sexes and virilization in girls. Thus, the rationale for lifelong treatment with steroids is glucocorticoid substitution and androgen suppression. In case of SW, additional substitution with mineralocorticoids is indicated (1,2,3). When caring for patients with CAH, special attention should be paid to the possible long-term complications, such as obesity, accelerated pubertal development, impaired neurological development, cardiovascular diseases and reduced final height (5).

Continuous glucose monitoring (CGM) is an established method for measuring glucose in the interstitial fluid in children and adults with type 1 diabetes (6,7,8). The advantages of this method are evident, especially in paediatrics. After application of the CGM device, glucose measurement in the interstitial fluid can be performed continuously for up to 14 days without further pricks in the skin, in contrast to the classical self-monitoring of blood glucose that requires multiple finger-sticks per day. There is a good correlation between blood glucose and tissue glucose (9). The last generation sensor from Abbott Diabetes Care (FreeStyle Libre 3®) used in this study showed a very good overall mean absolute relative difference of 7.9% in patients with type 1 diabetes mellitus (10). Very few studies are available on the use of CGM systems in non-diabetic patients (11,12,13,14). However, Shah et al. (15) recently presented a study on normal values of CGM profiles in children and adults. This important work can be used as a basis for evaluating glucose metabolism in hormone-related diseases. However, there are currently no prospective studies on glucose profiles of children and adolescents with CAH. Xiang et al. (16) reported an adult patient with CAH where cortisol dosage adjustment was facilitated by the use of a flash glucose monitoring system.

It is known that hypoglycaemia can occur in patients with CAH, especially under stress in infancy and early childhood (17,18,19,20,21). Episodes of nocturnal asymptomatic hypoglycaemia have also been reported under normal conditions (22). There are numerous reports of lethal outcomes of hypoglycaemic seizures and coma (23). A lack of counter-regulation by means of epinephrines from the adrenal medulla is also likely to be the cause of the hypoglycaemia (24). Standardized recommendations for glucose measurement do not exist for patients with CAH.

In CAH, in adolescence and adulthood, the focus changes to possible metabolic risk factors. Thus, in CAH there is an increased risk for visceral obesity, dyslipidemia, hypertension, venous thromboembolism, hyperinsulinism and insulin resistance. This in turn results in an increased risk for impaired fasting glucose (IFT), impaired glucose tolerance and thus type 2 diabetes (25,26,27). The use of CGM is well established in obesity research and adds to the methodological repertoire. While fasting glucose measurements in the morning, the measurement of glycosylated haemoglobin (HbA1c) and the oral glucose tolerance test provide important clinical data, the use of CGM can provide continuous data from patients' daily lives. Data in children and adolescents is very limited (28,29). Previous studies have specifically demonstrated insulin resistance and fasting hyperglycemia in children and adults with CAH (30,31). Another study in children showed an increased homeostasis model assessment for insulin resistance in children with CAH (32). However, altered parameters for insulin secretion and sensitivity could not be associated with an increased risk of type 2 diabetes (33). In this context, the known unfavorable influence of steroids on glucose metabolism should be noted.

The purpose of the present study was to examine CGM profiles of children and adolescents with CAH under different treatment regimens to investigate the following aspects: evaluating the time in range (TIR) according to time of day and night; occurrence of (asymptomatic) hypoglycaemia; occurrence of hyperglycaemia; or evidence of IFT depended on the treatment regimen.

Methods

Patients

This was a monocentric, prospective, observational study from December 2021 to December 2022 to determine the glucose profiles of patients with CAH undergoing different treatment regimens. All patients had genetically confirmed classical CAH (with and without SW). The exclusion criteria were the use of medication with an influence on glucose metabolism other than steroids and a special nutritional therapy or diet. The age range for the inclusion criteria was 4 to 18 years. As the sensor is approved for use from the age of 4 years, it was not possible to include younger children. Both patients and parents gave written informed consent/assent to participate in the study. All patients were seen at the Division for Paediatric Endocrinology at Dr. von

Hauner Children's Hospital based at the University Hospital Munich (Ludwig Maximilian University). The same team of doctors treated all patients. All study participants received hydrocortisone three times a day at the following times: in the morning between 7 and 9 am; at noon between 1 and 3 pm; in the evening between 8 and 10 pm. The intake times usually coincided with the intake of the three main meals. There was no documentation of physical activity, eating habits or meals.

Investigations

After medical consultation, the sensor was applied to the dorsal upper arm by a study doctor, as instructed by the manufacturer. Only the latest generation FreeStyle Libre 3® sensor was used (Abbott Diabetes Care Ltd., Range Road, Wittney, Oxon, OX29 OYL, United Kingdom). The patient and parents received no feedback from the sensor (blinded). There were no adverse events. All sensor data were complete according to the study protocol. The clinical characteristics were obtained through a review of patients' medical records with the following information extracted: age; sex; CAH type; weight; height; body mass index (BMI); BMI percentile; weight status category; height standard deviation score (HSDS); type of steroid replacement therapy; treatment pattern; waist circumference; pubertal stage; and other medications. The references of BMI-SDS were obtained from Kromeyer-Hauschild et al. (34). The references of HSDS were obtained from Prader et al. (35). The reference ranges for weight status category by percentile range were taken from Barlow (36).

This research related to human participants complied with all the relevant national regulations, institutional policies and was performed in accordance with the tenets of the Helsinki Declaration and was approved by the authors' Institutional Ethical Review Board and with the permission of the patients and their legal guardians. The study was approved in advance by the "Ethikkommission der Medizinischen Fakultaet" at the Ludwig Maximilian University in Munich (approval number: 21-0658, date: 10.09.2021).

Data Processing and Presentation

After completion of the observation phase, the tissue glucose values were extracted using the procedure specified by the manufacturer. This generates a file containing the following data over the entire observation period: continuous 5-minutes documentation of glucose values in mg/dL (blood glucose conversion factor: 1 mg/dL = 0.0555 mmol/L and 1 mmol/L = 18.018 mg/dL) and Glucose Management Indicator in %, that is the calculated value for HbA1c. Tissue glucose values were recorded as mean values with standard deviation over the entire observation period. The sum (n) of the individual measurements was calculated. Measurements were subdivided into day values (8 am to 8 pm) and night values (8 pm to 8 am). In addition, the observation period was divided into 6-hour segments to investigate the influence of different doses of hydrocortisone on tissue glucose values (6 am to 12 am; 12 am to 6 pm; 6 pm to 12 pm; 12 pm and 6 am).

The time for specific ranges of tissue glucose proportionally in % were analyzed, in terms of total, day and night values. Deviation from the reference values, as defined and published by Shah et al. (15) was investigated.

Furthermore, we were able to perform an averaged fasting glucose analysis. Here, the mean value of the 6 am glucose was determined over all examination days. The reference values (normal < 100 mg/dL and elevated > 100 mg/dL) are taken from Speiser et al. (37). Tissue glucose values below 60 mg/dL were considered hypoglycaemia.

Statistical Analysis

Due to the normal distribution of the single values for tissue glucose, the unpaired t-test was calculated to determine statistical significance. Significance was assumed when the p value was below 0.05. Statistical analysis was performed using Statistical Package for the Social Sciences software for Windows version 15.0 (IBM Inc., Armonk, NY, USA).

Results

Clinical-therapeutic Findings

The clinical characteristics of the patients are shown in Table 1. A total of 10 patients (six boys) were included with a median age was 11 years (range 6-15 years). Five patients were still prepubertal. One patient had a SV form of CAH. The median dose of hydrocortisone was 14.16 (7.05-20.98) mg per square metres of body surface per day (mg/m^2 BSA/day). Except for one patient (vitamin D), there was no comedication. The median dose for fludrocortisone was 0.05 mg per day absolute (range 0-0.125 mg/day). Four patients were obese, two were overweight and the remaining four were normal weight according to Barlow (36). The mean absolute values for BMI were 23.32 kg/m^2 (range 16.2-33.8 kg/m^2). As a further marker for the evaluation of weight status, we determined the waist circumferences. Based on the study by Maffeis et al. (38), two patients had normal waist circumferences, one patient had waist circumferences indicating overweight and five patients had waist circumferences indicating obesity. In two patients, the waist circumference was not recorded. The patients

were all treated with hydrocortisone as a glucocorticoid. The distribution of treatment regimens was as follows. No patient with was receiving a circadian regimen, six patients were on the reverse circadian regimen, one patient was receiving equal doses throughout the day, two patients had higher morning and evening doses (which were equal) compared to the afternoon dose, while one patient used another regimen (the lowest dose in the morning and higher and equal doses at noon and in the evening). Severe deviations of the metabolic parameters before and after the measurements shown here or adrenal crises were not observed (data not shown).

Average Fasting Hyperglycaemia and HbA1c

Table 2 shows the mean, total, day and night and every 6-hour period glucose values. The sum (n) of the individual measurements is shown in brackets. Three out of 10 patients showed morning fasting hyperglycaemia, which was defined as a fasting value >100 mg/dL (Table 3). The automatic algorithm of the FreeStyle Libre 3® CGM device allows the specification of a calculated value for HbA1c. The calculated mean value for HbA1c was 5.8% (range 5.7-6.0%).

Tissue Glucose Values by Time of Day

The CGM was conducted without interruptions for a mean of 205 (range 162-335) hours. The mean values including standard deviation for tissue glucose are shown in Table 2. The values are given as mean total values and mean values for the day and for the night. Remarkably, in four patients the mean values from 8 pm in the evening to 8 am in the morning were significantly higher ($p = 0.0001$) than from 8 am in the morning to 8 pm in the evening. All four patients were pubertal and all received reverse circadian glucocorticoid therapy. Two were obese and two were normal weight. In comparison, of the five prepubertal children, only

Table 1. Clinical and auxological characteristics of patients with CAH

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5		Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Age (years)		6	7	8	8	11		11	13	15	15	15
Sex (male/female)		M	M	M	F	M		F	M	F	F	M
CAH type (SW/SV)		SW	SW	SW	SW	SW		SW	SW	SW	SW	SV
Weight (kg)		19.8	20.5	32.5	36.0	58.0		39.8	51.8	82.0	79.5	77.0
Weight (Z-score)		-1.14	-0.77	+0.46	+1.4	+1.58		+0.03	-0.19	+2.16	+2.0	+1.29
Height (cm)		112.9	112.4	125.3	133.5	145.0		142.0	161.0	155.8	155.4	170.1
Height (SDS)		-1.6	-1.6	-1.5	+1.0	-0.5		-0.7	-0.2	-1.3	-1.4	0.0
BMI (percentile)		48th	66th	94th	94th	99th		75th	61st	>99th	>99th	96th
Weight status category (N/OW/OB)		N	N	OW	OW	OB		N	N	OB	OB	OB
BMI (kg/m^2)	Prepubertal	15.5	16.2	20.7	20.2	27.59	Pubertal	19.7	20.0	33.8	32.9	26.6
Waist circumference (cm)		54.0	52.5	69.0	Unknown	Unknown		70.0	76.0	115.0	97.0	84.5
Waist circumference (Z-score)		No ref.	No ref.	No ref.	No ref.	No ref.		+0.86	+0.72	+2.67	+2.23	+1.29
Pubertal state (Tanner)		Prepub.	Prepub.	Prepub.	Prepub.	Prepub.		P2, B2	P3, G3	Adult	Adult	Adult
HC regimen (distribution: morning-at noon-evening)		2.5-2.5-5.0	5.0-2.5-5.0	2.5-2.5-2.5	3.0-5.0-5.0	5.0-5.0-7.5		5.0-5.0-10.0	10.0-5.0-12.5	7.5-5.0-7.5	10.0-7.5-15.0	12.5-10.0-17.5
HC dose (mg/m^2 BSA/day)		12.69	15.63	7.05	11.26	11.45		15.96	18.07	10.62	17.55	20.98
FC dose (mg/day)		0.025	0.05	0.05	0.025	0.075		0.05	0.05	0.125	0.075	0
Other medication		None	None	None	None	None		None	None	None	None	Vitamin D
RR		Normal	Normal	Normal	Normal	Normal		Normal	Normal	Normal	Normal	Normal
Clinical signs of hyperinsulinism		None	None	None	None	None		None	None	None	None	None

BSA: body surface area, CAH: congenital adrenal hyperplasia, FC: fludrocortisone, HC: hydrocortisone, N: normal weight status category, OW: overweight status category, OB: obese weight status category, SV: simple virilizing, SW: salt wasting, M: male, F: female

Table 2. Tissue glucose values depending on the time of day and total wearing time of the CGM device in patients with CAH

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5		Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Wearing time CGM (h)		203	162	169	173	335		279	195	177	190	163
Glucose mean ± SD total		103 ± 18 (2423)	103 ± 16 (1928)	112 ± 13 (2026)	99 ± 13 (2068)	105 ± 16 (4010)		102 ± 16 (3558)	113 ± 15 (2350)	103 ± 15 (2118)	98 ± 14 (2273)	105 ± 17 (1949)
Glucose mean ± SD 8 am to 8 pm		106 ± 17 (1257)	109 ± 17 (958)	115 ± 12 (1019)	101 ± 15 (1064)	106 ± 18 (1996)		99 ± 15 (1782)	109 ± 14 (1184)	109 ± 17 (1092)	96 ± 13 (1121)	102 ± 19 (941)
Glucose mean ± SD 8 pm to 8 am	Prepubertal	100 ± 19 (1166)	97 ± 12 (970)	110 ± 14 (1007)	96 ± 11 (1004)	104 ± 13 (2015)	Pubertal	106 ± 15 (1776)	116 ± 16 (1166)	104 ± 14 (1026)	100 ± 13 (1152)	108 ± 16 (1008)
Glucose mean ± SD 6 am to 12 am		101 ± 21 (584)	105 ± 16 (434)	112 ± 13 (503)	95 ± 13 (504)	94 ± 12 (1008)		96 ± 12 (864)	108 ± 12 (575)	98 ± 13 (497)	92 ± 11 (545)	96 ± 10 (485)
Glucose mean ± SD 12 am to 6 pm		106 ± 17 (647)	109 ± 17 (500)	117 ± 14 (504)	102 ± 16 (560)	110 ± 17 (1003)		100 ± 17 (894)	111 ± 14 (585)	106 ± 19 (564)	97 ± 16 (576)	105 ± 21 (456)
Glucose mean ± SD 6 pm to 12 pm		109 ± 18 (616)	105 ± 15 (503)	117 ± 12 (504)	101 ± 13 (502)	115 ± 14 (991)		104 ± 16 (936)	115 ± 18 (614)	104 ± 15 (546)	100 ± 14 (576)	109 ± 18 (504)
Glucose mean ± SD 0 am to 6 am		95 ± 12 (576)	94 ± 9 (491)	103 ± 8 (504)	95 ± 9 (502)	102 ± 10 (1008)		108 ± 14 (864)	116 ± 16 (576)	106 ± 13 (504)	102 ± 11 (576)	109 ± 14 (504)

Notice: All values for tissue glucose are given in mg/dL ± SD. The number of measurements (n) is given in brackets.
am: ante meridiem, CGM: continuous glucose measurement, h: hours, pm: post meridiem, SD: standard deviation, CAH: congenital adrenal hyperplasia, CGM: continuous glucose monitoring

Table 3. Average fasting glucose at 6 am and calculated HbA1c in patients with CAH

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5		Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Mean TG	Prepubertal	82	90	101*	86	91	Pubertal	97	110*	90	94	104*
SD		7	10	3	6	9		12	11	11	8	6
n		8	6	7	7	14		13	8	7	8	7
GMI		5.8	5.8	6.0	5.7	5.8		5.8	6.0	5.8	5.7	5.8

Notice: Glucose values expressed in mg/dL, *Elevated fasting glucose value as defined in the method section.
HbA1c: glycosylated haemoglobin, GMI: glucose management indicator (= calculated HbA1c), n: quantity, SD: standard deviation. TG: tissue glucose, CAH: congenital adrenal hyperplasia

two were treated with reverse circadian regimen. These two patients showed no nocturnal abnormalities. As our patients usually take their medication at the same time as their meal, a direct influence of food or medication on tissue glucose levels cannot be differentiated. When the four pubertal patients were examined at 6-hour intervals, the values in the first segment from 6 am to 12 am were lower in all of them than in the evening between 6 pm and 12 pm ($p = 0.0001$) and in the night from 12 pm to 6 am ($p = 0.0001$). In the latter period, the effect of food can no longer be expected.

Comparison Between CAH and Control Population

Table 4 shows a comparison of tissue glucose values (percentage of time within a particular range) of patients with CAH with a healthy reference cohort (15), depending on time of day. No patients showed hypoglycaemia during the day or overall. Two patients (patient 9 and 10) showed nocturnal hypoglycaemia, but no clinical symptoms were reported by the patients or parents. It is worth mentioning that both patients were obese and received a reverse circadian therapy regimen. Overall, 6 out of 10 patients had low TIR (70-120 mg/dL) values. This finding was detected during the day in 8 of 10 patients and at night in 6 of 10 patients. Tissue glucose values above 140 mg/dL, above 160 mg/dL and above 180 mg/dL were found in 5 of 10 patients studied overall and during the day, and in 4 of 10 patients at night.

Table 4. Comparison of tissue glucose values (percentage of time within a particular range) of patients with CAH with a previously reported healthy reference cohort by time of day

		Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
>180 mg/dL total	0 am-12 pm	0	0	0.1	0	0.1	0.1	0	0	0	0.2
>160 mg/dL total		0.5	0.1	0.7	0	0.2	0.1	0.5	0.4	0	0.4
>140 mg/dL total		3.2	2.4	3.3	1.4	2.0	1.9	4.7	2.5	0.6	2.7
70-140 mg/dL total		95.8	97.1	96.9	98.2	98.0	97.2	95.0	97.1	98.5	96.5
70-120 mg/dL total		81.6	84.6	77.2	93.1	84.6	88.3	71.1	87.4	93.6	81.6
<70 mg/dL total		1.0	0.5	0	0.4	0.2	0.9	0.3	0.4	0.8	0.9
<60 mg/dL total		0.2	0.2	0	0	0	0.3	0.2	0	0.2	0.5
<54 mg/dL total		0	0	0	0	0	0.1	0.1	0	0.2	0.3
>180 mg/dL day	8 am-8 pm	0.1	0	0.1	0	0.2	0.1	0	0	0	0.3
>160 mg/dL day		0.6	0.1	0.9	0	0.2	0.2	0.4	0.3	0	0.6
>140 mg/dL day		4.2	3.2	4.3	1.9	2.6	1.6	4.3	2.7	0.8	3.0
70-140 mg/dL day		94.7	96.7	95.9	98.0	97.2	97.4	95.3	96.8	98.6	96.8
70-120 mg/dL day		76.8	80.0	70.8	91.3	80.2	89.4	74.1	86.4	92.5	82.7
<70 mg/dL day		1.0	0.1	0	0.2	0.2	1.0	0.4	0.6	0.6	0.2
<60 mg/dL day		0.3	0.1	0	0.1	0	0.3	0.2	0.1	0	0.1
<54 mg/dL day		0	0	0	0	0	0.1	0.1	0.1	0	0.1
>180 mg/dL night	8 pm-8 am	0	0	0	0	0	0	0	0	0	0
>160 mg/dL night		0	0	0	0	0	0	0.5	0.6	0	0
>140 mg/dL night		0	0	0	0	0	2.5	5.4	1.8	0	1.8
70-140 mg/dL night		99.1	100	100	98.8	100	97.0	94.6	98.2	98.4	95.4
70-120 mg/dL night		96.7	98.4	96.6	98.8	98.5	84.8	58.5	90.7	97.0	78.6
<70 mg/dL night		0.9	1.6	0	1.2	0	0.5	0	0	1.6	2.8
<60 mg/dL night		0	0.4	0	0	0	0.2	0	0	0.7	1.4
<54 mg/dL night		0	0	0	0	0	0	0	0	0.7	0.8

According to the time of day (day 8 am-8 pm, night 8 pm-8 am or total 0 am-12 pm), ranges of tissue glucose values were given in the first column. All tissue glucose values (indicated as a percentage of the total time within the specific range) that lie within the age-appropriate norm values for the specific range as published by Shah et al. (15) are highlighted in gray. All tissue glucose values outside the above-mentioned norm values are highlighted in light gray.

pm: post meridiem, am: ante meridiem, CAH: congenital adrenal hyperplasia

Discussion

In this study, we were able to use continuous tissue glucose measurement for the first time to systematically evaluate glucose profiles in patients with CAH. The average observation time of 205 hours was fairly long and compensated for the expected fluctuations between individual days (Table 2). A major distinctive feature of this study is the investigation of glucose levels in the context of the patients' regular everyday life. We compared the tissue glucose values overall and divided into day and night with the published reference values of Shah et al. (15). Only these published reference data were available for comparison. However, the reference data of Shah et al. (15) were collected using a different technical system, the Dexcom G6 CGM System (DexCom Inc., 6340 Sequence Drive, San Diego, CA 92121, USA). This may potentially affect the comparability of tissue glucose values. Overall, many subjects showed elevated tissue glucose levels (Table 4). In percentage terms, 60% had too many values outside the desired range of 70-120 mg/dL and even using an extended range (70-140 mg/dL) 40% of patients were still outside the range. In addition, we were also able to diagnose morning fasting hyperglycaemia in 3 out of 10 patients using CGM. Torky et al. (30) demonstrated fasting hyperglycaemia in over 93.0% of cases at one or more visits. In our cohort, fasting hyperglycaemia was present in fewer patients. As in the cohort of Torky et al. (30), one of the patients in our study with fasting hyperglycaemia was prepubertal and only 8 years old. Another study by Metwalley et al. (32) also found increased fasting glucose in children with CAH. It has been reported that the increased fasting hyperglycaemia in young patients with CAH seems to subside in young adulthood (30). However, in a large cohort of adults, impaired fasting blood glucose was found in 6-8% of adults (39). The data on evident diabetes mellitus type 2 in patients with CAH is inconclusive. While one study from Sweden reported an increased prevalence, this was not found in other cohorts (26). However, reduced insulin sensitivity has been repeatedly shown in other studies (40,41,42,43). The contribution of long-standing adrenomedullary hypofunction and intermittent iatrogenic hypercortisolism to insulin resistance has not yet been conclusively clarified (44). Hyperinsulinism is an independent risk factor for cardiovascular disease in non-diabetics (45). CGM technology may identify changes in glucose-insulin metabolism at a very early stage. Subtle abnormalities can also potentially be early warning signs. Thus, in terms of a primary preventive measure, one could probably reduce cardiovascular morbidity through regular screening and early intervention. For instance, the efficacy of insulin sensitizer (piaglitazone) has been shown in adult patients with CAH (46). However, whether insulin resistance is a condition that requires treatment in all patients will have to be investigated further. For example, compensation for insulin resistance via reduced hepatic insulin clearance has been shown in patients with CAH (47). With regard to hyperglycaemia, we identified four patients with significantly higher mean glucose values at night (8 pm to 8 am) than during the day (8 am to 8 pm). Remarkably, all four patients were of pubertal age and all received reverse circadian therapy (Tables 2, 4). It is difficult to separate the influence of hydrocortisone from the influence of food. However, it seems plausible that with the highest hydrocortisone dose in the evening, a tendency to hyperglycaemia may be increased at night. For a more precise distinction between the influence of therapy and eating behaviour, we also performed a 6-hour analysis of the mean values (Table 2). This showed highly significant lower values in the morning (6 am to 12 noon) compared to the evening (6 pm to 12 pm) and night (12 pm to 6 am) for these four patients. Overall, the values at night, which are presumably independent of food intake between 12 pm and 6 am, were still higher than in the morning and in the afternoon. The differences in absolute values must be considered relevant here, as there is no drop in value during the night. In addition, the CGM device gives a calculated value for HbA1c (Table 3), which was 5.8% on average and thus above the age-appropriate norm compared to data reported by Peplies et al. (48). The comparability of a measured and calculated HbA1c value can also be a source of inaccuracy. However, the clinically and biochemically adjusted increased dose of hydrocortisone, which is partly above the international recommendation, may have had a negative influence on glucose homeostasis.

With regard to hypoglycaemia, two patients had relatively frequent glucose levels below 54 mg/dL at night, but not during the day (Table 4). This lower threshold value of 54 mg/dL is internationally regarded as a reasonable lower limit for studies (49). However, it is also known that the sensitivity of all CGM devices decreases and false alarms can occur at low values (50). Since our patient population was blinded to the values, no capillary blood glucose measurement was performed for verification. This is always strongly recommended in an open use of CGM devices. Thus, there is a risk of inaccuracies in the hypoglycaemic range. However, both patients with evidence of hypoglycaemia at night showed increased mean values during the same period. This could be an indication of nocturnal glucose instability. In the context of the known studies on nocturnal hypoglycaemia in patients with CAH, the age of our two patients seems unusually old at 15 years and both patients were obese (17,18,19,20,21). Children younger than 4 years

were not included in the present study as the CGM device is only approved for use from this age onward.

Children and adolescents with CAH in this study had a calculated average HbA1c of 5.8% (Table 3), three children had fasting hyperglycaemia and 6 of 10 children had overall average values above the age-appropriate norm. In particular, all adolescents with reverse circadian therapy had higher tissue glucose values at night compared to during the day. In summary, reversed circadian therapy must be critically indicated in adolescents and may require special monitoring. Furthermore, when caring for patients with CAH, the focus must be on early indications of insulin resistance. However, the different values for BMI, age, gender, and pubertal stages limit comparability and statistical significance.

Study Limitations

The most relevant limitations of this study is the small number of cases, the lack of very young participants (< 4 years) and the technical measurement inaccuracy of the glucose sensors, especially in low ranges.

Conclusion

The use of CGM in patients with CAH may facilitate prompt identification of mean glucose values deviating from the reference population, thus providing an opportunity for early intervention. Based on individual glucose profiles, therapy dose, regimen and dietary habits or drug therapies should be discussed for the most severe cases. Especially for young children, the monitoring of nocturnal hypoglycaemia is potentially of great importance, for which further studies will be required.

We are convinced that this approach is in the best interest of personalised medical care for paediatric patients with CAH.

Ethics

Ethics Committee Approval: The study was approved in advance by the "Ethikkommission der Medizinischen Fakultaet" at the Ludwig Maximilian University in Munich (approval number: 21-0658, date: 10.09.2021).

Informed Consent: All patients and legal guardians provided written informed consent to participate in our study for continuous glucose measurement in congenital adrenal hyperplasia (CGM in CAH-Study).

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: Ilja Dubinski, Heinrich Schmidt, Design: Ilja Dubinski, Susanne Bechtold-Dalla Pozza, Hannah Franziska Nowotny, Nicole Reisch, Lea Tschaidse, Heinrich Schmidt, Data Collection or Processing: Ilja Dubinski, Susanne Bechtold-Dalla Pozza, Belana Debor, Nicole Reisch, Heinrich Schmidt, Analysis or Interpretation: Ilja Dubinski, Susanne Bechtold-Dalla Pozza, Hannah Franziska Nowotny, Nicole Reisch, Lea Tschaidse, Heinrich Schmidt, Literature Search: Ilja Dubinski, Belana Debor, Hannah Franziska Nowotny, Nicole Reisch, Lea Tschaidse, Heinrich Schmidt, Writing: Ilja Dubinski.

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