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Original article

10 patients, 10 years – Long term follow-up of cardiovascular risk factors in Glut1 deficiency treated with ketogenic diet therapies: A prospective, multicenter case series

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SUMMARY

Background and aims: Glut1 Deficiency (Glut1D) is caused by impaired glucose transport into brain. The resulting epileptic encephalopathy and movement disorders can be treated effectively by high-fat carbohydrate-restricted ketogenic diet therapies (KDT) mimicking fasting and providing ketones as an alternative cerebral fuel. Recently 6–24 months follow-ups of epileptic patients reported elevated blood lipids and intima thickening of the carotid artery raising concerns about potential cardiovascular risks by KDT. To clarify potential cardiovascular risks we performed a prospective 10 year follow up of 10 Glut1D patients.
Methods: Between August 2001 and January 2016 we enrolled Glut1D patients on KDT at two hospitals in Germany in this prospective, multicenter case series. The minimal follow up was 10 years. Standard deviation scores (SDS) of body mass index (BMI), total cholesterol (TC), HDL-/LDL cholesterol, and triglycerides (TG) before initiation of KDT were compared with respective values at 6 months, 2, 5 years, and 10 years after initiation. After 10 years on KDT cardiovascular risk, assessed by BMI, carotid intima-media thickness (CIMT) measurement, and blood pressure, was compared to a healthy reference population (n = 550).
Results: Baseline and 10 year follow-up investigations were available for 10 individuals with Glut1D on KDT. After two years on KDT BMI increased significantly, while total cholesterol, HDL-cholesterol, and LDL-cholesterol decreased. Within 3–5 years on KDT these differences disappeared, and after 10 years blood lipid parameters reflected the situation at initiation of KDT. Prior to KDT one child had dyslipidaemia, but no child after 10 years on KDT. No significant differences were observed with respect to BMI SDS ($p = 0.26$), CIMT ($p = 0.63$) or systolic and diastolic blood pressure (SDS $p = 0.11$ and $p = 0.37$, respectively) in Glut1D children treated with KDT for at least 10 years compared to healthy controls.
Conclusions: In contrast to previous short-term reports on adverse effects of KDT, 10-year follow-up did not identify cardiovascular risks of dietary treatment for Glut1D.

1. Introduction

Glut1 Deficiency (Glut1D) is a rare and treatable disorder of cerebral energy metabolism. A defect of the facilitated glucose transporter GLUT1 at the blood–brain barrier and in brain cells impairs glucose transport into the brain. The cerebral energy deficit results in impaired development, epilepsy, and complex movement

Abbreviations: BMI, body mass index; Glut1D, Glut1 Deficiency; KDT, ketogenic diet therapies; CSF, cerebral spinal fluid; CIMT, carotid intima-media thickness.

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disorder in children and adults [1–3]. In adolescents and adults, atypical manifestations such as paroxysmal exercise-induced dystonia and stomatin-deficient cryohydrocytosis enlarge the clinical spectrum [4]. The diagnosis of Glut1D is based on low CSF glucose concentrations termed hypoglycorrhachia and mutations in the *SLC2A1* gene. The condition can be treated effectively and exclusively by high-fat, carbohydrate-restricted ketogenic diet therapies (KDT). KDT mimic the metabolic state of fasting and ketones from dietary fat serve as an alternative fuel for the developing brain. As such, KDT in Glut1D currently are the treatment of choice from infancy into adulthood, which has raised concerns about potential long-term cardiovascular risks. Available data on KDT in intractable childhood epilepsy is restricted to follow-ups of six months with individual follow-up of up to three years. Several studies in approximately 400 children on KDT have addressed these concerns by investigating blood lipid profiles as well as carotid intimal wall thickness (CIMT) and vessel distensibility as measured by carotid artery ultrasound [5–10]. Results beyond 1–2 years on KDT are limited, although some studies report increased serum lipids [8,9] and intimal wall thickness changes [5,6,9]. For Glut1D, no data is available. To further clarify potential cardiovascular risks on KDT we performed a prospective long-term follow-up of $\geq$10 years in Glut1D patients on KDT.

2. Material and methods

2.1. Study design and participants

This is a prospective, observational multicenter case series of Glut1D patients on KDT. We enrolled 65 patients under 18 years of age (1 month - 18 years) diagnosed with Glut1D by hypoglycorrhachia and/or *SLC2A1* mutations, from August 2001 to January 2016, at Children's Hospitals of Aschaffenburg-Alzenau, Germany, and Essen University, Germany. The number of patients differed between centers contributing to this case series (Aschaffenburg-Alzenau: n = 38, Essen: n = 27). Follow-up investigations were routinely performed in both centers. Patients were assessed every 6–12 months for effects of KDT and cardiovascular risk by history, neurological examination, and lipid profiles. Collected data included gender, *SLC2A1* mutations, predominant clinical phenotype, and age at onset, type, duration, and ratio of KDT, weight, height, and blood pressure. Lipid profiles included total cholesterol, triglycerides, LDL-, and HDL cholesterol. Exclusion criteria were KDT less than 10 years, interruption of KDT for >six months, congenital hypertriglyceridemia or hypercholesterinemia, and intake of lipid reducers.

The case series was approved by the Internal Review Board of Wuerzburg University (reference number Reg. No. 268/15) and written consent was obtained from parents and patients $\geq$12 years of age.

2.2. Anthropometric measurements

Anthropometric measurements were obtained on each clinical follow-up. Body weight and height were recorded to the nearest 100 g and 0.5 cm, respectively. Height was measured with a Harpenden Stadiometer. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and transformed to standard deviation scores (SDS) using World Health Organization (WHO) reference values [11], which were also used to define overweight (including obesity; BMI SDS > 1) and obesity (BMI SDS > 2). Due to an initial problem in follow-up protocols no BMI measurements were available at 6 months. After ten years systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were obtained in all patients by using an automated oscillometric device at 2 min intervals after a non strenuous examination and additional 5 min rest. The measurements were taken using the right arm, in the sitting position with the elbow at the level of the atrium, using cuff sizes, which had to cover at least two-thirds of the upper arm length. The values were transformed to SDS using blood pressure percentiles by sex, age and height from non overweight children and adolescents in Germany [12].

2.3. Laboratory tests

Blood samples were collected from all participants following an overnight fast (>12 h). Lipid parameters were measured by standard protocols. Serum TG and TC levels were measured using enzymatic methods (Roche, Basel, Switzerland in 2004; Olympus, Tokyo, Japan in 2014). HDL-C and LDL-C levels were measured directly using an Olympus AU640 automatic chemistry analyzer (Olympus, Tokyo, Japan). Age-dependent reference values for lipid profiles in children were defined according to German normative values from 2016 [13]. Abnormal values were defined as >97th percentile for triglycerides, total cholesterol, and LDL-cholesterol, and <3rd percentile for HDL-cholesterol. Dyslipidemia was defined as the presence of any of the following four factors: high LDL-cholesterol, low HDL-cholesterol, high triglycerides, or high total cholesterol.

2.4. Carotid ultrasound

Effects on vascular function were assessed in each patient after 10 years on KDT by ultrasound of carotid intima-media thickness (CIMT) as a surrogate marker for subclinical atherosclerosis by a single experienced investigator. High-resolution B-mode carotid ultrasound was performed by a single investigator using linear array transducer (nominal band width 3–9 MHz) with 7.5 MHz center frequency [iU22 echo machine, Philips Medical Systems, Andover, MA, USA). Following a 15 min rest patients were examined in supine position and moderate neck extension with the head turned 45° away from the scanner. On ultrasound, CIMT was defined as the distance between two echogenic lines representing the lumen-intima interface and the media-adventitia interface of the carotid arterial wall [14] CIMT was measured in B-Mode according to the Mannheim consensus on the common carotid artery far wall, 1 cm proximal to the bulb at end-diastolic moment [15]. The cardiac cycle was simultaneously controlled with a 3-lead ECG. In each patient four measurements were performed, two on the left and two on the right common carotid artery, and CIMT was calculated as average mean value. After zooming and freezing the image, the CIMT was measured manually using electronic calipers. In adults, CIMT values >0.9 mm have been shown as a marker of cardiovascular risk caused by atherosclerosis [16]. No measurements of CIMT were obtained at initiation of the KDT as all patients were younger than 10 years. In this age group measurements of CIMT are practically limited due to small vessels and thus reference values are unreliable [17].

2.5. Statistical analysis

SDS values of BMI, of total, HDL and LDL cholesterol, as well as of triglycerides before initiation of KDT were compared to SDS values at 0.5/1/2/5/10 years after initiation of KDT, respectively, using the Wilcoxon signed rank test. BMI and lipid SDS values at initiation and after 10 years KDT, respectively, were compared to 0 (i.e. the median value in the normative data used for calculation of SDS) using the Mann–Whitney *U* test. 10-year BMI SDS, CIMT and blood pressure SDS values as well as the prevalences of

overweight and obesity were compared to a healthy untreated German reference population [18] using the Mann–Whitney U test and Chi–Square test, respectively. For this analysis, the reference data were restricted to n = 550 children aged 10–16 years in order to match the age range of the Glut1D children at their respective 10-year follow-up visit. As a sensitivity analysis, these associations were additionally adjusted for sex and age using linear and logistic regression, respectively. No lipid measurements were available for the reference group. The significance level was set to 0.05 for all statistical tests. All calculations were carried out with SAS 9.4 (SAS Institute Inc, Cary, North Carolina) and R 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

By January 2016 ten of 65 patients (15.38%) on KDT fulfilled the inclusion criteria and didn't meet the exclusion criteria. Fifty five patients were excluded for KDT <10 years (n = 30) or interruption of KDT for >six months (n = 15), congenital hypertriglyceridemia or hypercholesterinemia (n = 4), and intake of lipid reducers (n = 6). Clinical and laboratory findings of those reported are provided in Table 1.

3.1. Glut1D patients versus control population

The 10 Glut1D patients exposed to KDT were comparable to the healthy reference population with respect to gender (n = 5 (50%) compared to n = 264 (48%) females, p = 0.90) and age at their 10-year visit (median (interquartile range) age: 12.0 (10.3–13.9) compared to 11.8 (11.1–12.7) years, p = 0.88).

In the treatment group, one child (10.0%) was overweight and none obese, compared to 136 (25%, p = 0.28) overweight and 49 (9%, p = 0.32) obese children in the healthy reference population, respectively. Also, after adjustment for age and gender, no significant association was found between treatment group and BMI SDS (p = 0.14), CIMT (p = 0.72), systolic blood pressure SDS (p = 0.17), diastolic blood pressure SDS (p = 0.55), overweight (p = 0.31) or obesity (p = 0.64).

3.2. Comparison of carotid ultrasound, blood pressure, and BMI

No significant differences were observed with respect to BMI SDS (p = 0.26), CIMT (p = 0.63) or systolic and diastolic blood pressure SDS (p = 0.11 and p = 0.37, respectively) in Glut1D children treated with KDT for ≥ 10 years compared to healthy controls (Fig. 1).

3.3. Comparison of BMI and lipid values before and after treatment initiation

After two years on KDT BMI increased significantly, while total cholesterol, HDL-cholesterol, and LDL-cholesterol decreased (Table 2, Fig. 2a–d). Within 2–5 years on KDT these differences dissolved. Median triglyceride values increased at year 1, but returned to initial values thereafter (Fig. 2e).

At 5–10 years on KDT blood lipid parameters reflected the situation at initiation of KDT. Dyslipidemia based on high LDL and total cholesterol levels in one child prior to KDT resolved - no child was found to have dyslipidemia at 10 years on KDT. Average LDL-cholesterol SDS at initiation was significantly higher (p = 0.03) than in the normative data used for SDS calculation, while no such differences were observed at later time points or for other lipids or BMI (Table 2).

Table 1
Patients characteristics (n = 10 Glut1D patients on KDT for 10 years. Diagnosis of Glut1D is based on hypoglycorrhachia and/or mutations in the SLC2A1 gene.).

ID	Gender	Gene	Mutation	Predominant clinical phenotype	Age at onset initiation of KDT (years)	KD Type	KD ratio start vs. last	Current status	CIMT (mm)	BMI (kg/m^2)	Blood pressure systolic/diastolic (mmHg)
1	F	SLC2A1	Heterozygous deletion	Movement disorder with ataxia, spasticity, dystonia and paroxysmal events	0.23	classic	3:1/3:1	continued	0.38	17.10	102/65
2	F	SLC2A1	Mutation in Exon 4	Paroxysmal events, dyslexia	1.00	classic	2.5:1/3:1	continued	0.60	17.50	104/64
3	F	SLC2A1	c.680-1G>C splicesite	Movement disorder with ataxia, spasticity, dystonia	6.85	classic	3:1/2:1	continued	0.40	15.10	116/69
4	F	SLC2A1	c.653G>A Arg218His	Intellectual disability, severe movement disorder with ataxia, spasticity, dystonia, expressive speech disorder	3.92	classic	4:1/3:1	continued	0.52	20.10	111/68
5	F	SLC2A1	14bpins EXON 10 at the Carboxyl-terminus	Intellectual disability, movement disorder with ataxia, spasticity, dystonia and exercise-induced paroxysmal dyskinesias	2.01	classic	3:1/3:1	continued	0.54	15.70	109/75
6	M	none	No mutation detection	Intellectual disability, ataxic-hypotonic movement disorder, global speech disorder	5.03	classic	3:1/3:1	continued	0.53	15.90	121/76
7	M	SLC2A1	Polymorphism 224T>C; 578C>T; 767G>A; 1607T>C	No abnormalities	0.15	classic	4:1/3:1	continued	0.54	18.10	119/64
8	M	SLC2A1	Mutation in Exon 10	Intellectual disability, expressive speech disorder	1.91	classic	3:1/2.5:1	continued	0.40	22.20	110/66
9	M	SLC2A1	c.101A>G Asn34Ser	Intellectual disability	0.34	classic	4:1/2:1	continued	0.49	17.10	112/62
10	M	SLC2A1	Stop mutation E54.X (+/−) in Exon 3	Intellectual disability, movement disorder with ataxia, spasticity, dystonia, severe dysarthria	3.34	classic	2:1/2:1	continued	0.48	16.60	101/65

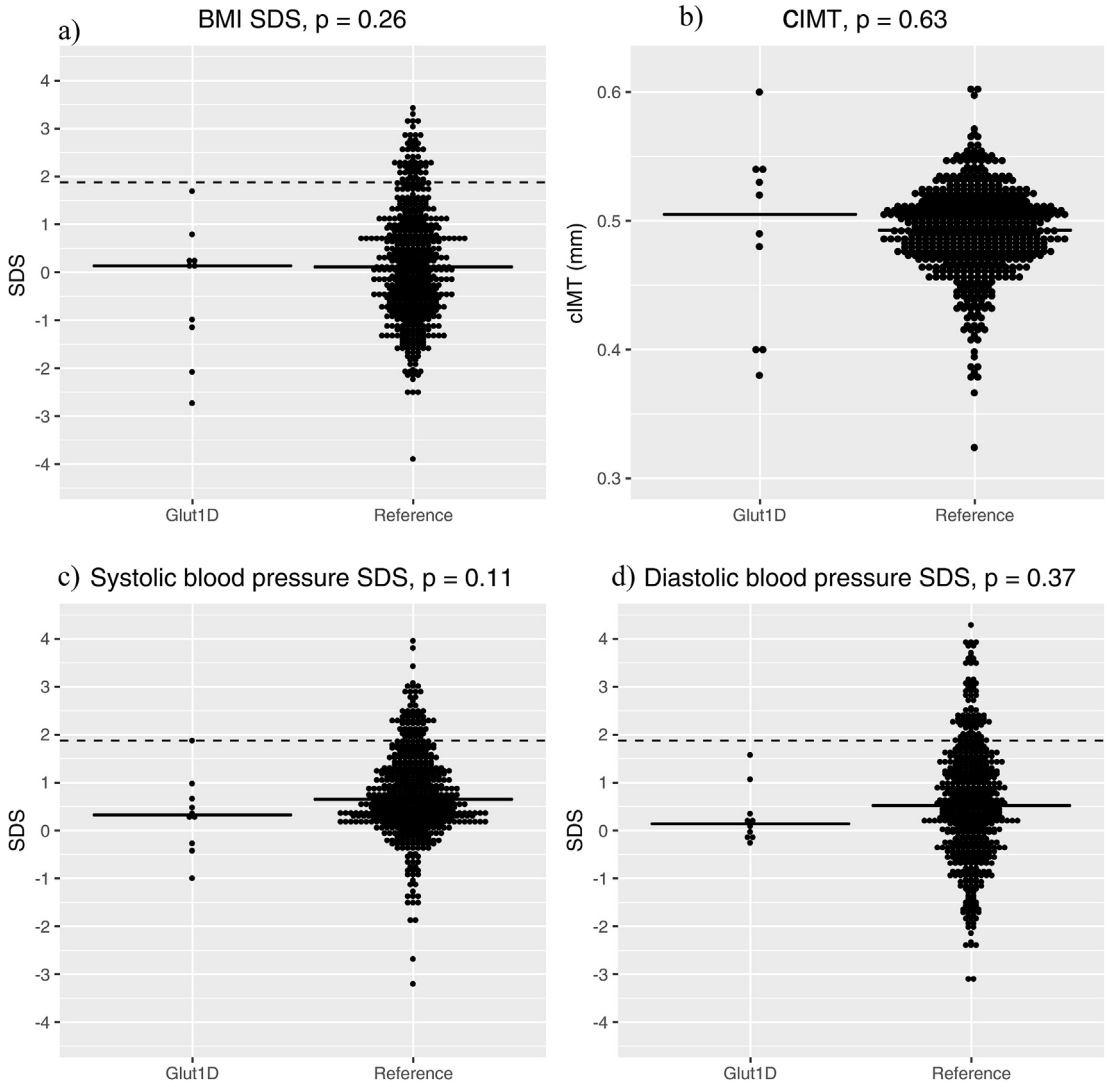

Fig. 1. Comparison of a) body mass index standard deviation scores (BMI SDS) and b) carotid intima media thickness (CIMT), c) systolic blood pressure SDS and d) diastolic blood pressure SDS of study cohort (Glut1D patients, n = 10) after 10 years of KDT and a healthy reference population (n = 550) 17. p-values were derived from Mann–Whitney U tests. The horizontal bars depict the median BMI SDS/CIMT in each group. The dashed lines indicate the 97th percentile in the respective reference population used for SDS calculation.

Table 2
Age- and sex-specific standard deviations scores (SDS) of body mass index (BMI) and lipid values of n=10 Glut1D children before and after initiation of ketogenic diet. Data are presented as median (interquartile range). p-values represent the comparison of each time point with before initiation and were derived from Wilcoxon signed rank tests.

	Before initiation	After 6 months	After 1 year	After 2 years	After 5 years	After 10 years
BMI SDS	−0.47 (−0.83, −0.24)	–	0.52 (−0.08, 1.18) p = 0.03	0.52 (−0.57, 1.29) p < 0.01	−0.26 (−0.79, 0.69) p = 0.11	0.14 (−1.15, 0.27) p = 0.32
Total cholesterol SDS	0.67 (−0.28, 1.07)	−0.51 (−0.94, 0.12) p = 0.048	0.33 (−1.18, 0.66) p = 0.63	0.11 (−1.17, 0.56) p = 0.28	0.01 (−0.33, 1.12) p = 0.56	−0.04 (−1.23, 1.61) p = 0.49
HDL cholesterol SDS	0.50 (−0.02, 1.22)	−0.54 (−1.09, −0.16) p < 0.01	−1.30 (−1.92, −0.63) p < 0.01	−0.06 (−1.13, 0.75) p = 0.03	0.08 (−0.29, 0.36) p = 0.08	0.23 (−0.12, 1.02) p = 0.49
LDL cholesterol SDS	1.03 (0.27, 1.64)[a]	−0.32 (−1.05, 1.53) p = 0.11	−0.38 (−0.68, 1.38) p = 0.23	−0.19 (−0.88, 1.67) p = 0.06	0.35 (−0.82, 0.76) p = 0.19	0.03 (−0.70, 1.47) p = 0.19
Triglycerides SDS	−0.36 (−1.04, 0.84)	0.61 (−0.38, 1.05) p = 0.049	0.77 (−0.20, 2.09) p = 0.049	−0.08 (−0.56, 1.09) p = 0.28	−0.01 (−0.66, 0.53) p = 0.38	−0.42 (−1.42, 0.02) p = 0.70

[a] Significantly different from 0 (p < 0.05).

4. Discussion

Current reports on cardiovascular risks of ketogenic diet therapies (KDT) have raised concerns about dietary treatment in Glut1 Deficiency (Glut1D). In particular, the concept that high-fat classical KDT are the only effective treatment for this entity is challenged by modified KDT [5]. Potential cardiovascular risks of KDT must be balanced with proven benefits for development, seizure control,

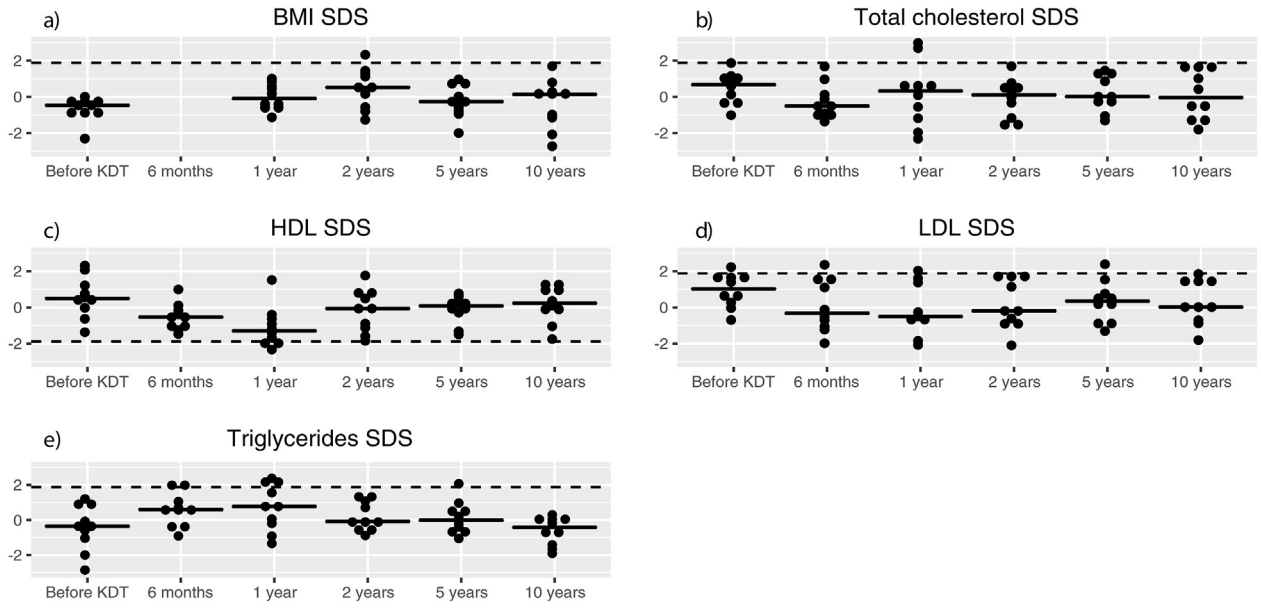

Fig. 2. 10-year-follow-up of BMI and lipid parameters of study cohort (n = 10). Time points range from initiation to 10 years on KDT. 2a) Time-course of BMI (no measurements at 6 months follow-up available). 2b–e) Time-course of lipid parameters. The horizontal bars depict the median SDS values at each time point. The dashed lines indicate the 3rd or 97th percentile (as appropriate) in the respective reference population used for SDS calculation.

and movement. Diets are initiated early and continued long-term to meet energy requirements of the developing brain [3,19]. Current reports on cardiovascular risk were based on 6–24 months follow-ups with conflicting results. Here we provide the first very long-term follow-up of ≥10 years on cardiovascular risk of KDT in Glut1D.

In contrast to the majority of studies reporting dyslipidemia on 6–24 months follow-up [8,9], our results indicate that initial dyslipidaemia may normalize over time (Fig. 2). This has been observed previously in single reports. In 12 children with intractable childhood epilepsy and hyperlipidemia prior to KDT, elevated total cholesterol and low-density lipoprotein normalized following 12 months on KDT [20]. Retrospective studies of patients with intractable epilepsy showed normal lipid parameters after discontinuation of KDT for more than three years [21,22], and a retrospective follow-up study of long-term outcome in children treated with KDT in the past did not demonstrate cardiovascular risks [23].

The encouraging finding of transient dyslipidemia over a 10-year period on KDT was supported by normal vascular function as measured by carotid artery ultrasound. Normal CIMT on KDT has also been described previously in single reports: Kapetanakis et al. investigated carotid artery function in 43 children ages 2–15 years on KDT and reported that arteries were less “distensible” at 3 and 12 months but returned to normal by 24 months - CIMT did not change nor correlated to total cholesterol or triglycerides [22]. Likewise, Coppola et al. also reported increased arterial stiffness as an early marker for vascular damage in 23 children and adults on KDT compared to 20 control children with epilepsy, but found no changes in CIMT. Similar results were found by Özdemir et al. in 52 children with refractory epilepsy - no changes in CIMT after 12.6 months on KDT were observed [9]. Elevation of total cholesterol, LDL-cholesterol, and triglycerides may have been due to the short follow-up period. In line with a previous report no gender differences in CIMT nor correlations of CIMT to BMI were found in healthy children younger than 15 years [24] (Fig. 1). Of note, initial hyperlipidemia in one patient normalized on KDT as described previously [20].

Glut1D is a very rare entity - consequently cohort size and external validity is limited. Other caveats include absent data on arterial stiffness determined by ultrasound, additional markers for cardiovascular risk such as homocysteine, lipoprotein (a) [25], oxidative stress, fat composition of KDT, and antiepileptic drug therapy [26]. The strength of this prospective case series is the unprecedented long-term follow-up of 10 years of KDT in Glut1D. Our data indicate that initial dyslipidemia caused by KDT may be transient and CIMT after 10 years on KDT remains normal. No changes in BMI or blood pressure parameters were observed on long-term KDT. We conclude that previous data on cardiovascular risks of KDT may be limited by inadequate follow-up – a period of at least five years appears necessary to assess the course of lipid parameters on KDT. Our findings encourage KDT as the treatment of choice for Glut1D. As effects of KDT in Glut1D and in intractable childhood epilepsy are comparable [27], our results also have implications for the use of KDT in several other diseases such as intractable childhood epilepsy and in metabolic disorders such as pyruvate dehydrogenase deficiency.

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Authors' roles

N. Heussinger: Organization, interpretation of data, manuscript draft, critical review, and correspondence.

A. Della Marina: neurological examiner, blood samples collection, critical review.

A. Beyerlein: statistical analysis, critical review of manuscript draft.

B. Leiendecker: Data collection, KDT supervision and critical review of manuscript draft.

S. Alves: Data collection, tables, logistics.

R. DallaPozza: statistics, critique, reference data.

J. Klepper: general clinical investigator, neurological examiner, follow-up concept, organization, manuscript draft, and critical review.

Declaration of interests

JK, ADM and BL received speaker honoraria and travel costs from Nutricia GmbH, Erlangen, Germany, and JK also from Vitaflo GmbH, Steinbach, Germany. All other authors declare no competing interests.

Responsibility

The corresponding author had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors have approved the final article.

Ethical compliance statement

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

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