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Long-term variation of dietary fiber intake in subjects with neurological diseases on a classic ketogenic dietary therapy

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Abstract

Background The classic Ketogenic Dietary Therapy (cKDT), traditionally considered low in fiber, has seen growing interest in improving its nutritional quality. This retrospective cohort study examined long-term changes in dietary fiber intake among paediatric patients with neurological diseases on cKDT, hypothesizing that the introduction of Foods for Special Medical Purposes (FSMPs) would increase fiber consumption without compromising nutritional status or diet efficacy.

Methods We included 20 patients on cKDT for at least two years. Changes in fiber intake were assessed by analyzing 3-day food diaries at 1 month post-initiation and at the most recent nutritional evaluation, with data compared to Italian Dietary Reference Values (LARN, 2024). Anthropometric and biochemical parameters were also collected.

Results Over an average observation period of 5.3 ± 2.9 years, data showed a significant increase in fiber intake from 8.7 ± 7.1 to 26.0 ± 14.9 g/day and from 6.8 ± 6.2 to 16.9 ± 11.1 g/1000 kcal ($p = 0.006$). This new intake level exceeded the LARN adequate intake (8.4 g/1000 kcal), with adherence percentage increasing from 80.8 ± 74.4% to 202.1 ± 131.5% ($p = 0.006$). The contribution of fiber from FSMPs increased from 28.4 ± 26.5% to 58.1 ± 21.3% ($p = 0.002$). Meanwhile, subjects' anthropometric and biochemical parameters, including ketones, remained stable, and biochemical markers indicated maintained ketosis (Capillary Ketones T0: 0.1 ± 0.1 vs. T1: 2.5 ± 1.4 mmol/L; $p = 0.001$).

Conclusions Our data show that fiber intake in patients on long-term cKDT has more than doubled, primarily due to FSMPs. No substantial changes were observed in measured parameters over follow-up, challenging the outdated perception of cKDT as a low-fiber diet. However, data regarding seizure frequency and specific gastrointestinal tolerability were not systematically collected.

Keywords Ketogenic diet · Long-term effect · Fiber

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Background

The classic ketogenic dietary therapy (cKDT) is a normocaloric, hyperlipidic, normoprotein, and low-carbohydrate diet designed to promote the constant production of ketone bodies (KBs), primarily acetoacetate and β-hydroxybutyrate. Its main goal is to mimic the effects of long-term fasting without depriving the body of the essential calories needed for growth and development [1–3]. Several hypotheses suggest that the diet's antiepileptic effects may be attributed to the production of KBs. These ketones are proposed to exert their therapeutic effects by altering mitochondrial function (e.g., promoting ATP synthesis and increasing mitochondrial biogenesis), reducing glutamate release and synaptic cleft concentration, enhancing γ-aminobutyric acid synthesis, and protecting neurons from oxidative stress through hypothesised mechanisms such as increased reduced glutathione and uncoupling protein expression [4–6]. Moreover, in GLUT1 Deficiency Syndrome, KBs can cross the blood-brain barrier via monocarboxylate transporters, which are unaffected by the Glut1 mutation. This enables KBs to act as an alternative energy source and compensate for the lack of glucose. These mechanisms collectively explain the use of the cKDT as a first-line therapy for GLUT1 Deficiency Syndrome, as well as a supportive treatment for various epileptic syndromes [3].

In the cKDT, the intake of each macronutrient is designed based on the ketogenic ratio, which is the ratio of the fat amount to the sum of the carbohydrate and protein amounts (both expressed in grams). The most common ratios used in clinical protocols are 4:1 and 3:1, which means 4–3 g of fat versus 1 g of protein plus carbohydrate. The choice of the ratio depends on age, individual production and brain sensitivity to KBs [2–4]. Specifically, fat intake comprises at least 87–90% of daily energy in a 4:1 or 3:1 ratio, while protein provides the minimum requirement for growth, and carbohydrates are severely restricted (often < 10–15 g per day).As a result, foods that are suitable for a KDT typically include those that are high in healthy fats and low in carbohydrates (fatty fish, vegetable oils, seeds, nuts, eggs, full-fat dairy), excluding all cereals and cereal products (pasta, bread, rice), fruit (excluding berries) and vegetables (including only leafy vegetables in limited quantities). These exclusions make cKDT a diet low in vitamins, minerals and, above all, fibre. The benefits of fiber intake are well known, including its role in promoting gut health, regulating blood sugar levels, and preventing constipation, which are crucial for overall well-being. A low-fiber diet, as typical of traditional cKDT providing a fiber intake of 4–6 g/1000 kcal (lower than Adequate Intake for children [7], can lead to gastrointestinal discomfort and long-term health issues such as an increased risk of colorectal cancer and cardiovascular diseases. Studies have shown that adequate fiber intake is associated with a reduction in these risks, highlighting the importance of maintaining fiber consumption even when on a restrictive diet like cKDT [8, 9].

To address these concerns, recent advancements have focused on the development of high-fiber special medical foods (FSMPs) [10]. The introduction of novel FSMPs with increased fiber content may lead to several effects. These innovations include the incorporation of soluble fibers such as psyllium husk and inulin, which can enhance fiber content without significantly impacting the carbohydrate restrictions crucial to maintaining ketosis [11]. Unlike other ketogenic approaches (e.g., Modified Atkins Diet), in a Classic KDT with such high fat ratios, it is extremely difficult to increase fiber through natural fruits and vegetables without exceeding the net carbohydrate limit and altering the ketogenic ratio. Consequently, typically only total fiber is analyzed, without distinguishing between soluble and insoluble fractions, which may have different physiological impacts. Nevertheless, soluble fibers, such as pectin, psyllium, and beta-glucan, can bind to bile acids in the intestine, excreting them rather than reabsorbing, which reduces fat absorption. Moreover, soluble fibers can form viscous gels in the gut, which slows the mixing of food with digestive enzymes and delays the absorption of fats, and increased fiber consumption can promote satiety, which may lead to a reduction in overall food intake [9, 12, 13].

To our knowledge, no study has yet comprehensively described the detailed amount of fiber intake and changes in dietary fiber over time in a cKDT. Therefore, this study aimed to investigate long-term changes in dietary fiber intake among individuals following this type of regimen. Additionally, the study sought to assess adherence to

fiber intake recommendations in the general population and explore potential differences in nutritional status based on fiber intake.

Methods

Study design and participants

The study was a multi-centre retrospective study involving 20 patients. The study protocol was approved by the ethics committee of the Fondazione IRCCS Policlinico San Matteo di Pavia (reference number 20180083746) and complied with all principles of the Declaration of Helsinki. All caregivers and parents provided written informed consent before the beginning of the study.

The patients were retrospectively recruited from the Paediatric Neurology Unit of the Vittore Buzzi Children's Hospital (Milan, Italy) and the Department of Child Neuropsychiatry of the Casimiro Mondino IRCCS Foundation (Pavia, Italy). Inclusion criteria were: (1) diagnosis of drug-resistant epilepsy or GLUT1 deficiency syndrome, (2) absence of cKDT introduction contraindications as defined by the latest Consensus [2, 3], such as β-oxidation defects, carnitine deficiency, pyruvate carboxylase deficiency, and porphyria, (3) age < 18 years, (4) access to the regional treatment plan for the distribution of FSMPs.

Neurological evaluations and electroencephalograms (EEGs) were conducted at baseline (pre-intervention) and annually thereafter. These assessments took place at the Paediatric Neurology Unit, "V. Buzzi" Children's Hospital in Milan and at the Department of Neurology and Child Psychiatry, Fondazione IRCCS Istituto Neurologico Casimiro Mondino in Pavia. Monitored neurological symptoms included seizure types and frequency, paroxysmal dyskinesia, spasticity, ataxia, dystonia, dysarthria, and muscle strength. Caregivers also provided daily observations of the patients' alertness, activity levels, and any seizure .

cKDT plans were implemented at both the International Center for the Assessment of Nutritional Status (ICANS) of the University of Milan and the Center for Research on Human Nutrition and Eating Disorders in Pavia according to the same guidelines [4].

Fiber intake changes were assessed by the analysis of 3-days food diary collected between the onset of the prescribed cKDT (T0) and the last nutritional evaluation occurred (T1). The average time elapsed between T0 and T1 was 5.3 ± 2.9 years. Fiber intake was compared with the Italian Dieraty Reference Values [7]. Data on anthropometric (body weight, height, circumferences, fat mass and fat free mass estimation through skinfold thickness measurement and bioimpedance evaluation) and biochemical parameters of interest were also collected in both evaluations.

Setting

Patients initiated the dietary protocol at home, progressively increasing the ketogenic ratio without fasting, following previously published guidelines [14]. Prior to beginning, each patient completed a dietary history with a dietician to evaluate caloric intake, intolerances, and food preferences. cKDT was tailored to each patient's energy expenditure and physical activity level. Caloric prescriptions were adjusted as necessary during follow-up. Participants received a normocaloric diet with a minimum of 0.7 g/kg protein, supplemented with a sugar-free multivitamin, multimineral, and potassium citrate, based on their sex and age. Allergies and food preferences were also considered.

Before starting the diet, patients and caregivers were counselled to address any questions and ensure understanding of the ketogenic dietary therapy, meal preparation, costs, and potential side effects. Patients began at home with a 1:1 ratio, gradually increasing to 2:1, and ultimately to 3:1 or 4:1. The final ratio depended on KDT tolerance and ketonemia trends. A typical daily meal plan consisted of three main meals and two snacks. Meals were constructed using high-fat bases (olive oil, butter, heavy cream, specific KDT formulas/FSMPs) combined

with calculated protein sources (eggs, meat, fish, cheese) and low-carbohydrate vegetables (leafy greens, zucchini, broccoli). FSMPs were integrated specifically as functional substitutes for pasta, bread, salty snacks, and sweets to improve compliance and quality of life. To ensure dietary variety and prevent over-reliance on medical foods, FSMPs were generally prescribed in quantities of 2–3 units per day per subject. Capillary ketonemia and ketonuria were measured daily by caregivers to ensure safety and diet compliance (target > 2.0 mmol/L). However, we only have data reported at specific times to assess compliance and safety.

Main outcomes: fiber intake

The assessment of changes in fiber intake was investigated by a 3-days food diary collected T0 (1 month ± 7 days after cKDT initiation) and at T1 (the most recent nutritional evaluation, mean follow-up 5.3 ± 2.9 years).

Caregivers filled the diaries reporting the type and the amount of each food and beverage consumed over a period of three non-consecutive days, including two weekdays and one weekend day to capture variations in ketogenic recipes. For each meal, they were asked to also list ingredients used for mixed dishes preparation, the brand of packaged foods consumed and the method of preparation, including the portion sizes of each food item using household measures (e.g. cups, tablespoons) or weigh foods with a kitchen 1 gram precision scale.

Diet records were analysed using MetaDieta 3.0.1 (Meteda s.r.l.) for macronutrient content, detailing carbohydrates, proteins and lipids into saturated fatty acids (SFA), based on CREA and BDA IEO food composition tables, and defining fiber as total dietary fiber (AOAC method). FSMPs used in this cohort were inserted in the database manually according to the nutritional values of the company's labels. All of them were typically high-fat, low-carbohydrate formulas, enriched with specific fibers such as inulin, psyllium, or oat fiber to support gastrointestinal health. The introduction of FSMPs was based on clinical judgment and product availability over the years, rather than a rigid systematic protocol. he introduction of FSMPs was based on clinical judgment and product availability over the years, rather than a rigid systematic protocol. Additionally, dietary fibre was counted as the total daily amount and distinguished from the amount derived FSMPs only.

Fiber intake was compared with the Italian Dietary Reference Values [7]. The adequacy index was calculated with the formula: daily nutrient intake/dietary reference values for sex and age × 100. We focused on total fiber and FSMP-derived fiber, as standard food composition databases are often imprecise regarding resistant and retrograded starch content, and the variability in home cooking/cooling procedures makes retrospective estimation of these fractions unreliable.

For the purposes of this study, "low fiber" was defined as an intake of less than 10 g/1000 kcal (internal median-split of fiber intake in this sample used for exploratory analysis)), while "high fiber" refers to intakes above this threshold. While the Italian LARN suggests an Adequate Intake (AI) of 8.4 g/1000 kcal, the higher internal threshold of 10 g/1000 kcal was chosen to statistically stratify the cohort into two distinct groups for comparison based on the observed distribution.

Nutritional status

A trained dietitian conducted anthropometric measurements following standard procedures, including body weight, height, and calculating body mass index (BMI). Sex-specific BMI-for-age percentiles and Z scores were derived from CDC growth charts, categorizing weight status. Waist circumference was measured with a non-elastic tape. Fat mass (FM) was estimated using the Brook (1971) and Siri (1961) equations. These equations calculate body fat percentage (FM%) from skinfold measurements taken with a caliper (Holtain T/W). Resting energy expenditure (REE) was measured after a 12–14 h fast using an open-circuit ventilated hood system (VMAX Sensor Medics 29). Biochemical parameters were analyzed from fasting blood samples, including glucose, cholesterol, triglycerides, liver enzymes, and insulin levels. While a glucose cutoff of 50 mg/dL is typically used to diagnose hypoglycemia, we used a higher threshold of 68 mg/dL. This is because counter-regulatory responses

often begin at this level [15]. Conversely, hyperglycemia was diagnosed at plasma glucose levels above 100 mg/dL [15]. Capillary ketonemia and ketonuria were also measured using specific diagnostic devices.

Statistical analysis

Continuous variables were reported as minimum, maximum, mean, and standard deviation (SD), and Median and Interquartile Range (IQR). Normality of data distribution was assessed using the Shapiro-Wilk test. A paired t-test or Wilcoxon signed-rank test (for skewed data) was used to compare values of dietary and nutritional variables at the cKDT initiation, as well as between patients with low and high fiber intake. The percentage change in nutritional status between baseline (T0, at the onset of cKDT) and the last nutritional evaluation occurred (T1) was calculated as ((T1-T0)/T0)×100. The Spearman correlation coefficient was calculated to assess the relationship between KR and fiber intake. Effect sizes with 95% confidence intervals (CI) were calculated for primary outcomes. This was a complete-case analysis; no data imputation was performed. All p-values were two-tailed, and statistical significance was defined as $p<0.05$. All analyses were performed using SPSS Statistics software, version 29.0 (IBM Corp.).

Results

Pre-intervention

We recruited 20 patients, 11 females and 9 males.

Table 1 shows clinical characteristics of all patients at the visit at the cKDT initiation.

At baseline, patients were on average normal weight (mean BMI 20.3 +/- 5.1 kg/m2) In particular, 12 (60%) were of normal weight, 1 (6%) presented with obesity, 5 (32%) were classified in the overweigh range t and 2 (12%) in the underweight one.

None of the patients had fasting blood glucose levels above 100 mg/dL or hypoglycemia. Mean total cholesterol (TC) and LDL cholesterol levels were adequate, less than 200 mg/dl and 130 mg/dl respectively, although three patients (15%) exceeded both parameters. HDL cholesterol levels were adequate in all the participants. Triglyceride levels were also adequate, with an average value below the recommended limit (150 mg/dl).

Post-intervention

Dietary composition

The average time elapsed between T0 and T1 was 5.3 ± 2.9 years.

Table 2 shows the average dietary composition of the patients at T0 and at T1.

The diet's composition remained largely consistent, with adjustments only to caloric and protein intake to accommodate expected growth. Table 2 indicates a significant increase in the average daily intake of protein (from 31.4 ± 13.7 to 42.2 ± 11.5 g/day; $p=0.003$) and fiber (from 8.7 ± 7.07 to 26.0 ± 14.9 g/day; $p=0.001$). However, only two patients (10%) reported a reduction in fiber intake due to the high ketogenic ratio of the prescribed diet (KR 3:1). Another change in fiber was the significant increase in grams per 1000 kcal, which has more than doubled from 6.8 ± 6.3 to 16.9 ± 11.0 ($p=0.006$).

Figure 1 shows adherence to the Italian LARN adequate intake (AI) for dietary fiber, expressed as percentage of AI. The LARNs define an Adequate Intake (AI) of 8.4 g/1000 kcal for children. The data indicate that adherence to the LARNs improved significantly during the dietary treatment, with average adherence values increasing from 80.8% (± 74.4) to 202.1% (± 131.5), exceeding the childhood adequate intake recommended. Moreover,

Table 1 Clinical and Anthropometric Characteristics of Patients at Ketogenic Diet Initiation (T0)

	Mean ± SD	Median [IQR]	Min - Max
Age (years)	10.8 ± 5.0	10.4 [7.4 - 13.0]	1.5 - 19.6
Anthropometric measurements			
Weight (kg)	38.9 ± 18.6	37.2 [28.1 - 52.5]	10.1 - 70.9
Weight Z-score	-0.1 ± 1.1	-0.1 [-0.9 - 0.6]	-2.2 - 2.3
Height (m)	1.34 ± 0.25	1.40 [1.19 - 1.53]	0.78 - 1.74
Height Z-score	-0.2 ± 1.2	-0.0 [-1.0 - 0.7]	-3.2 - 1.3
BMI (kg/m²)	20.2 ± 5.0	19.2 [16.5 - 23.8]	13.6 - 31.5
BMI Z-score	0.5 ± 1.1	0.6 [-0.2 - 1.5]	-1.6 - 2.4
Waist Circumference (cm)	66.7 ± 12.1	67.9 [60.0 - 72.5]	43.0 - 94.3
Waist Z-score	1.2 ± 1.2	1.3 [0.8 - 1.6]	-0.9 - 2.9
Body composition by skinfolds			
Fat Mass (%)	36.9 ± 8.7	35.6 [31.2 - 42.4]	24.6 - 58.2
Biochemical parameters			
Glucose (mg/dL)	83.4 ± 20.5	89.0 [84.5 - 91.5]	4.8 - 100.0
Insulin (µU/mL)	12.2 ± 11.1	8.7 [5.0 - 14.2]	1.0 - 42.6
Total Cholesterol (mg/dL)	171.5 ± 37.1	167.5 [140.5 - 195.5]	112.0 - 247.0
LDL Cholesterol (mg/dL)	102.4 ± 27.1	105.0 [81.0 - 116.0]	61.0 - 161.0
HDL Cholesterol (mg/dL)	56.4 ± 11.7	55.0 [48.5 - 64.0]	39.0 - 83.0
Triglycerides (mg/dL)	68.2 ± 27.0	65.5 [43.8 - 88.0]	32.0 - 133.0
AST (U/L)	20.5 ± 9.7	18.0 [13.8 - 24.8]	6.8 - 47.0
ALT (U/L)	13.7 ± 6.4	12.0 [10.0 - 17.6]	3.0 - 32.0
GGT (U/L)	13.3 ± 8.2	10.5 [8.0 - 14.8]	5.0 - 35.0
Creatinine (mg/dL)	0.3 ± 0.1	0.28 [0.22 - 0.36]	0.1 - 1.0
Urea (mg/dL)	19.0 ± 9.0	17.5 [12.0 - 24.0]	3.4 - 39.0
Uric acid (mg/dl)	4.7 ± 1.3	4.7 [3.8 - 5.6]	4.4 - 15.1

Values are presented as Mean ± Standard Deviation (SD) and Median [Interquartile Range: 25th - 75th percentile]. *BMI* Body Mass Index, *LDL* Low-Density Lipoprotein, *HDL* High-Density Lipoprotein, *AST* Aspartate Aminotransferase, *ALT* Alanine Aminotransferase, *GGT* Gamma-Glutamyl Transferase

Table 2 Changes in Macronutrient and Fiber Intake from Baseline (T0) to Follow-Up (T1)

	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Mean Diff (95%CI)	*p*-value
Diet composition						
Energy intake (kcal/day)	1604 ± 432	1754 [1194 - 1932]	1658 ± 497	1719 [1350 - 1966]	54 (-101 - 485)	0.994
Energy intake/BW (kcal/kg)	52.8 ± 19.7	49 [35 - 59]	46.3 ± 12	37.9 [33.5 - 54.0]	-6.5 (-16.6 - 3.6)	0.582
Protein (g/day)	31.4 ± 13.7	32.0 [27.3 - 43.7]	34.2 ± 11.5	32.0 [27.3 - 43.7]	+2.8 (0.2 - 5.4)	**0.033**
Protein/BW (g/kg)	1.1 ± 0.4	0.9 [0.8 - 1.2]	1.1 ± 0.1	1.0 [0.9 - 1.2	0.0 (-0.2 - 0.2)	0.546
Fat (g/day)	151 ± 48.8	153 [133 - 177]	160.3 ± 47.6	168 [92-186]	+9.3 (-21.3 - 39.9)	0.466
Fat (%)	79.4 ± 16.5	86.4 [80.8 - 89.8]	85.5 ± 5.6	85.6 [81.3 - 87.2]	+6.1 (-1.9 - 14.1)	0.258
SFA (g/day)	48 ± 19	45 [36 - 55]	46 ± 17	41.7 [27.0 - 56.2]	-2.0 (-13.4 - 9.4)	0.316
SFA (%)	22.9 ± 9.6	25.1 [21.2 - 27.4]	24.5 ± 5.2	22.7 [18.5 - 29.3]	+1.6 (-3.3 - 6.5)	0.848
Carbohydrate (g/day)	34.5 ± 44	17 [11 - 36]	24.9 ± 15.4	21.8 [12.7 - 25.6]	-9.6 (-32.1 - 12.9)	0.216
Carbohydrate (%)	7.9 ± 9.4	3.6 [2.8 - 10.2]	6.3 ± 3.9	5.4 [3.6 - 8.0]	-1.6 (-6.5 - 3.3)	0.516
Ketogenic ratio	2.6 ± 0.9	2.6 [2.0 - 3.2]	2.5 ± 0.8	2.5 [2.0 - 3.0]	-0.1 (-0.6 - 0.4)	0.978
Total Fiber (g/day)	8.7 ± 7.1	7.6 [2.3 - 11.5]	26 ± 15	20.1 [10.4 - 37.7]	17.3 (7.9 - 26.7)	**0.001**
Total Fiber (g/1000kcal)	6.8 ± 6.3	6.7 [2.1 - 11.1]	16.9 ± 11.1	14.0 [6.7 - 29.48]	10.1 (3.2 - 17.0)	**0.006**
of which						
Fiber FSMPs (g/day)	2.6 ± 6.9	0 [0 - 5.0	16.1 ± 11.1	16.1 [8.6 - 23.6]	13.5 (6.2 - 20.8)	**0.001**
Fiber FSMPs (%/Total fiber)	28.4 ± 26.5	14 [5.0 - 38.0]	61.1 ± 21.3	61.1 [46.7 - 75.5]	32.7 (13.2- 52.2)	**0.002**
	N	%	**N**	%		
Patients with low fiber intake	12	60	8	40	-	**0.041**

Values are presented as Mean ± Standard Deviation (SD) and Median [Interquartile Range: 25th - 75th percentile]. BW = Body Weight; SFA = Saturated Fatty Acids; FSMPs = Food for Special Medical Purposes

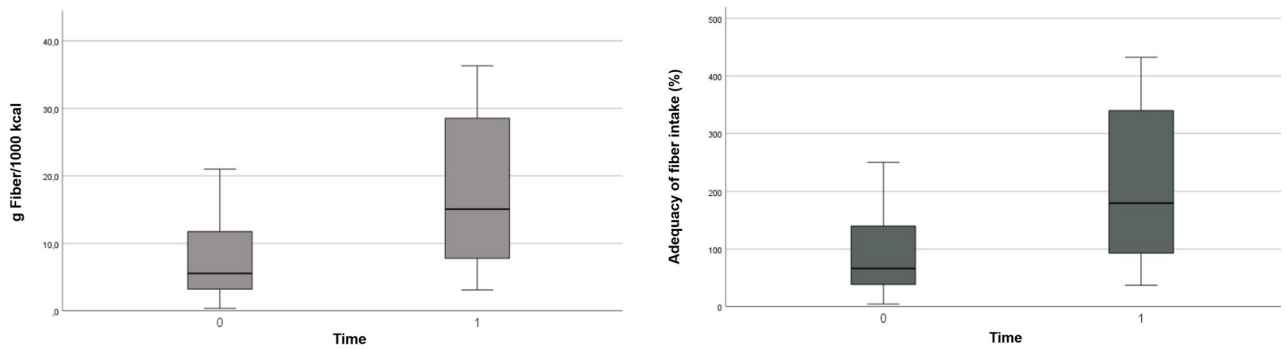

Fig. 1 Average adherence of fiber intake to Dietary Reference Values

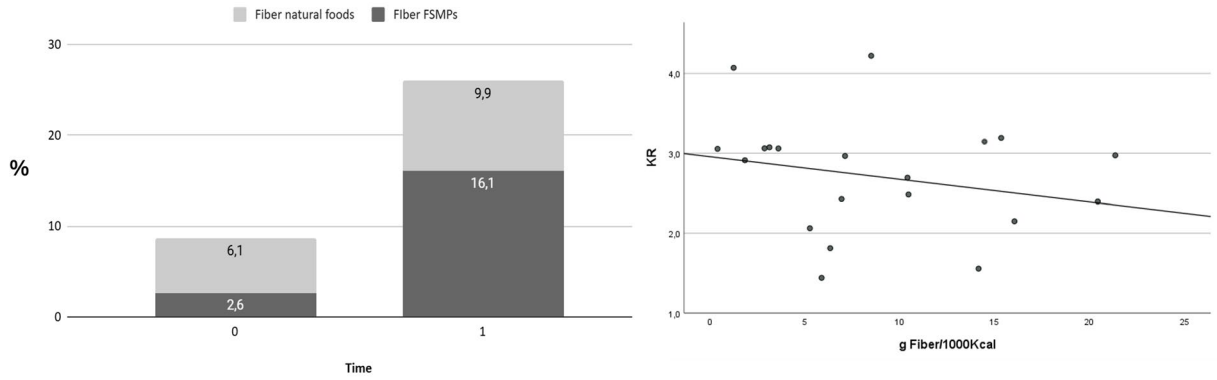

Fig. 2 Relation between natural foods' and FSMPs' fiber intake and ketogenic ratio

fiber from FSMPs significantly doubled over the years from 28.4±26.5%/total fiber to 61.1±21.3%/total fiber ($p=0.002$).

As a result, the percentage of natural food fiber intake decreased, while fiber from FSMPs more than doubled, highlighting the distinct contribution of supplements versus natural foods (vegetables and nuts). No correlation was found between KR and fiber intake (ρ=-0.398, $p=0.082$) as shown in Fig. 2. and No correlation was found between KR and fiber intake (ρ=-0.398, $p=0.082$) as shown in Fig. 2.

Nutritional status

Table 3 displays the comparison between the average values of these parameters measured at the study's outset and conclusion. Notably, significant increases in parameters such as age and fat-free mass are evident, along with a marked reduction in insulin levels. These trends were expected, aligning with the patients' growth and the implementation of the cKDT. Importantly, Table 3 demonstrates that capillary KBs increased significantly from T0 (0.1±0.1 mmol/L) to T1 (2.5±1.4 mmol/L, $p=0.001$). This significant rise confirms that the patients successfully achieved and maintained therapeutic ketosis over the 5-year period, despite the increase in fiber intake. Furthermore, the Respiratory Quotient (RQ) significantly decreased from 0.82±0.1 to 0.7±0.1 ($p=0.006$), indicating a metabolic shift towards exclusive fat oxidation, further corroborating the maintenance of a ketogenic state.

No other noteworthy changes in patients' conditions were reported during the treatment.

Table 3 Comparison of Anthropometric and Biochemical Parameters at Baseline (T0) and Follow-Up (T1)

	Mean ± SD	Median [IQR]	Mean ± SD	Median [IQR]	Mean Diff [95%CI]	*p*-Value
Age (years)	10.8 ± 5.0	10.4 [7.4 - 13.0]	14.2 ± 7.7	16.1 [2.8 - 19.9]	3.90 [0.74 -15.17]	**0.015**
Anthropometric measurements						
Weight (kg)	38.9 ± 18.6	37.2 [28.1 - 52.5]	45.3 ± 19.8	45.0 [27.6 - 58.9]	6.50 [0.98 -12.02]	**0.013**
Weight Z-score	-0.1 ± 1.1	-0.1 [-0.9 - 0.6]	-0.1 ± 1.4	-0.7 [-1.5 -0.4]	0.0 - [-0.8 -0.8]	0.281
Height (m)	1.34 ± 0.25	1.40 [1.19 - 1.53]	1.5 ± 0.2	1.54 [1.28 - 1.66]	0.14 [0.08 -0.21]	**0.001**
Height Z-score	-0.2 ± 1.2	-0.0 [-1.0 - 0.7]	-0.6 ± 1.6	-0.2 [-1.5 -0.3]	-0.4 - [-1.3 -0.5]	0.263
BMI (kg/m²)	20.2 ± 5.0	19.2 [16.5 - 23.8]	19.8 ± 4.7	19.7 [16.8 - 22.7]	-0.47 [-2.19 -1.25]	0.225
BMI Z-score	0.5 ± 1.1	0.6 [-0.2 - 1.5]	0.2 ± 1.6	0.14 [-0.16 - 0.84]	-0.28 [-1.78 -1.22]	0.124
Waist Circumference (cm)	66.7 ± 12.1	67.9 [60.0 - 72.5]	68.3 ± 8.3	67.1 [64.2 - 71.4]	-0.91 [-7.40 -5.57]	0.152
Body composition by skinfolds						
Fat Mass (%)	36.9 ± 8.7	35.6 [31.2 - 42.4]	29.2 ± 2.9	29.6 [19.3 - 34.8]	-7.7[-20.2 -4.8]	0.104
Fat Free Mass (%)	61.7 ± 6.6	61.7 [57.2 -66.2]	70.8 ± 3	70.4 [65.2 - 80.7]	9.1[5.7 -12.5]	**0.006**
Resting energy expenditure						
RQ	0.82 ± 0.1	0.83 [0.78 - 0.85]	0.7 ± 0.1	0.75 [0.73 - 0.80]	-0.05 [-0.10 --0.002]	0.003
REE (kcal/die)	1045 ± 301	1104 [783 - 1180]	1241 ± 320	1211 [1024 - 1329]	143.0 [4.8 -281.2]	0.307
Biochemical parameters						
Glucose (mg/dL)	83.4 ± 20.5	89.0 [84.5 - 91.5]	85.8 ± 8.9	86.0 [77.0 - 91.0]	-0.47 [-4.04 -3.10]	0.206
Insulin (µU/mL)	12.2 ± 11.1	8.7 [5.0 - 14.2]	7.9 ± 5.1	5.7 [4.1 - 11.4]	-3.43 [-9.59 -2.73]	0.137
Total Cholesterol (mg/dL)	171.5 ± 37.1	167.5 [140.5 - 195.5]	168.9 ± 40.8	174 [134 - 186]	-1.88 [-23.26 -19.51]	0.048
LDL Cholesterol (mg/dL)	102.4 ± 27.1	105.0 [81.0 - 116.0]	102.4 ± 34.9	101 [78 - 118]	0.36 [-17.79 -18.50]	0.297
HDL Cholesterol (mg/dL)	56.4 ± 11.7	55.0 [48.5 - 64.0]	59.4 ± 10.7	55 [49 - 76]	2.19 [-5.26 -9.63]	0.438
Triglycerides (mg/dL)	68.2 ± 27.0	65.5 [43.8 - 88.0]	58.9 ± 23.1	55 [43 - 67]	-10.00 [-25.56 -5.56]	**0.003**
AST (U/L)	20.5 ± 9.7	18.0 [13.8 - 24.8]	14.1 ± 6.7	13.8 [9.7 - 17.0]	-8.31 [-13.41 --3.20]	0.074
ALT (U/L)	13.7 ± 6.4	12.0 [10.0 - 17.6]	12.5 ± 5.5	12.0 [10.1 - 15.0]	-1.13 [-4.51 -2.25]	0.215
GGT (U/L)	13.3 ± 8.2	10.5 [8.0 - 14.8]	15.9 ± 8.1	15.8 [10.4 - 20.4]	1.20 [-4.70 -7.11]	0.472
Creatinine (mg/dL)	0.3 ± 0.1	0.28 [0.22 - 0.36]	0.3 ± 0.1	0.30 [0.23 - 0.37]	0.00 [-0.06 -0.06]	0.202
Urea (mg/dL)	19.0 ± 9.0	17.5 [12.0 - 24.0]	19.0 ± 5.0	19.0 [15.6 - 22.4]	0.00 [-4.83 -4.83]	0.070
Uric acid (mg/dl)	4.7 ± 1.3	4.7 [3.8 - 5.6]	5.6 ± 1.6	5.6 [4.5 - 6.7]	0.90 [-0.06 -1.86]	0.074
KBs (mmol/L)	0.1 ± 0.1	0.1 [0.0 -0.2]	2.5 ± 1.4	2.5 [1.6 - 3.4]	2.40 [1.74 -3.06]	**0.001**

Values are presented as Mean ± Standard Deviation (SD) and Median [Interquartile Range: 25th - 75th percentile]. *BMI* Body Mass Index, *RQ* Respiratory Quotient, *REE* Resting Energy Expenditure, *LDL* Low-Density Lipoprotein, *HDL* High-Density Lipoprotein, *AST* Aspartate Aminotransferase, *ALT* Alanine Aminotransferase, *GGT* Gamma-Glutamyl Transferase, *KBs* Blood Ketone Bodies

Differences in nutritional status between high- and low- fiber intake

At follow-up, 8 patients (40%) had low fiber intake, while the remaining 12 (60%) had a high fiber intake.

Patients with high-fiber cKDT were younger and had higher weight z-scores. There were no significant differences between the groups for other clinical parameters (see Table 4).

Discussion

Our findings challenge the traditional belief that cKDT is inherently low in fiber: these results indicate a notable increase in fiber intake, specifically soluble fiber, over a 5 year-long period in patients following the cKDT. This increase has probably been facilitated by specialized food supplements for medical purposes (FSMPs) consumption and the gradual introduction of low-carbohydrate, fiber-rich ingredients. No substantial changes were observed in nutritional status or in the potential impact of the dietary regimen on ketone bodies' production. On the contrary, it suggests a potential enhancement in dietary quality, although a substantial proportion of patients (40%) remain with low fiber consumption.

Table 4 Comparison of Patient Characteristics at Follow-Up (T1) by Fiber Intake Group

	Low fiber intake		High fiber		*p*-value
	N = 8		N = 12		
	Mean	SD	Mean	SD	
Age	15.3	8.9	9.5	5.9	**0.400**
Anthropometric measurements					
Weight (kg)	45	19.2	40	20	0.392
Weight z-score	-0.3	0.8	0.1	1.4	**0.042**
Height (m)	1.5	0.2	1.4	0.2	0.192
Height z-score	-0.6	1.3	-0.2	1.2	0.462
BMI (kg/m2)	20	4.5	20	5.3	0.713
BMI z-score	0.4	0.9	0.5	1.3	0.085
Waist Circumference (cm)	70.9	10.3	63.7	13.4	0.033
Waist Circumference z-score	1.6	1,025	1.3	0.9	0.733
Body composition by skinfolds					
Body fat (%)	30.2	17	27.2	15.8	0.897
Body fat z-score	0.2	0.9	0.1	0.8	0.596
Resting energy expenditure					
RQ	0.8	0.1	0.8	0.1	0.242
REE (kcal/die)	1198	307	1024	311	0.766
Biochemical parameters					
TC (mg/dl)	182	42	161	33	0.265
HDL-C (mg/dl)	60	15	54	10	0.068
LDL-C (mg/dl)	112	34	94	25	0.556
TG (mg/dl)	66	28	62	23	0.616
Glucose (mg/dl)	87	8	86	8	0.331
Insulin (mU/mL)	11	10.9	9.3	7	0.535
AST (U/L)	16.8	9.8	18.1	8.3	0.736
ALT (U/L)	12.9	5.6	12.4	4.8	0.704
GGT (U/L)	13.6	7.6	15.8	9.3	0.270
Urea (mg/dl)	18.5	9.5	19	7.5	0.946
Creatinine (mg/dl)	0.3	0.1	0.3	0.1	0.703
Uric acid (mg/dl)	4.5	1.3	4.2	1.4	0.159
KBs (mmol/L)	2.5	1.8	2.4	1.9	0.341

Comparison between high- and low-fiber intake groups revealed that individuals with lower fiber and FSMPs consumption had lower weight z-scores. This unexpected finding may be attributable to age-related differences in nutritional status between the groups and a cohort effect: younger patients recruited more recently may have had earlier access to a wider variety of palatable, fiber-fortified FSMPs compared to older patients who started the diet when options were more limited. Also, fiber-induced fluid shifts, particularly with highly fermentable fibers, potentially contributing to altered gut microbiome composition and fluid balance, could hypotheticallyplay a role. Further investigation with a deeper body composition analysis and assessment of gut microbiome and dietary factors is necessary to clarify these findings.

Scientific literature supports the idea that ketogenic dietary therapies can be modified to include adequate fiber, without compromising their therapeutic benefits. Historically, KDTs were perceived as low-fiber regimens, due to the restrictions on carbohydrate intake. Recent studies have explored various strategies to enhance fiber content while maintaining ketosis. For instance, incorporating low-carbohydrate, high-fiber foods such as non-starchy vegetables, nuts, and seeds can effectively increase fiber intake without significantly affecting the ketogenic state [16–21]. While maximizing fiber through low-carbohydrate vegetables is a viable and effective strategy in more flexible or lifestyle-driven ketogenic protocols, it remains highly constrained in strict clinical classic regimens, as cKDT, due to exceptionally rigid net carbohydrate limits. Furthermore, FSMPs rich in fiber represent an innovative approach to enhance dietary diversity and nutritional adequacy in ketogenic regimens. They often contain

soluble and insoluble fibers sourced from various plant- based ingredients like psyllium husk or oat fiber, offering a solution by providing alternative sources of dietary fiber. These fibers could contribute to reduce gastrointestinal discomfort, regulating bowel movements and promoting post-prandial fullness and intestinal health [16, 21, 22].

Fiber is essential for long-term management of conditions treated with KDTs, potentially impacting gut health, satiety, and metabolic regulation. Increased fiber intake may improve gastrointestinal function, mitigating KDT side effects like constipation, and could contribute to numerous health benefits, which in the general population include a reduced risk of cardiovascular disease.This is linked to fiber's ability to reduce waist circumference and cholesterol, as large waist circumference, even in children, is associated with increased visceral fat and risk of metabolic syndrome. Fiber promotes satiety, crucial in c KDT where high fat intake limits food volume. It achieves this by increasing bulk in the digestive tract, slowing gastric emptying (especially soluble fibers), and producing short-chain fatty acids (SCFAs) that influence appetite hormones [8, 9, 23]. In cKDT, where dietary adherence is challenging, fiber's satiating effect with smaller portions is particularly valuable. Furthermore, it supports bowel regularity and reduces the risk of common cKDT comorbidity like constipation [9, 16, 24].

The role of dietary fibre in shaping the microbiota is no less important, although direct measures were not included in this study. Many types of fiber act as prebiotics, serving as a food source for beneficial gut bacteria. These bacteria thrive on fiber, leading to an increase in their abundance and diversity. A healthy gut microbiota helps maintain the integrity of the gut barrier, preventing harmful substances from entering the bloodstream. Fiber can contribute to this by promoting the growth of beneficial bacteria that strengthen the gut lining. Certain types of fiber, such as soluble fiber, can help reduce inflammation in the gut. This is important because chronic inflammation has been linked to various health problems, including metabolic disorders that could occur also as comorbidity in neurological disease due to a prolonged high fat intake. Moreover, beneficial gut bacteria ferment fiber, producing SCFAs. These have numerous health benefits, including improved insulin sensitivity, reduced inflammation, and enhanced gut barrier function [25–28].

KDT can have a significant impact on the gut microbiota, varying significantly from person to person. This is due to the dramatic shift in macronutrient intake that occurs when following a KDT:

- KDTs are characterized by a very low intake of carbohydrates, which are the primary fuel source for many gut bacteria. This reduction can lead to changes in the composition of the microbiota, as some bacteria may struggle to adapt to the new energy source.
- KDTs involve a high intake of fats. While some unsaturated fatty acids can be beneficial for certain gut bacteria, excessive levels of saturated and unhealthy fats may promote the growth of less desirable bacteria.
- KDTs can alter bile acid metabolism, which can in turn affect the gut microbiota. Some studies have suggested that KDTs may increase the risk of gut dysbiosis, especially if not followed properly.

Despite all of these benefits, consuming excessive amounts of fibre can lead to a number of potential adverse effects, such as digestive discomfort (bloating, gas, abdominal cramps), constipation if too little water is consumed with insoluble fibre, or diarrhoea if too much water is consumed with soluble fibre, thereby worsening hydration [12, 20, 22]. In addition, excessive fibre intake may interfere with the absorption of minerals such as iron and calcium, potentially leading to deficiencies because of already reduced levels in cKDT, as well as with certain medications and supplements commonly used in cKDT [12, 20]. None of our patients reported anemia. While bone status data were not collected in the present study, our previous 5-year investigation demonstrated no changes in bone mineral density T-scores associated with the dietary intervention [29].

Concerning ketosis, fiber typically has minimal adverse effects because it does not significantly affect blood glucose levels or insulin secretion [30]. However, if soluble fibers such as pectin, psyllium and beta-glycan are high, they can bind to bile acids and form viscous gels in the intestine, excreting rather than reabsorbing bile acids and slowing the mixing of food with digestive enzymes, significantly delaying the absorption of fats. At clinical level, this could probably result in a slower ketone bodies' production. Future acute studies in subjects with chronic therapeutic ketosis, similar to our previous study in healthy subjects [30], will be useful to test the postprandial trend of ketone bodies after consuming such high-fiber meals.

In conclusion, our findings align with emerging evidence suggesting that dietary modifications, including increased fiber intake through specialized supplements, can be integrated into ketogenic protocols without undermining their therapeutic efficacy. This paradigm shifts challenges previous perceptions of ketogenic diets as inherently low in fiber and underscores the importance of individualized dietary approaches in medical nutrition therapy. Future research should continue to explore optimal dietary compositions that balance therapeutic goals with overall nutritional adequacy and long-term health outcomes, specifically through prospective studies with microbiome sequencing, bone mineral assessment and postprandial ketone studies.

This study has several strengths. Firstly, it has an adequate sample size given the pathology being studied, and features a long treatment duration, enabling comprehensive long-term analysis. Additionally, the collaboration between two multidisciplinary teams with extensive experience in KDT treatment is noteworthy. These national reference centers collaborated effectively, facilitating extensive patient recruitment and robust data collection. Furthermore, the study utilized gold standard methods such as the 3-day food diary for dietary data collection.

This study is not free of other limitations. Firstly, the absence of a control group remains a significant limitation inherent to such studies. Moreover, the small sample size limits the statistical power for detailed subgroup comparisons. Secondly, the reliance on caregiver-filled food diaries may introduce potential reporting bias. Furthermore, given the long observation period, specific FSMP formulations may have varied over time. Finally, as the study was conducted in specialized tertiary centres, the results may have limited generalisability to other clinical settings. A major limitation regarding the clinical efficacy of the treatment is the lack of systematic data collection on seizure frequency. However, it is important to note that our center's protocol requires diet discontinuation if no clinical benefit is observed after 6 months. The fact that this cohort remained on the diet for an average of over 5 years indirectly implies sustained clinical efficacy; otherwise, the therapy would have been suspended. Similarly, data on specific gastrointestinal symptoms and tolerability were not recorded, preventing an analysis of whether higher fiber intake reduced constipation or caused bloating in this specific cohort. Moreover, the lack of longitudinal continuous quantitative ketonemia data meant that the actual impact of the fibre increase on ketone production could not be statistically assessed. Despite this, as described above, the respiratory quotient made it possible to establish that the initial state of ketosis remained stable despite diet modificationa. Closely related to the assessment of fibre intake is the distinction between soluble and insoluble fibre which was not performed in this analysis. It would be useful to make this distinction when interpreting food diaries, as they have different effects, biological effects. Of particular interest could be soluble fibre, which, due to its chelating effect on certain organic molecules such as lipids, could reduce their bioavailability. This could lead to a shortage of lipids to produce ketones and thus a reduction in ketonemia. The distinction between soluble and insoluble fibre components could also be useful in the formulation of new FSMPs and in the evaluation of the gastrointestinal effects that the two fractions may cause.

In conclusion, our data show that over a 5-year period, fibre intake in cKDT more than doubled with FSMPs. This did not appear to affect nutritional status or reduce the impact of the diet on ketosis, and in fact may have improved dietary quality. These results challenge the outdated notion that cKDT is low in fibre and suggest that guidelines for optimal fibre intake need to be refined. Future studies are needed to assess the effect of changes in dietary fibre intake on ketosis, gut microbiota and mineral absorption.

Abbreviations

BMI	Body mass index
TC	Total cholesterol
LDL-C	Low-density lipoprotein cholesterol
HDL-C	High-density lipoprotein cholesterol
TG	Triglycerides
AST	Aspartate aminotransferase
ALT	Alanine transaminase

GGT	Gamma-glutamyl transferase
BW	Body weight
SFA	Saturated fatty acids
FSMP	Food for special medical purposes
cKDT	Classic Ketogenic Dietary Therapies
KR	Ketogenic Ratio
KBs	Ketone Bodies

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate The study protocol was approved by the ethics committee of the Fondazione IRCCS Policlinico San Matteo di Pavia (reference number 20180083746) and complied with all principles of the Declaration of Helsinki. All caregivers and parents provided written informed consent before the beginning of the study.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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