

Ketogenic Diet in patients with refractory epilepsy

Dieta Cetogénica en el paciente con epilepsia refractaria

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What do we know about the subject matter of this study?

Ketogenic diet (KD) is an effective non-pharmacological treatment for refractory epilepsy (RE) in the pediatric population and may diminish and eliminate seizures as well as reduce the use of anti-epileptic drugs.

What does this study contribute to what is already known?

We present a national experience of using KD in RE, with an important number of pediatric cases managed with ketogenic diet protocols according to each clinical condition, with good response in seizure control and no significant nutritional impact.

Abstract

Epilepsy affects 0.5 to 1% of the population. 25% of pediatric patients have drug-resistant epilepsy (DRE). Ketogenic Diet (KD) emerges as an effective, non-pharmacological treatment in this group. **Objective:** To describe the effect of KD on seizure control and nutritional status in children with DRE. **Patients and Method:** We reviewed the medical records of patients with DRE treated with KD, between 2008 and 2018, evaluating age, diagnosis, number of seizures, number of antiepileptic drugs used, clinical outcomes, and complications. The KD was initiated in all patients hospitalized for a period no longer than seven days, who were evaluated for their nutritional and anthropometric status, with weight and height measurements according to the clinical condition. **Results:** We analyzed 35 KD in 33 cases. The median age of KD initiation was 4.8 years with an interquartile range (IQR) of 2-3 to 6.8 years. Classical KD was used in 49% of patients, Modified Atkins Diet (MAD) in 37%, and Low-Glycemic Index Treatment (LGIT) in 14% of cases. The average duration was 13 months (SD 11 months). After three months of using KD, we observed at least 50% reduction of seizures in 82% (27/33) of the patients, out of these, 22.8% presented 90% or more reduction of seizures, and 20% ended up seizure-free. Adverse events were observed in 21 patients, mainly gastrointestinal (62%) and dyslipidemia (14%), without effect on height. All side effects resolved with medical management. **Conclusions:** KD is a useful treatment in pediatric patients with DRE without nutritional impact. The adverse events were easily controlled if the patients are evaluated by a multidisciplinary team, according to international guidelines.

Keywords:

Ketogenic Diet;
Refractory Epilepsy;
Atkins Diet;
Glycemic Index;
Dyslipidemia

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Introduction

Epilepsy is a clinical entity that affects 0.5% to 1% of the population¹. Sixty percent of the cases start during childhood¹ and about 25% of the patients present refractory epilepsy (RE)^{2,3}, which is defined as poor seizure control despite treatment with at least two antiepileptic drugs (AEDs), at adequate doses and during an appropriate time, leading to a neurological function deterioration and worsening the quality of life⁴⁻⁶. In these patients, it is proposed to add a ketogenic diet (KD) to the pharmacological treatment^{7,8}. KD consists of a high-fat, low-carbohydrate diet designed to simulate the biochemical effects of fasting^{3,8}.

There are different types of KD, and four of them have evidence supporting their use in RE^{8,9}. Classic KD (CKD) provides 90% of total daily calories as fat with the use of long-chain triglycerides (LCT) and 10% of the remaining calories as proteins and carbohydrates, establishing a caloric ratio between lipids and the sum of proteins plus carbohydrates of 4:1 or 3:1. Another is KD with medium-chain triglycerides (MCT), which produces a higher amount of ketones per gram of fat and provides 60% of calories as fat, where half of them may be MCT (percentage that varies according to tolerance), maintaining a 3:1 caloric ratio. Modified Atkins diet (MAD), which is less strict than the previous ones, provides a fixed amount of carbohydrates (10-15 g/d in children and 20 g/d in adults), with a caloric intake of proteins of 20%-30% and 60%-70% of fats. Finally, KD with low-glycemic index (LGID), provides 30-40 g of carbohydrates, with a glycemic index lower than 50, and 50%-60% of caloric intake as fat⁹.

The mechanism of action of KD as an anticonvulsant is not clearly identified. There have been numerous hypotheses about how it works, but none has been widely accepted as the sole mechanism behind its action. These are probably different mechanisms of action that act in parallel and synergistically¹⁰⁻¹².

Since KD entails a deficient intake of micronutrients, supplementation with vitamins, minerals, and trace-elements is essential^{9,13} and, considering that KD uses fat as the main source of energy, any congenital anomaly that affects lipid metabolism is a contraindication for its implementation¹⁴⁻¹⁶.

Several studies describe that the correct use of KD in subjects with RE reduces the number of seizures by at least 50% in half of the patients and a reduction of more than 90% in seizures in a third of them^{12,16-21}.

The objective of this publication was to describe the impact of KD on seizures frequency and nutritional status of pediatric patients with RE. Another publication reported the analysis of this group of patients regarding the effect of KD on seizure reduction according to the etiology of epilepsy and seizure type²².

Patients and Method

Design

We reviewed the medical records of all patients referred from the Child Neurology Service to the Child Nutrition team of the *Hospital Clínico San Borja Arriarán* (HCSBA), for treatment of RE using KD between 2008 and 2018.

Once the Neurology team indicated the KD, the Nutrition team evaluated the condition of the patient and her/his family to see the feasibility of its realization and assess adherence, providing information to parents and caregivers.

Patients and KD protocol

We analyzed the patients by sex, diagnosis, feeding route, number of AEDs used, and number of seizures/days reported by the caregiver at the time of starting the KD. Two cases were included who presented with status epilepticus, and therefore the number of seizures could not be quantified.

In all cases, patient started on KD during hospitalization for a period not exceeding seven days, where anthropometric nutritional assessment was performed with weight and height measurement according to the clinical condition. For this analysis, in 17 cases specific curves were used for patients with Cerebral Palsy²³, recording Body Mass Index/Age (BMI/A) and Height/Age (H/A) measured in percentiles and considering malnutrition in patients with BMI/A lower than Pc 5. In the remaining cases, we used WHO 2006 anthropometric standards²⁴ for children under 5 years old, recording BMI/A and H/A with Z-score measurement, and using WHO 2007 standards²⁵ for those over 5 years old, recording BMI/A and H/A with Z-score measurement. In patients analyzed with WHO curves, the usual cut-off points were used for nutritional diagnosis. At admission, laboratory tests were performed according to study protocol (Figure 1) and caregivers completed an education plan.

The type of KD was chosen considering the feeding route of the patients and the clinical condition of each one. In those who were fed orally, the preference was to use MAD and LGID modalities, which allows for improved adherence and tolerance due to better palatability. In patients fed enterally through gastrostomy (GTT), CKD 3:1 or 4:1 was preferred.

KD started without a fasting period or water restriction and was established from the beginning with full caloric intake, calculated according to their requirements. The ketogenic ratio was progressively increased until the objective of ketosis was achieved on the third day. Before 2015, ketosis was measured by ketonuria, considering as a positive value 3+, equivalent to 28 mmol/L. Since 2015, ketosis is measured by deter-

mining Beta-hydroxybutyrate levels in a blood sample, considering as positive a concentration higher than or equal to 2 mmol/L. Later, ketosis control was performed according to an outpatient protocol (Figure 1).

In the two cases with status epilepticus, KD was initiated with the patient monitored in the Intensive Care Unit. In both cases, CKD 4:1 was administered via enteral route through NGT and its implementation did not vary from what was described for the other patients.

All the patients were discharged with a set of menus elaborated in our center, personalized, and strictly calculated according to the Food Composition Table of the Institute of Nutrition and Food Technology (INTA) of the University of Chile²⁶.

In preschoolers with MAD, we used a lower percentage of proteins calories intake than the recommended one^{27,28}, in order to provide a diet with a more adequate protein intake for the age, using a P% of 15, keeping the carbohydrates intake mentioned in other publications²⁷⁻²⁹.

The lipids were calculated based on a fixed amount of oil rich in omega 3 (10 ml/d) and the difference was completed with equivalent percentages of olive oil and sunflower oil, in order to incorporate monounsaturated and polyunsaturated fatty acids into the diet, to achieve a ratio as close as possible to 1:1:1^{27,29}.

All patients received micronutrients and calcium supplements according to requirements (DRI). Egg intake was included in the menu to ensure proper Selenium intake²⁶. Vitamin D3 was administered at initial doses of 1,000 IU/d, which was adjusted based on serum concentrations of 25 OH vitamin D when it was available. Patients receiving treatment with Valproic Acid received supplementation with L-carnitine at doses of 50 mg/kg/d.

KD was maintained for 24 months in case of success and a maximum of 3 months in case of failure. In both situations, the diet was gradually withdrawn over 4 weeks. Outpatient follow-up was carried out at the Polyclinic of Nutrition with checkups visits at 1, 3, 6, 12, 18, and 24 months after starting the diet. At each visit, we evaluated anthropometric data and adequacy of caloric intake, with menu variations when necessary, request for lab tests according to the protocol (which included measurement of Beta-hydroxybutyrate in our hospital laboratory), detection of complications, and clinical follow-up, including the number of seizures reported by the caregiver.

A reduction in the number of seizures higher than or equal to 50% was considered a favorable response^{12,29}. Dyslipidemia was defined according to the cut-off points for blood lipids suggested by the AAP expert panel in 1992 and complemented in 2011 for Triglyceride (TG) and cholesterol HDL (C-HDL) levels³⁰⁻³².

Statistical Analysis

The results were summarized in a database in the Excel software. Statistical analysis was performed with the GraphPad Prism 8 software; quantitative variables were evaluated as median and interquartile range (IQR) or mean, standard deviation, and percentages. The Wilcoxon test for paired samples was used for the analysis of percentage of seizures reduction (Figure 2).

Ethics

This work was presented and approved on October 9, 2019, by the Scientific Ethical Committee of the Central Metropolitan Health Service of Santiago.

Results

We analyzed 35 KD in 33 patients with a median age of 4.8 years at the beginning of KD and IQR of 2.3-6.8 years, ranging from 4 months to 15 years.

Two patients discontinued the diet, which was later re-started by Neurology. Table 1 shows the general characteristics of the KD used, as well as their distribu-

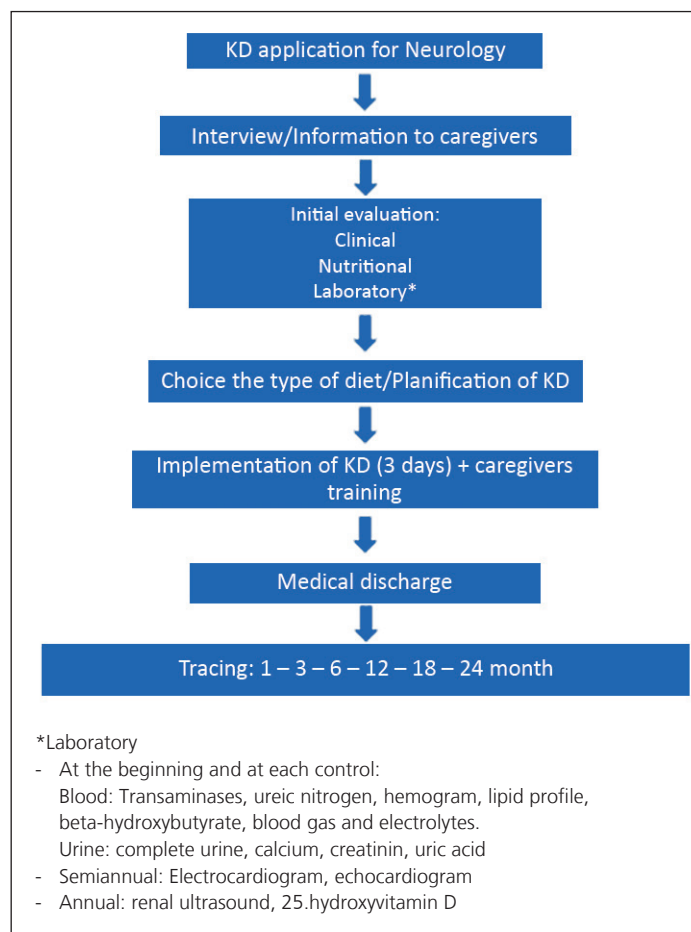


Figure 1. Ketogenic Diet protocol applied to the studied population.

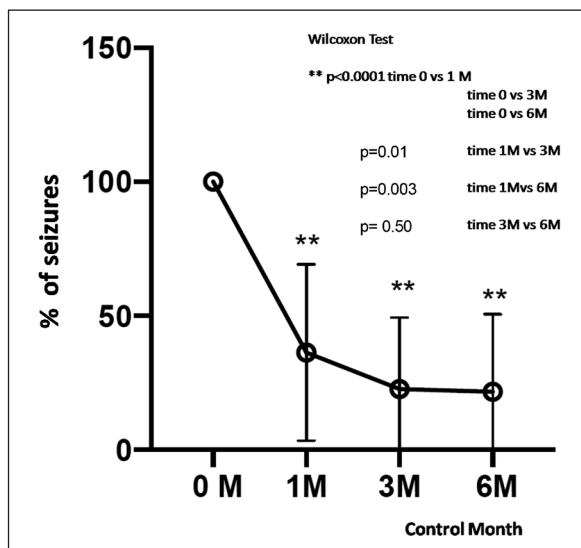


Figure 2. Percentage of epileptic seizures reduction over time.

tion according to diagnosis, and Table 2 shows the distribution of patients according to the type of KD used.

The nutritional status of the patients at the entry to the protocol was 22 eutrophic (63%), 3 at risk of malnutrition (8.5%), 2 undernourished (5.7%), 2

overweight (5.7%), and 6 obese (17.1%). At the time of withdrawal from the protocol, the distribution was 20 eutrophic (57.2%), 4 at risk of malnutrition (11.5%), 3 undernourished (8.5%), 6 overweight (17%), and 2 obese (5.7%). When comparing the condition of each patient at the beginning and end of the diet, 23 (65.7%) had no changes, 2 (5.7%) who started the diet at risk of malnutrition became undernourished, 2 (5.7%) who were eutrophic ended up at risk of malnutrition, and 2 (5.7%) who started eutrophic ended up overweight. 6 patients (17.1%) improved their anthropometry after having started with excess weight or underweight. In those patients who maintained the KD for at least six months, their height was not affected.

Out of the 35 KDs, 14 (40%) completed our protocol. 10 patients (28%) discontinued the diet within the first 3 months (six due to no response and four due to diet withdrawal). Of the remaining 11, only one patient discontinued the diet due to complications (recurrent diarrhea), and the others discontinued it earlier than planned due to difficulties in adherence.

After 3 months of beginning the protocol, only 6 cases had no good response, 4 of them decreased the seizure frequency, and the other 2 reduced their seizures by less than 50%. The remaining 29 cases presented a favorable response, in other words, a decrease

Table 1. Characteristics of the KD performed

| Variable | Categorization | Total (n) |
|--------------------------------|-------------------------|-----------|
| Sex | Female | 19 |
| | Male | 16 |
| Number of AEDs used | ≤ 2 | 5 |
| | 3 to 4 | 28 |
| | ≥ 5 | 2 |
| Number of seizures/day | < 5 | 5 |
| | 5 to 10 | 19 |
| | 11 to 30 | 9 |
| | Status | 2 |
| Feeding route | Enteral (GTT) | 14 |
| | Oral | 21 |
| Etiological Diagnosis Unknown* | | 17 |
| Syndrome | West Syndrome | 4 |
| | Lennox Gastaut Syndrome | 1 |
| | Ohtahara Syndrome | 1 |
| | Dosse Syndrome | 2 |
| | Rett Syndrome | 1 |
| Genetic | Dravet Syndrome | 2 |
| | Glut 1 Deficiency | 1 |
| Structural - Metabolic | Tuberous Sclerosis | 3 |
| | Herpetic Encefalopathy | 3 |

*17 KD performed in 15 patients. AEDs: Antiepileptic drugs. GTT: Gastrostomy.

Table 2. Distribution of patients according to the type of ketogenic diet (KD) used

| Type of KD | Total of KD | | Caloric percent of macronutrients | | | Ketogenic ratio |
|-----------------------|-------------|----|-----------------------------------|---------|---------|-----------------|
| | n | % | % F | % P | % CHO | |
| Classic KD | | | | | | |
| 4:1 | 12 | 35 | 90 | 6 | 4 | 4:1 |
| 3:1 | 5 | 14 | 85 - 87 | 8 - 10 | 4 - 7 | 3:1 |
| Modified Atkins diet* | 13 | 37 | 50 - 79 | 15 - 30 | 5 - 20 | 1.5:1 |
| Low Glycemic Index | 5 | 14 | 60 - 66 | 17 - 27 | 13 - 23 | 1.5:1 |

*13 KD performed in 11 patients. %F: caloric percent from fat. %P: caloric percent from protein. %CHO: caloric percent from carbohydrates.

of 50% or more in the number of seizures, distributed as follow: 14 decreased their seizures between 50 and 90%, 8 presented a decreased by more than 90%, and 7 evolved with total remission (Table 3). Notably, the two patients in status epilepticus also had a favorable response.

Figure 2 shows the clinical efficacy of KD, expressed as the percentage of seizures reduction observed between the start of the diet and after 1, 3, and 6 months of its implementation which was a decrease statistically significant.

In our series, we observed that 21 patients presented complications, most of them (13 cases) gastrointestinal, 11 cases of constipation, all satisfactorily managed with polyethylene glycol (PEG) at usual doses; a nine-month-old infant who presented several episodes of diarrhea requiring inpatient management, and a patient with repeated vomiting which ceased after changing his 4:1 CKD for a MAD type.

Regarding the rest of the complications observed, two patients using Topiramate presented mild metabolic acidosis with spontaneous resolution, without requiring the use of bicarbonate and with no clinical repercussions. Three patients presented renal lithiasis that was medically resolved by the Nephrology team using potassium citrate. Other three patients presented alteration in the lipid profile, all of them under 10 years old and of early-onset, detected in the 3-months visit. In two of them, both total cholesterol (TC) and triglycerides (TG) level increased; the first one with TC of 210 mg/dl and TG of 137 mg/dl and the second one with TC of 263 mg/dl and TG of 166 mg/dl. The third patient with lipid profile alteration presented only a TC increase of 246 mg/dl. All of them were treated with dietary measures, achieving plasma levels of TC less than 200 mg/dl and TG less than 100 mg/dl, thus decreasing their risk level according to international consensus cut-off points³⁰⁻³². Another three patients presented at the beginning of the diet TC above 200 mg/dl and all of them reached plasma TC levels lower than 200 mg/dl by adjusting the diet.

Table 3. Percentage reduction in epileptic seizures

| % reduction of seizures | N | Percent (%) |
|-------------------------|----|-------------|
| 0% | 4 | 11.4 |
| < 50% | 2 | 5.7 |
| 50 - 89% | 14 | 40 |
| 90% - 99% | 8 | 22.8 |
| 100% | 7 | 20 |

Discussion

As part of the treatment for RE in children, KD is widely validated in the literature, with efficacy ranging from 56% to 85% in reducing more than 50% of the seizures and achieving remission by 15% to 55% in these patients^{11,12}. This variability could be related to the baseline diagnoses since there would be neurological conditions that have reported better response^{4,5,29}.

In our experience, in 82.8% of the cases, we obtained a favorable response, defined as the reduction of the seizures to more than 50%, highlighting that 20% of the patients presented a total remission. A possible explanation for these results could be that, of our 18 cases with known syndromic diagnosis, a large percentage had syndromes and conditions associated with a greater probability of successful response to KD^{4,5,29}. Only five patients had a molecular diagnosis to determine the associated genetic mutations, out of which two had *SCN1A* mutation, which is one of those associated with better response³³. In the future, having this diagnostic tool could help us evaluate the response and favor the selection of patients appropriated for KD.

Another element to consider, which also appears in other reports with favorable response, is the education of caregivers²⁹. In our center, during the hospitalization, we implemented an intensive theoretical

and practical workshop to educate the caregivers and to ensure opportunities for them to ask in case of any doubt.

In two of the patients using the CKD 4:1, there was a decrease in seizures despite there was no ketonemia (measured with Beta-hydroxybutyrate during hospitalization). In both cases, there was use of drugs that interfere with glucose metabolism^{34,35}. The first one using growth hormone due to panhypopituitarism and the other one with recurrent obstructive conditions receiving budesonide oral inhalation, which when suspended reached ketosis. One possible explanation that has been proposed is that glucose restriction would play a role in the anticonvulsant effect, which is demonstrated by the effectiveness of low-glycemic index diets^{34,35}.

Many of the caregivers reported improvement in patients' level of alertness, which was an additional motivation to continue with the diet. Although this finding was not part of our analysis, it allows us to establish a new line of work by evaluating the subjective well-being of the patient and their caregivers. Already in 2006, Fasarat and Kossoff demonstrated that meeting or exceeding parental expectations for cognitive improvement was significantly associated with a longer duration of the diet³⁶.

Since 2008, there are publications about the use of KD in patients diagnosed with status epilepticus that presented good evolution^{38,39}. In our experience, both patients with this condition responded favorably. In recent literature, there are reports on the use of KD via parenteral route in this type of cases, which we consider interesting for possible future use^{37,38}.

Regarding the percentage of patients suspending the diet, our experience was similar to that described in other studies^{28,40-42}. At 6 months, 13 of the 35 cases (37%) quit the diet, most of them due to not following the menus. In this group are mainly those children who wander, feed themselves orally, and have autonomous access to foods other than those contained in their daily diet.

Several short- and long-term adverse effects are described in the literature as a result of high-fat content and low carbohydrate, fiber, and micronutrient intake^{29,43,44}. To decrease the risk of nutritional deficiencies, currently and in patients under two years of age, we use specific commercial formulas since they are in a critical period of growth.

In our series, the most frequent adverse events were gastrointestinal, where constipation was the most reported (31%). However, a 9-month-old infant receiving 3:1 CKD presented multiple hospitalizations associated with diarrhea and hydroelectrolytic alterations due to the KDs thus it was suspended. This was the only case of adverse events.

Our low incidence of dyslipidemia (8.5%) compared with the reported in other publications (14%-59%) could be explained because in all cases we tried to obtain a balanced relation of lipids, optimizing the intake of polyunsaturated fatty acids with a fixed amount of omega 3^{29,45}. Additionally, some studies that evaluate different distributions of the types of fats show that a greater proportion of polyunsaturated fatty acids would favor the presence of ketosis⁴⁶⁻⁴⁸.

In relation to the impact on growth, there is controversy in the literature, reporting growth deceleration in some cases^{29,44,49-53}. None of our patients with at least 6 months of treatment showed any decline of height during the use of KD which could be due to the fact that we did not restrict caloric intake. We believe it is very important to evaluate in the future the relationship between KD and growth, considering underlying pathology, nutritional, endocrine, and metabolic factors that could affect growth patterns.

In conclusion, the results of our experience show a therapeutic success similar to those described in expert centers²⁹, locally validating the incorporation of KD to the pharmacological treatment of RE in the pediatric age. Our work shows the evolution of an important number of patients, under an established follow-up protocol, where we adapted the type of diet to each patient according to their clinical characteristics, requirements, and food tolerance, which we assessed throughout the treatment period. It is worth to mention that there was no impact on height in patients who used the diet for more than three months. This experience will allow other areas of research to determine the impact of KD not only on the number of seizures but also on the quality of life and well-being of the patient and her or his environment.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors state that the information has been obtained anonymously from previous data, therefore, Research Ethics Committee, in its discretion, has exempted from obtaining an informed consent, which is recorded in the respective form.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

Financial Disclosure

Authors state that no economic support has been associated with the present study.

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