Incidence of potential adverse events during hospital-based ketogenic diet initiation among children with drug-resistant epilepsy

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Abstract
Objective: Due to the possibility of serious adverse events (AE), patients are commonly admitted to hospital for 3-5 days for ketogenic diet (KD) initiation. This study examined the incidence of potential AE during admission for KD initiation to investigate the possibility of safely initiating a KD at home.

Methods: Children with drug-resistant epilepsy (DRE) who were admitted to hospital for 5 days for KD initiation were retrospectively studied.

Results: A total of 66 children (59% female) were analyzed. The mean age at the initiation of the KD was 48.0 ± 38.4 months, and the mean weight was 14.6 ± 6.3 kg. The median number of anticonvulsant medications used at the time of KD initiation was 3. The etiology of the DRE was structural in 4.5%, hypoxic ischemic encephalopathy in 10.6%, genetic/metabolic in 31.8%, acquired in 10.6%, and unknown in 42.2%. The potential AE occurred in 28.7% of patients, including hypoglycemia (20%), hypoactivity (6.1%), somnolence (3%), and vomiting (7.6%). A univariate analysis of the clinical characteristics of the AE and no AE groups showed a statistically significant difference in weight (P = 0.003) and age (P = 0.033). The concurrent use of topiramate was found to have a near-significant association (P = 0.097) between the groups. The groups’ urine ketone levels on all 5 days were compared, and a statistically significant difference was found on day 3 (P = 0.026). A statistically significant difference in the serum bicarbonate levels (P = 0.038) was found between the patients taking topiramate and those not taking it.

Significance: The incidence of AE during admission for KD initiation was found to be low. The AE either required no intervention or were easily managed with simple interventions. Thus, in carefully selected patients, it may be possible to initiate a KD at home if the parents are adequately prepared and monitored.

Keywords: adverse events, children, drug-resistant epilepsy, initiation, ketogenic diet

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INTRODUCTION

A ketogenic diet (KD) is widely recognized as an effective treatment modality for children with drug-resistant epilepsy (DRE).1–4 A KD is a low-carbohydrate, high-fat regimen that induces ketone body production and so creates a metabolic state similar to fasting. The ketone bodies β-hydroxybutyrate and acetoacetate are used as the primary source of energy due to the absence of an adequate glucose supply. There are four types of KDs, namely the classic KD, the modified Atkins diet (MAD), the medium-chain triglyceride diet (MCTD), and the low-glycemic-index treatment (LGIT).5 These specialized diets need to be medically supervised so as to monitor potential adverse events (AE). The AE experienced during KD initiation are usually transient and able to be managed conservatively; however, serious complications require close monitoring.6,7 Major AE are rare during KD initiation, although they could include persistent emesis, persistent hypoglycemia, liver toxicity, severe metabolic acidosis, and the refusal of oral intake.8

Due to the possibility of serious AE occurring, it is common practice to admit patients to hospital for 3-5 days for KD initiation, especially in relation to the classic KD and the MCTD.9 The modified Atkins diet is usually initiated on an outpatient basis, and it has been found to be well tolerated.10 Similarly, the LGIT is also typically initiated on an outpatient basis.11 A small-scale prospective observational study designed to evaluate the feasibility of introducing an all-liquid KD in an outpatient setting demonstrated the safety of KD initiation in such a setting.4 The classic KD and the MCTD were also initiated at home in a randomized trial concerning the treatment of childhood epilepsy.12 The need for admission to hospital for several days for KD initiation can prove inconvenient for parents, and it also increases healthcare costs.13 This is a particularly significant limitation in developing countries, where around 80% of patients with epilepsy live.14

The present study examined the incidence of potential AE during the initiation of the classic KD in a hospital setting in order to assess the feasibility of safely initiating such a diet at home, which could potentially increase the utility of the KD, especially in the developing world.

METHODS

This single-center, retrospective chart-review study was conducted among a total of 66 children with DRE who began a KD at King Fahd Specialist Hospital Dammam (KFSHD), Saudi Arabia, between 2011 and 2019. The study was designed to examine the incidence of potential AE during KD initiation in a hospital setting. All the children admitted to the hospital for KD initiation during the period in question were included in the study. Hospital records were reviewed to ascertain the patients’ demographics (sex, age at the time of KD initiation), weight, antiepileptic drugs (AED) used at the time of KD initiation, history of gastroesophageal reflux disease (GERD), route of feeding (oral, nasogastric tube, gastrostomy tube), etiology, metabolic workup, serum bicarbonate levels, KD ratio, daily urine ketone levels, AE experienced during the week of admission (hypoglycemia, hypoactivity, somnolence, vomiting), and interventions performed to treat the AE. This study also considered the number of patients who could not tolerate the KD during admission and so had to discontinue the diet. If the KD was discontinued, the reason for discontinuation was noted. All the patients included in this study underwent serum fasting lipid profile and baseline metabolic screening, including serum ammonia, lactate, pyruvate, plasma acylcarnitine profile, urine acylcarnitine profile, plasma amino acids, urine amino acids, and urine organic acids, prior to KD initiation to rule out any possible contraindications or metabolic disorders requiring different treatment.

2.1 Dietary protocol and blood ketone level measurements

The patients were first evaluated by the pediatric neurol-

    | Key Points |
    |-----------------|
    | • The incidence of AE during a KD initiation was found to be low, and the AE were easily managed with simple interventions |
    | • Children less than 3 years old and underweight children are at higher risk of AE during a KD initiation |
    | • Serum bicarbonate levels should be closely monitored when initiating a KD in patients who are on topiramate, and supplementation should be initiated whenever necessary |
    | • KD initiation at home may be possible in carefully selected patients |
    | • Outpatient KD initiation could be an affordable and convenient treatment option for many |

ologist and KD nurse at their regular clinics. During these visits, a review of each patient’s medical history was performed and a physical examination was conducted. The patients’ families were provided with all the necessary KD-related education, and the relevant dietary restrictions and lifestyle implications were discussed. Those patients considered fit to begin a KD were admitted to the hospital.
for 5 days for KD initiation. A nonfasting, gradual-initiation protocol was followed. The KD was started at a 2:1 ratio (fat to protein plus carbohydrate) and then gradually increased as tolerated. The initial calorie need was individually calculated for each patient based on their regular dietary intake or predictive equations. The recommended dietary allowance (RDA) and reference daily intake (RDI) were used for the metabolically normal children with a body composition, activity level, and growth rate that were all normal. The resting energy expenditure (REE) was used to determine the energy needs of the children who engaged in very little movement. Only 75% of the RDA was calculated for the nonambulatory and developmentally delayed children. The patients' energy and protein needs during adolescence were calculated based on their height rather than their weight. The patients' diets were supplemented with recommended vitamins and minerals.

The ratio of the diet was modified as necessary to maintain urine ketosis and to avoid acidosis, hyperketosis, and hypoglycemia. For the first 2 days, the diet was administered at a ratio of 2:1, which was altered according to the individual patient's needs, the investigation results, and the level of patient/family compliance. After 2 days, and if adequate ketosis (urine ketones between 80 and 160 mg/dL) was achieved, the ratio was maintained. If satisfactory urine ketones were not achieved, the ratio was gradually increased up to 4:1. If the patient's urine ketones were consistently 160 mg/dL, the ratio was reduced to 1.5:1 and the patient was monitored for signs of excess ketosis, such as rapid panting when breathing, increased heart rate, facial flushing, irritability, vomiting, and unexpected lethargy. A ketone level measurement was performed twice daily, usually in the morning and the evening, during the period of hospital admission. The patients' blood glucose levels were measured every 6 hours using a glucometer. Hypoglycemia was defined as blood glucose levels of less than 2.7 mmol/L. If a patient experienced hypoglycemia, either with or without symptoms, 30 mL of juice was administered. Seizures and any AE were monitored on a daily basis.

The caloric intake was adjusted to maintain an ideal body weight for each patient's height and an ideal body mass index based on the patient's weight gain or loss while following a KD. The recipes were planned on the basis of the preferences of the child and their family. The menus included traditional Saudi food in order to increase their palatability and so help to ensure patient compliance. More specifically, a Saudi-style KD was designed featuring extra virgin olive oil as the principal source of monounsaturated fats. Those patients who had a nasogastric tube (NGT) or a gastrostomy tube (GT), or who were under the age of 1 year and had feeding problems, received a commercial KD formula (KetoCal, Nutricia Inc) along with different supplements, including Polycose, Fantomalt, and Bene protein. Fluids were not restricted. The patients were discharged on either day 4 or 5, and they were followed closely by the dietician at the outpatient clinic and by phone.

2.2 | Statistical analysis

All the statistical analyses in the present study were performed using the Statistical Package for the Social Sciences version 22.0 (SPSS Inc). The continuous and categorical variables were reported as the mean ± the standard deviation or median [25-75 percentiles] and as numbers (%), respectively. The categorical data were analyzed using Pearson's chi-square test. Logistic regression models were used for the independent variables both separately (univariate) and collectively (multivariable). An adverse event was treated as a binary outcome (yes/no) to assess the associations with the predictor variables of interest with 95% confidence intervals. The comparisons of the mean values were analyzed using a two-tailed t-test. The significance level for all the tests was P < 0.05.

3 | RESULTS

A total of 66 children (59% female) with DRE who began a KD in a hospital setting were analyzed in the present study. The patients' baseline characteristics are presented in Table 1. The mean age at the time of KD initiation was 48.0 ± 38.4 months. The youngest patient was 7 months old, while the oldest patient was 13 years old. The mean weight at the time of KD initiation was 14.6 ± 6.3 kg. The median number of anticonvulsant medications used at the time of KD initiation was three. The majority of patients were fed by mouth (72.7%). The etiology of the patients' DRE was as follows: structural (n = 3, 4.5%), hypoxic ischemic encephalopathy (n = 7, 10.6%), genetic/metabolic (n = 21, 31.8%), acquired (n = 7, 10.6%), and unknown (n = 28, 42.2%). The notable etiologies in each group were as follows: structural (agyria–pachygyria complex, lissencephaly with no genetic mutation, focal cortical dysplasia), genetic/metabolic (Trisomy 21, NCL2, Ring Ch-17, Deletion 15q11.2-13.1, SCN2A, SCL2A1, POLG, SCN8A, FOLR1, WWOX, STXBP1, FRRS1L, RELN, KCNT1, SCN9A, CYFIP2, JMJD1C), acquired (FIRES, febrile illness-related epilepsy syndrome), and unknown (Aicardi syndrome). Epileptic spasms (ES) were present in 53% of patients. None of the patients had an abnormal comprehensive metabolic panel. In the majority of patients, the maximum KD ratio at the time of discharge was between 2:1 and 3:1 (92.4%). In one patient, the ratio was decreased to 1.5:1 on day 3, as the patient developed vomiting after reaching a urine ketone level of 160 mg/dL. In one patient (aged 5 years and 3 months) with Doose syndrome and a mutation in the GABRG2 gene, the KD was started very
slowly at a ratio of 1:1 and the patient was discharged on a 1.5:1 ratio due to concerns regarding dietary adherence.

Potential AE occurred in 19 children (28.7%), including hypoglycemia (n = 13, 20%), hypoactivity (n = 4, 6.1%), somnolence (n = 2, 3%), and vomiting (n = 5, 7.6%) (Figure 1). Further details concerning the children who experienced AE are presented in Table 2. A univariate analysis of the clinical characteristics of the AE and no AE groups was performed (Table 3). A statistically significant difference in weight ($P = 0.003$) and age ($P = 0.033$) was found between the AE and no AE groups. In the AE group, the reported AE occurred more commonly in children aged less than 3 years (Figure 2). There was no statistically significant difference found in terms of the number of anticonvulsants used at the time of KD initiation between the two groups, although the concurrent use of topiramate was found to have a near-significant association ($P = 0.097$) with the AE group. Further, there was no statistically significant difference found between the two groups with regard to the route of feeding and history of GERD. The urine ketone levels on all 5 days were compared in both groups, and a statistically significant difference was found on day 3 ($P = 0.026$) (Figure 3). A statistically significant difference in the serum bicarbonate levels ($P = 0.038$) was found between the patients who were taking topiramate and the patients who were not taking it.

The identified AE either required no intervention or could be managed with simple interventions such as the administration of juice and the adjustment of the KD ratio. During admission, the KD was not discontinued in any patient due to AE, and none of the patients had to be transferred to the pediatric intensive care unit.

4 | DISCUSSION

The 2018 updated recommendations of the international ketogenic diet study group report that most centers still routinely admit patients for KD initiation. Every center has its own protocol for doing so, and the duration of admission usually ranges between 3 and 5 days. In contrast, the MAD is

### TABLE 1 Characteristics of patients

| Characteristics                      | Values         |
|--------------------------------------|----------------|
| Female, n                            | 39 (59.0%)     |
| Age at the initiation of the KD, mean ± SD, mo | 48.0 ± 38.4 |
| Weight upon initiation of KD, mean ± SD, kg | 14.6 ± 6.3 |
| No. of prior anticonvulsants, median | 3             |
| Treatment with topiramate at the initiation of the KD, n | 31 (46.9%) |
| History of GERD, yes                  | 12 (18.8%)     |
| Route of feeding, n                   |                |
| PO                                   | 48 (72.7%)     |
| NGT                                  | 5 (7.5%)       |
| G-tube                               | 13 (19.6%)     |
| Etiology, n (%)                      |                |
| Structural                           | 3 (4.5%)       |
| HIE                                  | 7 (10.6%)      |
| Genetic/metabolic                    | 21 (31.8%)     |
| Acquired                             | 7 (10.6%)      |
| Unknown                              | 28 (42.2%)     |
| Epileptic spasms, n                  | 35 (53.0%)     |
| Abnormal metabolic workup, n         | 0              |
| Serum bicarbonate levels             | 21.4 ± 3.1     |
| Max KD ratio reached, n              |                |
| 1.5:1                                | 2 (3.0%)       |
| 2:1                                  | 20 (30.3%)     |
| 2.5:1                                | 14 (21.2%)     |
| 3:1                                  | 27 (40.9%)     |
| 4:1                                  | 3 (4.5%)       |
| Urine ketones (mg/dL, mean ± SD)     |                |
| Day 1                                | 1.3 ± 5.7      |
| Day 2                                | 19.9 ± 30.3    |
| Day 3                                | 65.1 ± 56.8    |
| Day 4                                | 79.7 ± 46.4    |
| Day 5                                | 102.4 ± 43.6   |
| Adverse events                       |                |
| Hypoglycemia                         | 13 (20%)       |
| Vomiting                             | 5 (7.6%)       |
| Hypoactivity                         | 4 (6.1%)       |
| Somnolence                           | 2 (3.0%)       |

Abbreviations: GERD, gastroesophageal reflux disease; G-tube, gastrostomy tube; KD, ketogenic diet; NGT, nasogastric tube; PO, per oral; SD, standard deviation.
| Case # | Age (m) | Gender (M/F) | Weight (kg) | Metabolic work up | GERD (Y/N) | Feeding (PO/NG/GT) | AEDS at KD initiation | KD ratio at discharge | Ketone level at discharge | Adverse events | Intervention |
|--------|---------|--------------|-------------|-------------------|------------|-------------------|----------------------|----------------------|------------------------|----------------|-------------|
| 1      | 28      | F            | 9           | UR                | Y          | GT                | LEV, LTG             | 3:1                  | 3                      | Hypoglycemia | 30 mL juice given via GT None |
| 2      | 10      | F            | 9           | UR                | N          | PO                | VPA, LEV             | 2:1                  | 4                      | Hypoglycemia | 30 mL juice given |
| 3      | 26      | F            | 13          | UR                | N          | PO                | VGB, CZP, TPM        | 2:1                  | 3                      | Hypoglycemia | 30 mL juice given |
| 4      | 28      | M            | 11          | UR                | N          | PO                | LTG, CZP, LEV, TPM   | 3:1                  | 4                      | Hypoglycemia | 30 mL juice given |
| 5      | 95      | F            | 16          | UR                | N          | PO                | LEV, PHB             | 2:1                  | 3                      | Hypoactivity | None |
| 6      | 25      | F            | 10          | UR                | N          | PO                | VGB, TPM, LEV        | 3:1                  | 4                      | Somnolence   | None |
| 7      | 42      | F            | 12          | UR                | N          | PO                | LEV, PHB, TPM        | 2:1                  | 3                      | Hypoglycemia | 30 mL juice given |
| 8      | 43      | M            | 12          | UR                | N          | PO                | TPM, LEV, CZP        | 3:1                  | 3                      | Hypoglycemia | 30 mL juice given None |
| 9      | 25      | F            | 8           | UR                | N          | PO                | VGB, CZP, TPM        | 2:1                  | 3                      | Hypoglycemia | 30 mL juice given |
| 10     | 16      | F            | 8           | UR                | Y          | GT                | LEV, TPM, VGB        | 2:1                  | 4                      | Hypoglycemia | 30 mL juice given |
| 11     | 15      | F            | 10          | UR                | N          | PO                | TPM, VGB             | 2.5:1                | 3                      | Hypoactivity | None |
| 12     | 19      | F            | 10          | UR                | N          | PO                | PHB, LEV, CZP, TPM   | 2.5:1                | 2                      | Hypoglycemia | 30 mL juice given |
| 13     | 11      | F            | 7           | UR                | Y          | NGT               | VGB, PHB, CZP        | 2.5:1                | 3                      | Hypoglycemia | D10 None |
| 14     | 46      | F            | 18          | UR                | N          | PO                | CZP, LEV, VPA, TPM   | 2.5:1                | 4                      | Hypoglycemia | 30 mL juice given None |
| 15     | 93      | M            | 14          | UR                | Y          | PO                | TPM, VPA, LEV        | 4:1                  | 3                      | Vomiting     | None |
| 16     | 29      | F            | N/A         | UR                | N          | NGT               | TPM, VPA, VGB        | 1.5:1                | 4                      | Vomiting     | Feeding held and gradually reintroduced at ratio 1.5:1 |

(Continues)
usually initiated on an outpatient basis. Caution is taken during KD initiation because the diet is known to sometimes be associated with serious AE, which can have life-threatening consequences. Examples of the AE that can stem from KD initiation include severe hypoglycemia and metabolic acidosis. This retrospective study was conducted to examine the incidence of potential AE during KD initiation in a hospital setting.

Potential AE occurred in 28.7% of patients included in the present study, including hypoglycemia, hypoactivity, somnolence, and vomiting. The most common AE was hypoglycemia. The identified AE either required no intervention or were easily managed with simple interventions such as the administration of juice or the reduction in the ratio of the diet.

### TABLE 3

| Variable                              | Adverse event (n = 19) | No adverse event (n = 47) | P value |
|---------------------------------------|------------------------|---------------------------|---------|
| Percentage                            | 28.7%                  | 71.2%                     | 0.001   |
| Gender (F)                            | 14 (73.6%)             | 25 (53.1%)                | 0.129   |
| Age (mo)                              | 32.3 ± 24.2            | 54.4 ± 41.4               | 0.033   |
| Weight (kg)                           | 11 ± 2.9               | 16.1 ± 6.6                | 0.003   |
| No. of prior anticonvulsants, median  | 2.7 ± 1                | 3.0 ± 0.6                 | 0.360   |
| Treatment with topiramate             | 12 (63.1%)             | 19 (40.4%)                | 0.097   |
| History of GERD                       | 5 (26.3%)              | 7 (14.8%)                 | 0.283   |
| Route of feeding, n                   | 14 (73.6%)             | 34 (72.3%)                | 0.912   |
| PO                                    |                       |                           | 0.584   |
| NGT + GT                              | 5 (26.3%)              | 13 (27.6%)                |         |
| Etiology, n (%)                       | 0                      | 3 (6.3%)                  |         |
| Structural                            | 2 (10.5%)              | 5 (10.6%)                 | 0.257   |
| HIE                                   | 5 (26.3%)              | 16 (34.0%)                | 0.016   |
| Acquired                              | 3 (15.7%)              | 4 (8.5%)                  | 0.705   |
| Epileptic spasms                      | 12 (63.1%)             | 23 (48.9%)                | 0.302   |
| Urine ketones                         | 1.5 ± 4.7              | 1.1 ± 6.1                 | 0.807   |
| Day 2                                 | 21.3 ± 29.8            | 19.4 ± 30.8               | 0.822   |
| Day 3                                 | 89.4 ± 66.9            | 55.3 ± 49.7               | 0.026   |
| Day 4                                 | 79.4 ± 48.3            | 79.8 ± 46.1               | 0.974   |
| Day 5                                 | 105.2 ± 44.6           | 101.2 ± 43.6              | 0.741   |

Abbreviations: GERD, gastroesophageal reflux disease; G-tube, gastrostomy tube; HIE, hypoxic ischemic encephalopathy; NGT, nasogastric tube; PO, per oral.
in the diet being better tolerated while still maintaining its efficacy.\textsuperscript{18} We followed a nonfasting, gradual-initiation protocol, which could explain the low incidence of potential AE among our cohort. The use of a KD is contraindicated for certain metabolic disorders, for example, carnitine deficiency, fatty acid oxidation defects, and pyruvate carboxylase deficiency, and care should be taken to rule out such metabolic disorders prior to initiating the diet.\textsuperscript{7}

DRE during infancy can be associated with epileptic encephalopathy caused by either genetic or metabolic etiologies. The patients who experience such epileptic encephalopathy are not usually candidates for epilepsy surgery, although the use of a KD has proven to be an effective treatment modality for them.\textsuperscript{19–21} However, some studies have reported a higher incidence of AE in children who were younger at the time of KD initiation, especially with regard to hypoglycemia.\textsuperscript{8} Similarly, among our cohort, we found that those children who were less than 3 years old were more likely to experience AE. van der Louw et al\textsuperscript{22} excluded children aged less than 12 months from their study on the outpatient initiation of a KD due to the relatively high risk of hypoglycemia. In another study, around 37\% of infants discontinued the KD as a result of the complications they experienced.\textsuperscript{20} We also found that those children with a lower weight were also at a higher risk of developing AE. Therefore, we suggest caution when initiating a KD in infants and young children aged less than 3 years old and in children with a lower weight, especially when the diet is initiated on an outpatient basis.

Patients in whom a KD is initiated are usually on multiple AED. Those patients who are on certain AED, for example, TPM, could be at an increased risk of experiencing AE. TPM is a carbonic anhydrase inhibitor that could lead to decreased levels of serum bicarbonate and so cause metabolic acidosis.\textsuperscript{23} A KD, which works via the production of ketone bodies, can predispose patients to metabolic acidosis due to the fact that ketone body metabolism produces protons and pH-lowering metabolic products.\textsuperscript{24} Takeoka et al\textsuperscript{25} showed that a large decrease in the serum bicarbonate levels occurred at the time of KD initiation in patients who were on TPM; therefore, patients’ bicarbonate levels should be carefully monitored in the case of TPM and KD cotreatment. In our cohort, the AE observed during KD initiation also showed a near-significant level of correlation with the concurrent use of topiramate. The serum bicarbonate levels were found to be low in those patients who were on topiramate, and further, the use of topiramate reached statistical significance within the AE group. Thus, it is recommended that the serum bicarbonate levels be closely monitored when initiating a KD in patients who are on topiramate and, whenever necessary, bicarbonate supplementation should be initiated to prevent severe metabolic acidosis. In the present study, we also found that the ketone levels of the patients in the AE group were significantly higher when compared to those in the no AE group on day 3. This sudden increase in the ketone levels seen on day 3 could explain the observed side effects. Moreover, it could serve as a biomarker for predicting the occurrence of AE and so allow for necessary precautions and early interventions to be put in place to avoid AE.

There are four treatment options available for DRE, namely medication, KD, neurostimulation devices (eg,
vagus nerve stimulation and responsive neurostimulation), and epilepsy surgery. In developing countries, where around 80% of patients with epilepsy live, some treatment options, including newer AED, may not be available, while expensive treatment options may not be affordable. Cost-effective, sustainable epilepsy care options are thus needed to decrease the treatment gap between developed and developing countries. In a multinational survey involving 41 countries, the majority of KD centers expressed their desire to increase their patient numbers.26 A KD can be an effective and affordable treatment option for the vast majority of epilepsy patients. Since admission to hospital for 3-5 days in order to initiate a KD could prove both expensive and inconvenient for patients and their families, KD initiation on an outpatient basis among carefully selected patients, coupled with good communication and close monitoring, could be an affordable and beneficial treatment option for many.

ACKNOWLEDGMENTS
The authors would like to thank participants and their family members.

CONFLICT OF INTEREST
Neither of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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REFERENCES
1. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. Lancet Neurol. 2008;7:500–6.
2. Thiele EA. Assessing the efficacy of antiepileptic treatments: the ketogenic diet. Epilepsia. 2003;44(suppl 7):26–9.
3. Kang HC, Chung DE, Kim DW, Kim HD. Early- and late-onset complications of the ketogenic diet for intractable epilepsy. Epilepsia. 2004;45:1116–23.
4. Weijenberg A, van Rijn M, Callenbach PMC, de Koning TJ, Brouwer OF. Ketogenic diet in refractory childhood epilepsy. Child Neurol Open. 2018;5:2329048X18779497.
5. Kessler SK, Neal EG, Camfield CS, Kossoff EH. Dietary therapies for epilepsy: future research. Epilepsy Behav. 2011;22(1):17–22. https://doi.org/10.1016/j.yebeh.2011.02.018
6. Duchowny MS. Food for thought: the ketogenic diet and adverse effects in children. Epilepsy Curr. 2005;5:152–4.
7. Kossoff EH, Zupec-Kania BA, Avvin S, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving dietary therapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. Epilepsia Open. 2018;3:175–92.
8. Lin A, Turner Z, Dooerler SC, Stanfield A, Kossoff EH. Complications during ketogenic diet initiation: prevalence, treatment, and influence on seizure outcomes. Pediatr Neurol. 2017;68:35–9.
9. Liu YM. Medium-chain triglyceride (MCT) ketogenic therapy. Epilepsia. 2008;49(suppl 8):33–6. https://doi.org/10.1111/j.1528-1167.2008.01830.x
10. Sharma S, Sankhyan N, Gulati S, Agarwala A. Use of the modified Atkins diet for treatment of refractory childhood epilepsy: a randomized controlled trial. Epilepsia. 2013;54(3):481–6. https://doi.org/10.1111/epi.12069
11. Pfeifer HH, Lyczkowski DA, Thiele EA. Low glycemic index treatment: implementation and new insights into efficacy. Epilepsia. 2008;49:42–5. https://doi.org/10.1111/j.1528-1167.2008.01832.x
12. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. Epilepsia. 2009;50(5):1109–17. https://doi.org/10.1111/j.1528-1167.2008.01870.x
13. Kinderen RJ, Lambrechts DA, Wijnen BF, Postulart D, Aldenkamp AP, Majoie MH, et al. An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: an interim analysis. Epilepsia. 2016;57:41–50. https://doi.org/10.1111/epi.13254
14. Birbeck GL. Epilepsy care in developing countries: part I of II. Epilepsy Curr. 2010;10(4):75–9. https://doi.org/10.1111/j.1535-7511.2010.01362.x
15. Ballaban-Gil K, Callahan C, O’Dell C, Pappo M, Moshé S, Shinnar S. Complications of the ketogenic diet. Epilepsia. 1998;39:744–8. https://doi.org/10.1111/j.1528-1157.1998.tb01160.x
16. Dong WK, Hoon CK, Jung CP, Heung DK. Benefits of the nonfasting ketogenic diet compared with the initial fasting ketogenic diet. Pediatrics. 2004;114(6):1627–30.
17. Park JC, Kim HD. Benefits of nonfasting ketogenic diet in intractable childhood epilepsy as compared with initial fasting ketogenic diet. Epilepsia. 2001;42(suppl 7):214–5.
18. Bergqvist AGC, Schall JI, Gallagher PR, Cnaan A, Stallings VA. Fasting versus gradual initiation of the ketogenic diet: a prospective, randomized clinical trial of efficacy. Epilepsia. 2005;46:1810–9. https://doi.org/10.1111/j.1528-1167.2005.00282.x
19. Hong AM, Turner Z, Hamdy RF, Kossoff EH. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia. 2010;51:1403–7. https://doi.org/10.1111/j.1528-1167.2010.02586.x
20. Eun SH, Kang HC, Kim DW, Kim HD. Ketogenic diet for treatment of infantile spasms. Brain Dev. 2006;28:566–71.
21. Thammongkol S, Vears DF, Bicknell-Royle J, Nation J, Draffin K, Stewart KG, et al. Efficacy of the ketogenic diet: which epilepsies respond? Epilepsia. 2012;53:e55–9.
22. van der Louw EJTM, Desadens R, Vehmeijer FOL, van der Sijs H, Catsman-Berrevoets CE, Neuteboom RF, et al. Concomitant lamotrigine use is associated with decreased efficacy of the ketogenic diet in childhood refractory epilepsy. Seizure. 2015;32:75–7.
23. Sacré A, Jouret F, Manicourt D, Devuyst O. Topiramate induces type 3 renal tubular acidosis by inhibiting renal carbonic anhydrase. Nephrol Dial Transplant. 2006;21(10):2995–6.
24. Masino SA, Rho JM. Mechanisms of ketogenic diet action. In: Noebels JL, Avoli M, Rogawski MA, et al., editors. Jasper's Basic Mechanisms of the Epilepsies [Internet]. 4th edition. Bethesda (MD): National Center for Biotechnology Information (US); 2012. Available from: https://www.ncbi.nlm.nih.gov/books/NBK98219/

25. Takeoka M, Riviello JJ Jr, Pfeifer H, Thiele EA. Concomitant treatment with topiramate and ketogenic diet in pediatric epilepsy. Epilepsia. 2002;43:1072–5.

26. Kossoff EH, McGrogan JR. Worldwide use of the ketogenic diet. Epilepsia. 2005;46:280–9.

How to cite this article: Mir A, Albaradie R, Alamri A, et al. Incidence of potential adverse events during hospital-based ketogenic diet initiation among children with drug-resistant epilepsy. Epilepsia Open. 2020;5:596–604. https://doi.org/10.1002/epi4.12442