Potassium citrate and metabolic acidosis in children with epilepsy on the ketogenic diet: a prospective controlled study

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ABBREVIATION
AED Antiepileptic drug

AIM To investigate if potassium citrate, a mild alkaline compound, can prevent metabolic acidosis in children with epilepsy treated with the ketogenic diet without reducing antiepileptic efficacy.
METHOD In this prospective controlled study, we investigated the frequency of initial uncompensated metabolic acidosis in 51 participants. There were 22 participants with and 29 without potassium citrate supplementation. The ketogenic diet was used as add-on treatment to children with drug resistant epilepsy. We also estimated the proportion of participants with a greater than 50% seizure reduction after 7 months.
RESULTS None of the 22 participants (15 males, seven females; median age 1y 7mo, interquartile range [IQR] 3y 3mo) with, and 10 of 29 (12 males, 17 females; median age 6y 1mo, IQR 4y 8mo) without potassium citrate developed metabolic acidosis (odds ratio=0.04, 95% CI 0.00–0.75 [$p<0.01$]); median pH 7.32 vs 7.24; [$p<0.001$]), and median bicarbonate 19.7mmol/L vs 14.0mmol/L ($p<0.001$). The number of seizures was reduced by more than 50% in 9 of 22 with potassium citrate and 8 of 29 participants without potassium citrate, 7 months after introducing a ketogenic diet ($p=0.4$).
INTERPRETATION In the ketogenic diet, potassium citrate supplementation can prevent metabolic acidosis, without reducing antiepileptic efficacy.

Two randomized controlled studies[1,2] have indicated that the efficacy of the ketogenic diet is at least equivalent to antiepileptic drug (AED) treatment in drug-resistant epilepsies.

The ketogenic diet increases the acid load due to conversion of fat to ketone bodies, leading to a liability for uncompensated metabolic acidosis in the initial phase and chronic low-grade metabolic acidosis.[3] The initial uncompensated acidosis might lead to dehydration and excessive weight loss if left untreated. Chronic metabolic acidosis is also accompanied by side-effects such as kidney stone formation and loss of bone mineral content.[4] Given the disadvantages and risk of non-compliance, practical implementation of the ketogenic diet is considered more complicated than treatment with conventional AEDs,[1] therefore, it is rarely used as first line treatment of epilepsy.

Citrate is an organic anion that produces bicarbonate when metabolized in the liver,[5] and thus acts as an alkalizing agent. It has been proposed as a substance that can reduce ketogenic-diet induced metabolic acidosis.[6] In renal diseases, potassium citrate is used to prevent metabolic acidosis and to improve bone mineral density.[7,8] Citrate is also used to prevent nephrolithiasis by counteracting urinary acidosis and hypocitraturia induced by the ketogenic diet.[9–11]

In this study, we defined 'uncompensated' metabolic acidosis as a state with clinical signs of metabolic acidosis (nausea, vomiting, and somnolence) accompanied by a blood pH of less than 7.30. The aim of this study was to investigate if potassium citrate supplementation can prevent uncompensated metabolic acidosis and related symptoms without affecting seizure frequency in ketogenic diet treatment for intractable epilepsy.

METHOD

Participants

All participants (except one with GLUT1 deficiency [OMIM #134140]) eligible for the study had tried at least five AEDs without a satisfactory response. Thus, they represented the most difficult-to-treat or 'super-resistant' among our patients with drug-resistant epilepsy. Relevant patient data, such as age at ketogenic diet initiation, sex, number of AEDs in use, epilepsy syndrome, and intellectual disability (Tables 1 and 2) were systematically

collected and registered from the medical charts. The degree of intellectual disability was assessed using the International Classification of Diseases, 10th edition[12] criteria and was divided into IQ less than 35, profound and severe intellectual disability; IQ 35 to 70, mild and moderate intellectual disability; and IQ greater than 70, without intellectual disability. We used a historical prospective controlled study design.[13] The ketogenic diet was administered between 2005 and 2012 at Oslo University Hospital. Thirty-eight of the participants in our report have been included in a collaborative Scandinavian multicenter study.[10] In the present study, seizure frequency was measured before and after 7 months of ketogenic diet treatment and the number of participants with a more than 50% seizure reduction was presented. We also evaluated time participants needed to reach the ketogenic ratio they had at the end of the first in-patient stay and how high this ratio was. Clinical evaluation of the signs of metabolic acidosis was performed during introduction of the diet. In the 29 patients not treated with potassium citrate, serum pH and bicarbonate concentrations were only registered when clinical signs of acidosis occurred. In the 22 patients treated with potassium citrate, the median pH and bicarbonate concentration were calculated from three serum pH and bicarbonate concentrations registered within the first 2 weeks after starting the diet.

Table 1: Participant characteristics in 51 children with drug-resistant epilepsy treated with ketogenic diet

	Potassium citrate supplementation	
Variable	Group 1: No supplement (*n*=29)	Group 2: Supplement (*n*=22)
Sex, *n* (%)		
Males	12 (41)	15 (68)
Females	17 (59)	7 (32)
Intellectual disability, *n* (%)		
Profound or severe	19 (66)	18 (82)
Moderate or mild	10[a] (34)	4[a] (18)
Cerebral palsy, *n* (%)	12 (41)	7 (32)
Age at onset of epilepsy, median (IQR), y:mo	0:7 (1:10)	0:2 (0:9)
Age at ketogenic diet start, median (IQR), y:mo	6:1 (4:1)	1:7 (3:3)
Seizure types, *n* (%)		
One seizure type	4 (14)	8 (36)
Multiple seizure types	25 (86)	14 (64)
Seizures per day at onset, median (IQR)	7.5 (8.5)[b]	50 (41)[b,c]
Type of epilepsy, *n* (%)		
Generalized	8 (28)	6 (27)
Focal/multifocal	8 (28)	10 (45)
Combined focal and generalized	9 (31)	3 (14)
Unknown	4 (14)	3 (14)
AEDs tried before onset of ketogenic diet, median (IQR)	8 (4)	8 (3)
AEDs used at onset of ketogenic diet, median (IQR)	2 (1)	3 (1)

[a]One participant in Group 1 and one in Group 2 did not have intellectual disability. [b]Seizures that exceeded 50/d were not counted. [c]Two participants with status epilepticus. IQR, interquartile range; AED, antiepileptic drug.

What this paper adds

- Citrate supplementation prevents metabolic acidosis in children treated with a ketogenic diet.
- Efficacy of the ketogenic diet is not affected by supplementation with citrate.
- Citrate supplementation does not affect beta-hydroxybuturate concentration.
- Potassium citrate reduces the time needed to reach an optimal ketogenic ratio.

Diet administration

The ketogenic diet was started without prior fasting as add-on therapy to daily AEDs. The necessary intake of calories was based on the nutritional status and level of physical activity of the participants and complied with the Norwegian recommended intake for age and weight.[14] Vitamins and mineral supplements were within the norm recommended by the World Health Organization. All participants were kept in hospital for 2 to 3 weeks after treatment onset. Four participants were fed via a nasogastric tube and 23 via gastrostomy when the diet was initiated (Table 3). We regarded a ketogenic ratio of 4:1 (3:1 in infants <1y) to be a necessary but restrictive precondition to obtain a seizure-reducing effect, except in participants who became seizure free with a lower ketogenic ratio. An increase in the ketogenic ratio increased the efficacy of the ketogenic diet in some patients while others achieved seizure freedom on a lower ratio.[15]

Potassium citrate supplementation

In 2007, we became aware of a report suggesting that potassium citrate could prevent nephrolithiasis caused by the ketogenic diet.[9] This prompted us to start oral administration of potassium citrate in participants starting the ketogenic diet after April 2007. Potassium citrate was administered as oral Polycitra-K crystals (2mEq/kg/d up to a maximum dose of 60mEq/d) and was started simultaneously with the ketogenic diet in 22 participants. The 29 participants who were started on the diet before May 2007 did not receive potassium citrate.

Statistical analysis

The association between citrate supplementation and metabolic acidosis, efficacy of the ketogenic diet, and the tendency to develop nephrolithiasis respectively, was estimated as odds ratio with 95% confidence intervals using Fisher's exact test.

Serum pH and bicarbonate concentration were compared between participants not treated with citrate who developed acidosis and participants treated with citrate who did not develop acidosis using the Mann–Whitney *U* test. Beta-hydroxybuturate concentration in serum, age at start of ketogenic diet, ketogenic ratio at the end of the first hospital in-patient stay, and the number of days needed to reach the ketogenic ratio, were compared between groups treated and not treated with potassium citrate using the Mann–Whitney *U* test. The association between citrate supplementation, body mass index (BMI), and enteral feeding was compared

Table 2: Classification of epilepsy and etiology in 51 participants with drug resistant epilepsy[a]

	Potassium citrate supplementation	
Variable	Group 1: No supplement (*n*=29)	Group 2: Supplement (*n*=22)
Electro-clinical epilepsy syndromes (*n*=22)	West (*n*=2); Dravet (*n*=1); Doose (*n*=2); Lennox–Gastaut (*n*=5)[b,c]	West (*n*=3); Dravet (*n*=1); Doose (*n*=1); Lennox–Gastaut (*n*=2)[b]; migrating epilepsy of infancy (*n*=3)[d]; early myoclonic encephalopathy (*n*=2)[e]
Cortical malformation (*n*=7)	Lissencephaly (*n*=3)[b]; cortical dysplasia (*n*=1)	Lissencephaly (*n*=2)[b,f]; hemimegalencephaly (*n*=1)
Perinatal risk factors (*n*=6)	Asphyxia (*n*=2)[c]; cerebral stroke (*n*=2)[g]	Sinus venous thrombosis (*n*=1); cerebral stroke (*n*=1)
Post infectious (*n*=1)		Post-herpes encephalitis (*n*=1)
Genetic disorders (*n*=15)	Rett syndrome (*n*=2); Down syndrome (*n*=2)[g]; partial trisomy 13/monosomy 5p (*n*=1); tuberous sclerosis (*n*=1); GLUT 1 (*n*=1)	Wolf Hirschhorn syndrome (*n*=1); polymerase gamma gene mutation (*n*=1); potassium channel gene mutation (*n*=3)[d]; *CDKL5* mutation (*n*=1)[e]; Miller-Dieker syndrome (*n*=1)[f]; congenital disorder of glycosylation (*n*=1)
Unknown (*n*=8)	(*n*=7)	(*n*=1)

[a]According to a modified version of the proposed classification system by the International League against Epilepsy.[16] [b]One participant in Group 1 and one in Group 2 had combined lissencephaly and Lennox–Gastaut syndrome. [c]One participant with combined perinatal asphyxia and Lennox–Gastaut syndrome. [d]Two participants with migrating epilepsy of infancy and potassium channel gene mutations. [e]One participant with early myoclonic encephalopathy due to *CDKL5* mutation. [f]One participant with lissencephaly due to Miller-Dieker syndrome. [g]One participant with combined perinatal cerebral stroke and Down syndrome.

between participants treated with citrate and participants not treated with citrate and between those who did and who did not develop acidosis using the Mann–Whitney *U* test for BMI and χ^2 test for enteral feeding. PASW Statistics for Windows, version 18 (IBM Corporation, Armonk, NY, USA) was used for all statistical analysis. We considered *p*-values less than 0.05 as significant.

The regional ethics committee of the South Eastern part of Norway (REC South-East) approved the study and the committee's recommendations have been adhered to. The study was conducted in accordance with the ethical standards in the revised Helsinki Declaration of 1983. As our study was designed as a historical prospective study, dispensation from individual informed consent was obtained from the Data Protection Official and REC South-East.

RESULTS

We present the results of 51 participants treated with the ketogenic diet; 29 did not receive potassium citrate supplementation (Group 1: 12 males, 17 females; median age 6y 1mo, interquartile range [IQR] 4y 8mo), and 22 received supplementation (Group 2: 15 males, seven females; median age 1y 7mo, IQR 3y 3mo). General participant characteristics are listed in Table 1 and classification of epilepsy is shown in Table 2.

None of the 22 participants given potassium citrate supplementation developed uncompensated metabolic acidosis, whereas 10 of 29 who did not receive potassium citrate did (OR<0.04; 95% CI 0.00–0.75 [p<0.01]). All participants who developed uncompensated acidosis had clinical symptoms of metabolic acidosis such as nausea, vomiting, and somnolence. These symptoms could not be explained by other causes and were relieved when the participants received carbohydrates. Metabolic acidosis developed between 2 and 7 days (median 4d) after onset of ketogenic diet treatment. At the time of acidosis, the ketogenic ratio was registered in all 10 participants and ranged between 1.5 and 4 (median 2.25), beta-hydroxybuturate concentration was measured in five participants and varied between 4.0mmol/L and 6.0mmol/L (median 5.25mmol/L). Values greater than 6.0mmol/L were not possible to distinguish due to the measurement method.

Within the group not treated with citrate (Group 1), BMI, measured when the ketogenic diet was initiated, varied between 11.6 and 17.3 (median 14.8, IQR 3.1) in participants who developed acidosis and between 13.9 and 22.3 (median 16.4, IQR 2.5) in participants who did not develop acidosis (p=0.02). In the group treated with citrate (Group 2), BMI varied between 13.1 and 21.4 (median 16.1, IQR 3.3). We also compared participants who did not receive citrate (Group 1) and developed acidosis with participants who received citrate (Group 2) and did not develop acidosis and found that p=0.2 (Table 3). Of the 29 participants not treated with citrate, 14 received enteral feeding and 15 oral feeding: five of the participants who received enteral feeding and five who received oral feeding developed acidosis (p=0.9). Of the 22 participants treated with citrate, 13 received enteral feeding and none developed acidosis (Table 3).

Three participants in Group 1 discontinued the ketogenic diet because of acidosis and one participant in Group 2 discontinued the ketogenic diet because of aspiration pneumonia in the course of the first 2 weeks. We chose to keep the participant with aspiration pneumonia in the analysis. The difference in the number of participants who developed metabolic acidosis between the two groups was significant. This was also the case if the participant who ended the ketogenic diet due to aspiration pneumonia was excluded from the analysis (odds ratio=0.04; 95% CI 0.00–0.75 [p<0.05]). Participants in Group 1 with clinical signs of metabolic acidosis had lower serum pH and bicarbonate concentration than participants in Group 2 without clinical signs of metabolic acidosis (Table 3). There was no

Table 3: Comparison of data between groups that received and did not receive potassium citrate supplementation

Variable	Potassium citrate supplementation: Group 1: No supplement (*n*=29)	Potassium citrate supplementation: Group 2: Supplement (*n*=22)	*p*
Clinical ketoacidosis, *n* (%)			
Yes	10 (34)	0 (0)	
No	19 (66)	22 (100)	<0.01[a]
Serum pH			
Median	7.24	7.32[b]	
IQR	0.06	0.04	
n (%)	6/10[c,d]	12 (55)	<0.01[e]
Serum bicarbonate			
Median (mmol/L)	14	19.7 [b]	
IQR	2.5	5.8	
n (%)	6/10[c,d]	12 (55)	<0.01[e]
Body mass index at start of the diet			
Median	14.8	16.1	
IQR	3.1	3.3	
n (%)	10/10[d]	15 (68)	0.2[e]
Beta-hydroxybuturate max[f]			
Median (mmol/L)	5.3	5.6	
IQR (mmol/L)	1.7	1.4	
n (%)	17 (59)	17 (77)	0.9[e]
Beta-hydroxybuturate min[g]			
Median (mmol/L)	2.7	2.6	
IQR (mmol/L)	1.4	1.4	
n (%)	17 (59)	17 (77)	0.8[e]
Number of participants with >50% seizure reduction			
n (%)	8 (28)	9 (41)	0.4[a]
Number of days to achieve final ketogenic ratio[h]			
Median	9	4	
IQR	7	9	
n (%)	23 (79)	19 (86)	<0.01[e]
Ketogenic ratio when discharged from hospital[h]			
Median	3	3.5	
IQR	1.3	1.0	
n (%)	26 (90)	20 (91)	<0.001[e]
Enteral feeding, *n* (%)	14 (48)	13 (59)	0.6[i]

[a]Fisher's exact test. [b]Median of at least three values measured before discharge from hospital. [c]Data were registered in 6 out of 10 participants when there were clinical signs of metabolic acidosis. [d]Only data on participants who developed acidosis. [e]Mann–Whitney *U* test. [f]The highest value measured before discharge from hospital. Values >6mmol/L were not possible to distinguish due to the measurement method. [g]The lowest value measured before discharge from hospital. [h]Ketogenic ratio when the participant was discharged from hospital after 2 to 3 weeks. [i]χ^2 test. IQR, interquartile range.

difference in serum beta-hydroxybuturate concentration between the groups (Table 3). Nephrolithiasis developed in two of the 29 participants not treated with potassium citrate and in none of the 22 patients treated with potassium citrate (p=0.5). No participant was lost to follow-up and all participants eligible for the study were included in the analysis.

DISCUSSION

We found that supplementation with potassium citrate in ketogenic diet treatment prevents uncompensated metabolic acidosis (Table 3). We believe that these results can be generalized to all individuals treated with the ketogenic diet, since citrate is metabolized to bicarbonate in the liver and thus acts as a mild alkalizing compound. Citrate has briefly been mentioned as a substance that reduces symptoms of initial metabolic acidosis in the ketogenic diet.[17] However, the dosage used, or the efficacy obtained, has not been specified previously. Potassium citrate supplementation did not affect the serum beta-hydroxybuturate concentration and the long-term efficacy of the ketogenic diet in our study. Even if acute metabolic acidosis is known to be anticonvulsive, it is important to diminish its acute symptoms in order to improve adherence to the diet and diminish long-term side-effects of chronic metabolic acidosis, including possible proconvulsive effects.[6]

BMI did not differ between participants who developed acidosis and participants treated with citrate who did not develop acidosis. However, among participants not treated with citrate, the risk of developing acidosis was higher in participants with a lower BMI when the ketogenic diet was initiated (p=0.02). In participants without potassium citrate supplementation, we gradually introduced the ketogenic diet to avoid metabolic acidosis. Supplementation with potassium citrate contributed to a faster tolerance at the onset of the ketogenic diet, which reduced the time needed to reach an optimal ketogenic ratio (Table 3). At the end of the trial, participants who received potassium citrate supplementation were started directly on a 3:1 or 4:1 ketogenic ratio without developing symptoms of metabolic acidosis. Our result could be of special interest in an outpatient setting where it is important to avoid metabolic acidosis and, according to our results, in participants with a low BMI.

Another area for consideration is treatment with ketogenic diet in refractory status epilepticus in the intensive care unit. In refractory status epilepticus it is important to terminate seizures as soon as possible and thus start directly with a high ketogenic ratio. If ketogenic diet is introduced rapidly, ketosis can be reached faster, but there is also an increased risk of acidosis.[17] Acidosis due to ketogenic diet might be confused with other underlying causes of metabolic acidosis in the intensive care unit such as hypoxia and can lead to premature discontinuation of the diet in this setting.[18] Thus, potassium citrate can be used as ketogenic diet supplementation, not only to prevent nephrolithiasis, but also to prevent initial symptoms and side-effects related to metabolic acidosis, without reducing ketonemia and efficacy.

It could be argued that the different median age at initiation of the diet in the two groups (Group 1: 6y 1mo, Group 2: 1y 7mo [p<0.01]) could interfere with the results. A lower age at the start of the ketogenic diet indicates lower ketogenic ratio because of higher risk of early symptoms of metabolic acidosis. The dietary acid load per kilogram of body weight is higher in infants than in older children[19,20] and the normal serum bicarbonate concentration is lower.[21] The ketogenic diet ratio was increased to a higher level in a shorter time among the younger children in Group 2 (Table 3) and treatment with potassium citrate could be one explanation as to why these children did not develop metabolic acidosis.

None of the 22 patients started on potassium citrate developed nephrolithiasis during the 7 months follow-up, compared to two of the 29 not treated with potassium citrate, a non-significant result (p=0.5). According to earlier studies,[9–11] citrate supplementation protects against nephrolithiasis in ketogenic diet treatment.

One weakness of the study is the lack of pH and bicarbonate values in some participants with ketoacidosis (Table 3). However, all four participants without measurements of serum bicarbonate concentration had typical symptoms of metabolic acidosis that could possibly not be explained by other causes. The symptoms also resolved after treatment with glucose. Chronic, low-grade reduction of pH has been documented in the ketogenic diet.[3] An increased rate of kidney stone formation and loss of bone mineral content with fractures are described side effects of the ketogenic diet that might be related to chronic acidosis.[22] It is known from studies on acidosis-producing diets, with a high amount of animalic protein and sodium chloride, that even low-grade reduction of pH and bicarbonate within the normal range over time predisposes to kidney stone formation, increased bone resorption, reduced bone mineral density, loss of muscle mass, and other side effects.[4]

In this study we have no long-term follow up measurements of serum pH or bicarbonate concentration. In one study by McNally et al.,[11] there was no difference in serum bicarbonate concentrations between participants who received and who did not receive citrate 3 months after starting the ketogenic diet. A possible explanation for the difference between our study and this study regarding acidosis is that the tendency to develop acidosis is at its highest in the initial phase, as development of renal compensatory mechanism takes several days.[23] This explanation is supported by the fact that we later could increase the ketogenic ratio in several of the participants who developed acidosis without a relapse of acidosis. Another difference between the two studies is that we used the subgroup of participants who developed acidosis for comparison of pH and bicarbonate values while McNally et al. used all participants without citrate supplementation for comparison. It has previously been shown that potassium citrate effectively normalized chronic metabolic acidosis and increased serum bicarbonate in renal transplant patients[8] and in patients with renal tubular acidosis.[7] Further studies are needed to investigate if potassium citrate also affects chronic metabolic acidosis and related side effects in patients treated with the ketogenic diet.

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REFERENCES

1. Neal EG, Chaffe H, Schwartz RH, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008; **7**: 500–6.
2. Lambrechts D, de Kinderen RJA, Vles JSH, de Louw AJ, Aldenkamp AP, Majoie HJM. A randomized controlled trial of the ketogenic diet in refractory childhood epilepsy. *Acta Neurol Scand* 2017; **135**: 678.
3. Yancy WS Jr, Olsen MK, Dudley T, Westman EC. Acid-base analysis of individuals following two weight loss diets. *Eur J Clin Nutr* 2007; **61**: 1416–22.
4. Carnauba RA, Baptistella AB, Paschoal V, Hübscher GH. Diet-induced low-grade metabolic acidosis and clinical outcomes: a review. *Nutrients* 2017; **9**: E538.
5. Halperin ML. Metabolism and acid-base physiology. *Artif Organs* 1982; **6**: 357–62.
6. Yuen AWC, Walcutt IA, Sander JW. An acidosis-sparing ketogenic (ASK) diet to improve efficacy and reduce adverse effects in the treatment of refractory epilepsy. *Epilepsy Behav* 2017; **74**: 15–21.
7. Domrongkitchaiporn S, Pongskul C, Sirikulchayanonta V, et al. Bone histology and bone mineral density after correction of acidosis in distal renal tubular acidosis. *Kidney Int* 2002; **62**: 2160–6.
8. Starke A, Corsenca A, Kohler T, et al. Correction of metabolic acidosis with potassium citrate in renal transplant patients and its effect on bone quality. *Clin J Am Soc Nephrol* 2012; **7**: 1461–72.
9. Sampath A, Kossoff EH, Furth SL, Pyzik PL, Vining EP. Kidney stones and the ketogenic diet: risk factors and prevention. *J Child Neurol* 2007; **22**: 375–8.
10. Hallböök T, Sjölander A, Åmark P, Miranda M, Bjurulf B, Dahlin M. Effectiveness of the ketogenic diet used to treat resistant childhood epilepsy in Scandinavia. *Eur J Paediatr Neurol* 2015; **19**: 29–36.
11. McNally MA, Pyzik PL, Rubenstein JE, Hamdy RF, Kossoff EH. Empiric use of potassium citrate reduces kidney-stone incidence with the ketogenic diet. *Pediatrics* 2009; **124**: e300–4.
12. World Health Organization. ICD-10 Guide for Mental Retardation, 1996. Available from www.who.int/mental_health/media/en/69.pdf (accessed 6th October 2019).
13. Rothman KJ. Modern Epidemiology, 3rd ed. Philadelphia: Liippincott, Williams and Wilkins, 2008.
14. Becker W, Lyhne N, Pedersen AN, et al. Nordic Nutrition Recommendations 2004 – integrating nutrition and physical activity. *Scandinavian J Nutrit* 2004; **48**: 178–87.
15. Wirrell EC. Ketogenic ratio, calories, and fluids: do they matter? *Epilepsia* 2008; **49**(Suppl 8): 17–9.
16. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010; **51**: 676–85.
17. Bergqvist AG, 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.
18. Cervenka MC, Hocker S, Koenig M, et al. Phase I/II multicenter ketogenic diet study for adult superrefractory status epilepticus. *Neurology* 2017; **88**: 938–43.
19. Kalhoff H, Manz F, Kiwull P, Kiwull-Schöne H. Food mineral composition and acid-base balance in preterm infants. *Eur J Nutr* 2007; **46**: 188–95.
20. Kalhoff H, Manz F. Nutrition, acid-base status and growth in early childhood. *Eur J Nutr* 2001; **40**: 221–30.
21. Edelmann CM, Soriano JR, Boichis H, Gruskin AB, Acosta MI. Renal bicarbonate reabsorption and hydrogen ion excretion in normal infants. *J Clin Invest* 1967; **46**: 1309–17.
22. Bergqvist AG, Schall JI, Stallings VA, Zemel BS. Progressive bone mineral content loss in children with intractable epilepsy treated with the ketogenic diet. *Am J Clin Nutr* 2008; **88**: 1678–84.
23. Hamm LL, Nakhoul N, Hering-Smith KS. Acid-base homeostasis. *Clin J Am Soc Nephrol* 2015; **10**: 2232–42.