1st European Conference on GLUT1 Deficiency

Milan, Italy 7th- 8th October 2016

LONG TERM MANAGEMENT OF KEOGENIC DIET

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Long-term management of the diet

Long-term is usually defined as duration of the diet for over 6 months which is the rule in GLUT1-DS patients

Long term management requires a combined effort of the keto-team and of the patient/families

We aim at

- Prevention of long-term medical side effects
- Prevention of decline in compliance

Epilepsia, **45**(9):1116–1123, 2004
Blackwell Publishing, Inc.

Early- and Late-onset Complications of the Ketogenic Diet for Intractable Epilepsy

*Hoon Chul Kang, *Da Eun Chung, †Dong Wook Kim, and ‡Heung Dong Kim

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TABLE 3. *Early- and late-onset complications of the ketogenic diet*

	No. of patients (%)		
	Early onset	Late onset	Early and late onset
Dehydration[a]	60 (46.5)		
Gastrointestinal discomfort[b]	50 (38.7)	36 (27.9)	13 (10.1)
Infectious disease[c]	12 (9.3)	27 (20.9)	5 (3.9)
Lipoid aspiration pneumonia	3 (2.3)	6 (4.7)	1 (0.8)
Lipid profiles			
Hypertriglyceridemia	35 (27.1)	26 (20.2)	15 (11.6)
Hypercholesterolemia	19 (14.7)	25 (19.4)	3 (2.3)
Hypo HDL[d] cholesterolemia	5 (3.9)	1 (0.8)	
Hyperuricemia	34 (26.4)	10 (7.8)	
Symptomatic hypoglycemia[e]	9 (7.0)	1 (0.8)	1 (0.8%)
Hypoproteinemia	7 (5.5)	5 (3.9)	
Hypomagnesemia	6 (4.7)	14 (10.9)	1 (0.8)
Repeated hyponatremia	6 (4.7)		
Hepatitis	3 (2.3)	7 (5.4)	
Acute pancreatitis	1 (0.8)		
Persistent metabolic acidosis	1 (0.8)		
Osteopenia		19 (14.7)	
Renal stone		4 (3.1)	
Hydronephrosis		1 (0.8)	
Iron-deficiency anemia		2 (1.6)	
Secondary hypocarnitinemia		2 (1.6)	
Cardiomyopathy		1 (0.8)	

Long-term side effects

Potential long-term side effects of KD include:

- Gastrointestinal disorders
- Linear growth failure
- Increased risk of cardiovascular diseases
- Hyperuricemia and nephrolitiasis
- Osteopenia and changes in body composition
- Micronutrient deficiences

Long-term side effects in *drug-resistant epileptic children* on KD

Author, year	Patients, Diet	Mean duration	Side effetcs
Dressler et al 2010, retrospecitve	50 pts on classic KD 2.5:1 – 4:1	1,2 yrs (6 mos - 3,8 yrs)	Adverse effects 28% carnitine deficiency moderate growth impairment one case of kidney stones
Caraballo et al 2011, retrospective	216 pts on classic KD 2.5:1 – 4:1	3,5 yrs (1 -12 yrs)	Gastrointestinal disorders 33% hypercalciuria or hyperlipidemia 12% ; kidney stones 3%
Wibisono et al 2015, retrospective	48 pts on classic, MCT or MAD	Median of 16 mos	Constipation 65%; Dislipidemia 40% Growth retardation 30%
Lambrechts et al , 2015 prospective	48 pts on MCT diet	10 mos	Constipation 65%; growth retardation 30% and Dislipidemia 40%

Gastrointestinal disorders

The KD lacks fiber and bulk, fat lowers the esophageal sphincter tone, slows gastric emptying and decreases intestinal transit time.

As a consequence, gastrointestinal problems can occur

- Constipation
- Worsening of pre-existing gastro-esophageal reflux disease (GERD)

All children need to evaluate at baseline and the diet has to be modifyed accordingly

Constipation can be treated adding non absorbable fiber and increasing fluid intake or sugar-free laxatives

Mild GERD can be treated with specific drugs

Increased risk of cardio-vascular diseases

High dietary fatty acid consumption, particularly long-chain saturated fatty acids, has a well-known negative effect on

- blood lipids (hypercholesterolemia and hypertriglyceridemia) and
- endothelial function

As a consequence, the continuous use of KD for several decades could increase cardiovascular risk.

Increased risk of cardiovascular disease: hyperlipidemia

Hyperlipidemia is not an inevitable consequence of KD
Studies conducted to date on cardiovascular risk factors are controversial

Genetics and the ***composition of the fat*** in the child's diet appear to play important factors in the development of hyperlipidemia

Prevention

proper counseling from the dietician regarding the fat and cholesterol sources in the child's meals

Monitoring of lipid profile (increased frequency if family dyslipidemia)

Growth failure

This problem has been mainly described in *epileptic children* due to:

- restriction in energy or protein intake
- decrease in Insulin growth factor-1

Prevention:
Antropometric measurements at each
Re-evaluation of energy and protein re
When growth retardation occurs prote
maximized, consideration for ratio decrease and calorie
adjustments made if possible

Hyperuricemia and nephrolitiasis

The KD results in many metabolic changes that predisposes to nephrolithiasis; uric acid levels are elevated, the ketone bodies are acidic and determine an acidic urine PH, hypercalciuria and low urine citrates all contribute to kidney stone formation

Prevention:

Preventive use of potassium citrate

Routine monitoring for renal stones (urine analysis, kidney scan)

Good hydration is suggested to further minimize the risk of stone formation

Micronutrient deficiencies

Due to the limited food choice, the ketogenic diet is deficient in vitamins and minerals

Supplementation with sugar-free products need to be continued for the *entire duration of the diet* to avoid *deficiencies*

Evaluation of micronutrient content of current diet by the dietician

Serum levels of specific micronutrient (i.e. carnitine, vitamin D)

Compliance to the supplementation need to be routinely checked

Osteopenia and changes in body composition

Osteopenia and fractures have been reported in several studies on long-term KD due to micronutrient deficiencies (calcium and vitamin D) and chronic acidosis

The risk of osteopenia in refractory epilepsy is higher than in GLUT1 patients due the use of ***multiple AEDs*** with known deleterious effect on bone health or ***low motility***

Evaluation of micronutrient content of current diet by the dietician

Serum levels of specific micronutrient (i.e. vitamin D)

Bone Mineral Density at baseline and yearly on the diet

Prevention of long-term side effects

Table 2. Pre-KD evaluation

Neurologic evaluation
Etiology
Seizure type
Seizure frequency
AEDs and other medication review
EEG/Holter EEG
MRI
Cognitive/development assessment
Full serum and urine metabolic evaluation
Pediatric evaluation
ECG if history of heart disease
Abdomen ultrasound
Laboratory analysis
Nutritional evaluation
Baseline weight, height, and ideal weight for stature
Body mass index (BMI)
Skinfold thickness measurement
Dietary history
Bioelectrical impedance analysis
Indirect calorimetry[a]
Dual energy x-ray absorptiometry (DEXA)[a]
Counseling

[a]If these last two tests are not available, the use of predictive equations of basal metabolic rate and wrist x-ray could be performed

To prevent long-term side effects a complete baseline evaluation of clinical condition and nutritional status is necessary

Long-term side effects

How frequent are long-term side effects

In GLUT1-DS patients?

Epilepsia, 53(9):1503–1510, 2012
doi: 10.1111/j.1528-1167.2012.03592.x

FULL-LENGTH ORIGINAL RESEARCH

Glucose transporter type I deficiency syndrome: Epilepsy phenotypes and outcomes

*Amanda W. Pong, †Brianna R. Geary, ‡Kris M. Engelstad, §Ashwini Natarajan, ‡Hong Yang, and *‡¶Darryl C. De Vivo

Retrospective chart review of 87 patients followed up for 6 yrs on average. All patients evaluated annually by a neurologist, a ketogenic dietician, a research coordinator and in specific cases a movement disorder specialist

Long-term KD management

- 82% (71 patients) treated with KD for more than 5 yrs
- KD up to 4:1 used to achieve a blood beta-hydrobutirate of 4 – 5 mM

«***No instances of osteoporosis, hyperlipidemia, incresed hepatic enzymes or dyscrasia in this cohort***. »

«***Compliance problems*** were reported by 13 families ; still 5 of 13 patients were able to achieve seizure freedom, suggesting that even imperfect maintenance of the KD may be of benefit, at least in terms of seizure control.

Seizure Control and Acceptance of the Ketogenic Diet in GLUT1 Deficiency Syndrome: A 2- to 5-Year Follow-Up of 15 Children Enrolled Prospectively

J. Klepper[1]
H. Scheffer[2]
B. Leiendecker[1]
E. Gertsen[1]
S. Binder[1]
M. Leferink[2]
C. Hertzberg[3]
A. Näke[4]
T. Voit[1]
M. A. Willemsen[5]

Klepper J et al. Seizure Control and … Neuropediatrics 2005; 36: 302–308

15 children followed **prospectively for 2.0 – 5.5 yrs**

LCT KD 3:1 supplemented with multivitamins, calcium, minerals

Fluids were not restricted

Patients were assessed at 6–12-month intervals

Adverse effects of the diet such as growth retardation, kidney stones, pancreatitis, prolonged QT intervals or cardiomyopathy, impaired platelet function, or optic neuropathy were monitored but not recognized in any patient in this series; **hypercholesterolemia** elevated in 2/15; **carnitine levels reduced** in 6/15

Satisfaction with the practicability of the diet in daily life was ranked high by 7/24 (29%) parents, moderate by 13/24 (54%) parents, and **poor** by 4/24 (**17%**) parents. Parents and caretakers reported an improved alertness, demeanour, physical and mental endurance on the ketogenic diet.

DEVELOPMENTAL MEDICINE & CHILD NEUROLOGY ORIGINAL ARTICLE

Use of modified Atkins diet in glucose transporter type 1 deficiency syndrome

SOFIANE AMALOU[1] | DOMITILLE GRAS[1] | ADINA ILEA[1] | MARIE-ODILE GRENECHE[1] | LAURENT FRANCOIS[1] | VANINA BELLAVOINE[1] | CATHERINE DELANOE[2] | STÉPHANE AUVIN[1,3,4]

Retrospective observational study of 10 children

Diet : MAD introduced during 2-week hospitalization without fasting with supplements as needed

Patients were assessed every 3 mos

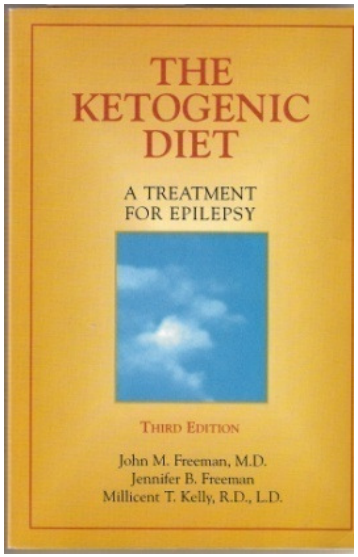
Mean duration on the diet 2,5 years (6 mo - 6 y)

Compliance: BHB measured at home 3 times a week and levels of ketosis were recorded in calendars

No major side effects observed in the long-term

GE symptoms (constipation) at start

Our experience



Since1994: classic KD according to the John Hopkins Hospital protocol

Since 2008 :

- At home initiation
- Without fasting
- No calorie or fluid restriction
- Gradual increase in ketogenic ratio

Dietary treatment

- After a complete neurological and nutritional assessment and dietary counselling, our patients are prescribed a classical KD to be initiated at home without fasting with a gradual increase in ketogenic ratio.
- ***The final ratio is dependent upon the child's age , diet tolerance and achievement of an optimal level of ketosis by measuring blood beta-hidroxybutirate aiming for levels of 2 – 5 mmol/L***
- Sugar-free vitamins and minerals are prescribed according to Italian Reference Values for age + potassium citrate to prevent nephrolitiasis

Long-term follow-up

Table 5. Recommendations for aspects of a follow-up KD clinic visit[a]

Nutritional assessment (registered dietitian)
Obtain height weight, ideal weight for stature, growth velocity, BMI when appropriate
Review appropriateness of diet prescription (calories, protein, and fluid)
Review vitamin and mineral supplementation based on dietary reference intake guidelines
Assess compliance to therapy
Adjust therapy if necessary to improve compliance and optimize seizure control
Medical evaluation (neurologist)
Efficacy of the diet (is the KD meeting parental expectations?)
Anticonvulsant reduction (if applicable)
Should the KD be continued?
Laboratory assessment
Complete blood count with platelets
Electrolytes to include serum bicarbonate, total protein, calcium, magnesium, and phosphate
Serum liver and kidney profile (including albumin, AST, ALT, blood urea nitrogen, creatinine)
Fasting lipid profile
Serum acylcarnitine profile
Urinalysis
Urine calcium and creatinine
Anticonvulsant drug levels (if applicable)
Optional
Serum β-hydroxybutyrate (BOH) level
Zinc and selenium levels
Renal ultrasound
Bone mineral density (DEXA scan)
EEG

[a]Visits should be at least every 3 months for the first year of the KD.

After 1 year every 6-12 months
Phone or mail-contacts as needed

Epilepsia, 50(2):304–317, 2009
doi: 10.1111/j.1528-1167.2008.01765.x

SPECIAL REPORT

Optimal clinical management of children receiving the ketogenic diet: Recommendations of the International Ketogenic Diet Study Group

Table 4. Follow-up KD management

Neurologic assessment
Neurologic evaluation (at 1–3–6–12 months)
Electroencephalography (at 1–3–6–12 months)
Review efficacy of the diet
Cognitive/development evaluation (at 6–12 months)
Pediatric assessment
Electrocardiography (every 6 months)
Abdominal echo (every 6 months)
Laboratory evaluation (at 1–3–6–12 months)
Complete blood count with plates
Serum liver and kidney tests
Blood sugar level
Electrolytes
Blood gas analysis
Laboratory evaluation (at 3–6–12 months)
Fasting lipid profile
Parathormone and vitamin D
Osteocalcin (if osteopenia)
Urinalysis and 24 h urine calcium and creatinine (only if previously altered)
Anticonvulsant drug levels
Nutritional assessment
Assess compliance to therapy
Height and body mass index (BMI)
Skinfold thickness measurements
Bioelectrical impedance analysis
Indirect calorimetry (each 3 months)
Dual energy x-ray absorptiometry or wrist x-ray (every 6–12 months)
Review appropriateness of diet prescription (calories, protein, and fluid)
Review vitamin and mineral supplementation

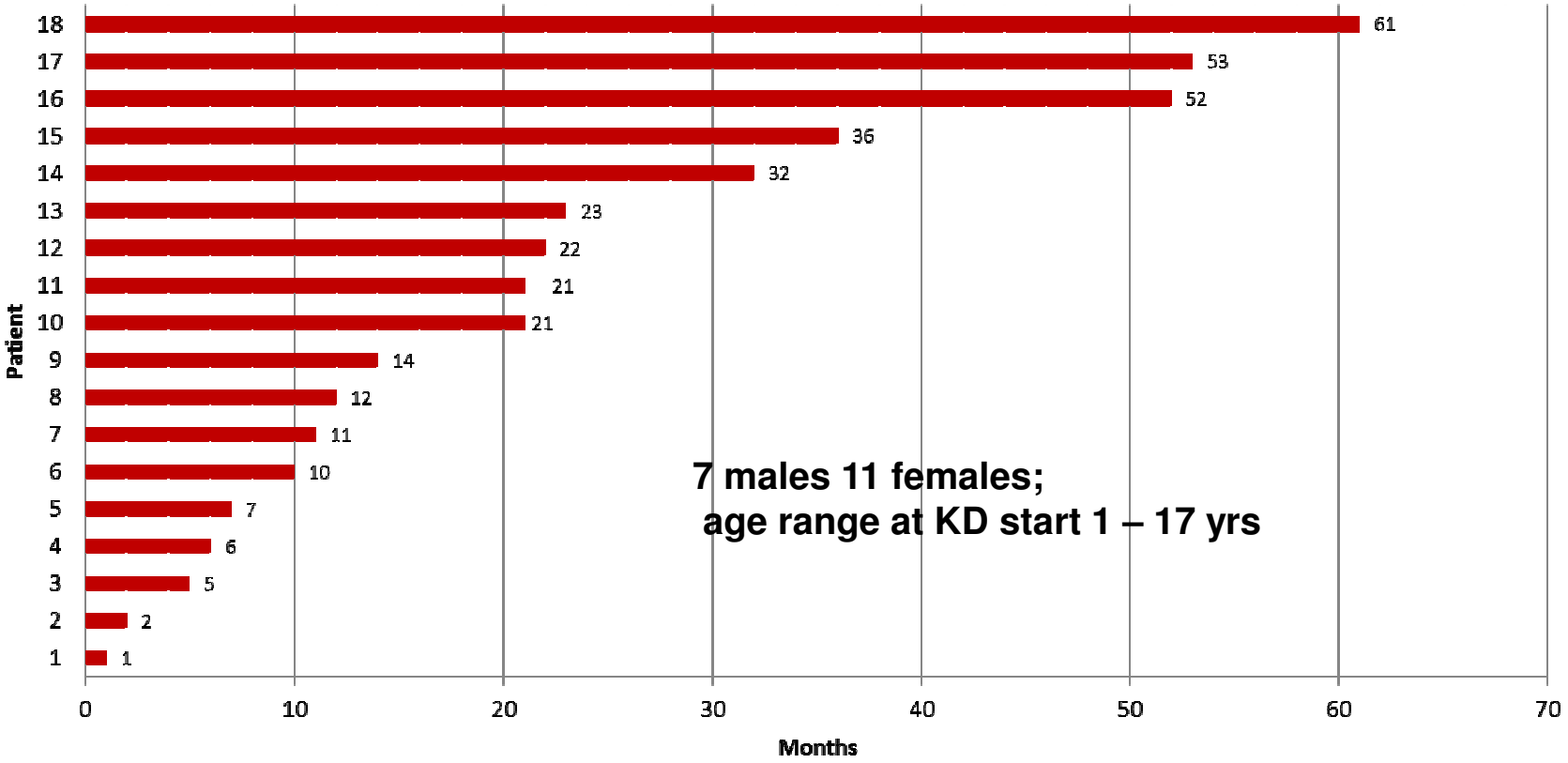
Epilepsia, 52(Suppl. 2):83–89, 2011
doi: 10.1111/j.1528-1167.2011.03010.x

DRAVET SYNDROME

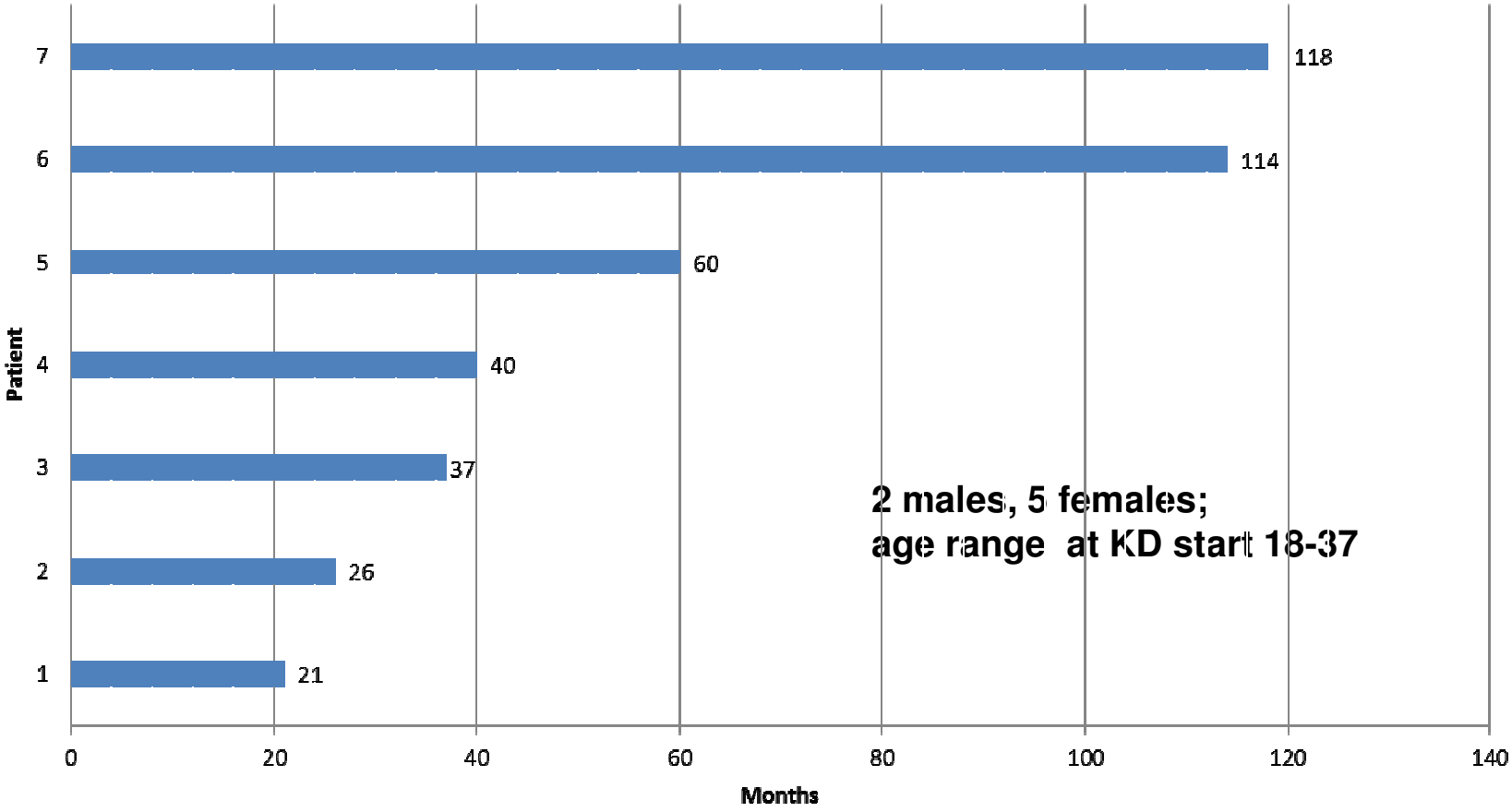
The ketogenic diet for Dravet syndrome and other epileptic encephalopathies: An Italian consensus

*Pierangelo Veggiotti, †Alberto Burlina, ‡Giangennaro Coppola, §Raffaella Cusmai, *Valentina De Giorgis, ¶Renzo Guerrini, **Anna Tagliabue, and ††Bernardo Dalla Bernardina

GLUT1-DS children on KD



GLUT1-DS adults on KD



Macronutrient composition of ketogenic diets

Table 1
Daily dietary intake before and after the beginning of the ketogenic diet.

	Baseline		6 months		*p* value
	Mean	Standard deviation	Mean	Standard deviation	
Energy intake (kcal/24 h)	1487	448	1512	331	ns
Energy intake (kcal/kg)	59	23	58	21	ns
Fat (g/kg)	2.5	1.0	5.9	1.8	<0.001
Fat (% energy)	37	5	89	2	<0.001
Saturated fat (% energy)	10	4	21	5	<0.001
Monounsaturated fat (% energy)	13	2	27	4	<0.001
Polyunsaturated fat (% energy)	3	1	9	6	<0.001
Protein (g/kg)	2.5	1.1	1.0	0.3	<0.001
Protein (% energy)	16	3	8	2	<0.001
Carbohydrates (g/kg)	6.9	3.0	0.5	0.2	<0.001
Carbohydrates (% energy)	47	8	3	1	<0.001

ns indicates nonsignificant differences.

We use MCT oil at low percentage to increase ketosis when necessary

Examples of Italian recipies

PAZIENTE MASCHIO
11 ANNI
Dieta chetogenica da 1760 kcal con rapporto 4 : 1

PRIMA COLAZIONE

BAVARESE ALLA FRAGOLA

Panna fresca	50 g
Burro	30 g
Nocciole	15 g
Fragole	13 g
Colla di pesce e saccarina	q.b.
Formaggino	37 g

Ammollare un pezzo di colla di pesce in acqua calda. Metterla nel contenitore della bavarese ed aggiungere l'esatta quantità di panna. Aggiungere il burro ammorbidito a temperatura ambiente. Dolcificare con saccarina liquida ed aggiungere l'aroma di vaniglia. Mettere la bavarese in frigorifero e prima di servire aggiungere la fragola, una piccola foglioina di menta e le nocciole tritate grossolanamente. Servire il formaggio a parte con una tazza di tè al gelsomino dolcificato con saccarina.

PRANZO O CENA

COCKTAIL DI GAMBERETTI

Gamberetti freschi	57 g
Lattuga	46 g
Avocado	60 g
Salsa cocktail	13 g
Lardo	12 g
Olio	25 g

Pesare i gamberetti già puliti e cuocerli sotto il grill. Salare e pepare. Mondare, lavare e pesare la lattuga.
Mettere sul fondo di una coppetta da macedonia una foglia di insalata sulla quale adagiare i crostacei, l'avocado, il lardo tagliato a dadini ed il resto della lattuga. Emulsionare la salsa cocktail con l'olio e condire tutto.

PRANZO O CENA

PIATTO TIROLESE IN SALSA DI AVOCADO

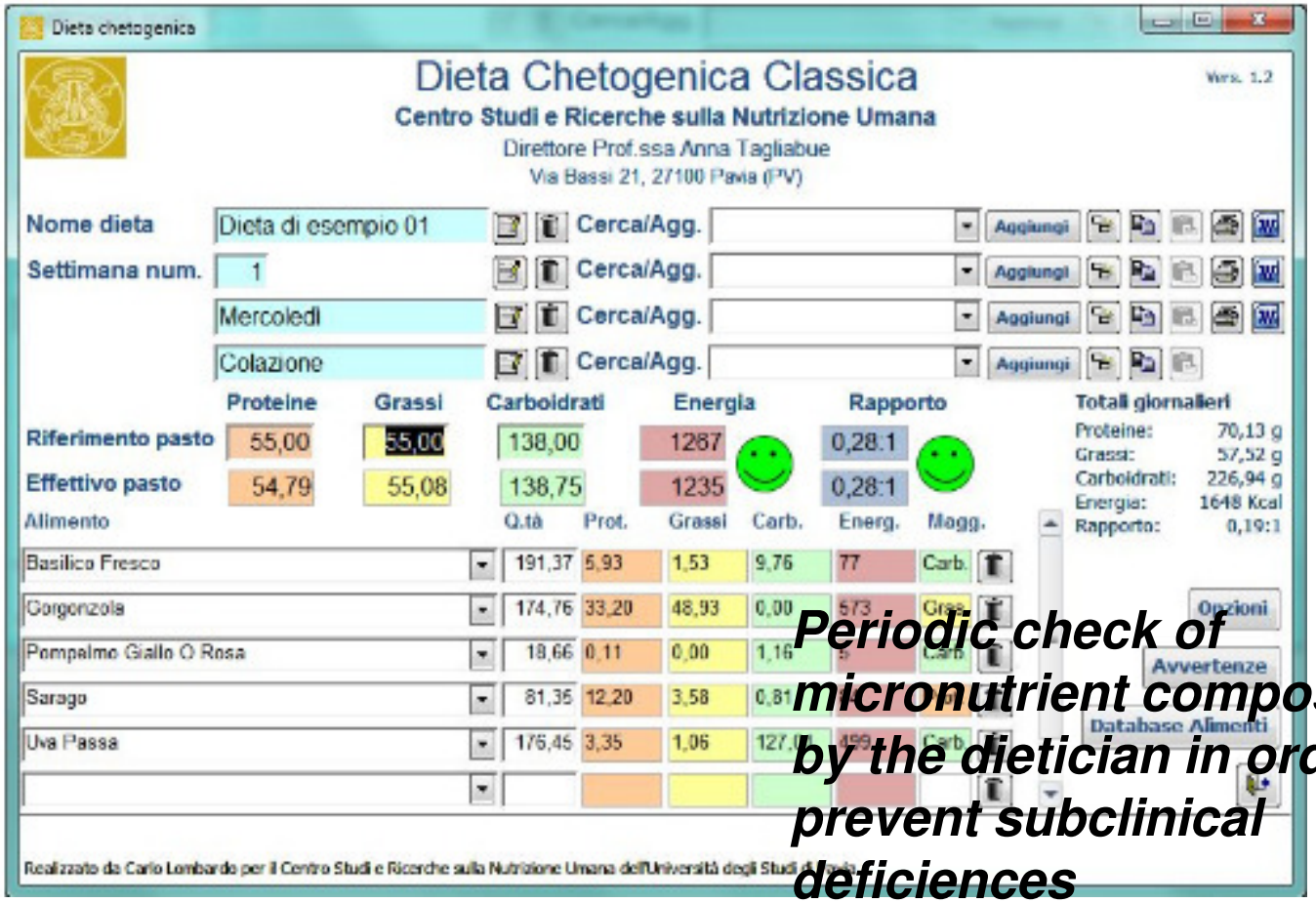
Wurstel	63 g
Pomodori da insalata	63 g
Avocado	55 g
Maionese	20 g
Olio d'oliva	14 g

Pesare ed arrostire in forno i wurstel bucandoli in superficie. Tagliare e pesare i pomodori dopo averli fatti sgocciolare. Preparare la salsa di avocado tagliando con la mezzaluna il frutto quindi aggiungere la maionese stemperata nell'olio. Con questa salsina condire i pomodori.

At first the diet is prepared by the dietician according to each patient requirements and modified by e-mail or at follow-up visits

In the long-term we suggest to use the keto-calculator to improve independence

Keto kalculator with Italian foods



Periodic check of micronutrient compostion by the dietician in order to prevent subclinical deficiences

Long-term monitoring

- Standard care of patients involve regular medical and nutritional follow-up every three months in the first year and six months thereafter
- ***Continuos support of patients and families*** is secured by ***e-mail or phone contacts*** in order to check compliance, tolerability, modify recipies if requested or solve troubles

Monitoring form

Week 48

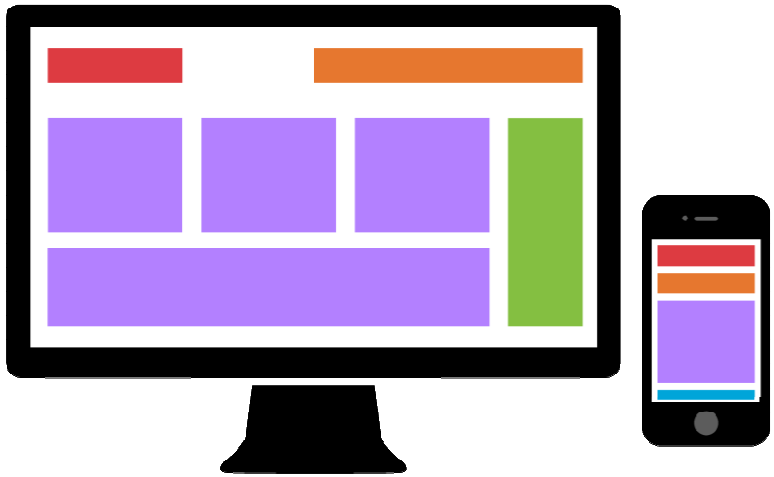
DATA	DIETA	CHETOS 8	CHETOS 20	Glicemia 8	Glicemia 20	n° CRISI	liquidi	*NOTE*
5/9/16	2:1	nm	nm	nm	nm	-		nessun significativo cambiamento rispetto alle settimane
6/9/16	2:1	2,5	3,7	83	76	-		precedenti
7/9/16	2:1	3,6	3,2	nm	nm	-		
8/9/16	2:1	2,2	2,4	95	80	-		
9/9/16	2:1	nm	nm	nm	nm	-		
10/9/16	2:1	2,4	2,6	87	92	-		
11/9/16	2:1	nm	nm	nm	nm	-	4,5 l /sett	

KD-Helper Project

How is it made?

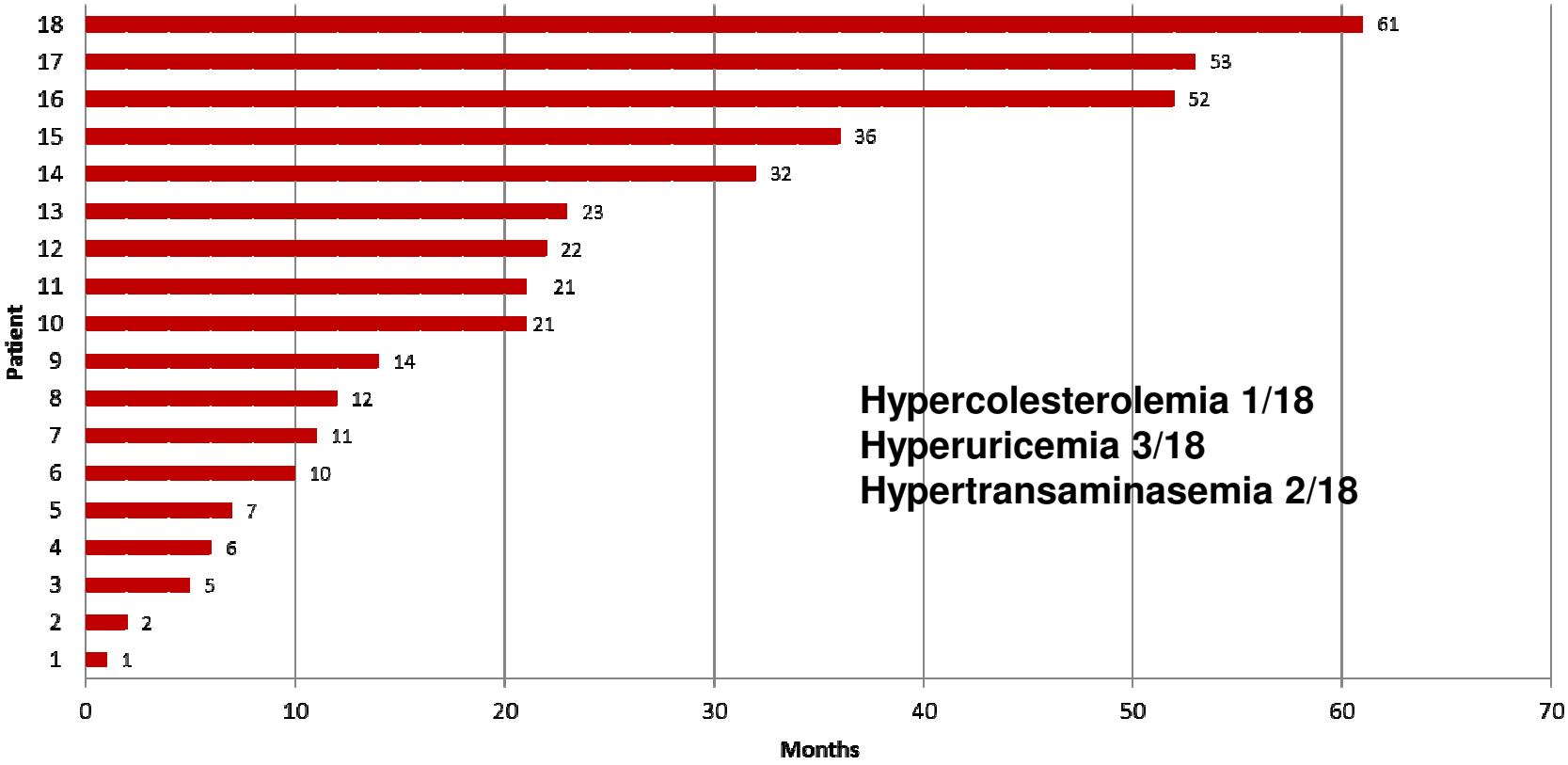
Main parts of the project

- Mobile application
  - For patients and families:
- Web service
  - For healt-care providers

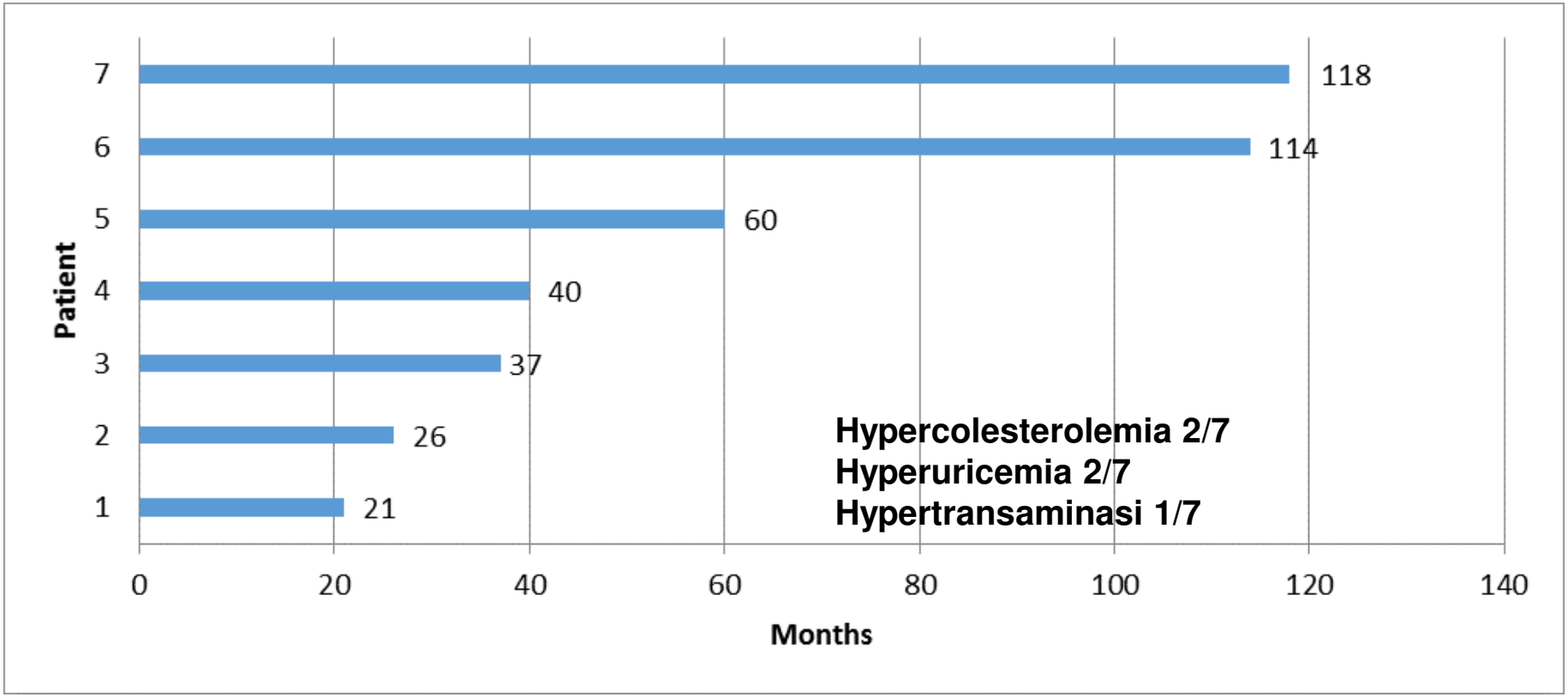


The system does not jeopardize the patient-physician relationship, on the contrary it improves communication

Long-term side effects in GLUT1-DS children on KD



Long-term side effects in GLUT1-DS adults on KD



Original article

Effects of the ketogenic diet on nutritional status, resting energy expenditure, and substrate oxidation in patients with medically refractory epilepsy: A 6-month prospective observational study

Anna Tagliabue [a,*], Simona Bertoli [b], Claudia Trentani [a], Paola Borrelli [c], Pierangelo Veggiotti [d]

18 children
8 males; 10 females
Mean age 12 yrs

Table 2
Nutritional status, resting energy expenditure, and substrate oxidation at baseline and after 6 months of KD.

	Baseline		6 months		*p* value
	Mean	Standard deviation	Mean	Standard deviation	
Body height *z*-score	−0.72	1.70	−0.76	1.73	ns
Body weight *z*-score	−0.81	2.42	−0.86	2.47	ns
BMI *z*-score	−1.33	2.17	−1.10	2.11	ns
REE (predicted, kcal)	1277	258	1233	224	ns
REE (measured, kcal)	1107	277	1081	237	ns
REE (%, measured versus predicted)	−16.4	12.1	−15.7	12.6	ns
REE/body weight (kcal/kg)	33.3	14.3	32.4	11.1	ns
REE/fat free mass (kcal/kg)	48.5	21.3	43.5	16.2	ns
Respiratory quotient	0.80	0.06	0.72	0.05	< 0.001
Fat oxidation (mg/min)	50.9	25.2	97.5	25.7	< 0.001
Carbohydrate oxidation (mg/min)	72.5	54.1	21.5	48.2	< 0.001

Clinical Nutrition 2012

Nutrition. 2015 Jul-Aug;31(7-8):981-7. doi: 10.1016/j.nut.2015.02.017. Epub 2015 Mar 31.

ELSEVIER FULL-TEXT ARTICLE

Short-term effects of ketogenic diet on anthropometric parameters, body fat distribution, and inflammatory cytokine production in GLUT1 deficiency syndrome.

Bertoli S[1], Neri IG[2], Trentani C[3], Ferraris C[3], De Amicis R[2], Battezzati A[2], Veggiotti P[4], De Giorgis V[5], Tagliabue A[3].

Table 2. Anthropometric measurements and biochemical parameters in 10 children undergoing a 3-months KD

	Preintervention		Postintervention		*P value*
	Mean	SD	Mean	SD	
Metabolic Parameters					
Blood glucose, mg/dl	80,9	12,5	77,6	7,2	0,245
Insulin, µU/ml	6,0	3,2	3,0	2,0	**0,001**
HOMA index	1,2	0,6	0,6	0,4	**0,002**
QUICKI index	0,38	0,03	0,44	0,05	**0,002**
Triglycerides, mg/dl	63,7	20,2	85,8	53,2	0,306
Total cholesterol, mg/dl	182,8	26,0	209,9	60,0	0,246
LDL cholesterol, mg/dl	110,6	19,0	132,8	52,6	0,269
HDL cholesterol, mg/dl	57,9	13,1	58,1	12,7	0,794
Total cholesterol/HDL cholestero	3,3	0,7	3,8	1,5	0,461
LDL cholesterol/HDL cholesterol	2,0	0,5	2,4	1,2	0,380
Uric Acid, mg/dl	4,1	1,4	5,8	2,1	**0,048**
Creatinine, mg/dl	0,4	0,1	0,4	0,2	**0,015**

After intervention:

- lower insulin levels and higher insulin sensitivity
- no significant changes in blood glucose and lipid profile
- increase in uric acid in 30%

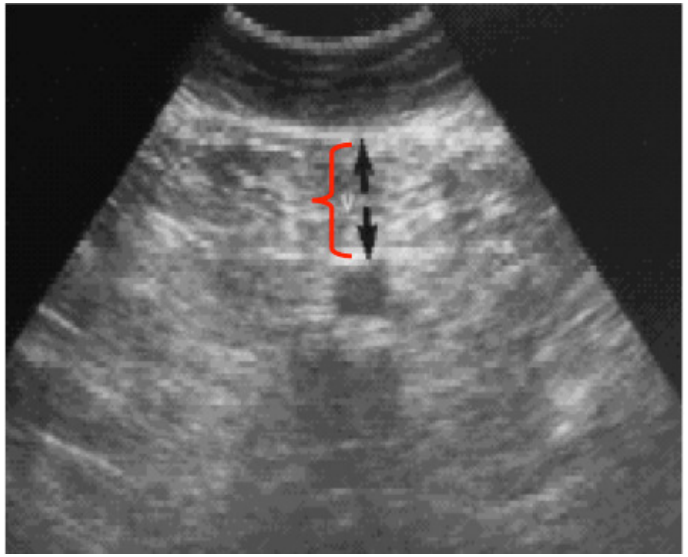


Table 2. Anthropometric measurements and biochemical parameters in 10 children undergoing a 3-months KD

	Preintervention		Postintervention		*P value*
	Mean	SD	Mean	SD	
Nutritional Status Parameters					
Body weight, kg	31,9	19,5	31,9	17,3	0,972
BMI, kg/m2	16,9	5,7	16,8	4,7	0,751
BMI z-score	-0,88	1,60	-0,63	1,51	0,421
Waist, cm	61,6	15,5	60,9	14,4	0,570
Waist z-score	0,02	0,72	-0,10	0,92	0,164
Bicipital skinfold, mm	6,4	2,9	7,0	3,5	0,492
Tricipital skinfold, mm	10,0	4,0	11,4	4,8	0,141
Subscapular skinfold, mm	7,6	4,5	7,1	2,7	0,647
Suprailiac skinfold, mm	11,3	7,6	11,7	6,0	0,679
% Body fat	18,2	5,9	20,4	5,1	0,290
SAT, mm	1,1	1,5	0,5	0,4	0,358
VAT, mm	2,8	1,3	3,2	0,8	0,257
SAT/VAT	0,3	0,3	0,2	0,1	0,565

Table 3. Infiammatory and adipose tissue activity biomarkers in 10 children undergoing a 3-months KD

	Preintervention		Postintervention		*P value*
	Mean	SD	Mean	SD	
Infiammatory biomarkers					
High sensitivity c-protein reactive, mg/l	1,0	1,7	1,4	2,1	0,119
Tumor necrosis factor alfa pg/ml	0,2	0,6	0,5	0,9	0,574
Interlukine 6, pg/ml	1,9	0,5	2,6	1,5	0,219
Adipose tissue activity biomarkers					
Fatty free acid , mM/serum	0,6	0,3	0,8	0,2	0,097
Leptin, ng/ml	14,6	19,3	8,7	7,6	0,248
Adiponectin, µg/ml	27,3	27,4	34,7	21,7	0,422

All data are expressed as means ± SD.

Bertoli et al 2015

No changes in anthropometry visceral and subcutaneous fat

In the short term KD does not affect inflammatory cytokines production and abdominal fat distribution despite being a high-fat diet.

The Ketogenic Diet in Children with Glut1 Deficiency Syndrome and Epilepsy

MARKUS RAUCHENZAUNER, MD, JÖRG KLEPPER, MD, PD, BÄRBEL LEIENDECKER, GERHARD LUEF, MD, PROFESSOR, KEVIN ROSTASY, MD, PD, AND CHRISTOPH EBENBICHLER, MD, PROFESSOR

The effects of a long-term ketogenic diet in children with Glut1 deficiency syndrome on metabolism are unknown. Our results indicate a characteristic effect of a long-term ketogenic diet on glucose and lipid homeostasis in Glut1 deficiency syndrome. Although serum lipids and apolipoproteins reflect a proatherogenic lipoprotein profile, adipocytokine constellation is not indicative of enhanced cardiovascular risk. *(J Pediatr 2008;153:716-8)*

Seizure 23 (2014) 260–265

Contents lists available at ScienceDirect

Seizure

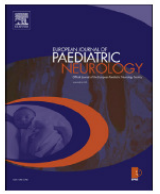
journal homepage: www.elsevier.com/locate/yseiz

The impact of the ketogenic diet on arterial morphology and endothelial function in children and young adults with epilepsy: A case–control study

Giangennaro Coppola [a,*], Francesco Natale [b], Annarita Torino [a], Rosanna Capasso [c], Alfredo D'Aniello [a], Erica Pironti [a], Elena Santoro [a], Raffaele Calabrò [b], Alberto Verrotti [d]

EUROPEAN JOURNAL OF PAEDIATRIC NEUROLOGY 18 (2014) 489–494

Official Journal of the European Paediatric Neurology Society



Original Article

Effects of ketogenic diet on vascular function

M. Kapetanakis [a], P. Liuba [b], M. Odermarsky [b], J. Lundgren [a], T. Hallböök [a,]*

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Nutrition 30 (2014) 726–728

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

International ward rounds

Long-term effects of a ketogenic diet on body composition and bone mineralization in GLUT-1 deficiency syndrome: A case series

Simona Bertoli M.D. [a], Claudia Trentani R.D. [b], Cinzia Ferraris R.D. [b], Valentina De Giorgis M.D. [c], Pierangelo Veggiotti M.D. [c], Anna Tagliabue M.D. [b,*]

[a] International Centre for the Assessment of Nutritional Status (ICANS), Department of Food Environmental and Nutritional Sciences (DeFENS), University of Milan, Milan, Italy
[b] Human Nutrition and Eating Disorder Research Center, Department of Public Health, Experimental and Forensic Medicine University of Pavia, Pavia, Italy
[c] Department of Neuroscience, IRCCS "C. Mondino" Foundation, Pavia, Italy

- Three young ambulatory women diagnosed in ***early adulthood*** with paroxismal movement disorders as the most relevant and disabling symptom
- Normocaloric KD (3:1) supplemented with vitamins and minerals according to requirements and potassiun citrate
- After beginning of **KD (3:1)** there was a complete disappearance of symptoms and an improvement in muscle strenght
- After 5 yrs on the diet no significant changes in body composition and bone mineral density

Long-term side effects

Physicians and patients should be aware of the possible long-term side effects of the diet, so that they can be carefully monitored and successfully prevented or treated as appropriate.

The risk of side effects, in any case, should be carefully weighed against the benefits of the diet

With appropriate implementation of the diet and monitoring ***the frequency of side effects is limited*** and only in a few cases leads to in interruption

Long-term management of the diet

Long-term is usually defined as duration of the diet for over 6 months which is the rule in GLUT1-DS patients

Long term management requires a combined effort of the keto-team and of the patient/families

We aim at

- Prevention of long-term medical side effects
- Prevention of decline in compliance

Prevention of decline in compliance

Decline of compliance is frequent mainly in adolescents

What can we do?

- consider a reduction in ketogenic ratio to increase carb content or switch to alternative diets (MAD)
- empower families in self-management
- suggest to contact ***family association*** for exchange of information and support
- Investigate the underlying issues
- consider a psychological support for patient or families

A survey

In order to take into consideration long-term difficulties we have e-mailed a short questionnaire to *50 Italian families on KD* (both epilepsy and GLUT1-DS patients)
The majority of them are on the diet > 12 months

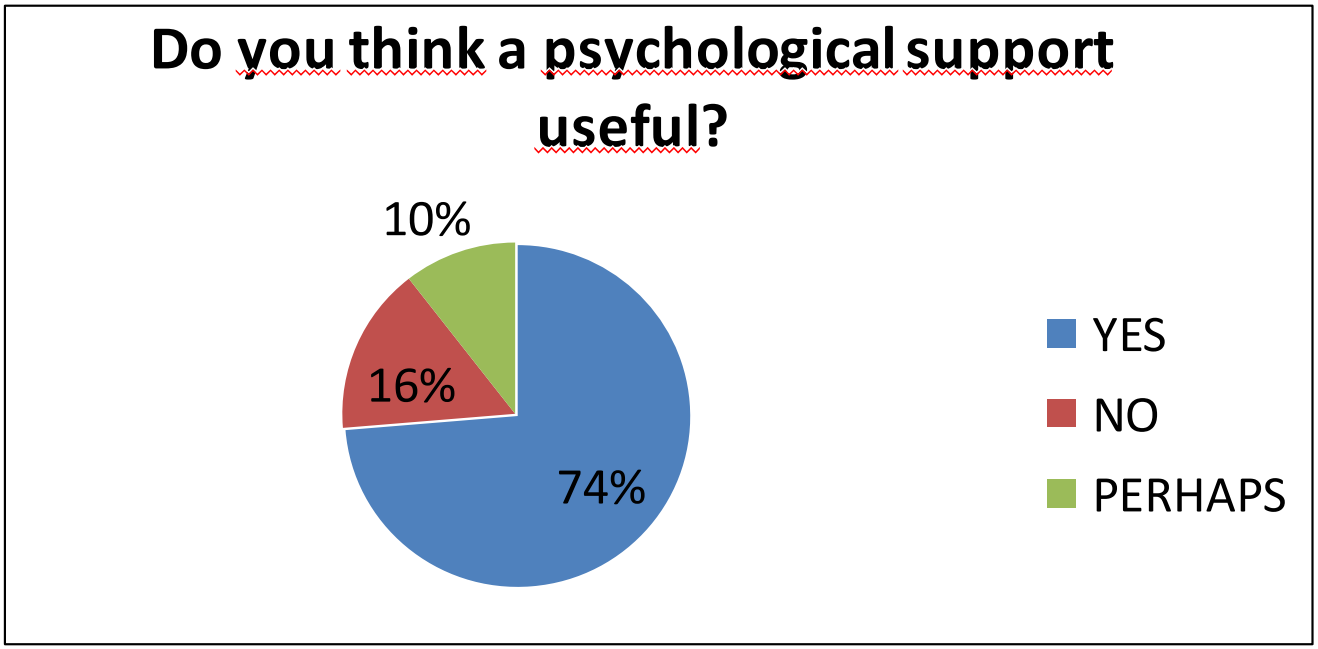
Which are the main difficulties ?

- The diet is too restrictive
- To share meals with younger sisters or brothers
- Eating out
- Find ketogenic products (expensive)

A survey

Which are the strategies to overcome difficulties with acceptance of the diet?

«To explain the importance of the therapy «

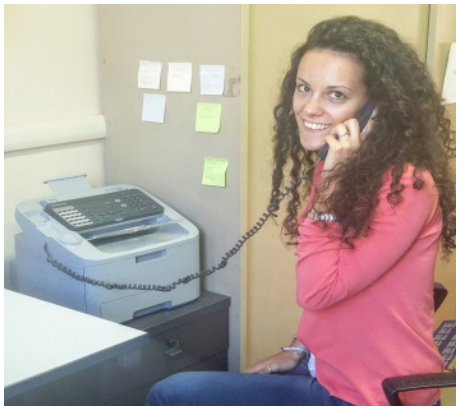


Conclusions

- Long-term management requires a combined effort of the keto-team and patient/families
- Side effects can be prevented by long-term monitoring; when they occur, they can be treated and the diet can be continued
- A guided self-management of the diet is useful
- Alternative diets may be considered to avoid side effects and improve tolerability
- Psychological support of patients, especially adolescents, and families may be required

And special thanks to

Claudia Trentani



Monica Guglielmetti

Cinzia Ferraris

Samantha Citrini

Sara Bellodi

University Course on ketogenic dietary therapies – 2nd edition Pavia 15 – 17 June 2016

Macro and micronutrient composition of supplemented ketogenic diets

	kcal	Carbohydrates (g)	Carbohydrates/kg (g)	Proteins (g)	Lipids (g)	Cholesterol (mg)	Dietary fibers (g)
Patient #1	1800	10.80	0.19	47.30	174.20	202.9	6.25
Patient #2	1900	11.30	0.19	50.00	183.80	130.4	5.18
Patient #3	1900	10.30	0.20	51.00	185.14	189.9	5.0

	Thiamin mg/day	Riboflavin mg/day	Niacin mg/day	Vitamin A g RE/day	Vitamin D µg/day	Vitamin C mg/day	Calcium mg/day	Phosporus mg/day	Potassium* mg/day	Sodium mg/day	Iron mg/day	Zinc mg/day	Copper mg/day
Patient #1	1.8	2.1	24.2	911	7.5	95	1000	786	2900*	1273	18.5	12.6	1.2
Patient #2	2.0	2.5	27.6	1050	7.5	90	1320	910	2960*	1740	20.5	14.4	1.3
Patient #3	1.7	2.2	21.0	1200	7.5	100	1000	800	2750*	875	21.0	12.0	1.2

Abbreviations: RE, retinol equivalent. *Given as potassium citrate.

Nutrition Journal

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Research

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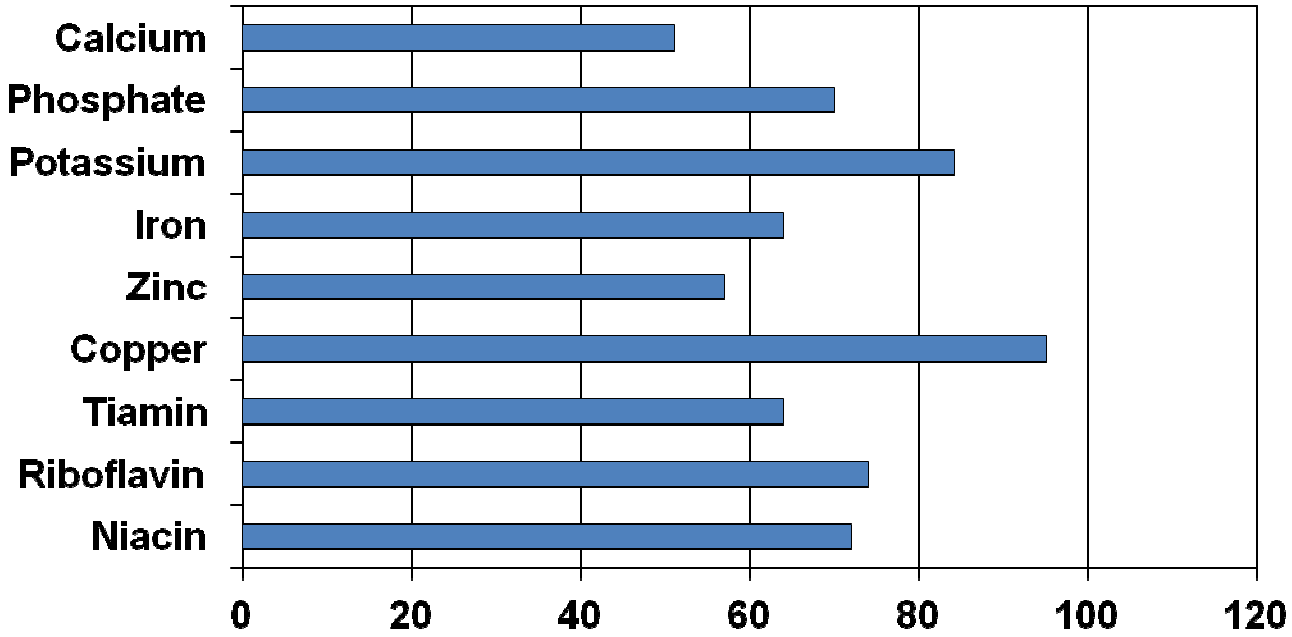
Evaluation of nutritional status in children with refractory epilepsy

S Bertoli*[1], S Cardinali[3], P Veggiotti[3], C Trentani[2], G Testolin[1] and A Tagliabue[2]

Address: [1]International Centre for the Assessment of Nutritional Status (ICANS), University of Milan, Italy, [2]Human Nutrition and Eating Disorders Research Centre, University of Pavia, Italy and [3]Child Neuropsychiatry Department, Casimiro Mondino Foundation, University of Pavia, Italy



Adequacy index (intake / recommended intake for sex and age * 100) for minerals and vitamins intake in 17 Italian children affected by IE before KD

Calcium and Vitamin D Dietary Reference Intakes

TABLE 1. Calcium and vitamin D dietary reference intakes by life stage

Life-stage group (age and gender)	Calcium		Vitamin D		
	RDA (mg/d) (intake that covers needs of ≥97.5% of population)	UL (mg/d)[a]	RDA (IU/d) (intake that covers needs of ≥97.5% of population)	Serum 25OHD level (ng/ml) (corresponding to the RDA)[b]	UL (IU/d)[a]
1–3 yr (M+F)	700	2500	600	20	2500
4–8 yr (M+F)	1000	2500	600	20	3000
9–13 yr (M+F)	1300	3000	600	20	4000
14–18 yr (M+F)	1300	3000	600	20	4000
19–30 yr (M+F)	1000	2500	600	20	4000
31–50 yr (M+F)	1000	2500	600	20	4000
51–70 yr (M)	1000	2000	600	20	4000
51–70 yr (F)	1200	2000	600	20	4000
71+ yr (M+F)	1200	2000	800	20	4000
Pregnant or lactating (F)					
14–18 yr	1300	3000	600	20	4000
19–50 yr	1000	2500	600	20	4000
Infants					
0–6 months (M+F)	200[c]	1000	400[c]	20	1000
6–12 months (M+F)	260[c]	1500	400[c]	20	1500

M, Male; F, female. EARs for calcium were 500 mg/d for ages 1–3 (M+F); 800 mg/d for ages 4–8 and 19–50 (M+F), and ages 51–70 (M); 1000 mg/d for ages 51–70 (F) and 71+ (M+F); and 1100 mg/d for ages 9–18 (M+F). EAR for vitamin D was 400 IU/d for all life-stage groups.

[a] UL indicates level above which there is risk of adverse events. The UL is not intended as a target intake (no consistent evidence of greater benefit at intake levels above the RDA).

[b] Measures of serum 25OHD levels corresponding to the RDA and covering the requirements of at least 97.5% of the population.

[c] Reflects AI reference value rather than RDA. RDAs have not been established for infants.

Institute of Medicine, 2010

Journal of Human Nutrition and Dietetics

CLINICAL NUTRITION

The effect of the classical and medium chain triglyceride ketogenic diet on vitamin and mineral levels

S. S. Christodoulides,*† E. G. Neal,* G. Fitzsimmons,* H. M. Chaffe,* Y. M. Jeanes,† H. Aitkenhead* & J. H. Cross*

*UCL-Institute of Child Health & Great Ormond Street Hospital for Children NHS Trust, London, UK
†Health Sciences Research Centre, Roehampton University, London, UK

Background: The risk of nutritional deficiency in children on restrictive dietary treatments and a ***lack of ketogenic diet (KD)-specific UK supplements*** raises concerns about micronutrient status.

Vitamin A, E, zinc, selenium and magnesium levels were therefore examined in children with intractable epilepsy treated with the KD.

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	KD classica		KD con MCT	
	basale	Dopo 12 mesi	basale	Dopo 12 mesi
Vitamina A (umol/L)	1,41	1,13*	1,52	1,81*
Vitamina E (umol/L)	22,67	33,20*	22,32	23,31**
Zinco (umol/L)	11,15	12,23	12,15	12,40
Selenio (umol/L)	0,97	0,89	0,92	0,87
Magnesio (mmol/L)	0,88	0,82**	0,86	0,84

*** p < 0,001; ** p < 0,05**

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Conclusions: Changes in plasma vitamins A and E and the decline in magnesium status after 12 months of KD treatment suggest that micronutrient status may be suboptimal in this group and that ***available formulations for KD supplementation may need reviewing***

Changes in micronutrient intake

	Mean ± SD	DRI 4 – 8 yrs	DRI 9 – 13 yrs	
Calcium (mg) ↓	381.4±189.8	800	1300	
Phosphorus (mg)	478.6±196.9	500	1250	
Potassium (mg) ↓	914.3±317.1	3238	4500	
Iron (mg) ↓	4.0±1.6	10	8	
Zinc (mg) ↓	3.3±1.2	5	8	
Copper (mg)	0.5±0.2	0.4	0.7	
Thiamin (mg) ↓	0.4±0.2	0.6	0.9	
Riboflavin (mg)	0.6±0.2	0.6	0.9	
Niacin (mg) ↓	5.1±2.3	8	12	
Vitamin C (mg)	43.5±14.3	25	45	
Vitamin A (ug RE)	471.3±296.4	400	600	

Integratori vitaminico minerali
esempi di composizione

Prodotto	*Vit A*	*Vit D*	*Vit E*	*Vit K*	*Vit C*	*Vit B1*	*Vit B2*	*Niacina*	*Vit B6*	*Ac Fol*	*Vit B12*	*Ac Pant*	*Biotina*
A adulti*	800 µg	5 µg	10 mg	30 µg	60mg	1,4 mg	1,6 mg	18 mg	2 mg	200 µg	1 µg	6 mg	150 µg
A baby ***	320 µg	8 µg	5 mg	30 µg	45 mg	0,7 mg	1,1 mg	11 mg	0,7 mg	130 µg	1 µg	6 mg	24 µg
B adulti **	300 µg	1 µg	10 mg	/	150 mg	20 mg	5 mg	50 mg	10 mg	/	5 µg	11,6 mg	2,3 µg
B baby **	300 µg	2,5 µg	5 mg	/	22,5 mg	0,45 mg	0,45 mg	6 mg	0,45 mg	75 µg	5 µg	2 mg	10 µg

*** No carboidrati; ** 1,2 g carboidrati; *** 4,88 g carboidrati**

Integratori vitaminico minerali
esempi di composizione

Prodotto	*Ca*	*P*	*K*	*Na*	*Fe*	*Zn*	*Cr*	*Cu*	*I*	*Mg*	*Mn*	*Mo*	*Se*	*Cl*
*A adulti**	162 mg	125 mg	40 mg	/	14 mg	7,5 mg	25 mg	0,7 mg	150 mg	100 mg	2,5 mg	25 mg	25 mg	36,3 mg
*A baby****	240 mg	242 mg	170 mg	/	6,8 mg	6 mg	/	0,4 mg	90 mg	80 mg	1 mg	/	15 mg	/
*B adulti **	51 mg	45 mg	/	/	1,25 mg	0,5 mg	/	0,1 mg	/	5 mg	0,5 mg	/	/	/
*B baby **	120 mg	/	/	/	6 mg	4 mg	12,5 mg	0,4 mg	60 mg	25 mg	1 mg	0,1 mg	12,5 mg	/

*** No carboidrati; ** 1,2 g carboidrati; *** 4,88 g carboidrati**

La dieta chetogenica compromette la crescita?

Author	Follow-up period	Number of subjects (age, yrs)	Protein content	Caloric restriction at initiation	Height percentile or zscores	Weight percentile or zscores
Neal et al, 2007	Prospective 12 months	75 (50 ambulatory) (2- 16)	Adequate	intermediate	decrease	decrease
Groesbeck et al, 2006	retrospective 6 years	28 (7 – 23)	Adequate	YES	decrease	decrease
Peterson et al, 2005	retrospective 12 months	33 (1 – 20)	Adequate	NO	decrease	decrease
Williams et al, 2002	retrospective 6 months	21 (1 – 15.5)	0.95g / kg weight	YES	decrease	decrease
Vining et al,2002	prospective 2 years	237 (0 - 10)	Adequate	YES	decrease	decrease
Liu et al, 2003	prospective 4 months	14 (1 – 16)	1 g / kg weight	YES	No change	decrease