La dieta chetogenica nel paziente neurologico adulto

Cherubino DI LORENZO

Il sottoscritto Cherubino DI LORENZO
ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,

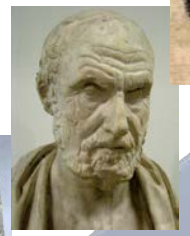
dichiara

☒ *che negli ultimi due anni ha avuto rapporti diretti di finanziamento con i seguenti soggetti portatori di interessi commerciali in campo sanitario:*

- *Eli Lilly*
- *Novartis*
- *Molteni*
- Dr Schär

STORY OF KETOGENESIS IN NEUROLOGICAL DISORDERS

1792 b.C
Hammurabi
Codex



IV sec. b.C.
Hippocrates
Theory of
humors

30-33 A.D.
Jesus of
Nazareth
(Mc.9.28;
Mt17.21)

78e ANNÉE

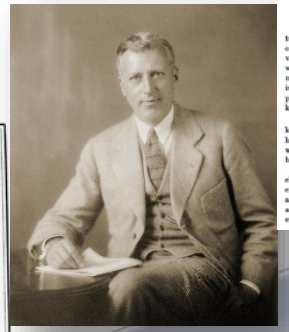
Revue de Thérapeutique

MÉDICO-CHIRURGICALE

1911

PARIS

1911
Guelpa & Marie
La lutte contre
l'epilepsie par la
desintoxication et
par la reeducation
alimentaire



1921
Russell Wilder
Ketogenic diet

SOME EFFECTS OF A
KETOGENIC DIET

BY

RICHARD W. B. ELLIS, M.A., M.D.

(From the Children's Department, Westminster Hospital, London).

The following study is based on the administration of a ketogenic diet to twenty children between the ages of three and eight years, the majority of cases being chosen with the purpose of testing tolerance to a high fat diet in various conditions. The diet employed, the details of which are given below, was found with slight modification for age to be sufficient to produce a marked ketosis in two to three days in most cases; where it was ineffective in four days, the added factor of restricted fluid intake was employed. A positive ferric-chloride test in the urine was taken as the criterion of an adequate ketosis, since Rothera's test is too sensitive to be of equal value.

Post-anæsthetic vomiting.—The first point investigated was the effect of ketosis on post-anæsthetic vomiting. It is well known that starvation, and hence vomiting, will produce ketosis in the human subject; the point at issue was whether ketosis, however produced, would in the post-anæsthetic state be likely to result in excessive vomiting.

A preliminary comparison was made between two groups each of seven children who were subjected to tonsillectomy. It was not possible to keep the experimental condition exactly uniform for each child as regards operation and anæsthetic, but the former consisted of tonsillectomy by dissection in each case, and the anæsthetics employed were ethyl chloride for induction followed by ether.

1930s
Ketogenic diet
in several
neurologic and
non-neurologic
disorders

THE CHARLIE FOUNDATION

1997
Charlie
Foundation

«First do not
harm»

NIH National Library of Medicine
National Center for Biotechnology Information

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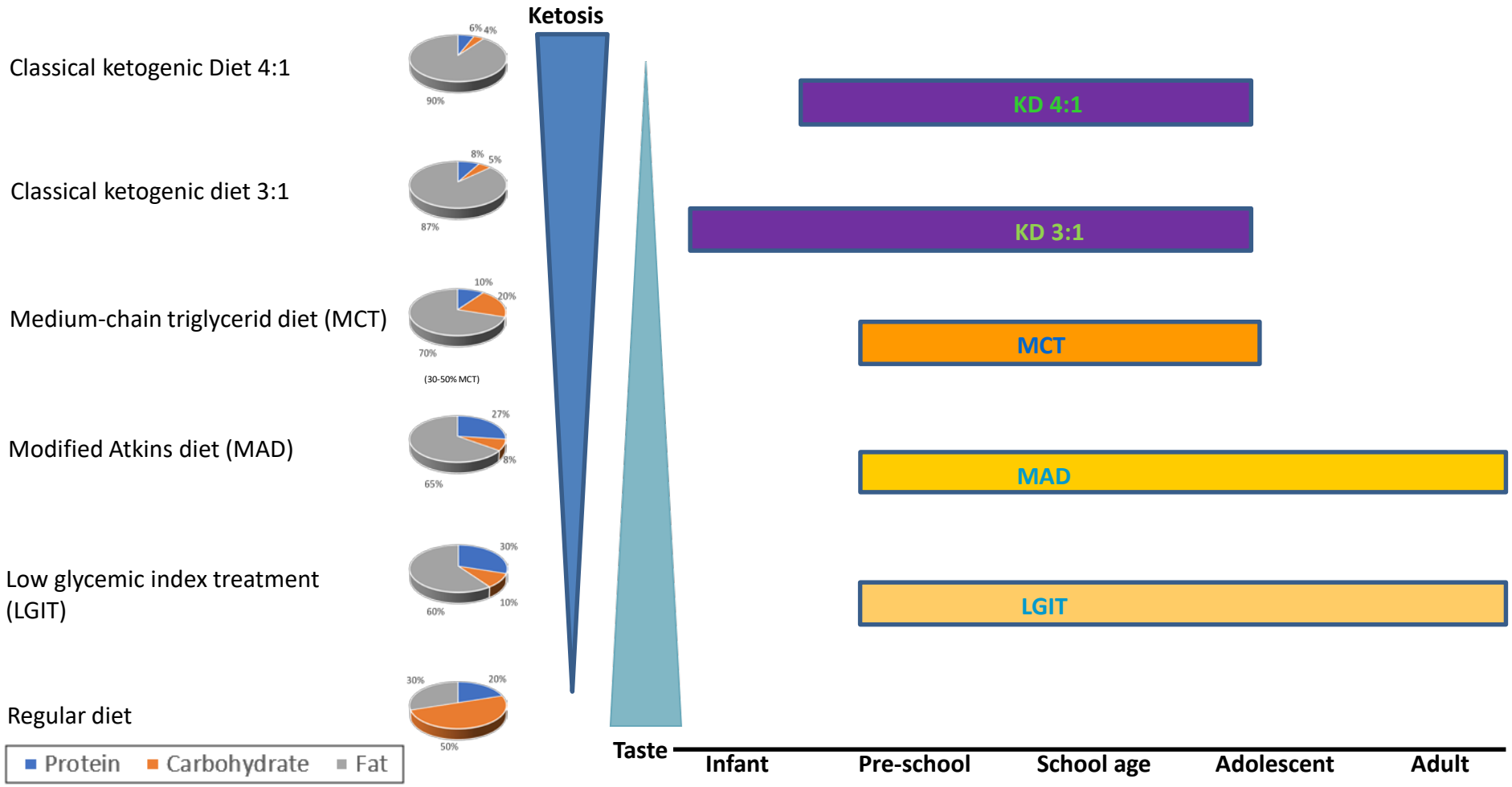
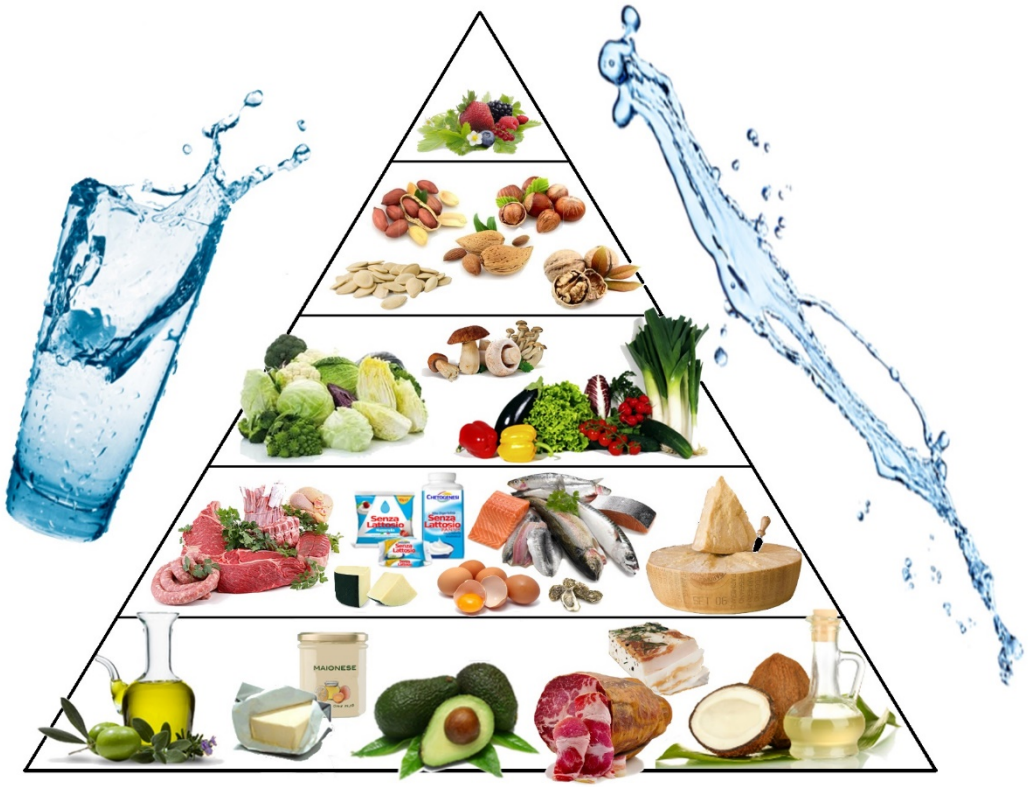
2017
More than 365
publications in
one year on
Pubmed with
the keywords
«Ketogenic
diet».


Ketosis
Classical ketogenic Diet 4:1
6%
4%
90%
Classical ketogenic diet 3:1
8%
5%
87%
Medium-chain triglycerid diet (MCT)
10%
20%
70%
(30-50% MCT)
Modified Atkins diet (MAD)
27%
8%
65%
Low glycemic index treatment (LGIT)
30%
10%
60%
Regular diet
30%
20%
50%
Protein
Carbohydrate
Fat
KD 4:1
KD 3:1
MCT
MAD
LGIT
Taste
Infant
Pre-school
School age
Adolescent
Adult

The Ketogenic Food Pyramid

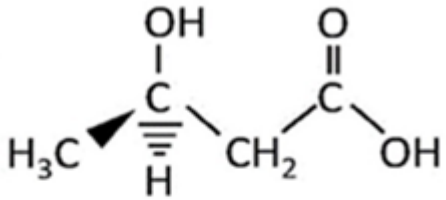


Omnivore vs Vegan

KDA Ketogenic Diet ACADEMY

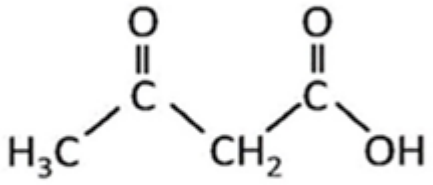
SINut Società Italiana di Nutraceutica

A



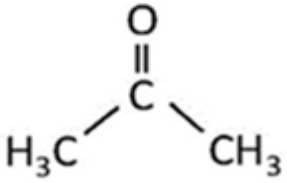
β-hydroxybutyrate

B

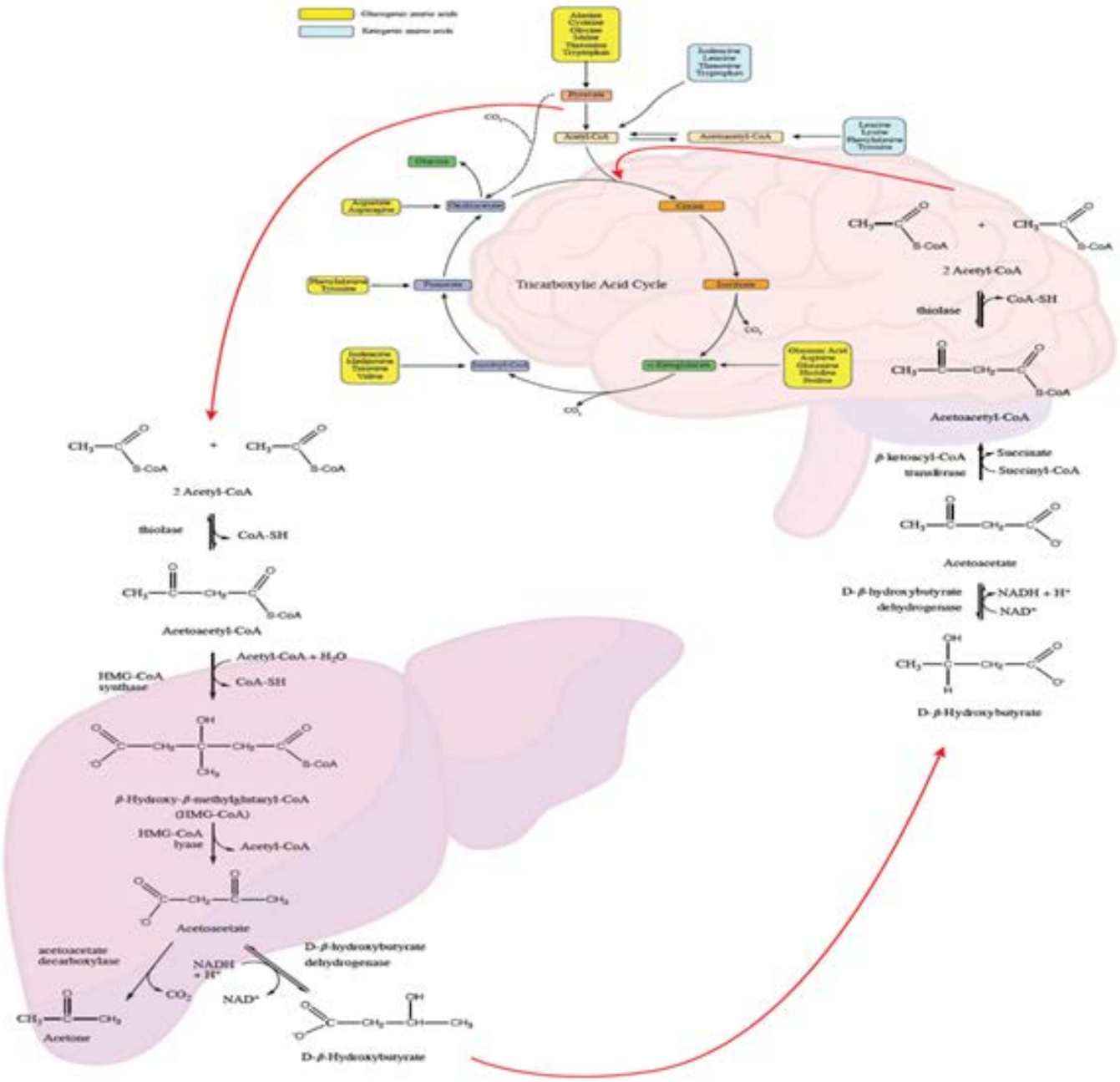


Acetoacetate

C



Acetone



KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

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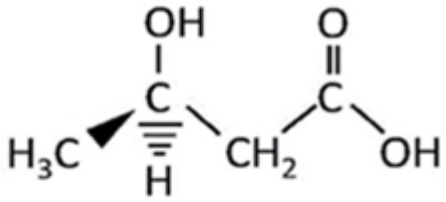
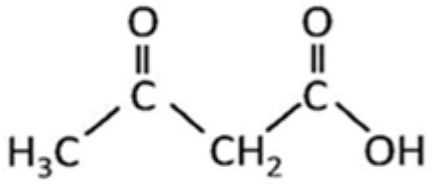


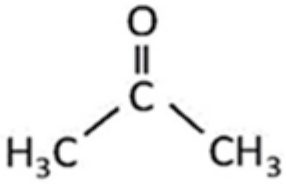
β-hydroxybutyrate

B

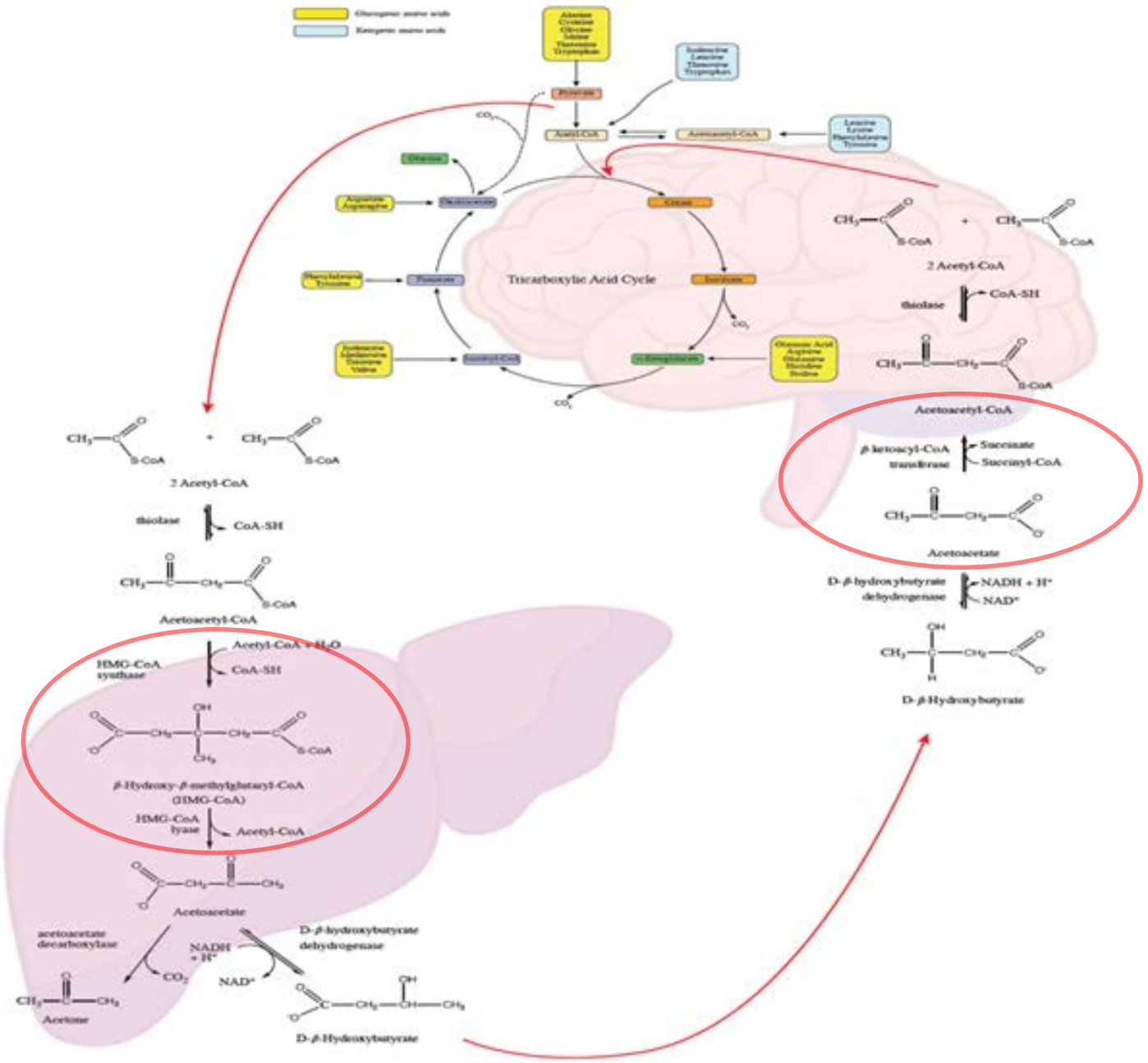


Acetoacetate

C



Acetone



Jasper's Basic Mechanisms of the Epilepsies
Fourth Edition
Edited by Jeffrey L. Noebels, Massimo Avoli, Michael A. Rogawski, Richard W. Olsen, Antonio V. Delgado-Escueta
NCBI Bookshelf Online Book Version

Mechanisms of Ketogenic Diet Action

Susan A. Masino
Neuroscience Program and Psychology Department, Trinity College, Hartford, CT (USA)

Jong M. Rho
Departments of Pediatrics and Clinical Neurosciences, Alberta Children's Hospital, University of Calgary Faculty of Medicine, Calgary, Alberta (Canada)

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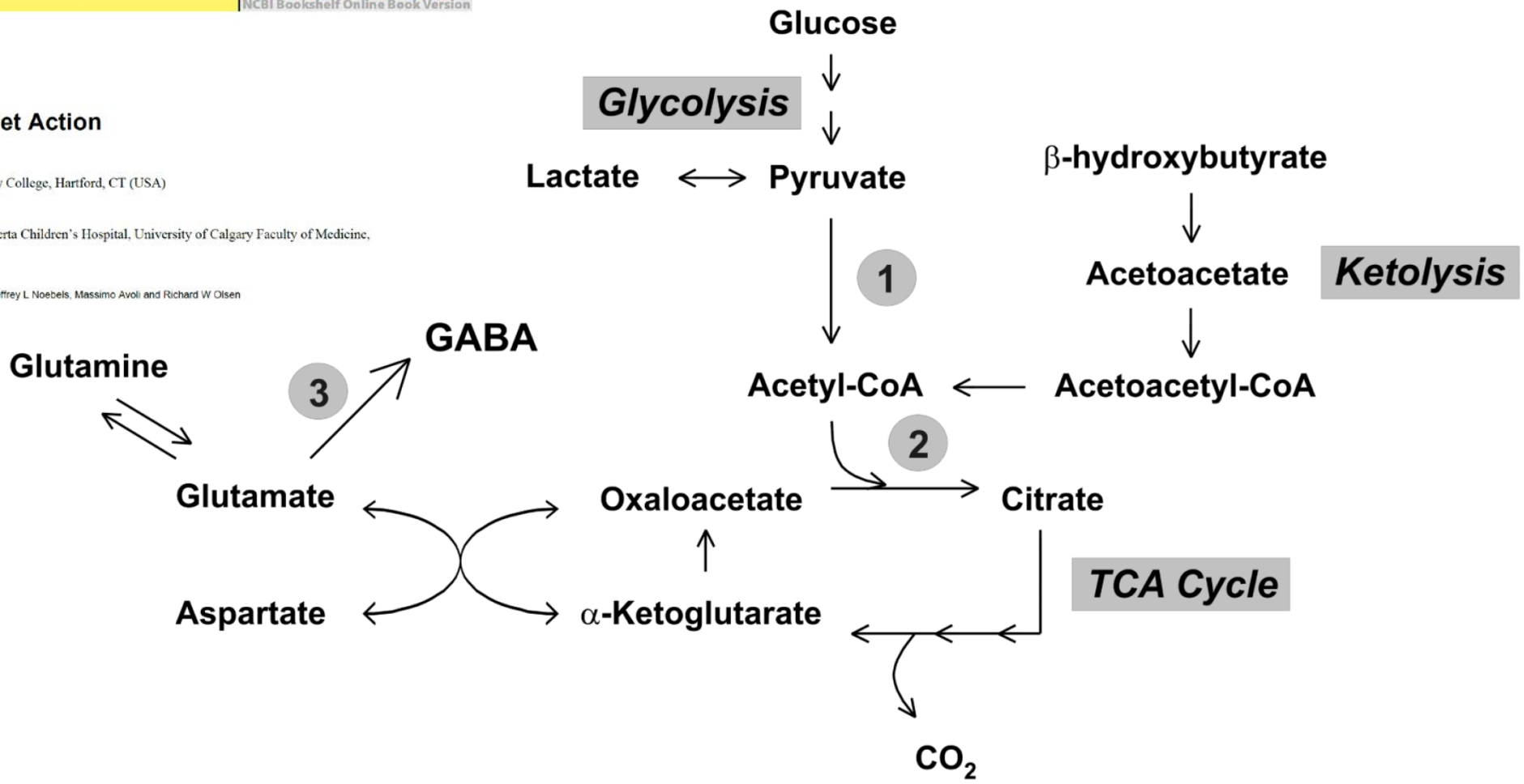
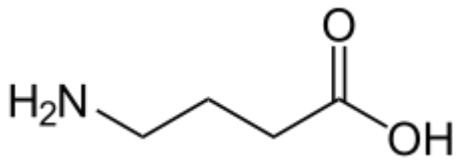


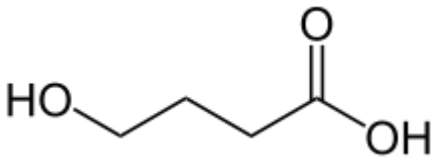
Figure 2. The metabolic inter-relationships between brain metabolism of glutamate, ketone bodies and glucose

GABAergic effect of ketone bodies

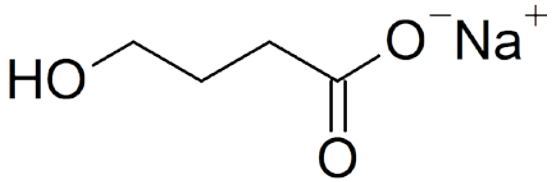
- Gamma-aminobutyric acid (GABA)



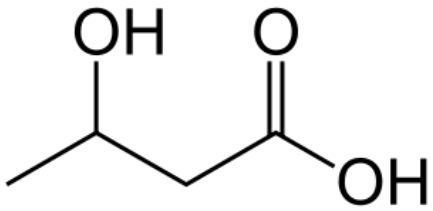
- Gamma-hydroxybutyric acid (GHB)



- Sodium Oxybate

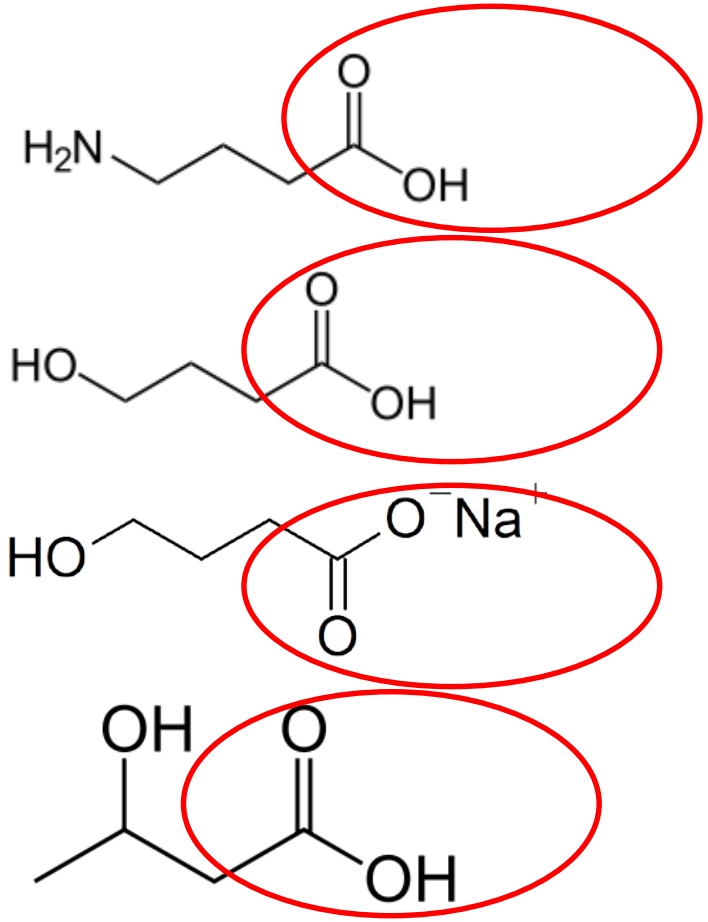


- Beta-hydroxybutyric acid (BHB)



GABAergic effect of ketone bodies

- Gamma-aminobutyric acid (GABA)
- Gamma-hydroxybutyric acid (GHB)
- Sodium Oxybate
- Beta-hydroxybutyric acid (BHB)



KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

ANSA.it › Cronaca › **Conduttore tv arrestato: 'Non spaccio, cerco di curarmi'**

Conduttore tv arrestato: 'Non spaccio, cerco di curarmi'

Così Ciro Di Maio al gip. Legale: 'Segue un perco

Redazione ANSA

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15:22

NEWS

Schweizerische Eidgenossenschaft
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Confederaziun svizra

Ufficio federale della sanità pubblica UFSP

Termini dall'A alla Z

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Ufficio federale della sanità pubblica UFSP › Vivere in salute › Ambiente & salute › Prodotti chimici › Prodotti chimici da A-Z › GHB

‹ Prodotti chimici

Prodotti chimici da A-Z

GHB, GBL, BD - Inibitori della volontà

Gocce KO, liquid ecstasy, droga dello stupro, il GHB finisce regolarmente sui giornali. Versato nelle bevande, rende la vittima manipolabile e priva di volontà, talvolta facendole perdere i sensi. Alcune informazioni...

Dietro le complicate designazioni chimiche gamma-idrossibutirrato (GHB), gamma-butirrolattone (GBL) e butandiolo (BD) si celano tre sostanze simili, meglio conosciute come gocce KO o Liquid Ecstasy. Per le loro caratteristiche, si prestano particolarmente per scopi subdoli: si tratta di polveri incolori o di liquidi dal sapore salato o leggermente saponoso, praticamente inodori. Sono idrosolubili e possono essere aggiunte facilmente alle bevande di nascosto. Già quindici minuti dopo l'assunzione si manifesta uno stato di euforia che si trasforma poi in stanchezza. Le gocce KO rafforzano inoltre gli effetti di altre droghe assunte contemporaneamente. Se il dosaggio è eccessivo, insorgono nausea, stati di stordimento e profonda incoscienza, insufficienza respiratoria. Al risveglio, le vittime non ricordano più nulla. In caso di avvelenamento, i pazienti devono essere sottoposti a sorveglianza medica e, se del caso, a respirazione artificiale. Il consumo occasionale non genera dipendenza, ma se assunte a lungo in dosi elevate, queste sostanze creano dipendenza fisica e psichica.

Contatto

Ufficio federale della sanità pubblica UFSP
Divisione prodotti chimici
Schwarzenburgstrasse 157
3003 Berna
Svizzera
Tel. +41 58 462 96 40
E-mail
Stampare contatto

Pediatr Neurol. 2007 May ; 36(5): 281–292.

The Neuropharmacology of the Ketogenic Diet

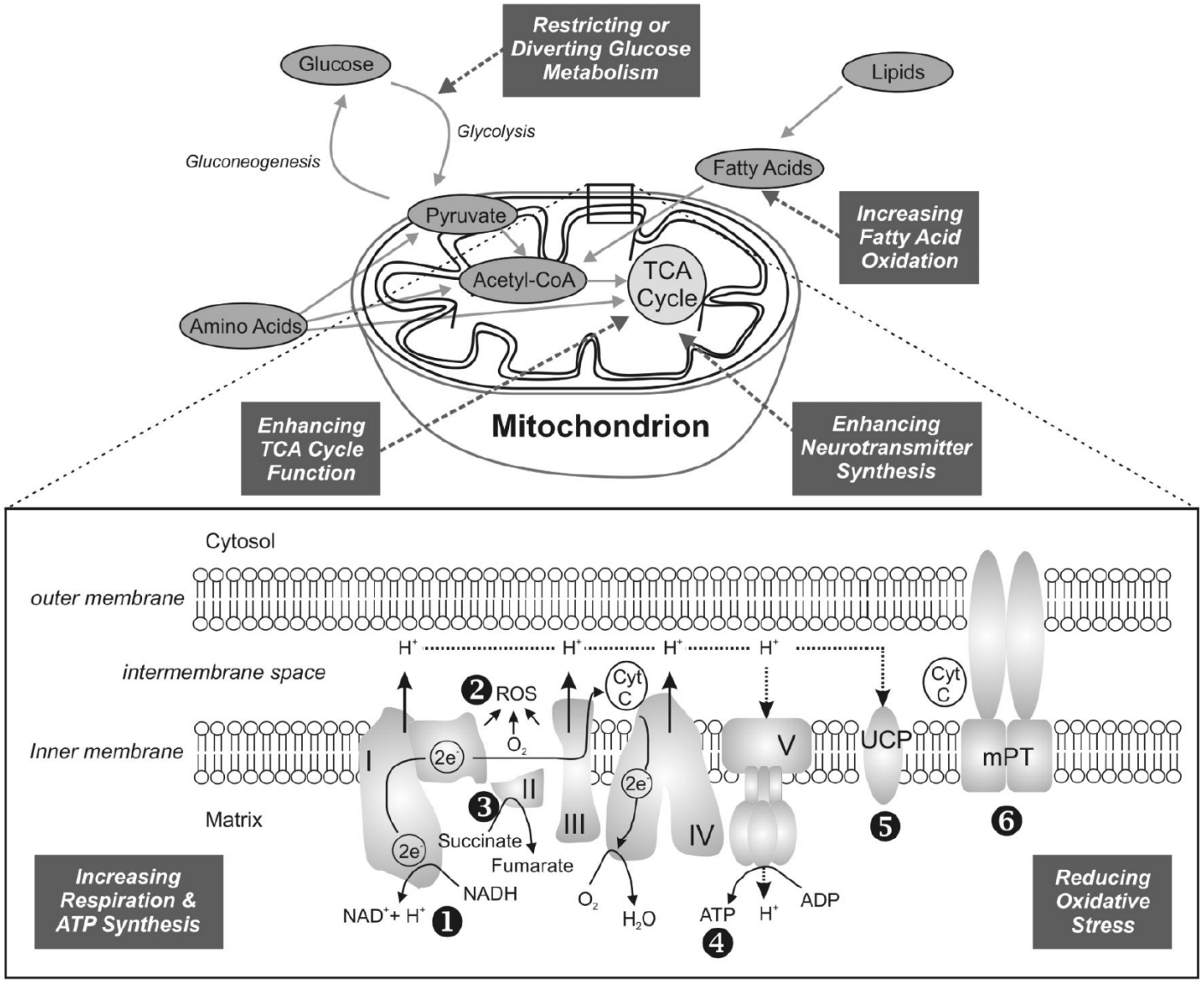
Adam L. Hartman, MD[*,†], **Maciej Gasior, MD, PhD**[†], **Eileen P. G. Vining, MD**[*], and **Michael A. Rogawski, MD, PhD**[†,‡]

Effects on Energy Metabolism

During consumption of the ketogenic diet, ketone bodies replace glucose as a source of energy for the brain. These ketone bodies may be a more efficient source of energy per unit oxygen than glucose [76]. In addition, the ketogenic diet causes a coordinated upregulation of mitochondrial genes and genes involved in energy metabolism, and appear to stimulate the biogenesis of mitochondria as assessed by electron microscopy [39]. Together, the availability of a more efficient fuel and an increase in the number of mitochondria provide an increase in cellular energy production capacity and reserves. It seems plausible that the greater energy reserve would enhance the capacity of neurons to withstand metabolic challenges and could account for the ability of the diet to confer neuroprotection in models of neurodegenerative diseases or stroke [5]. It also has been proposed that effects of the ketogenic diet on brain energetics contribute to the seizure protection conferred by the diet [37,42], although there is little experimental support for this concept.

KD and Mitochondria

Jasper's Basic Mechanisms of the Epilepsies



Electron Transport & Oxidative Phosphorylation

Ketone Bodies Mediate Antiseizure Effects through Mitochondrial Permeability Transition

Do Young Kim, DVM, PhD,[1] Kristina A. Simeone, PhD,[2]
Timothy A. Simeone, PhD,[2] Jignesh D. Pandya, PhD,[3] Julianne C. Wilke, BS,[1]
Younghee Ahn, PhD,[4] James W. Geddes, PhD,[3] Patrick G. Sullivan, PhD,[3] and
Jong M. Rho, MD[4]

Objective: Ketone bodies (KB) are products of fatty acid oxidation and serve as essential fuels during fasting or treatment with the high-fat antiseizure ketogenic diet (KD). Despite growing evidence that KB exert broad neuroprotective effects, their role in seizure control has not been firmly demonstrated. The major goal of this study was to demonstrate the direct antiseizure effects of KB and to identify an underlying target mechanism.
Methods: We studied the effects of both the KD and KB in spontaneously epileptic *Kcna1*-null mice using a combination of behavioral, planar multielectrode, and standard cellular electrophysiological techniques. Thresholds for mitochondrial permeability transition (mPT) were determined in acutely isolated brain mitochondria.
Results: KB alone were sufficient to: (1) exert antiseizure effects in *Kcna1*-null mice, (2) restore intrinsic impairment of hippocampal long-term potentiation and spatial learning–memory defects in *Kcna1*-null mutants, and (3) raise the threshold for calcium-induced mPT in acutely prepared mitochondria from hippocampi of *Kcna1*-null animals. Targeted deletion of the cyclophilin D subunit of the mPT complex abrogated the effects of KB on mPT, and in vivo pharmacological inhibition and activation of mPT were found to mirror and reverse, respectively, the antiseizure effects of the KD in *Kcna1*-null mice.
Interpretation: The present data reveal the first direct link between mPT and seizure control, and provide a potential mechanistic explanation for the KD. Given that mPT is increasingly being implicated in diverse neurological disorders, our results suggest that metabolism-based treatments and/or metabolic substrates might represent a worthy paradigm for therapeutic development.

ANN NEUROL 2015;00:000–000

KDA Ketogenic Diet ACADEMY

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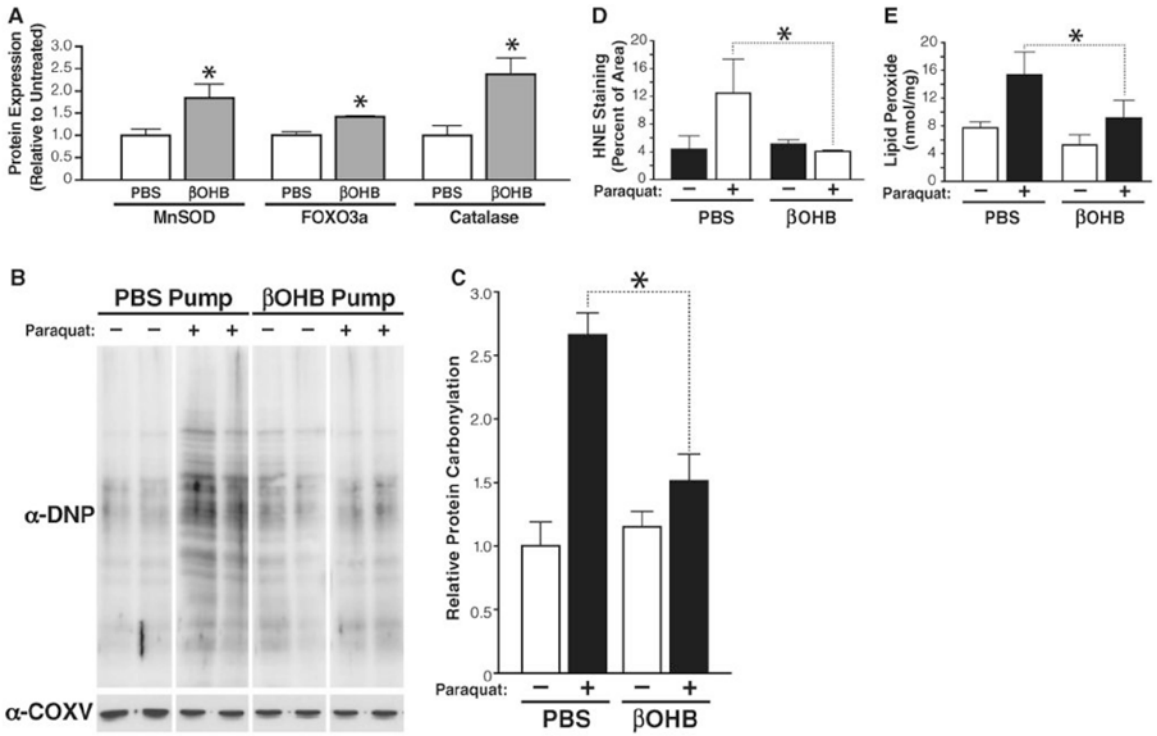

Fig. 4.
Protective effect of βOHB treatment against oxidative stress. (**A**) Amounts of catalase, MnSOD, or FOXO3A measured by protein immunoblotting in kidney tissue from 16-week-old mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$); mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**B**) Protein carbonylation in kidney samples from mice implanted with an osmotic pump delivering PBS or βOHB (as in Fig. 2; $n = 3$) and treated with paraquat (50 mg/kg) or vehicle for 2 hours. Car-bonylation was measured by immunoblotting with anti-DNP. All samples were run on a single gel; after imaging, lanes were rearranged for presentation. (**C**) Quantification of protein carbonylation in (B). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**D**) Sections of kidney obtained from the same mice as in (B) were stained with anti-4-HNE and quantified (see fig. S16 for primary picture). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions. (**E**). Lipid peroxides were quantified in mice kidneys (LPO assay kit, Cayman, Ann Arbor, MI). Mean ± SE, $*P < 0.05$ by t test between PBS and βOHB conditions.

Science. 2013 January 11; 339(6116): 211–214. doi:10.1126/science.1227166.

Suppression of Oxidative Stress by β-Hydroxybutyrate, an Endogenous Histone Deacetylase Inhibitor

Tadahiro Shimazu[1,2], **Matthew D. Hirschey**[1,2], **John Newman**[1,2], **Wenjuan He**[1,2], **Kotaro Shirakawa**[1,2], **Natacha Le Moan**[3], **Carrie A. Grueter**[4,5], **Hyungwook Lim**[1,2], **Laura R. Saunders**[1,2], **Robert D. Stevens**[6], **Christopher B. Newgard**[6], **Robert V. Farese Jr.**[2,4,5], **Rafael de Cabo**[7], **Scott Ulrich**[8], **Katerina Akassoglou**[3], and **Eric Verdin**[1,2,*]

Epigenetics regulation
&
Oxidative stress reduction

Ketogenic Diet and Cortical Spreading Depression

Available online at www.sciencedirect.com
ScienceDirect
Neuroscience Letters 434 (2008) 66–70
Neuroscience Letters
www.elsevier.com/locate/neulet

Effects of short-term and long-term treatment with medium- and long-chain triglycerides ketogenic diet on cortical spreading depression in young rats

Marcela de Almeida Rabello Oliveira[a], Terezinha da Rocha Ataíde[b], Suzana Lima de Oliveira[b], Ana Luíza de Melo Lucena[b], Carla Emmanuela Pereira Rodrigues de Lira[a], Anderson Acioli Soares[a], Clarissa Beatriz Santos de Almeida[a], Adriana Ximenes-da-Silva[a,*]

[a] *Laboratório de Eletrofisiologia e Metabolismo Cerebral, Instituto de Ciências Biológicas e da Saúde, Universidade Federal de Alagoas, 57.010-020, Maceió, AL, Brazil*
[b] *Laboratório de Nutrição Experimental, Faculdade de Nutrição, Universidade Federal de Alagoas, 57.010-020, Maceió, AL, Brazil*

Received 14 September 2007; received in revised form 7 January 2008; accepted 16 January 2008

Abstract

The ketogenic diet (KD) is a high fat and low carbohydrate and protein diet. It is used in the clinical treatment of epilepsy, in order to decrease cerebral excitability. KD is usually composed by long-chain triglycerides (LCT) while medium-chain triglycerides (MCT) diet is beginning to be used in some clinical treatment of disorders of pyruvate carboxylase enzyme and long-chain fatty acid oxidation. Our study aimed to analyze the effects of medium- and long-chain KD on cerebral electrical activity, analyzing the propagation of the phenomenon of cortical spreading depression (CSD). Three groups of weaned rats (21 days old) received, for 7 weeks, either a control (AIN-93G diet), or a MCT-KD (rich in triheptanoin oil), or a LCT-KD (rich in soybean oil). They were compared to another three groups (21 days old) receiving the same diets for just 10 days. CSD propagation was evaluated just after ending the dietary treatments. Results showed that short-term KD treatment resulted in a significant reduction of the CSD velocity of propagation (control group: 4.02 ± 1.04 mm/min; MCT-KD: 0.81 ± 1.46 mm/min and LCT-KD: 2.26 ± 0.41 mm/min) compared to the control group. However, long-term treatment with both KDs had no effect on the CSD velocity (control group: 3.10 ± 0.41 mm/min, MCT-KD: 2.91 ± 1.62 mm/min, LCT-KD: 3.02 ± 2.26 mm/min) suggesting that both short-term KDs have a positive effect in decreasing brain cerebral excitability in young animals. These data show for the first time that triheptanoin has an effect on central nervous system.
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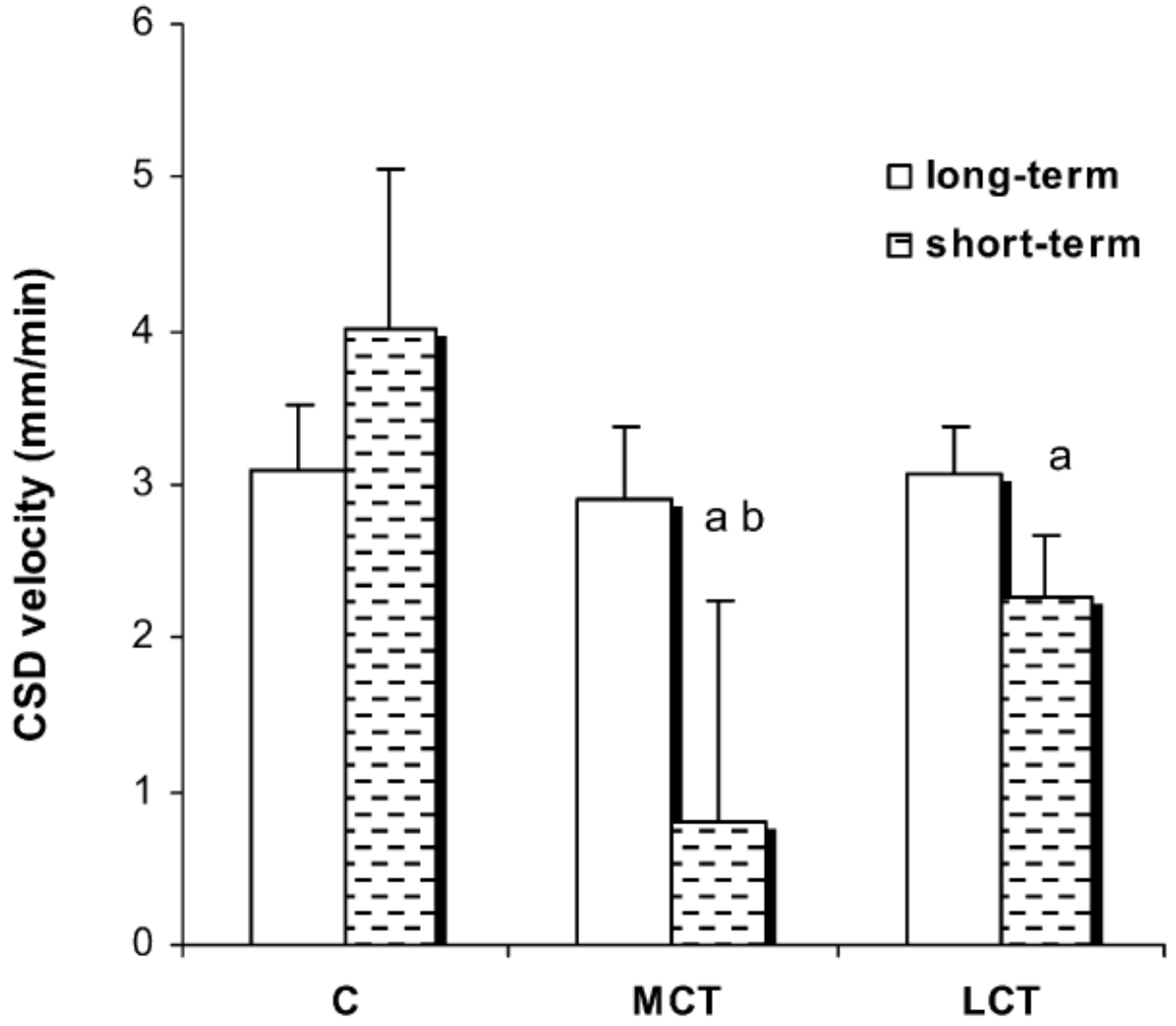
Keywords: Ketogenic diet; Triheptanoin; Cerebral metabolism; Spreading depression



KDA Ketogenic Diet ACADEMY
npj | Biofilms and Microbiomes
www.nature.com/npjbiofilms
SINut Società Italiana di Nutraceutica

ARTICLE OPEN

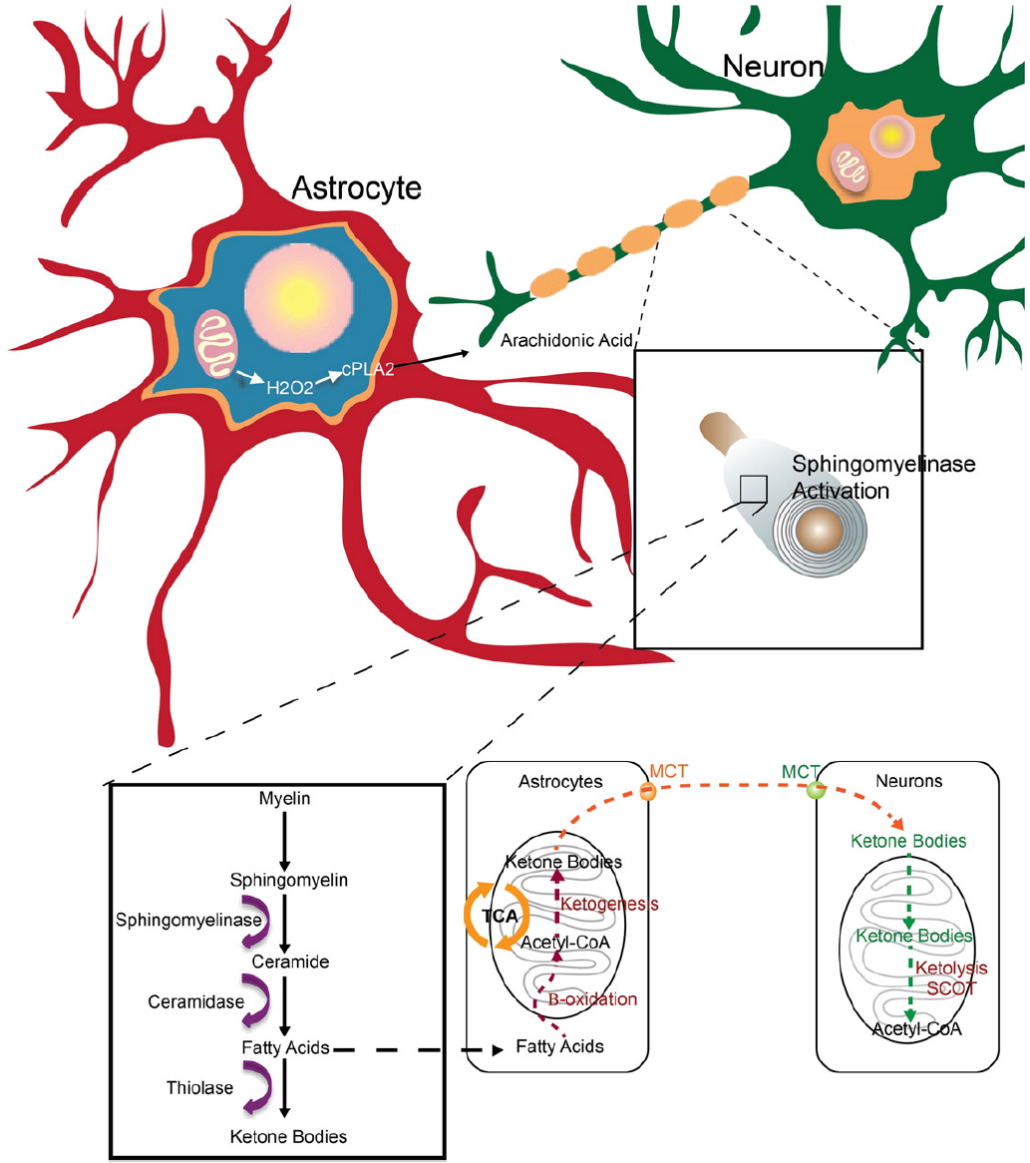
The ketogenic diet influences taxonomic and functional composition of the gut microbiota in children with severe epilepsy

Marie Lindefeldt[1], Alexander Eng[2], Hamid Darban[3], Annelie Bjerkner[4], Cecilia K Zetterström[5], Tobias Allander[4], Björn Andersson[3], Elhanan Borenstein[2,6,7,8,9], Maria Dahlin[1] and Stefanie Prast-Nielsen[10]

The gut microbiota has been linked to various neurological disorders via the gut–brain axis. Diet influences the composition of the gut microbiota. The ketogenic diet (KD) is a high-fat, adequate-protein, low-carbohydrate diet established for treatment of therapy-resistant epilepsy in children. Its efficacy in reducing seizures has been confirmed, but the mechanisms remain elusive. The diet has also shown positive effects in a wide range of other diseases, including Alzheimer's, depression, autism, cancer, and type 2 diabetes. We collected fecal samples from 12 children with therapy-resistant epilepsy before starting KD and after 3 months on the diet. Parents did not start KD and served as diet controls. Applying shotgun metagenomic DNA sequencing, both taxonomic and functional profiles were established. Here we report that alpha diversity is not changed significantly during the diet, but differences in both taxonomic and functional composition are detected. Relative abundance of bifidobacteria as well as *E. rectale* and *Dialister* is significantly diminished during the intervention. An increase in relative abundance of *E. coli* is observed on KD. Functional analysis revealed changes in 29 SEED subsystems including the reduction of seven pathways involved in carbohydrate metabolism. Decomposition of these shifts indicates that bifidobacteria and *Escherichia* are important contributors to the observed functional shifts. As relative abundance of health-promoting, fiber-consuming bacteria becomes less abundant during KD, we raise concern about the effects of the diet on the gut microbiota and overall health. Further studies need to investigate whether these changes are necessary for the therapeutic effect of KD.

npj Biofilms and Microbiomes (2019)5:5 ; https://doi.org/10.1038/s41522-018-0073-2

L.P. Klosinski et al. / EBioMedicine 2 (2015) 1888–1904

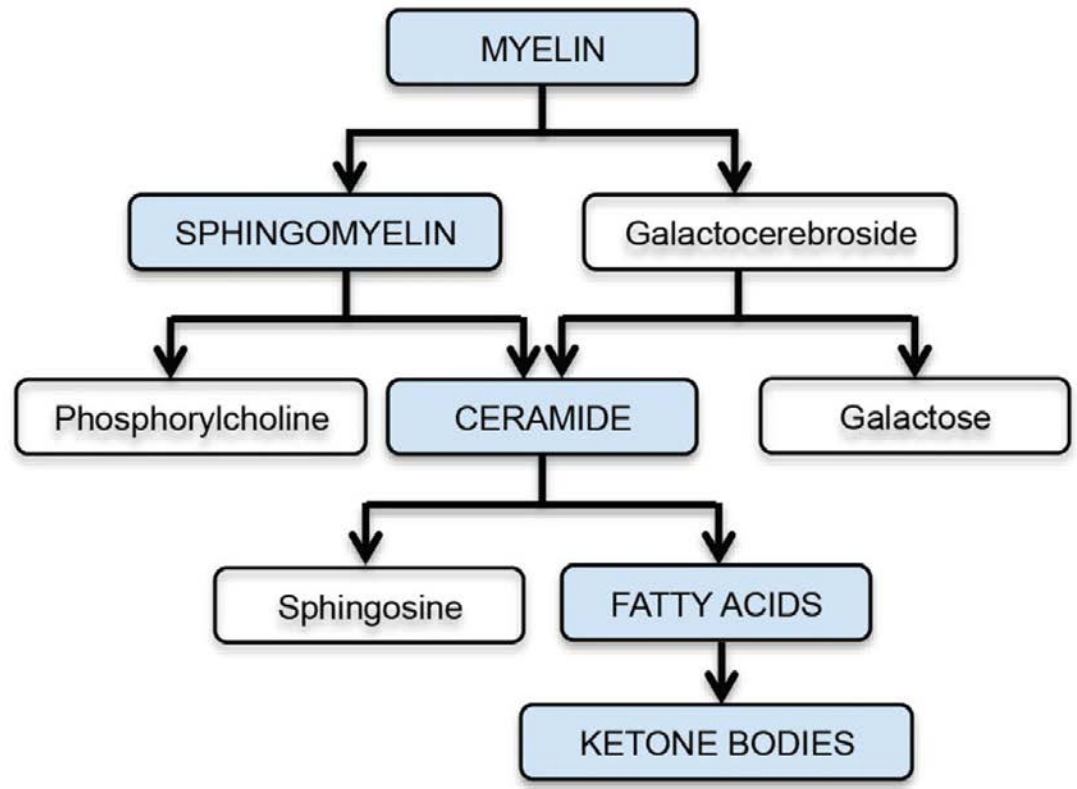


Research Article

White Matter Lipids as a Ketogenic Fuel Supply in Aging Female Brain: Implications for Alzheimer's Disease

Lauren P. Klosinski [a], Jia Yao [b], Fei Yin [b], Alfred N. Fonteh [c], Michael G. Harrington [c], Trace A. Christensen [d], Eugenia Trushina [d,e], Roberta Diaz Brinton [a,b,f]

L.P. Klosinski et al. / EBioMedicine 2 (2015) 1888–1904



KD in GLUT1 and Pyruvate dehydrogenase deficit

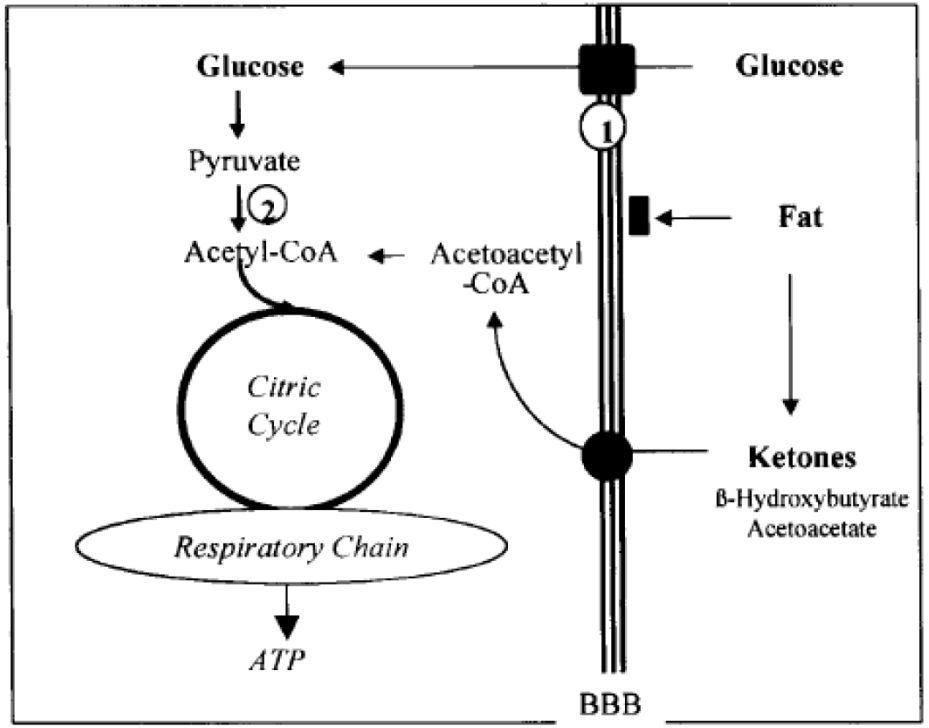
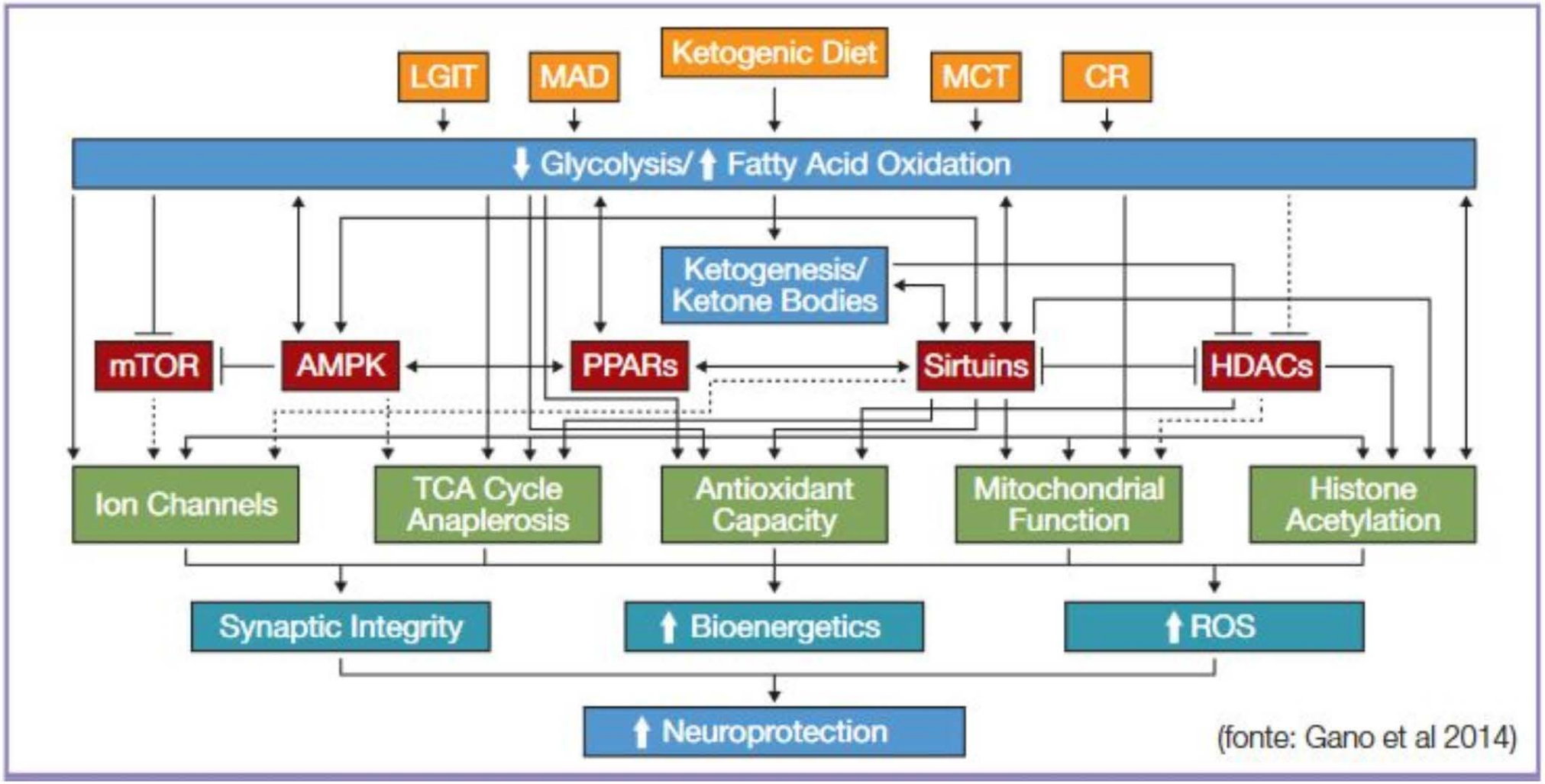


Figure 1 Ketosis and brain energy metabolism. Glucose enters the brain via the facilitated glucose transporter GLUT1 (■); ketones penetrate the blood–brain barrier (BBB) via the MCT1-transporter (●). Both substrates enter the citric acid cycle as acetyl-CoA for energy production. ① GLUT1 DS is caused by a defect in GLUT1-mediated glucose transport into brain. ② Pyruvate dehydrogenase deficiency impairs acetyl-CoA production. In both conditions, ketones bypass the transport/enzyme defect as acetoacetyl-CoA and provide acetyl-CoA.

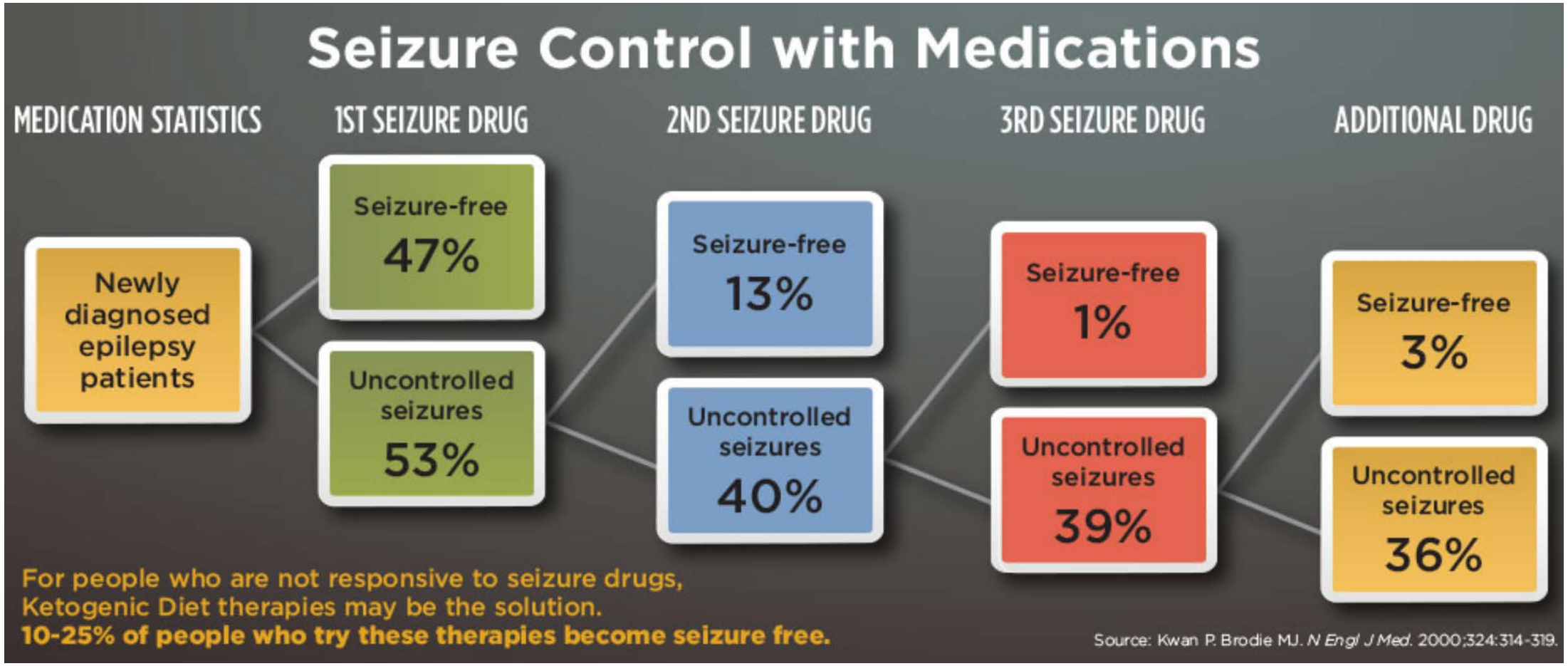


(fonte: Gano et al 2014)

Ketogenic diet and Epilepsy

Ketogenic diet and Epilepsy

Why?



KDA Ketogenic Diet ACADEMY

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TABLE 1.2

Outcomes of the Ketogenic Diet: Johns Hopkins Patients, 1998

NUMBER INITIATING	SEIZURE CONTROL AND DIET STATUS	TIME AFTER STARTING THE DIET		
		3 MONTHS	6 MONTHS	12 MONTHS
Total: N = 150	100% seizure free	4 (3%)	5 (3%)	11 (7%)
	> 90%	46 (31%)	43 (29%)	30 (20%)
	50%-90%	39 (26%)	29 (19%)	34 (23%)
	< 50%	36 (24%)	29 (19%)	8 (5%)
	Continued on diet	125 (83%)	106 (71%)	83 (55%)
	Discontinued diet	25 (17%)	44 (29%)	67 (45%)

Source: From Freeman JM, Vining EPG, Pillas DJ, et al. The efficacy of the ketogenic diet—1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998;102:1358–1363.

After 1 year of diet, the 50% of patients had at least a 50% reduction of attaks

Ketogenic Diet (KD) in Adults

- Is KD effective also in adults? Which other indications? Are there pubblished evidences? It is a recent achivement?

Ketogenic Diet (KD) in Adults

- Is KD effective also in adults? Which other indications? Are there pubblished evidences? It is a recent achivement?

EPILEPSY IN ADULTS

RESULTS OF TREATMENT BY KETOGENIC DIET IN ONE HUNDRED CASES *

CLIFFORD J. BARBORKA, M.D.

ROCHESTER, MINN.

The largest study to date of the ketogenic diet for adults, published in *Archives of Neurology* in 1930.

Efficacy of and Patient Compliance with a Ketogenic Diet in Adults with Intractable Epilepsy: A Meta-Analysis

Fang Ye, Xiao-Jia Li, Wan-Lin Jiang, Hong-Bin Sun, Jie Liu

Department of Neurology, Sichuan Provincial Academy of Medical Sciences & Sichuan Provincial People's Hospital, Chengdu, China

ORIGINAL ARTICLE

J Clin Neurol 2015;11(1):26-31

Studies of Effectiveness of Ketogenic Diets in Adults

AUTHOR	YEAR	NO. OF ADULTS	DIET	AGE RANGE	SEIZURES	SEIZURE FREE
Barborka	1928	48	KD	18-45	17 (35%)	7 (15%)
Barborka	1930	81	KD	18-56	47 (58%)	11 (14%)
Schlf	1998	1	MCT	20	1 (100%)	1 (100%)
Sirven	1999	11	KD	19-45	7 (88)%	0 (0%)
Kossoff	2003	3	Atkins	18-52	1 (33%)	0 (0%)
Kossoff	2008	30	MAD	18-53	15 (50%)	1 (3%)
Carrette	2008	8	MAD	30-54	3 (38%)	0 (0%)
Mosek	2009	9	KD	18-45	2[a] (22%)	0 (0%)
Klein	2010	12	KD	25-65	10 (83%)	1 (8%)
Smith	2011	18	MAD	18-55	3 (17%)	0 (0%)
Cervenka	2012	25	MAD	18-66	6 (24%)	1 (4%)
Lambrechts	2012	15	KD	18-40	3 (20%)	0 (0%)
Kossoff	2012	6[b]	MAD	18-44	4 (67%)	1 (17%)
Ramm-Pettersen	2013	2	MAD	18-51	2 (100%)	1 (50%)
Nei	2014	28[c]	KD	18-51	15 (54%)	1 (4%)

*All other patients stopped the study before the 12-week endpoint.
[b]Initial study of eight patients included two teenage girls whose results were not included in this table.
[c]Initial study of 29 patients included one 11-year-old girl whose results were not included in this table, following communication with the author.

Ketogenesis
and
Migraine

KD and Migraine

History

1928

An Experience with a Ketogenic in Migraine*

By Truman G. Schnabel, M.D., Philad

THE practice of dietary restriction for the control of hemicranial attacks is well known and doubtless dates back to a time when men or perhaps more often women first experienced such crises. Some migraine victims, long before consulting a physician, have learned to associate their sickness with the ingestion of certain foods and have accordingly omitte them from their dietary often w satisfactory results. The practice been further extended by phys who interdict for their patie nearly as feasibility permits of the three great food grou this course has undoubtedl gested by patients ther they have offered the o an increased intake of drates, proteins, or f lowed by sick head striction in one of food has seemin fit. Here and own initiativ dividuals h longed or p headaches not w fect as it would seem a

who have Up to planatio appar or p tro

*Read before the American Colle Physicians, March 8, 1928, New Orleans, La.

341

1930

Volume 91 Number 24

KETOGENIC DIET—BA

MIGRAINE

RESULTS OF TREATMENT BY KETOGENIC DIET IN FIFTY CASES *

CLIFFORD J. BARBORKA, M.D.

ROCHESTER, MINN.

Early in my experience with the ketogenic diet,[1] it was tried in cases of migraine. Since then Lennox and Cobb,[2] in their monograph on epilepsy, have stated that it would be of interest to know whether the induction of acidosis is of benefit in cases of migraine. Since the original report from the Mayo Clinic,[3] Schnabel[4] has reported his experience with a ketogenic diet in cases of migraine.

Some of the recent etiologic theories and therapeutic suggestions are of interest in considering the justification of a ketogenic regimen in cases of migraine. R. and S. Weissmann-Netter[5] found apparent changes in the acid-base balance: the hydrogen ion concentration and alkali reserve are normal in the periods of freedom from

attention an effort The su nomenon and his as lactic man the work in others hav of an alle posed the with intoleri theory. Th from the us proteins. Chiray,[13] and Huntsin problem from liver and duo biliary stasis a ture has emph is presented of

TABLE 1.—Observations on Patients Whose Conditions

Case	Age	Sex*	Attacks Before Treatment	Disease, Years	On Diet, Months
1	28	♀	About once a week, lasting two to three days	13	21
2	26	♀	Twice a week, lasting about two days	19	7
3	29	♀	Two to three time a week, lasting twelve to eighteen hours	19	20
4	27	♀	Once a week, lasting twelve to thirty-six hours	27	9
5	23	♀	Two to three a month, lasting two to three days	6	23
6	44	♀	At least two a month	26	16
7	21	♀	One to two a week, lasting several hours	4	14
8	50	♀	One to two a week, lasting one to two days, sometimes at thirty-eight; no alteration in attacks	23	16
9	23	♀	Cyclic vomiting beginning at age of two years; migraine at 14; attacks about every five to six weeks	21	13
10	31	..	One to two a week	21	19
11	30	♀	Three to six weeks	17	13
12	27	♀	One to three a week lasting about twelve hours	14	9
13	54	♂	Cyclic migraine thirty-eight years; abdominal migraine last two years	8	36
14	35	♀	Every two to four weeks	8	9

* In the tables, ♂ indicates male; ♀, female.

2006

182

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1. *BusinessWeek.* September 5, 2005; 78.
2. Silberstein SD, Neto W, Schmitt J, Jacobs D. Topiramate in migraine prevention. *Arch Neurol.* 2004;61:490-495.

Can Ketosis Help Migraine Sufferers? A Case Report

The ketogenic diet has long been used in the treatment of severe epilepsy in children, adolescents, and adults and seems to be well tolerated.[1,2,3] Even less stringent diets, such as the Atkins diet, have shown promise in the treatment of seizures and have been shown to have antidepressant properties.[4,5]

My wife began having severe headaches in elementary school. The headaches worsened during her teenage years and were officially diagnosed as migraines. The family history is significant for severe migraines on the paternal side. The migraines were described as a "throbbing, burning, hot knife" sensation in one temple. During her adulthood, the headaches progressed and were occurring many times a week. She tried multiple lifestyle changes without any change in the frequency of the headaches. Exercise, dieting, and two pregnancies did not alter the frequency.

Numerous medications were prescribed by neurologists over the years. Agents that helped the most included Imitrex, Amerge, and Floricet. Pharmacy profiles show that in 2004, at the age of 43, the patient was filling prescriptions about every 6 weeks for: Imitrex 50 mg #18, Amerge 2.5 mg #9, and Fioricet #30.

In an effort to lose the weight gained during pregnancy, the patient enrolled in a diet program under medical supervision. Patients undergo a modified fast, taking 3 to 4 high-protein, low-carbohydrate shakes a day. Each shake is 200 calories, and the shakes are the sole calorie source. Ketosis is

Upstate Medical University
Syracuse, NY

January 2006

induced and monitored on a weekly basis. A caloric restriction of 600 to 800 calories per day is maintained. Blood pressure, blood chemistries, and electrocardiograms are monitored regularly. Most patients stay in ketosis for 4 months or longer, depending on how much weight needs to be lost.

After going into ketosis, my wife went from having almost daily headaches to being completely free of migraines. Her last migraine was in late April, 2004. She maintained ketosis and the modified fast for almost 7 months and then went off her fast and began to eat regular foods. She has continued to be headache-free. She has now gone from daily migraines to going 14 months without an attack and has gradually reintroduced trigger foods such as alcohol and chocolate without getting a headache.

In conclusion, ketosis appears to have cured my wife's migraines. Other refractory migraine sufferers might be willing to enter a period of ketosis to rid them of their headaches. This letter is submitted with the hope of stimulating further research to confirm the benefits of a ketogenic diet on migraines.

R. Scott Strahlman, MD
Department of Pediatrics
Columbia Medical Practice
Columbia, MD, 21045
The Johns Hopkins Hospital
Baltimore, MD, 21205

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2. Mady MA, et al. The ketogenic diet: adolescents can do it, too. *Epilepsia.* 2003;44:847-851.
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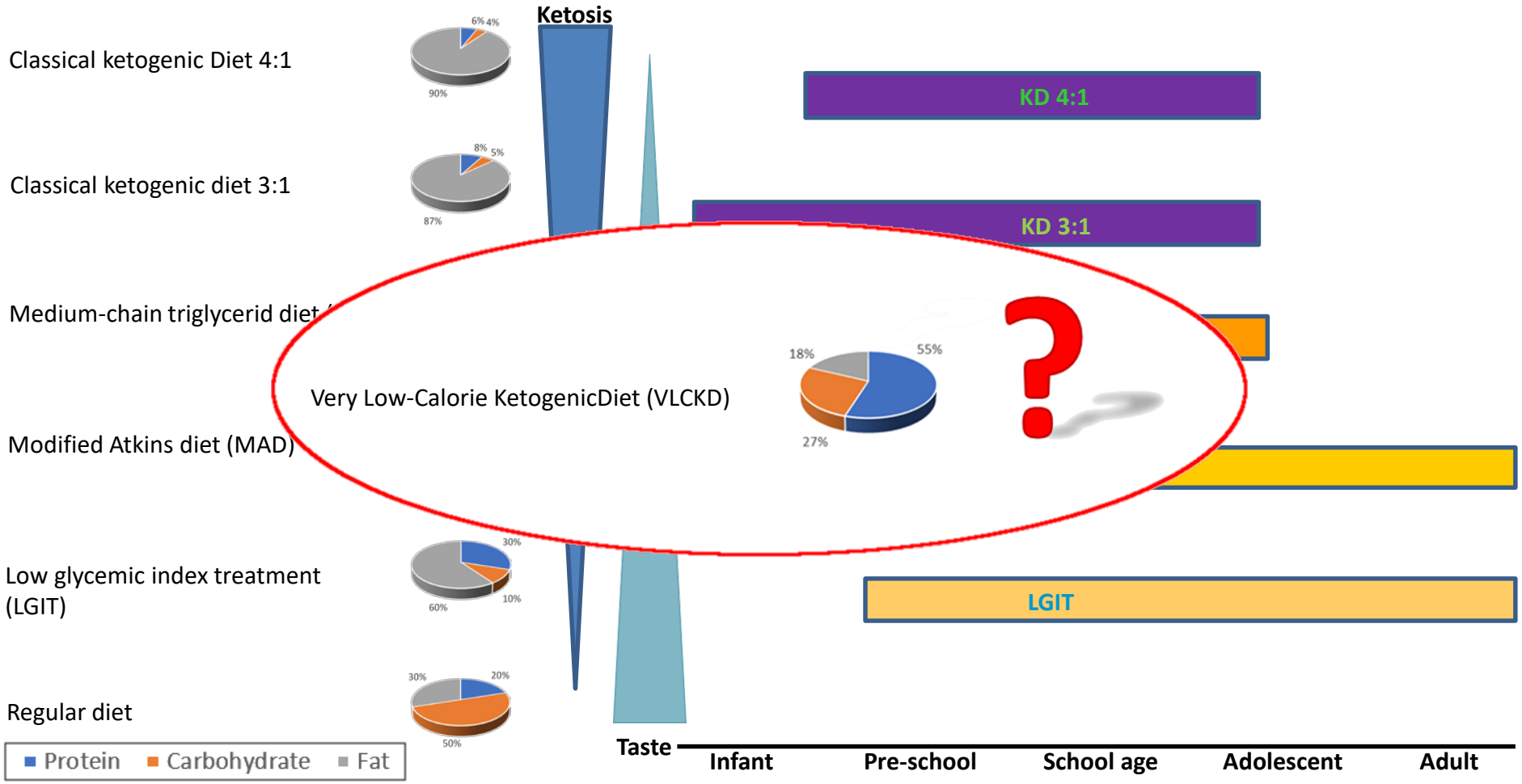
5. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. *Biol Psychiatry.* 2004;56:981-983.


Ketosis
Classical ketogenic Diet 4:1
6%
4%
90%
KD 4:1
Classical ketogenic diet 3:1
8%
5%
87%
KD 3:1
Medium-chain triglycerid diet
Very Low-Calorie KetogenicDiet (VLCKD)
18%
55%
27%
Modified Atkins diet (MAD)
Low glycemic index treatment (LGIT)
30%
10%
60%
LGIT
Regular diet
30%
20%
50%
Protein
Carbohydrate
Fat
Taste
Infant
Pre-school
School age
Adolescent
Adult

KDA Ketogenic Diet ACADEMY

Diet transiently improves migraine in two twin sisters: possible role of ketogenesis?

Functional Neurology 2013; 28(4): 305-308

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Patient Zero

Cherubino Di Lorenzo, PhD[a]
Antonio Currà, PhD[b]
Giulio Sirianni, MD[c]
Gianluca Coppola,PhD[d]
Martina Bracaglia, MD[e]
Alessandra Cardillo, MD[b]
Lorenzo De Nardis, MD[b]
Francesco Pierelli, MD[f]

[a] Don Carlo Gnocchi Onlus Foundation, Milan, Italy
[b] Department of Medical-Surgical Sciences and Biotechnologies, A. Fiorini Hospital, Terracina, LT, Sapienza University of Rome Polo Pontino, Latina, Italy
[c] Wellness Medicine, Krom Genetics Institute, Rome, Italy
[d] G.B. Bietti Foundation-IRCCS, Department of Neurophysiology of Vision and Neurophthalmology, Rome, Italy
[e] Department of Medical and Surgical Sciences and Biotechnologies and ICOT, "Sapienza" University of Rome Polo Pontino, Latina, Italy
[f] IRCCS Neuromed, Pozzilli (IS), Italy

Correspondence to: Cherubino Di Lorenzo
E-mail: cherub@inwind.it

Summary

The ketogenic diet is a high-fat, low-carbohydrate diet long used to treat refractory epilepsy; ketogenesis (ketone body formation) is a physiological phenomenon also observed in patients following low-carbohydrate, low-calorie diets prescribed for rapid weight loss.
We report the case of a pair of twin sisters, whose high-frequency migraine improved during a ketogenic diet they followed in order to lose weight.
The observed time-lock between ketogenesis and migraine improvement provides some insight into how ketones act to improve migraine.

KEY WORDS: ketogenic diet, migraine, prophylaxis, weight loss.

Pt1	Months											
Days	January	February	March	April	May	June	July	August	September	October	November	December
1	3		Diet on	2		Diet on			Diet on			
2	3			2	2	2						
3	3				3							
4					2						2	
5		2									2	
6		3			3		2			2		
7	2				3		3			3		
8	3	3			2					2		
9	3	3							1*			
10		3							1*			
11	3							2				
12	3				3			2				
13		2			2			2				
14		3		2								2
15		3		3							2	1
16	3										2	
17	3									2	2	
18	2	3								2		
19												
20												
21												
22	3	2										2
23		3					2					2
24		3					2					3
25		3										
26	2	2										
27	3							2				2
28	3		Diet off	2		Diet off		2	Diet off		2	3
29				3							2	
30				1				2				
31								2				
	6/15/1.3	5/14/1.4	0/0/0	3/7/0.5	3/8/0.7	1/1/0.1	2/4/0.3	3/7/0.5	1/2/0.1	2/5/0.3	3/7/0.5	3/7/0.5

ORIGINAL ARTICLE

Migraine improvement during short lasting ketogenesis: a proof-of-concept study

C. Di Lorenzo[a], G. Coppola[b], G. Sirianni[c], G. Di Lorenzo[d], M. Bracaglia[e], D. Di Lenola[e], A. Siracusano[d], P. Rossi[f,g] and F. Pierelli[h]

[a]Don Carlo Gnocchi Onlus Foundation, Milan; [b]Department of Neurophysiology of Vision and Neurophthalmology, G.B. Bietti Foundation – IRCCS, Rome; [c]Wellness and Dietary Medicine, Krom Genetics Institute, Rome; [d]Department of Systems Medicine, University of Rome 'Tor Vergata', Rome; [e]Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina; [f]Headache Clinic, INI, Grottaferrata, RM; [g]University Consortium for Adaptive Disorders and Head Pain (UCADH), Pavia; and [h]IRCCS – Neuromed, Pozzilli, IS, Italy

European Journal of Neurology 2015, **22:** 170–177

doi:10.1111/ene.12550

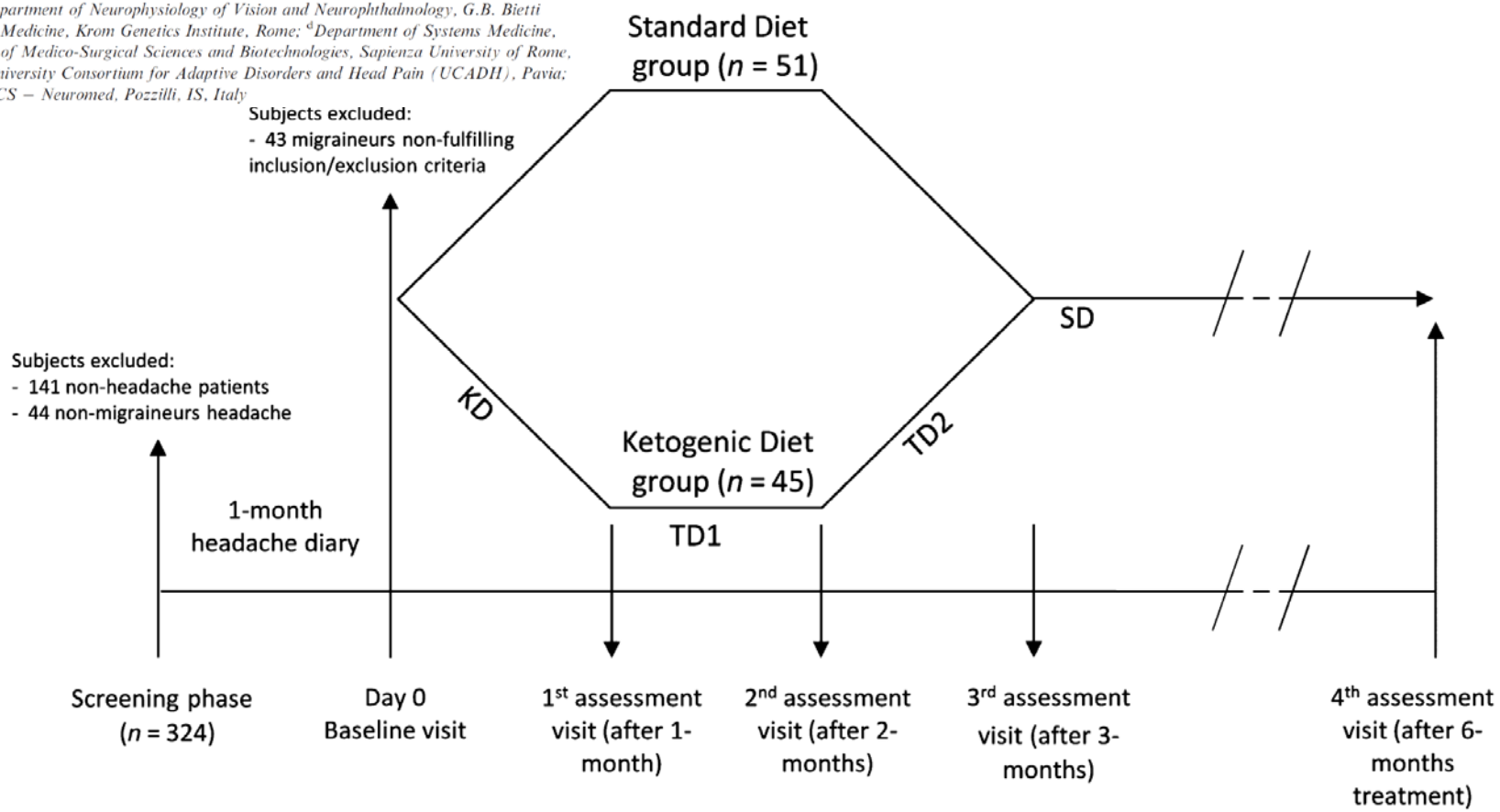

Figure 1 Outline of the study design. SD, standard low-calorie diet; KD, ketogenic very-low-calorie diet, supplemented by nutraceutical integrators; TD1, transitional diet supplemented by nutraceutical integrators; TD2, transitional diet without nutraceutical integrators.

European Journal of Neurology 2015, 22: 170–177

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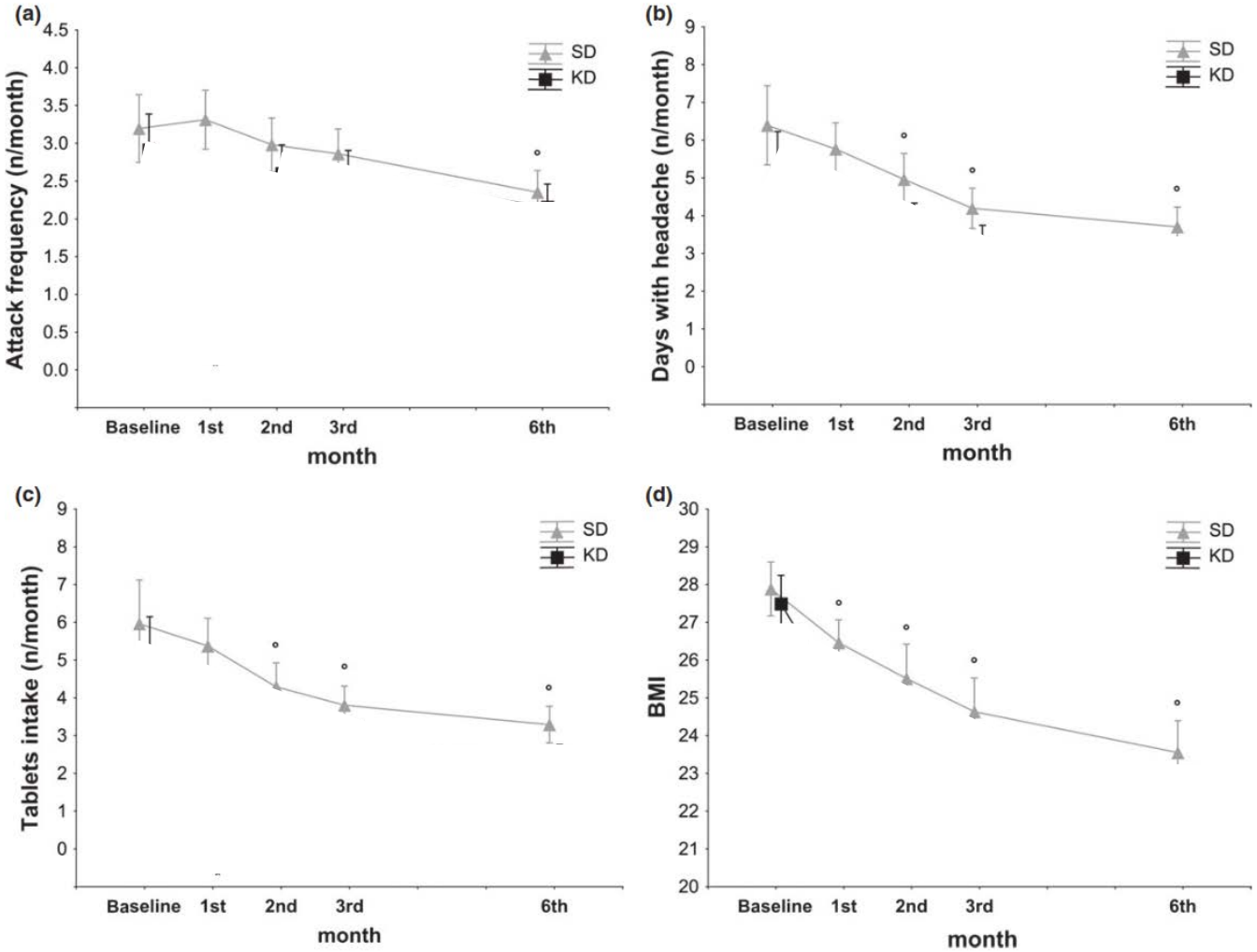

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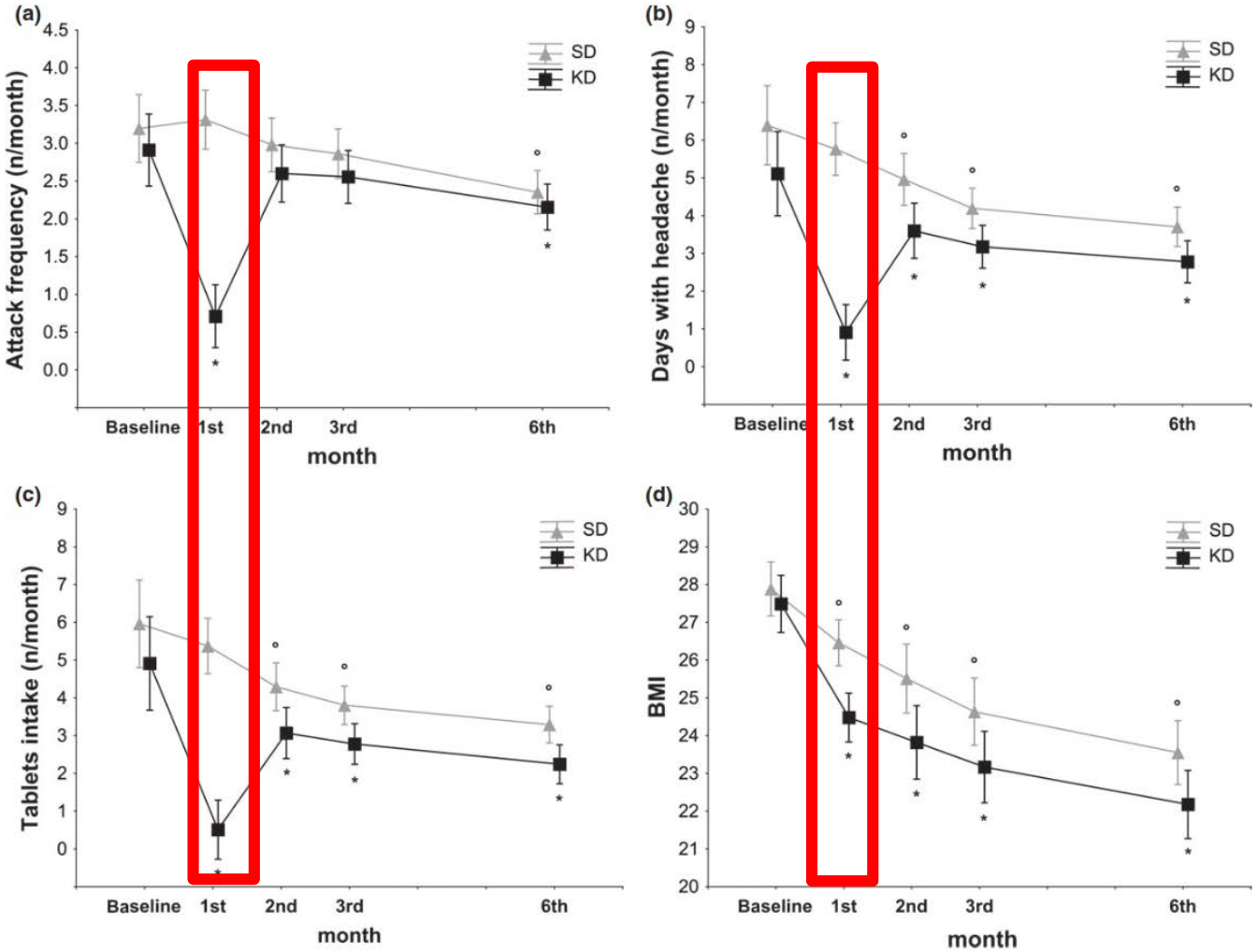

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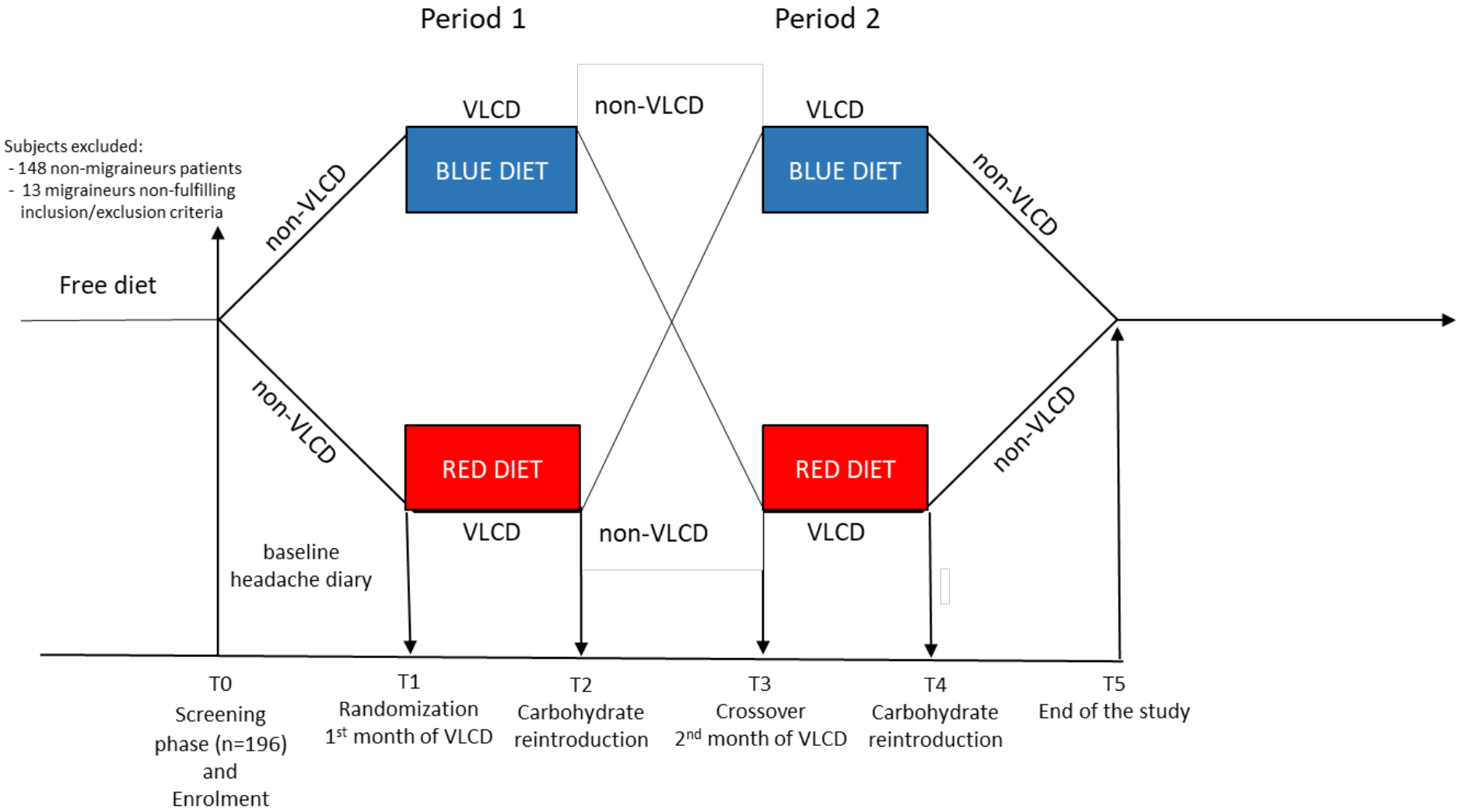
Article

A Randomized Double-Blind, Cross-Over Trial of very Low-Calorie Diet in Overweight Migraine Patients: A Possible Role for Ketones?

Cherubino Di Lorenzo [1,*], Alessandro Pinto [2], Roberta Ienca [2], Gianluca Coppola [3], Giulio Sirianni [4], Giorgio Di Lorenzo [5,6], Vincenzo Parisi [7], Mariano Serrao [2], Alessandra Spagnoli [8], Annarita Vestri [8], Jean Schoenen [9], Lorenzo M Donini [2] and Francesco Pierelli [2,10]



Nutrients **2019**, *11*, 1742; doi:10.3390/nu11081742

KDA Ketogenic Diet ACADEMY
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Article

A Randomized Double-Blind, Cross-Over Trial of very Low-Calorie Diet in Overweight Migraine Patients: A Possible Role for Ketones?

Cherubino Di Lorenzo [1,*], Alessandro Pinto [2], Roberta Ienca [2], Gianluca Coppola [3], Giulio Sirianni [4], Giorgio Di Lorenzo [5,6], Vincenzo Parisi [7], Mariano Serrao [2], Alessandra Spagnoli [8], Annarita Vestri [8], Jean Schoenen [9], Lorenzo M Donini [2] and Francesco Pierelli [2,10]

Results. Out 35 enrolled patients, six dropped at the first month of diet: all followed the “blue” diet; 29 completed the study.

Responder rate (number of patients with a headache frequency reduction ≤50%):
- 26 of 29 patients (74.28% of intention to treat (ITT) patients) responded to the “red diet”;
- 2 (5.7% of ITT patients) responded to the “blue diet”.

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When the blind was broken, we found out that the “red diet” was the ketogenic diet (VLCKD) and the “blue diet” was the non-ketogenic (VLCnKD).

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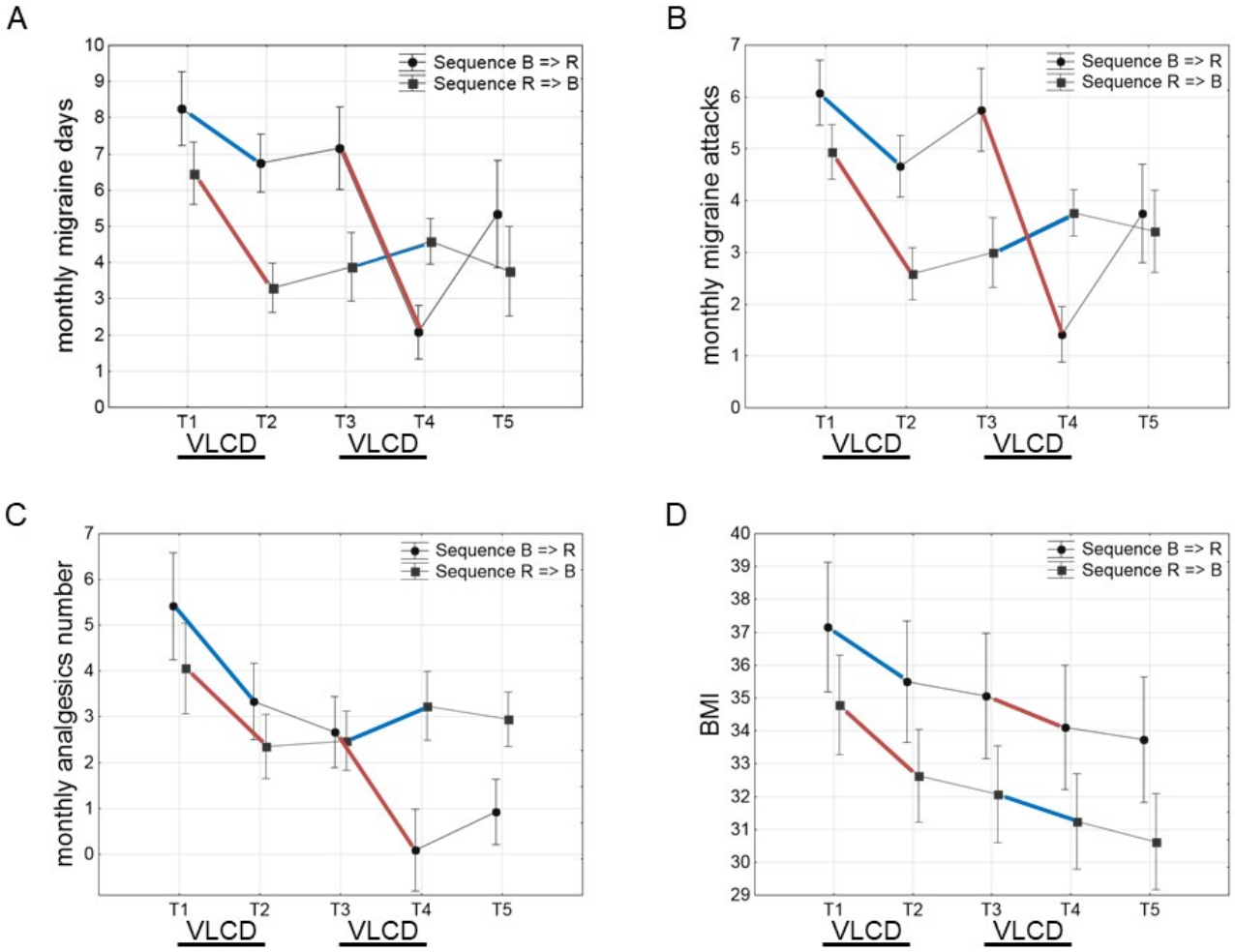

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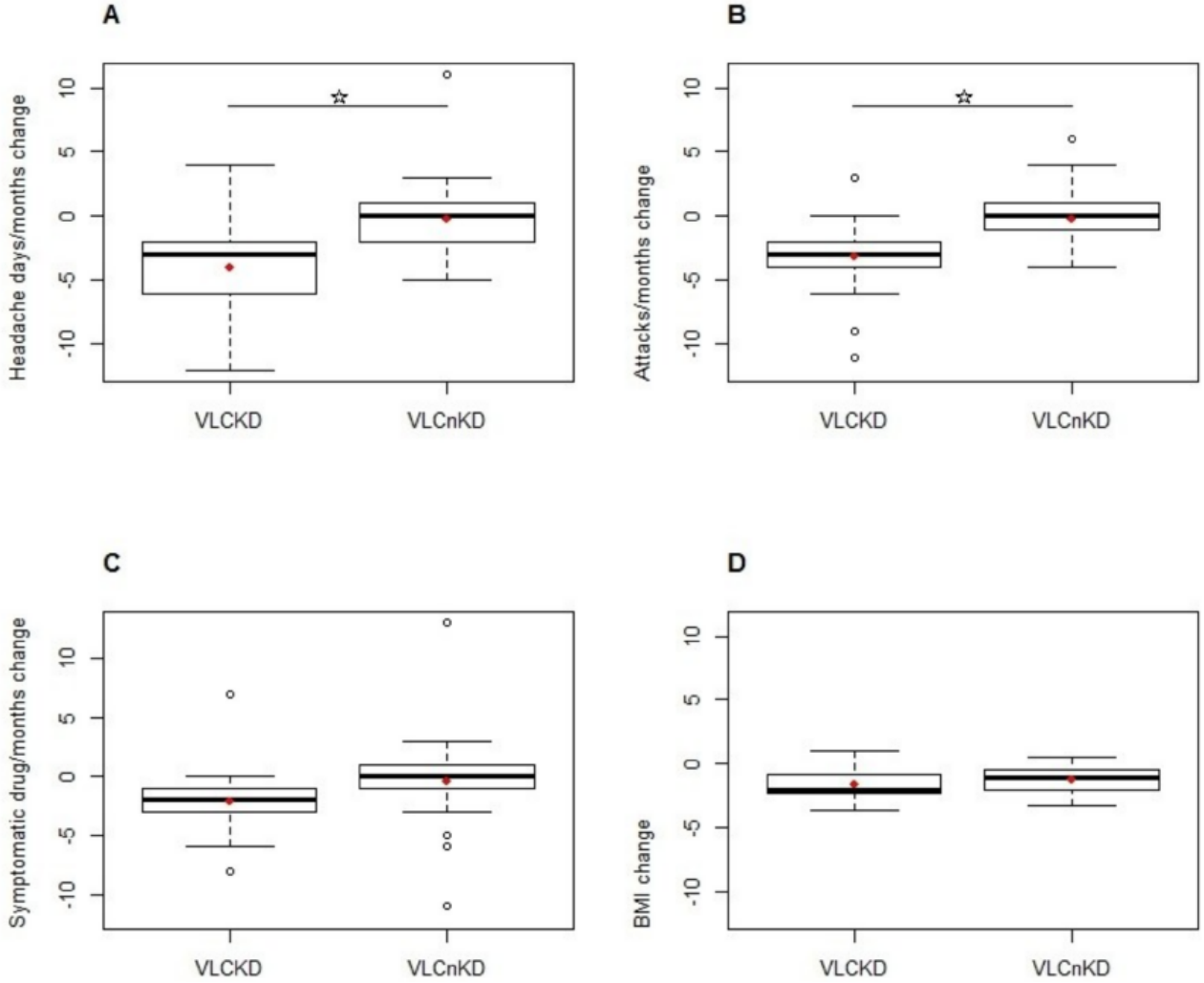

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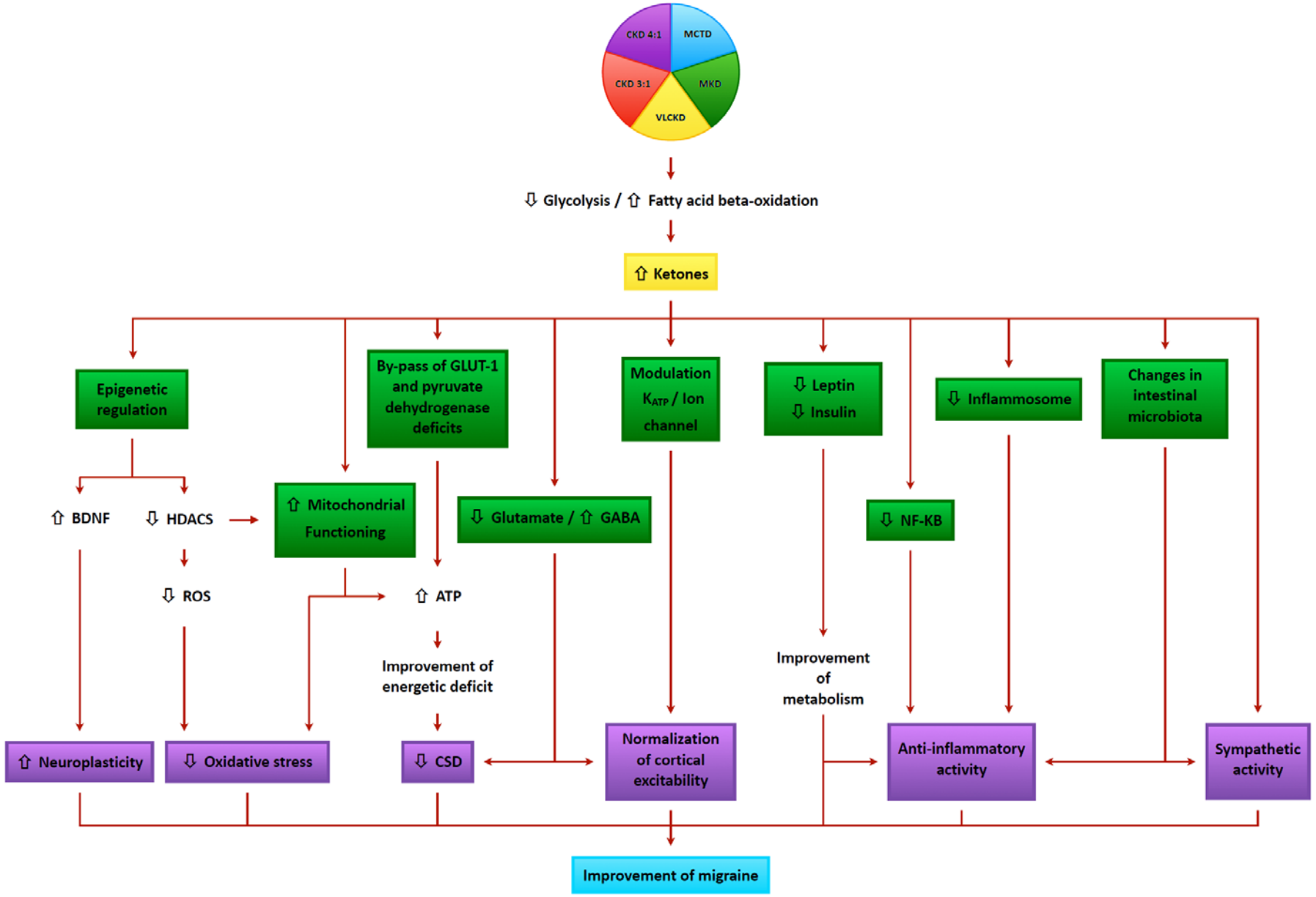
Number Needed to Treat (NNT)

$$\frac{1}{(\text{responders to VLCKD/Total patients}) - (\text{responders to VLCnKD/Total patients})}$$

(NNT = the number of patients who need a specific treatment compared to placebo to prevent one additional migraine attack)

NNT			
CGRP Monoclonal Antibodies	onabotulinumtoxinA	Topiramate	KD
3.2-5.9	8-12	4	2


CKD 4:1
MCTD
CKD 3:1
MKD
VLCKD
⇩ Glycolysis / ⇧ Fatty acid beta-oxidation
⇧ Ketones
Epigenetic regulation
By-pass of GLUT-1 and pyruvate dehydrogenase deficits
Modulation K_{ATP} / Ion channel
⇩ Leptin
⇩ Insulin
⇩ Inflammosome
Changes in intestinal microbiota
⇧ BDNF
⇩ HDACS
⇧ Mitochondrial Functioning
⇩ Glutamate / ⇧ GABA
⇩ NF-KB
⇩ ROS
⇧ ATP
Improvement of energetic deficit
Improvement of metabolism
⇧ Neuroplasticity
⇩ Oxidative stress
⇩ CSD
Normalization of cortical excitability
Anti-inflammatory activity
Sympathetic activity
Improvement of migraine

KD and Cluster headache (The suicide headache!)

Lifetime prevalence 124 per 100,000 (≅ 1‰)

1-year prevalence of 53 per 100,000

Overall sex ratio (M:F) 4.31:1

Episodic vs. Chronic CH ratio 6.0:1.

Chronic CH sex ratio (M:F) 15.0:1

Episodic CH sex ratio (M:F) 3.8:1

The worst pain of your life!

KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

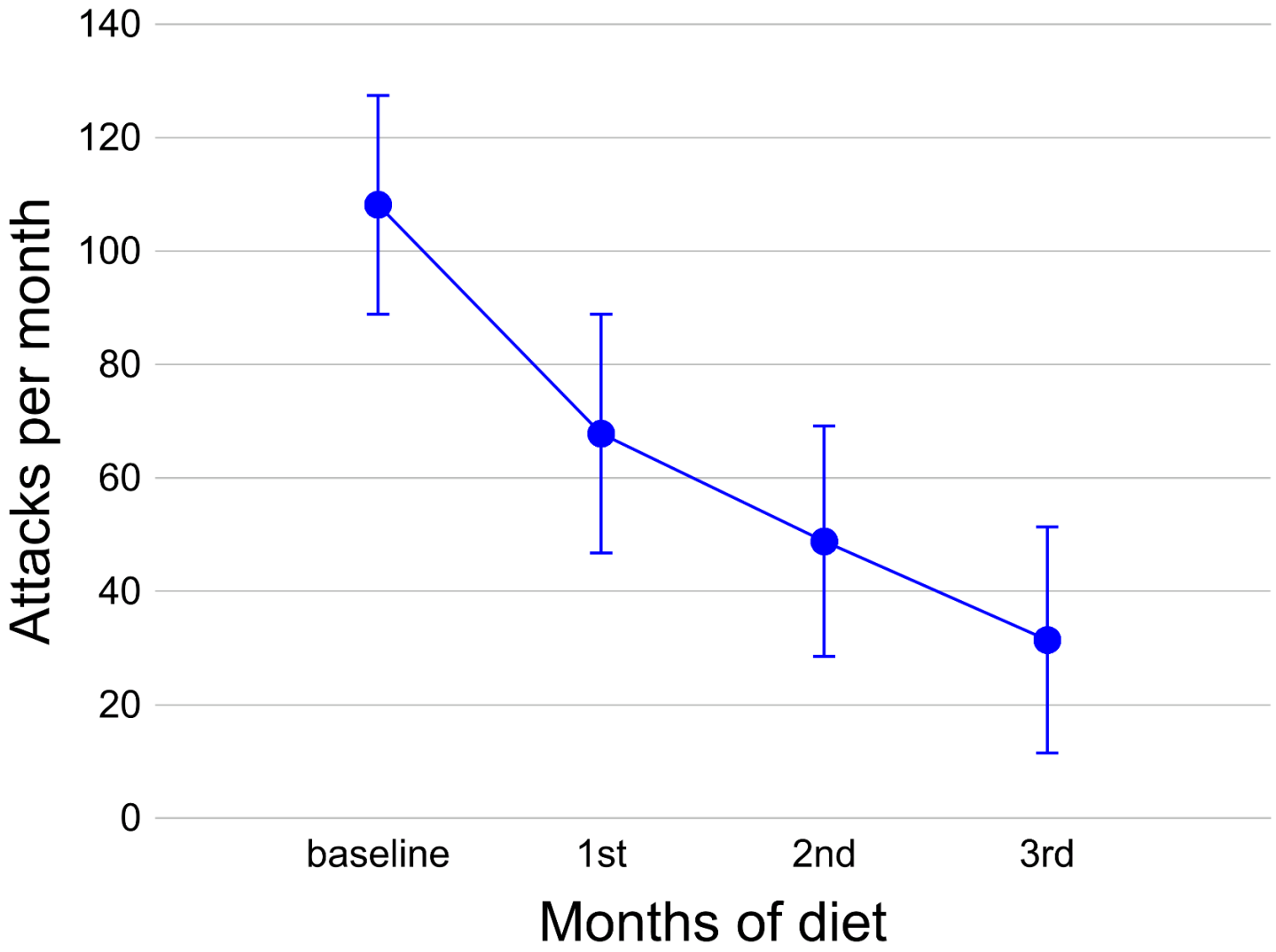
frontiers in Neurology

ORIGINAL RESEARCH
published: 12 February 2018
doi: 10.3389/fneur.2018.00064

Efficacy of Modified Atkins Ketogenic Diet in Chronic Cluster Headache: An Open-Label, Single-Arm, Clinical Trial

Cherubino Di Lorenzo[1], Gianluca Coppola[2], Davide Di Lenola[3], Maurizio Evangelista[4], Giulio Sirianni[5], Paolo Rossi[6], Giorgio Di Lorenzo[7], Mariano Serrao[3] and Francesco Pierelli[3,8]*

We enrolled 30 consecutive drug resistant (or not compliant) patients with cluster headache and propose them to follow a KD for at least 12 weeks.



Which kind of diet in adult patients?

Very low calorie ketogenic diet (VLCKD)
VS.
Classic or Modified ketogenic diet

Very low calorie diets (VLCDs)

- 400 (600 in Europe) – 800 Kcal/day
- Low carbohydrate: Ketogenic (**VLCKD**)
- Hihg carbohydrate: non-Ketogenic (**VLCnKD**)

VLCKD

- The vantages of KD + prolonged fasting
- Limits: duration

Diet discontinuation

- Reduces the ketogenic ratio (up to 1:1)
- Increase low GI carbohydrates, slowly
- Set with the patient the target diet
  - LOGIT?
  - Zone diet?
  - Mediterranean diet?
  - Never come back to high-carb diet, anyway

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nutrients

MDPI

Review

Applications of Ketogenic Diets in Patients with Headache: Clinical Recommendations

Cherubino Di Lorenzo [1,*], Giovanna Ballerini [2], Piero Barbanti [3,4], Andrea Bernardini [5], Giacomo D'Arrigo [6], Gabriella Egeo [3], Fabio Frediani [6], Riccardo Garbo [5], Giulia Pierangeli [7,8], Maria Pia Prudenzano [9], Nicoletta Rebaudengo [10], Grazia Semeraro [11], Giulio Sirianni [11], Mariarosaria Valente [5,12], Gianluca Coppola [1], Mackenzie C. Cervenka [13] and Giovanni Spera [14]

MONITORING				
Before starting	Every day	Every 6 months	Every 12 months	In case of non-response to KD
Complete blood count Glycemia*	Headache diaries	Complete blood count Glycemia*	BMD/DEXA Abdominal ultrasonography	Evaluation of ketones (blood, urine or breath)
Basal insulin	Eating diaries	Basal insulin		
OGTT (Glycemic level, Insulin level)		Total cholesterol		
Total cholesterol		LDL, HDL, Tg		
LDL, HDL, Tg		Direct bilirubin		
Direct bilirubin		Indirect bilirubin		
Indirect bilirubin		GOT e GPT Uricemia/Azotemia Creatininemia		
GOT e GPT Uricemia/Azotemia Creatininemia		Homocysteinemia Protein electrophoresis Na, K, Cl,		
Homocysteinemia Protein electrophoresis Na, K, Cl, Ca, P, Mg		Ca, P, Mg Folates		
Folates		Vitamin B12		
Vitamin B12		Vitamin D		
Vitamin D		Urinalysis		
Urinalysis		EKG		
EKG		Blood pressure		
Blood pressure		Weight		
Weight				

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SIDE EFFECTS		
COMMON	INFREQUENT	VERY INFREQUENT
Muscle cramps **Fatigue** **Hypotension** **Constipation** **Undesired weight loss**	Hyperlipidemia Gallbladder stones Menstrual irregularity Alopecia Nail fragility	Nausea Vomiting Abdominal pain Diarrhoea Prurigo pigmentosa (keto rash)* Mood disorders*

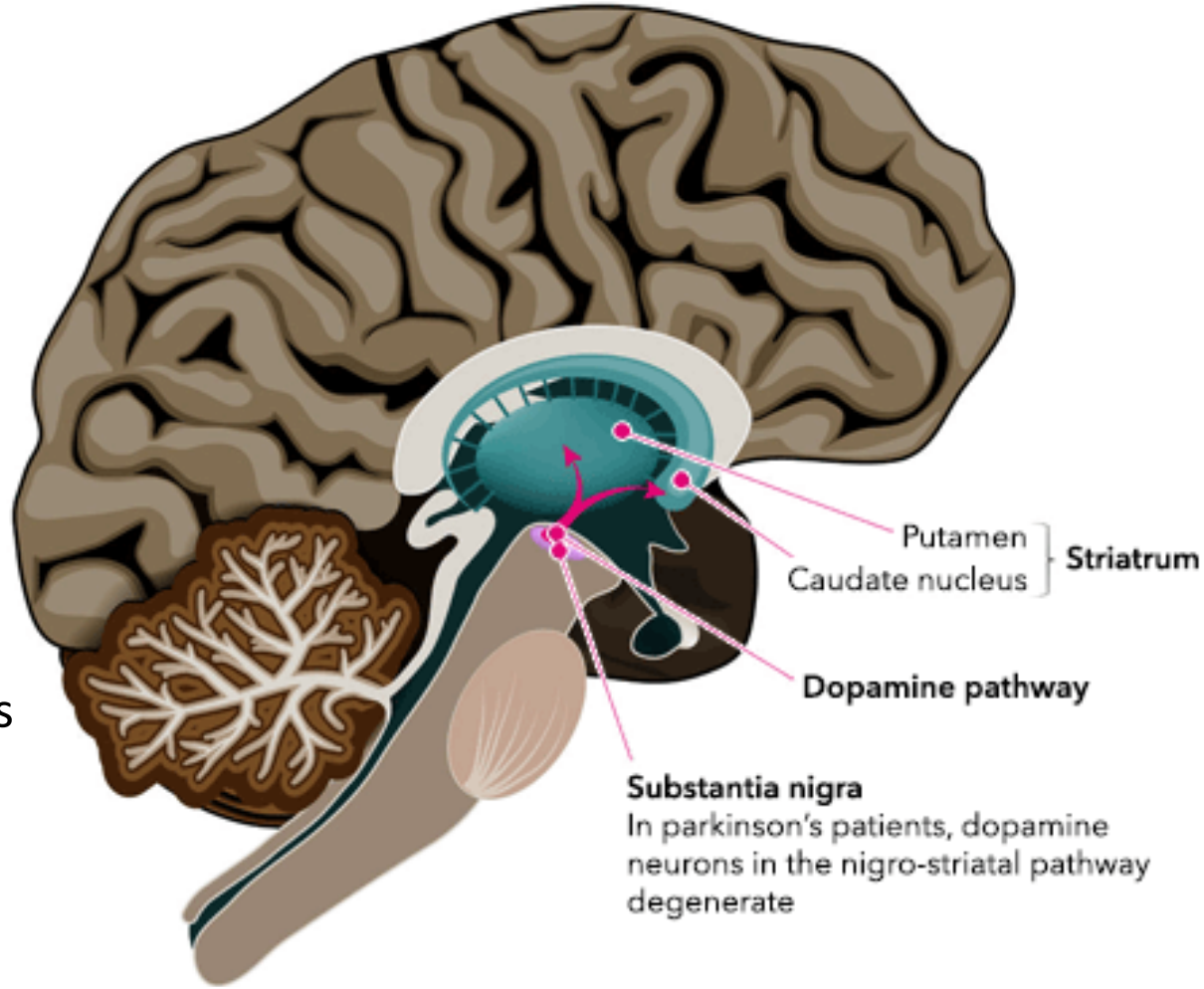
Ketogenesis
and
Neurodegenerative disorders

Ketogenesis in Parkinson Disease

Parkinson's Disease (PD) is a progressive neurological condition generally indicated by nerve cell damage and cell death. It results from a deterioration of dopamine producing cells in the brain (an area known as substantia nigra).

The specific cause of PD is believed to be genetic abnormalities and/or environmental triggers such as infections. These causes affect mitochondrial function by increasing oxidative stress in the body, which is believed to be a key driver in the deterioration of the dopamine producing cells in the brain.

Under normal conditions, when oxidative stress occurs in the body, there are systems that are available to help counteract the negative effects. However, when the system becomes over loaded (as in the case of PD), they are unable to deal with the pressure and so free radicals (also known as Reactive Oxygen Species; ROS) are formed which cause cell death and destruction.



Treatment of Parkinson disease with diet-induced hyperketonemia: A feasibility study

Abstract—Ketones may bypass the defect in complex I activity implicated in Parkinson disease (PD). Five of seven volunteers with PD were able to prepare a "hyperketogenic" diet at home and adhere to it for 28 days. Substituting unsaturated for saturated fats appeared to prevent cholesterol increases in four volunteers. Unified Parkinson's Disease Rating Scale scores improved in all five during hyperketonemia, but a placebo effect was not ruled out.

NEUROLOGY 2005;64:728–730

T.B. VanItallie, MD; C. Nonas, RD; A. Di Rocco, MD; K. Boyar, NP; K. Hyams, RD; and S.B. Heymsfield, MD

Table 2 *Unified Parkinson's Disease Rating Scale (UPDRS) scores in five patients with Parkinson disease (PD) at baseline and after 28 days* of adherence (final) to a hyperketogenic diet (total changes and changes by category)*

Patient no.	Mentation and mood	ADL	Motor function	Treatment complications	Totals	Decreases in total score, %
1	3.0/2.0	2.5/3.0	5.5/3.75	0/0	11.0/8.75	21
2	3.0/0.0	9.0/4.0	18.5/12.5	0/0	30.5/16.5	46
3	2.0/1.0	13.0/6.5	15.0/7.25	1.0/2.0†	31.0/16.75	46
4	3.0/3.25	4.0/3.0	6.25/5.0	6.5/4.0	19.75/15.25	23
5	3.0/0.5	7.0/0.75	9.75/1.00	3.0/2.0	22.75/4.25	81

Scores by category (baseline/final values). All patients were evaluated in their best "on" state.

* After 21 days in patient 4.

† Patient 3 reported feeling overmedicated with increased dyskinesia after 3 weeks on the hyperketogenic diet. Thus, at the end of her 4th week on the diet, her carbidopa/levodopa dose was reduced from 1,100 to 1,000 mg/day.

ADL = activities of daily living.

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Realtà Sannita

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Uno studio di Villa Margherita

Dieta chetogenica e malattia di Parkinson

Come è ormai noto, la dieta chetogenica, applicata sin dal lontano 1921 negli USA per il trattamento dell'epilessia farmaco-resistente, è diventata anche in Italia un trattamento di prima linea laddove i farmaci anticonvulsivi non sono più efficaci.

Tale dieta consiste in un apporto estremamente ridotto in carboidrati, elevato in grassi e normale in proteine. Negli ultimi 20 anni questo approccio si è dimostrato essere efficace nel trattamento di patologie quali epilessia, morbo di Alzheimer, morbo di Parkinson, sclerosi laterale amiotrofica, obesità, diabete di tipo I e II, dolore e processi infiammatori in generale, trauma cranico ed alcuni tra i tumori più invasivi.

Tali risultati sono stati osserne dei linfociti;

- riduzione dello stress ossidativo.

Negli ultimi dieci anni, la letteratura scientifica a sostegno delle proprietà benefiche della dieta chetogenica a carico del sistema nervoso è aumentata considerevolmente, lasciando tuttavia dei campi ancora inesplorati. Valutati nel loro insieme, i dati sperimentali ci portano a sostenere che lo stato metabolico della chetosi potrebbe essere di ampio beneficio in pazienti affetti dal morbo di Parkinson, agendo da stabilizzante bioenergetico, anche grazie all'assorbimento della L-Dopa. Inoltre, studi su modelli animali hanno evidenziato come uno dei metaboliti che si generano in corso di questo regime dietetico, il beta-idrossibutirrato, ricolti i dati demografici ed anamnestici, da quanto tempo sono affetti dalla patologia, il loro peso, altezza e indice di massa corporea. I criteri di esclusione principali saranno: stadi avanzati della malattia, utilizzo di Duodopa® (un gel a somministrazione intestinale continua a base di levodopa e carbidopa, somministrato per infusione intestinale), stitichezza acuta, comorbidità neurodegenerative o disturbi psichiatrici, precedenti di abuso di alcool o droghe, casi di trauma cranico, patologie a carattere cardiovascolare, epilessia concomitante e gravi segni di depressione.

Anche i pazienti diabetici saranno esclusi dallo studio.

I pazienti ammessi, saranno poi valutati per qualità della vita e scala dei sintomi non motori tramite analisi del movimento

RESEARCH ARTICLE

WILEY Biomedical Chromatography

A new validated HPLC method for the determination of levodopa: Application to study the impact of ketogenic diet on the pharmacokinetics of levodopa in Parkinson's participants

Fawzy Elbarbry[1] | Van Nguyen[1] | Alar Mirka[2] | Heather Zwickey[3] | Richard Rosenbaum[2]

[1] School of Pharmacy, Pacific University, Hillsboro, OR, USA

[2] Legacy Research Institute, Portland, OR

[3] Helfgott Research Institute, National University of Natural Medicine, Portland, OR, USA

Correspondence
Fawzy Elbarbry, School of Pharmacy, Pacific University, Hillsboro, OR, US 97123, P: (503) 352-7356.
Email: fawzy.elbarbry@pacificu.edu

Funding information
Legacy Good Samaritan Foundation

Abstract

A simple, accurate, and reproducible HPLC-UV method has been developed and validated for the quantification of levodopa (L-Dopa) in human plasma. The method involves a simple protein precipitation procedure to extract both L-Dopa and methyldopa, the internal standard. The chromatographic analysis was achieved on a Shimadzu LC 20A HPLC system equipped with a Zorbax Eclipse XDB C_{18} column and an isocratic mobile phase consisting of 20 mM KH_2PO_4 (pH 2.5) and methanol (95:5, v/v) run at a flow rate of 1 mL/min. The UV detection wavelength was set at 230 nm. The method exhibited good linearity ($R^2 > 0.999$) over the assayed concentration range (0.1–10 μg/mL) and demonstrated good intra- and inter-day precision and accuracy (relative standard deviations and the deviation from predicted values were <15%). This method was also successfully applied for studying the potential effect of ketogenic diet on the pharmacokinetics of L-Dopa in Parkinson's participants. Our data analysis indicates that ketogenic diet does not significantly affect the pharmacokinetics of L-Dopa.

KEYWORDS

HPLC, ketogenic diet, L-Dopa, Parkinsonism, pharmacokinetics, validation

RESEARCH ARTICLE

Low-Fat Versus Ketogenic Diet in Parkinson's Disease: A Pilot Randomized Controlled Trial

Matthew C.L. Phillips, MSc, FRACP,[1*] Deborah K.J. Murtagh,[2] Linda J. Gilbertson, BLitComm, PGCert(Nursing),[1]
Fredrik J.S. Asztely, PhD, FRACP[1,3] and Christopher D.P. Lynch, MD, FRACP[1]

	Low-fat group (n=23)			Ketogenic group (n=24)			
	Baseline	Week 8	Change	Baseline	Week 8	Change	*P* Value (between groups)
Part 1 (nonmotor daily living experiences)	8.96 ± 4.34	7.96 ± 6.56	**−0.99 ± 3.63**	11.15 ± 4.15	6.57 ± 4.09	**−4.58 ± 2.17**	<0.001
Part 2 (motor daily living experiences)	11.13 ± 5.59	9.80 ± 6.81	**−1.33 ± 3.28**	12.75 ± 5.30	9.62 ± 5.64	**−3.13 ± 4.01**	0.11
Part 3 (motor examination)	34.93 ± 13.40	26.36 ± 13.58	**−8.58 ± 5.50**	36.48 ± 13.29	30.20 ± 12.88	**−6.27 ± 4.07**	0.055
Part 4 (motor complications)	4.33 ± 4.44	3.54 ± 4.86	**−0.79 ± 2.71**	4.90 ± 3.95	3.33 ± 3.02	**−1.56 ± 2.45**	0.32
Weight (kg)	78.13 ± 19.45	73.26 ± 17.99	**−4.87 ± 2.47**	83.71 ± 19.38	79.34 ± 17.13	**−4.37 ± 3.00**	0.55
BMI	26.96 ± 6.35	25.28 ± 5.95	**−1.67 ± 0.79**	27.77 ± 5.29	26.31 ± 4.46	**−1.46 ± 1.01**	0.30
HbA1C (mmol/mol)	34.67 ± 5.22	34.18 ± 3.74	**−0.49 ± 2.72**	36.15 ± 8.60	34.72 ± 5.68	**−1.42 ± 4.12**	0.095
Triglycerides (mmol/L)	1.71 ± 0.88	1.45 ± 0.55	**−0.26 ± 0.74**	1.81 ± 1.18	1.71 ± 0.81	**−0.10 ± 0.63**	0.46
HDL (mmol/L)	1.51 ± 0.47	1.40 ± 0.38	**−0.11 ± 0.22**	1.50 ± 0.44	1.89 ± 0.75	**+0.40 ± 0.59**	<0.001
LDL (mmol/L)	2.74 ± 0.82	2.35 ± 0.77	**−0.40 ± 0.30**	2.73 ± 1.06	3.42 ± 1.37	**+0.70 ± 0.67**	<0.001
Total cholesterol (mmol/L)	5.03 ± 1.00	4.40 ± 0.93	**−0.63 ± 0.51**	5.03 ± 1.05	5.98 ± 1.39	**+0.94 ± 0.80**	<0.001
Urate (mmol/L)	0.30 ± 0.08	0.28 ± 0.08	**−0.02 ± 0.03**	0.30 ± 0.08	0.33 ± 0.08	**+0.03 ± 0.05**	<0.001
CRP (mmol/L)	2.95 ± 2.99	1.95 ± 1.79	**−1.00 ± 3.57**	1.95 ± 1.59	2.24 ± 1.26	**+0.29 ± 1.93**	0.10

Values are presented as mean ± standard deviation.
Bolded values highlight changes in scores and parameters; due to round-off, some change values differ by 0.01 from the absolute value differences.
P values refer to changes in scores and parameters between (not within) groups.

Movement Disorders, Vol. 33, No. 8, 2018

Ketogenesis in Dementia

Alzheimer (AD) as Type 3 Diabetes (a modern disease?)

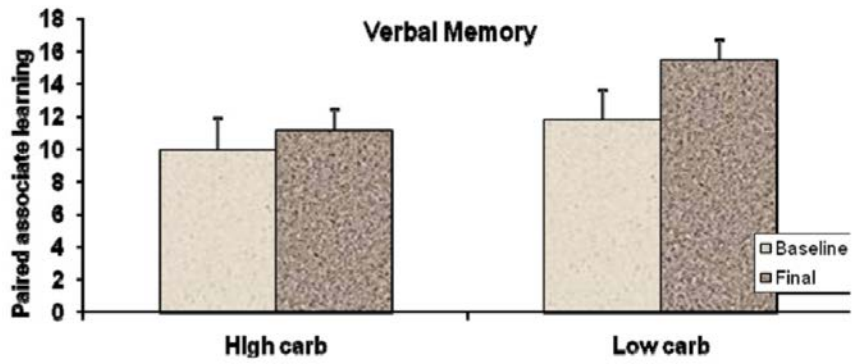
- Insulin resistance in the AD brain without diabetes.
- Alteration of insulin and IGF signaling in AD brain.
- Alteration of lipid metabolism in in AD brain.

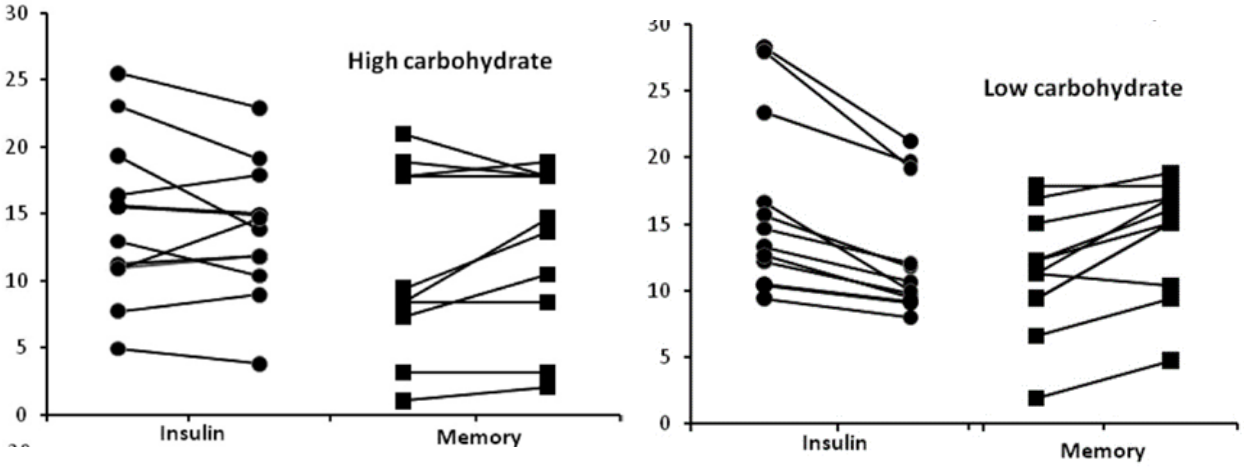
The first case:
Auguste Deter, 51 y.o.
(1906)

- Impaired glucose metabolism expose the brain to a chronic reduction of energetic substrates (neurodegeneration)
- Tau gene expression and phosforylation are regulated by insulin and IGF
- Amyloid beta deposits into the AD brain is similar to the amyloid protein found in pancreas of diabetic patients.

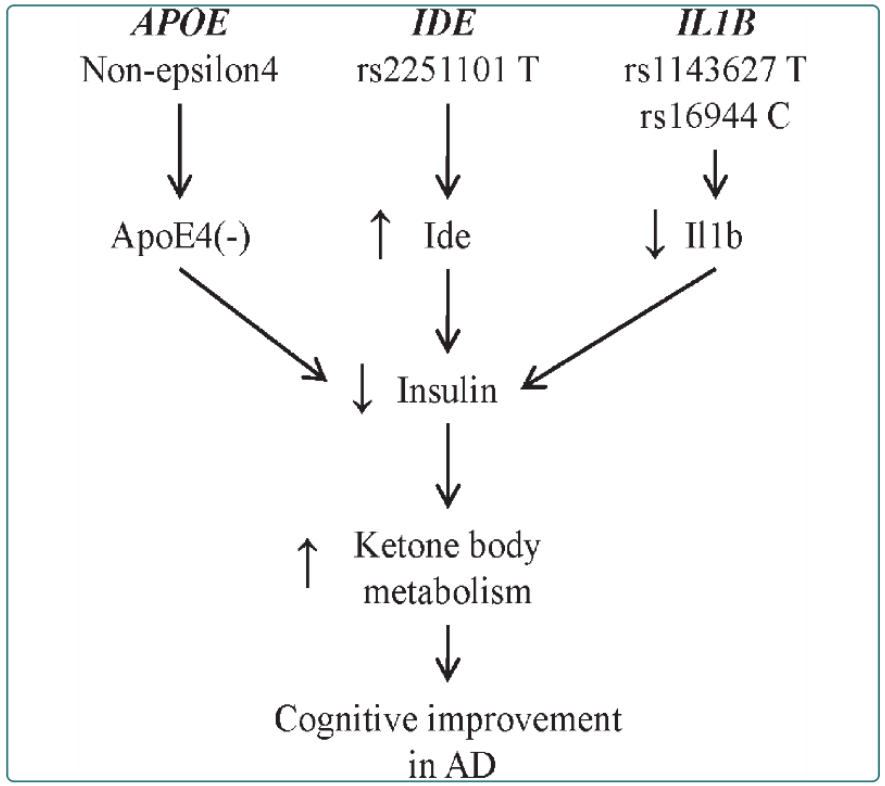
Dietary ketosis enhances memory in mild cognitive impairment

Robert Krikorian[a,*], Marcelle D. Shidler[a], Krista Dangelo[b], Sarah C. Couch[b], Stephen C. Benoit[a], Deborah J. Clegg[c]





R. Krikorian et al. / Neurobiology of Aging 33 (2012) 425.e19–425.e27



Pharmacogenetic analysis of the effects of polymorphisms in *APOE*, *IDE* and *IL1B* on a ketone body based therapeutic on cognition in mild to moderate Alzheimer's disease; a randomized, double-blind, placebo-controlled study

Henderson and Poirier

BioMed Central

Henderson and Poirier *BMC Medical Genetics* 2011, **12**:137
http://www.biomedcentral.com/1471-2350/12/137 (12 October 2011)

ELSEVIER

Neurobiology of Aging 25 (2004) 311–314

NEUROBIOLOGY OF AGING

www.elsevier.com/locate/neuaging

Brief communication

Effects of β-hydroxybutyrate on cognition in memory-impaired adults

Mark A. Reger[a,b], Samuel T. Henderson[c], Cathy Hale[d], Brenna Cholerton[a,b], Laura D. Baker[a,b], G.S. Watson[a,b], Karen Hyde[a], Darla Chapman[a], Suzanne Craft[a,b,*]

[a] Geriatric Research, Education and Clinical Center, Veterans Affairs Puget Sound Health Care System, 1660 South Columbian Way, S-182-GRECC, Seattle, WA 98108-1532, USA

[b] Department of Psychiatry and Behavioral Sciences, University of Washington School of Medicine, Seattle, WA 98195, USA

[c] Accera, Inc., Aurora, CO 80010, USA

[d] Department of Psychology, University of Puget Sound, Tacoma, WA, USA

Received 24 September 2002; received in revised form 30 January 2003; accepted 27 March 2003

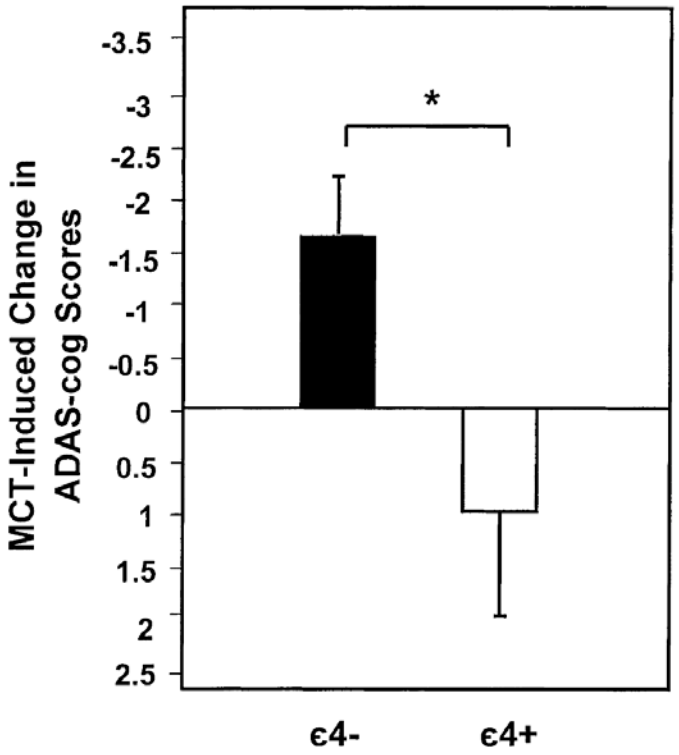


Fig. 1. ADAS-cog mean change with MCT treatment; benefits of treatment depended on $\varepsilon 4$ status ($^{*}P = 0.039$). Note: negative scores indicate improvement on the ADAS-cog.

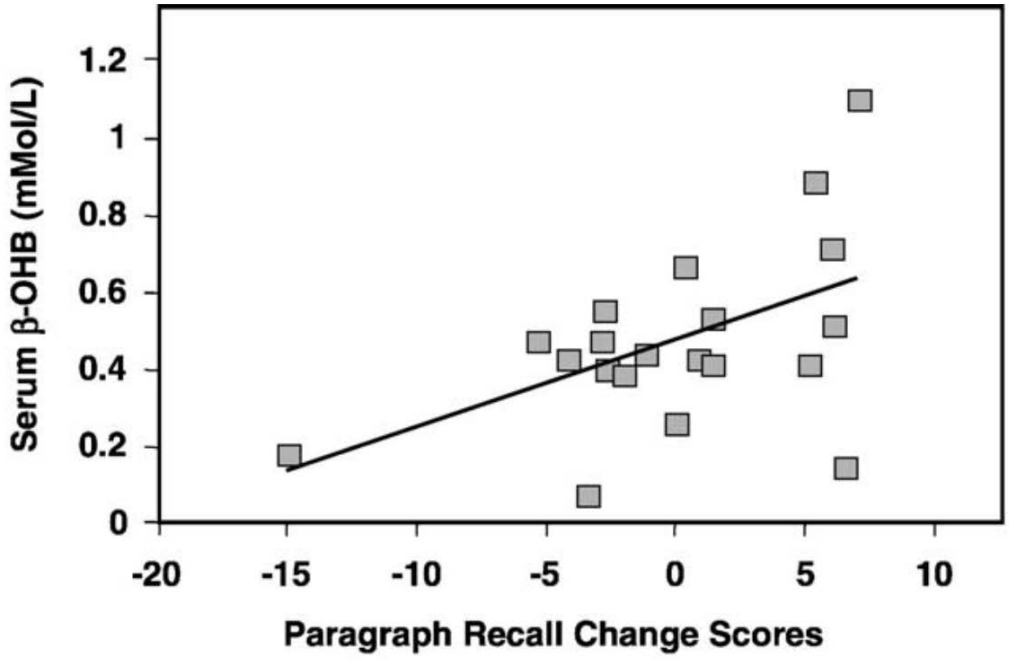


Fig. 2. Relationship between β-OHB levels at the time of cognitive testing and the change in paragraph recall following MCT treatment; $r = 0.50$, $P = 0.02$.

BBA Clinical 3 (2015) 123–125

Contents lists available at ScienceDirect

BBA Clinical

journal homepage: http://www.journals.elsevier.com/bba-clinical/

Commentary

Pilot feasibility and safety study examining the effect of medium chain triglyceride supplementation in subjects with mild cognitive impairment: A randomized controlled trial

Candida J. Rebello[a,b], Jeffrey N. Keller[a], Ann G. Liu[a], William D. Johnson[a], Frank L. Greenway[a,*]

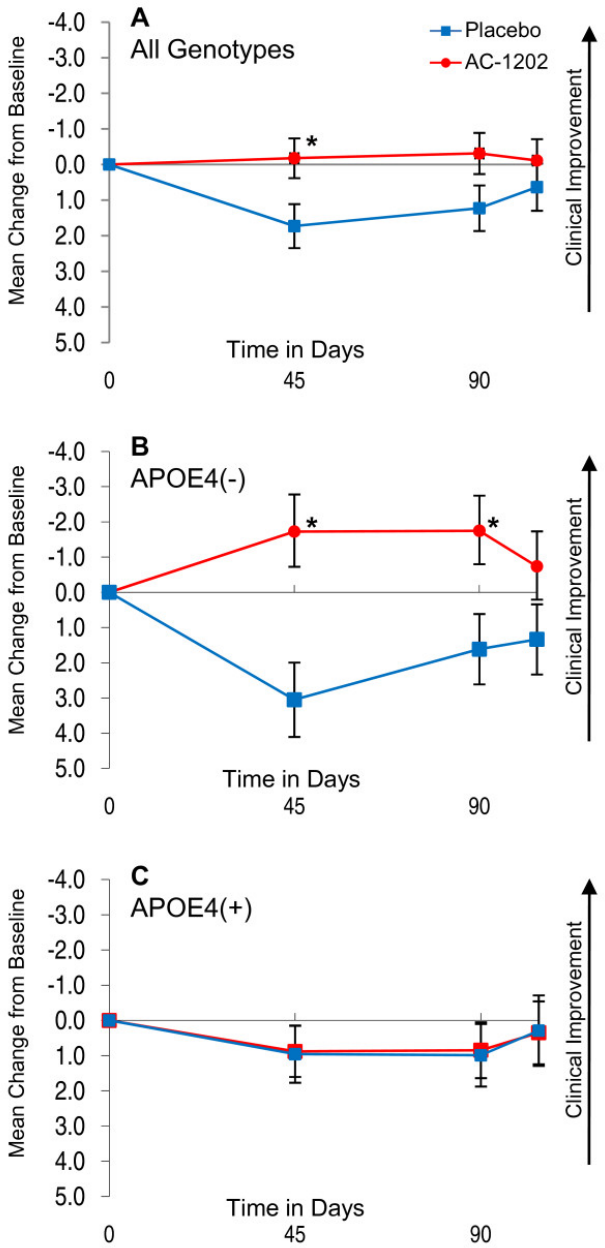
[a] Pennington Biomedical Research Center, Louisiana State University System, 6400 Perkins Road, Baton Rouge, United States
[b] School of Nutrition and Food Sciences, Louisiana State University, Baton Rouge, United States

Results: Intake of MCT oil increased serum ketone bodies and improved memory, while intake of placebo did not show improvement in any of the cognitive measures tested.

Conclusions: Consumption of 56 g/day of MCTs for 24 weeks increases serum ketone concentrations and appears to be a candidate for larger randomized control trials in the future that quantify the modulation of cognitive function through supplementation with ketone precursors, in patients with MCI.

Study of the ketogenic agent AC-1202 (that increases BHB levels in blood) in mild to moderate Alzheimer's disease: a randomized, double-blind, placebo-controlled, multicenter trial

[Henderson et al., 2009]



Mean change in ADAS-Cog scores from Baseline in the ITT population w/LOCF and stratified by APOE4 carriage status. Y axis is change from Baseline. X axis is time in days. Red circles and lines represent subjects taking AC-1202. Blue squares and lines represent subjects taking Placebo. Error bars represent standard error of the mean. Asterisks (*) indicate a significant (p-value < 0.05) difference in mean change from Baseline between AC-1202 and Placebo. **A)** Intention to treat subjects (N = 77AC, N = 63PL) administered AC-1202 demonstrate a significant difference from Placebo at Day 45. **B)** Genotyped subjects lacking the APOE4 allele (APOE4(-)) (N = 29AC, N = 26PL) and administered AC-1202 demonstrate a significant difference from Placebo at Days 45 and 90. **C)** Genotyped subjects carrying the APOE4 allele (APOE4(+)) (N = 38AC, N = 31PL) do not differ from Placebo at any time point.

Phillips *et al. Alzheimer's Research & Therapy* (2021) 13:51
https://doi.org/10.1186/s13195-021-00783-x

Alzheimer's Research & Therapy

KDA Ketogenic Diet ACADEMY

SINut Società Italiana di Nutraceutica

RESEARCH Open Access

Randomized crossover trial of a modified ketogenic diet in Alzheimer's disease

Matthew C. L. Phillips[1*], Laura M. Deprez[1,2], Grace M. N. Mortimer[3], Deborah K. J. Murtagh[3], Stacey McCoy[4], Ruth Mylchreest[1], Linda J. Gilbertson[1], Karen M. Clark[1], Patricia V. Simpson[1], Eileen J. McManus[1], Jee-Eun Oh[1], Satish Yadavaraj[1], Vanessa M. King[5], Avinesh Pillai[6], Beatriz Romero-Ferrando[1], Martijn Brinkhuis[7], Bronwyn M. Copeland[8], Shah Samad[9], Shenyang Liao[9] and Jan A. C. Schepel[1]

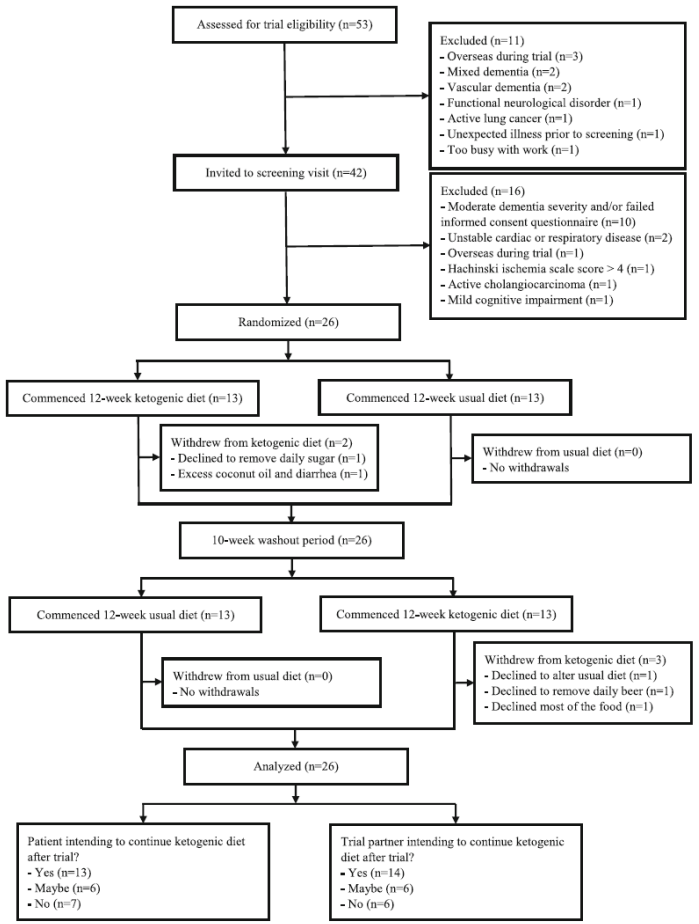


Fig. 1 Patient flow, showing all exclusions and withdrawals

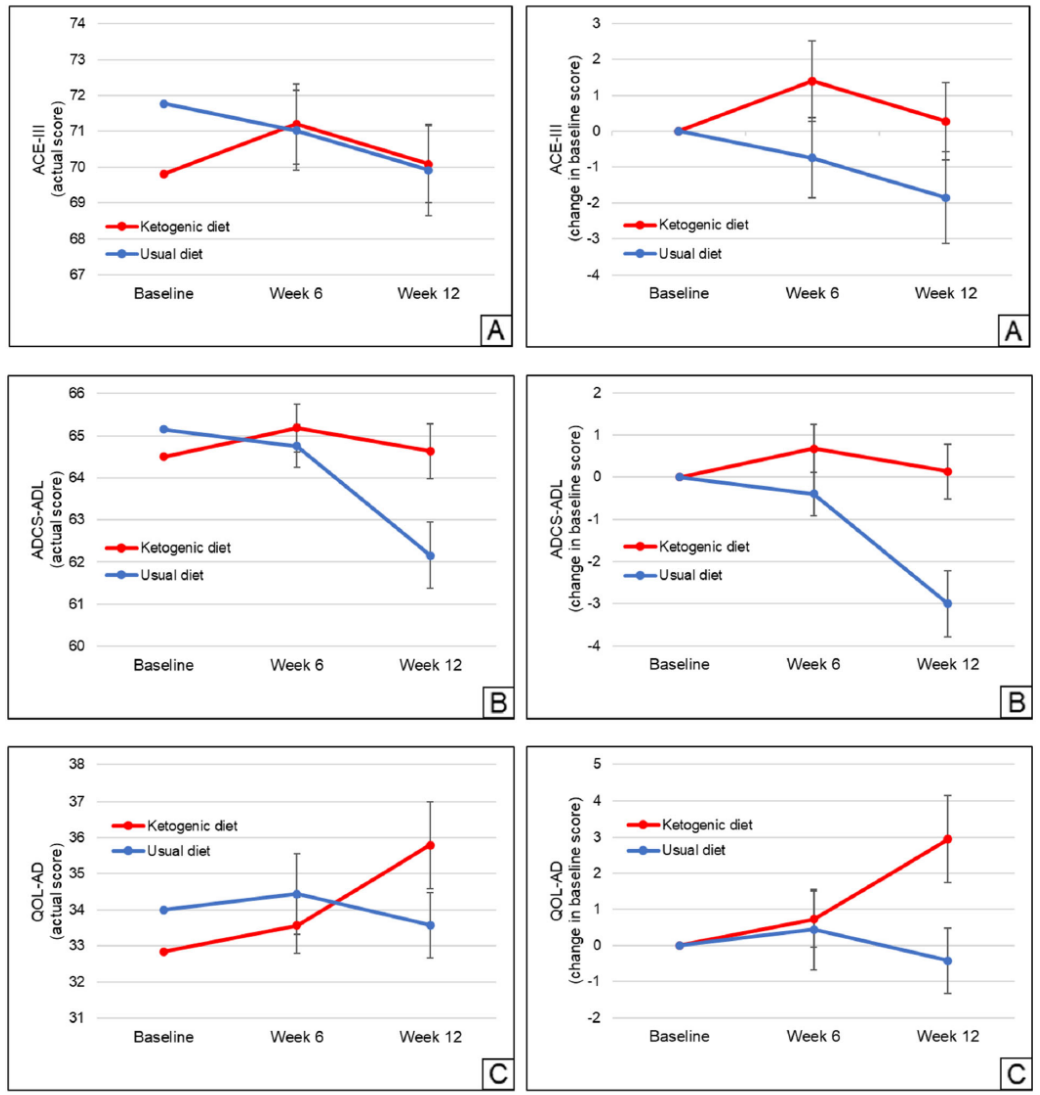


Fig. 3 Mean within-individual changes in **a** cognition (ACE-III), **b** daily function (ADCS-ADL), and **c** quality of life (QOL-AD) scores (both the actual scores as well as changes in baseline scores are shown) for all randomized patients ($n = 26$ for ketogenic diet, $n = 26$ for usual diet). Regarding withdrawals, all data up to the point of withdrawal are shown, with regression imputation used to calculate values for the week(s) post-withdrawal. Error bars indicate standard error

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Ketogenesis in Multiple Sclerosis

frontiers in Microbiology

ORIGINAL RESEARCH
published: 28 June 2017
doi: 10.3389/fmicb.2017.01141

Reduced Mass and Diversity of the Colonic Microbiome in Patients with Multiple Sclerosis and Their Improvement with Ketogenic Diet

Alexander Swidsinski[1,2], Yvonne Dörffel[3], Vera Loening-Baucke[1], Christoph Gille[1], Önder Göktas[1], Anne Reißhauer[1], Jürgen Neuhaus[4], Karsten-Henrich Weylandt[5], Alexander Guschin[6] and Markus Bock[7]*

Conclusions: Colonic biofermentative function is markedly impaired in MS patients.The ketogenic diet normalized concentrations of the colonic microbiome after 6 months.

KDA Ketogenic Diet ACADEMY

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Contents lists available at ScienceDirect

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EBioMedicine Published by THE LANCET

Ketogenic diets attenuate cyclooxygenase and lipoxygenase gene expression in multiple sclerosis

Markus Bock [a,b,*], Mirjam Karber [c], Hartmut Kuhn [a]

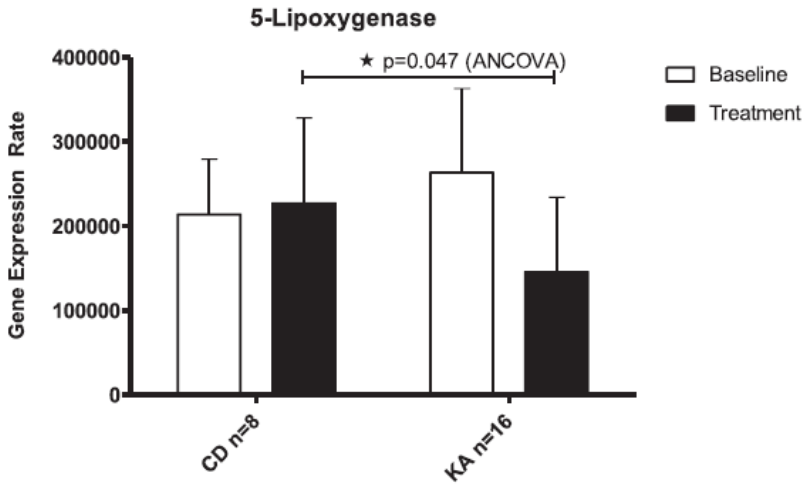

Fig. 2. Ketogenic approaches (KA) lower ALOX5 expression in the inter-group comparison to common western diet (CD). Comparison of ALOX5 gene expression during caloric restriction and adapted ketogenic diet (pooled ketogenic approach group, n = 16) with common western diet (control diet). Data were measured at baseline and retested between day 8 and 17 after the onset of dietary intervention. See also supplemental Fig. S2a–c for COX1, COX2, and ALOX15 expression results. Data represent mean ± standard error of the mean (SEM). *p ≤ 0.05, analysis of covariance (ANCOVA) to adjust for baseline dependencies.

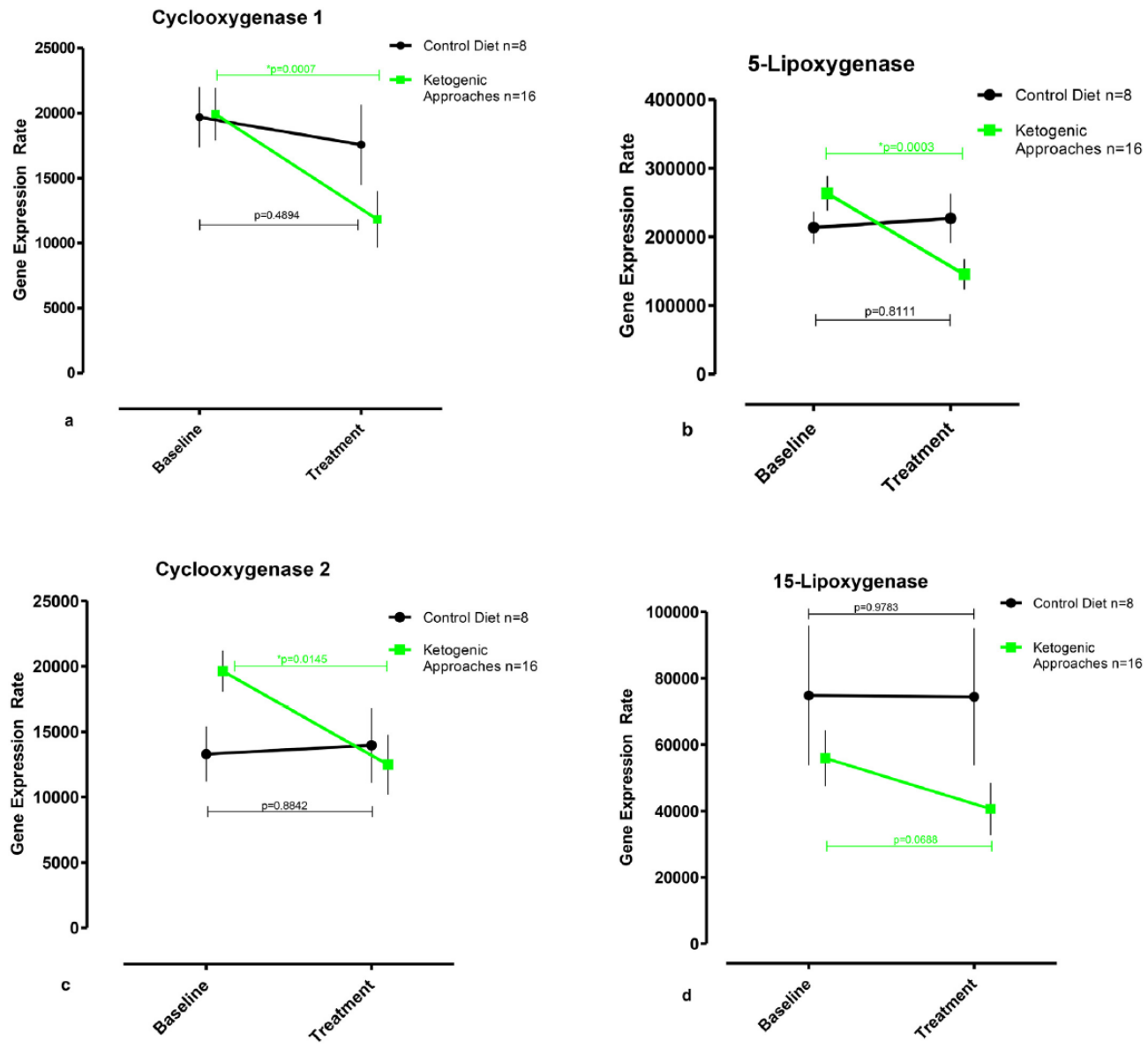

Fig. 1. Intra-group comparison - Ketogenic approaches lower the gene expression of pro-inflammatory enzymes involved in eicosanoid biosynthesis. (a–d) Alterations of gene expression induced by caloric restriction/adapted ketogenic diet (ketogenic approaches) when compared with common western diet (control diet). The steady state concentrations (copy numbers of target gene mRNA per 10^6 copies of GAPDH mRNA) for the following transcripts were evaluated: a) COX1, b) ALOX5, c)COX2, and d) LOX15. Data represent mean ± standard error of the mean (SEM) and were measured at baseline and retested between day 8 and 17 after the onset of dietary intervention. Horizontal bars indicate paired t-Test analysis.

Pilot study of a ketogenic diet in relapsing-remitting MS

J. Nicholas Brenton, MD, Brenda Banwell, MD, A.G. Christina Bergqvist, MD, Diana Lehner-Gulotta, RDN, CNSC, Lauren Gampper, BA, Emily Leytham, BA, Rachael Coleman, MPH, and Myla D. Goldman, MD, MSc

Correspondence
Dr. Brenton
jnb8h@virginia.edu

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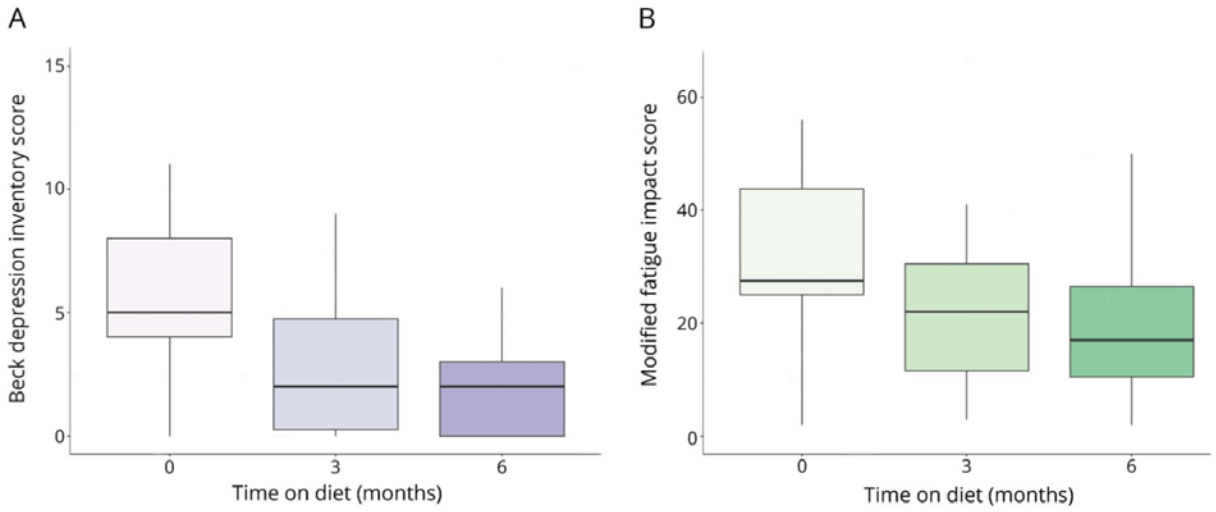
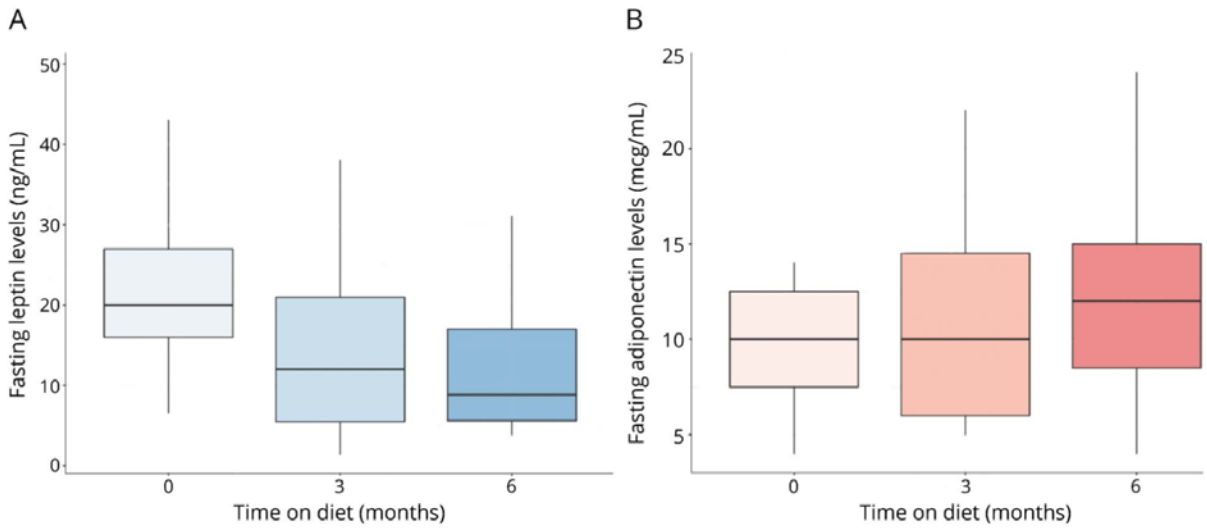
Figure 1 Subject-reported outcomes for subjects compliant to KD^{MAD} at 3 (n = 19) and 6 months (n = 15) for depression



(A) Depression scores as a function of time adhering to a modified KD (as assessed by the Beck Depression Inventory) and (B) fatigue levels as a function of time adhering to a modified KD fatigue (as assessed by the Modified Fatigue Impact Scale). Boxplots demonstrate the median and interquartile range. Whiskers represent the range. KD = ketogenic diet.

Figure 2 Change in baseline fasting serologic adipokine levels for compliant subjects at 3 (n = 19) and 6 months (n = 15) on KD^{MAD}



(A) Serologic leptin as function of time adhering to modified KD and (B) serologic adiponectin as a function of time adhering to modified KD. Boxplots demonstrate the median and interquartile range. Whiskers represent the range. KD = ketogenic diet.

Ketogenesis in Neurodegenerative and Neuroinflammatory disorders: when and who?

Ketogenesis in neurodegenerative and neuroinflammatory disorders?

- In obese patients
- In case of metabolic syndrome
- In early stages of disease?

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Ketogenesis in Stroke and TBI

Brain Research 1667 (2017) 11–18

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Brain Research

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Research Report

Ischemic preconditioning with a ketogenic diet improves brain ischemic tolerance through increased extracellular adenosine levels and hypoxia-inducible factors

Qi Yang [a,1], Min Guo [a,1], Xun Wang [a], Yanxin Zhao [b], Qi Zhao [c], Hongyan Ding [a], Qiang Dong [a,*], Mei Cui [a,*]

[a] Department of Neurology, Huashan Hospital, State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai 200040, China
[b] Department of Neurology, The 10th People's Hospital, Tongji University, Shanghai 200072, China
[c] BinZhou Medical University, 346 Guanhai Road, Yantai, Shandong 264003, China

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ABSTRACT

Ischemic tolerance reduces brain damage and neurological dysfunction after brain ischemia. A ketogenic diet (KD) has disease-modifying effects in several neurodegenerative disorders. In this study, we fed mice with a KD for three weeks and performed reversible middle cerebral artery occlusion (MCAO) in the animals. KD-fed mice had a significantly reduced infarct volume, increased regional cerebral blood flow (rCBF) and extracellular adenosine levels in both the ischemic and the reperfusion phases. *In vitro* and *in vivo* experiments revealed that the KD-induced neuroprotection was mediated through the adenosine A1 receptor. The KD increased Akt and ERK1/2 phosphorylation via A1R activation. Besides, the KD also upregulated robustly HIF-1α/HIF-2α and HIF regulated genes, such as *VEGF* and *EPO*. A three-week preconditioning period with a KD improved ischemic tolerance in mice with MCAO. The underlying mechanisms might include elevated extracellular adenosine levels, and increased Akt and ERK1/2 phosphorylation via A1 adenosine receptor activation, together with upregulated HIFs and HIF-regulated genes.

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Journal of Neuroscience Research 82:413–420 (2005)

Age-Dependent Reduction of Cortical Contusion Volume by Ketones After Traumatic Brain Injury

M.L. Prins,* L.S. Fujima, and D.A. Hovda

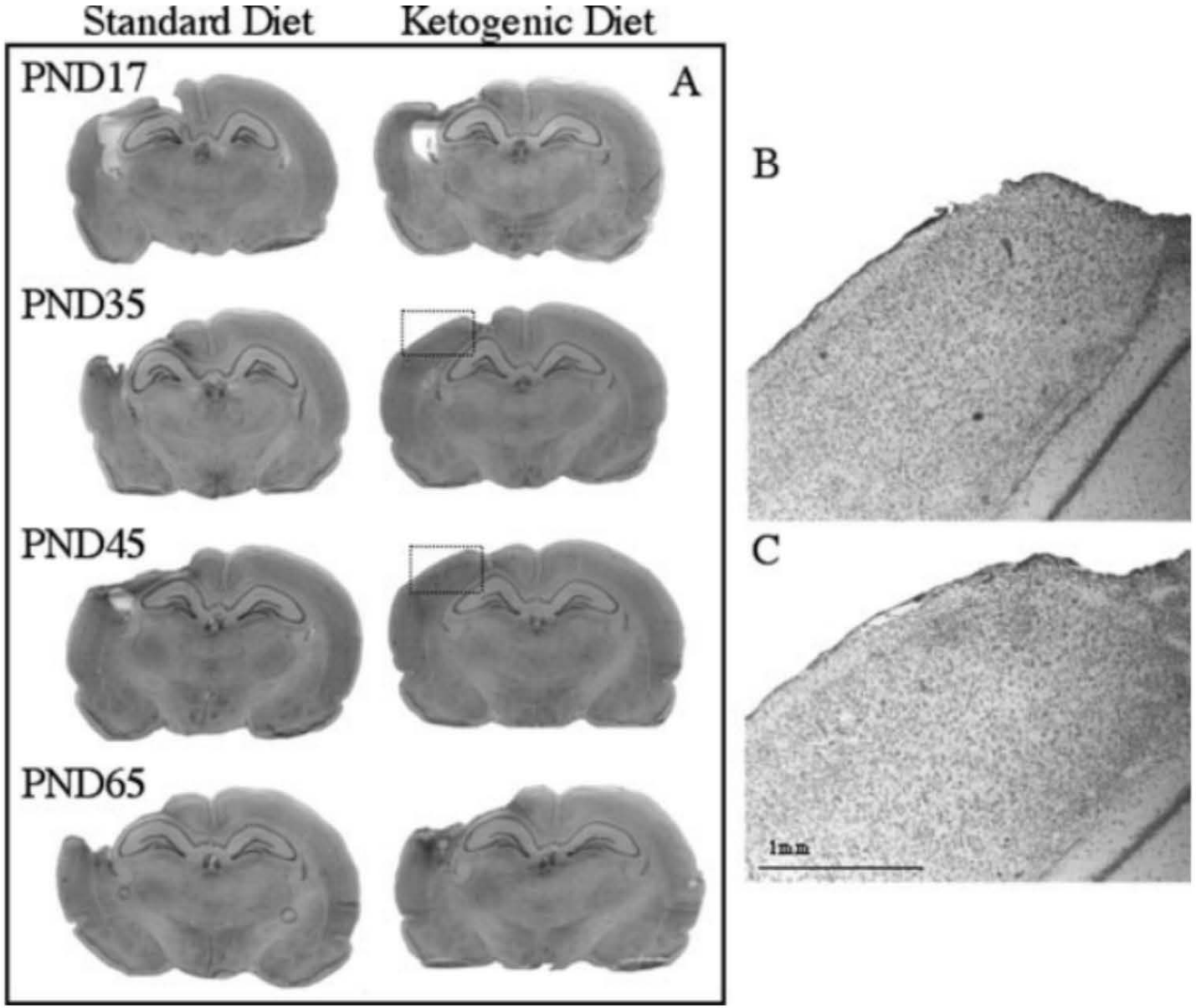

Fig. 2. Cresyl violet-stained coronal sections of standard and ketogenic (KG)-fed animals 7 days after controlled cortical impact (CCI) injury for postnatal day 17 (PND17), PND35, PND45, and PND65 animals. Dotted rectangles mark spared cortical areas that are magnified (4×) among PND35 (**B**) and PND45 (**C**) KG-fed animals. Scale bar = 1 mm.

NEUROLOGICAL RESEARCH
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ARTICLE

Inducing ketogenesis via an enteral formulation in patients with acute brain injury:a phase II study

Hayden White[a], Balasubramanian Venkatesh[b], Mark Jones[c], Peter S. Kruger[d], James Walsham[e] and Hesly Fuentes[f]

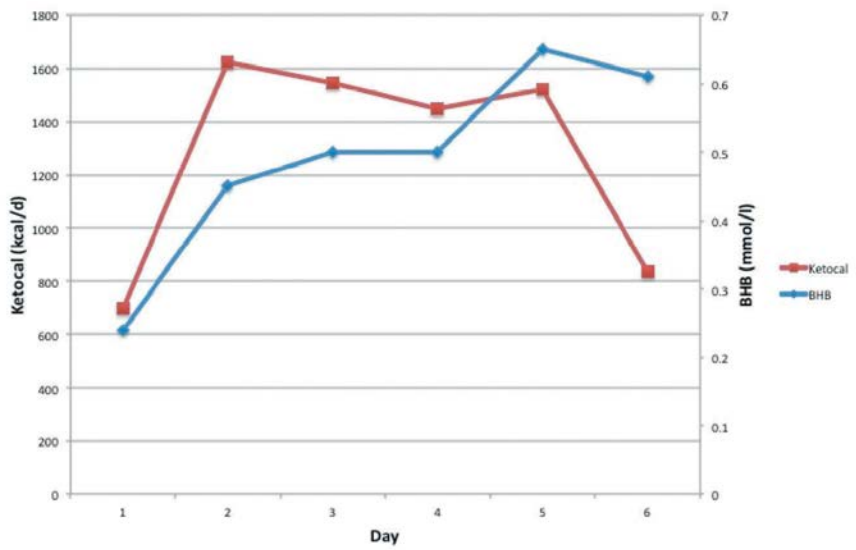

Figure 6. Daily plasma BHB concentration compared with total daily calories from Ketocal (kcal/day).
BHB – beta-hydroxybutyrateetahydroxybutyrate.

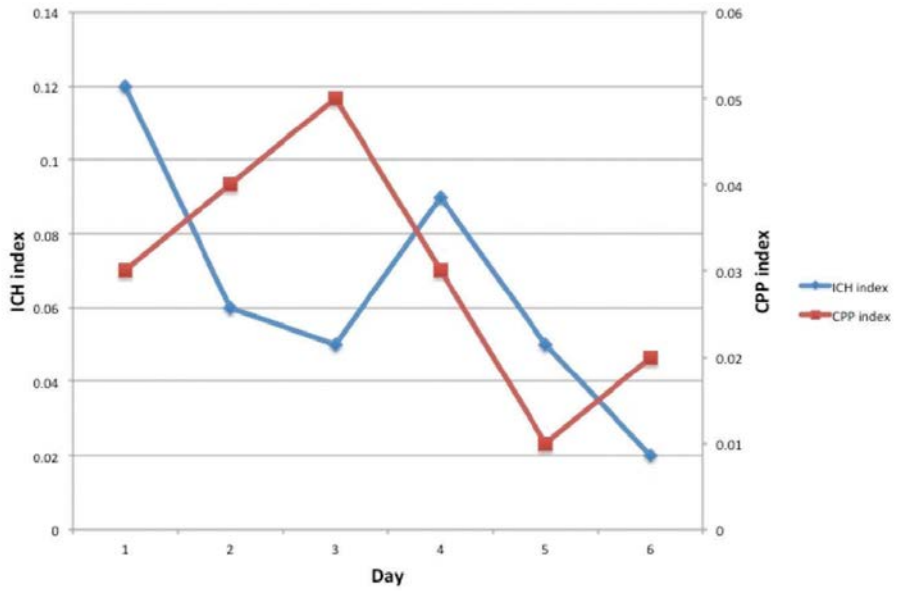

Figure 8. Daily ICH index compared with daily CPP index.
ICH index – intracranial hypertension index; CPP index – cerebral hypoperfusion index (see text for calculation).

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The Ketogenic Diet in the Treatment of Post-concussion Syndrome—A Feasibility Study

Michael A. Rippee[1,2], Jamie Chen[2] and Matthew K. Taylor[3,4]*

ORIGINAL RESEARCH
published: 10 September 2020
doi: 10.3389/fnut.2020.00160

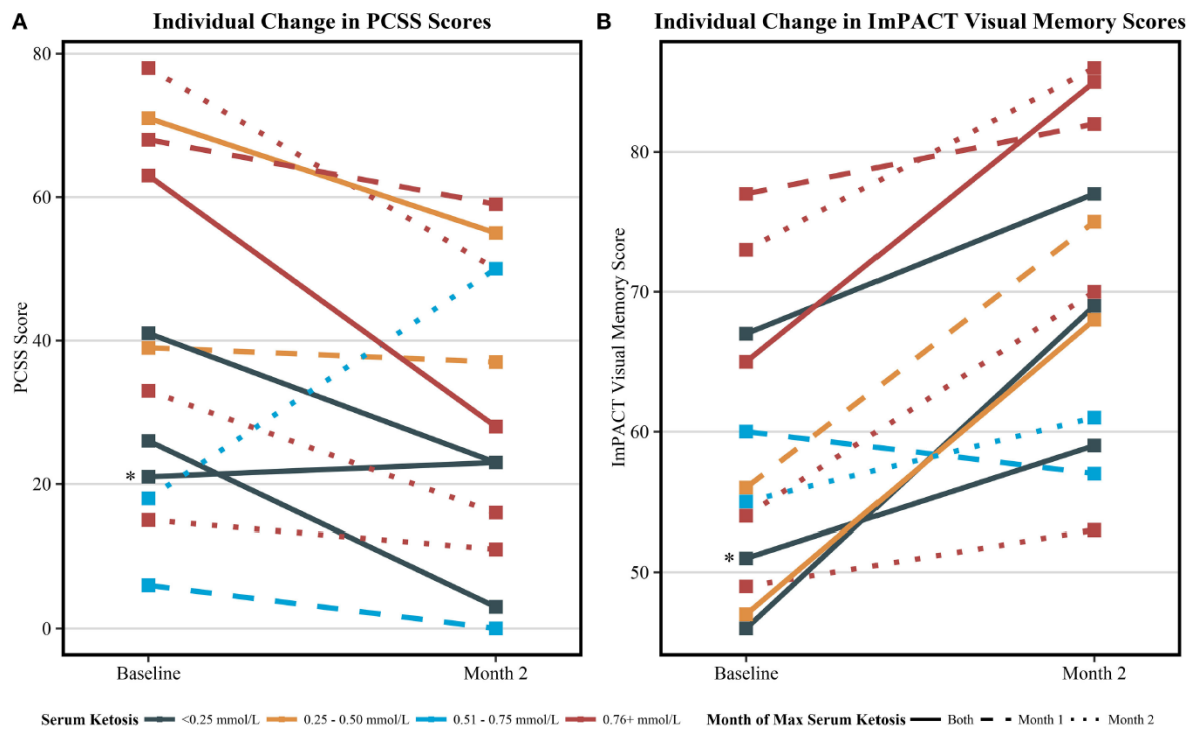

FIGURE 2 | Individual change in symptom and visual memory scores among all completing participants ($n = 12$). **(A)** The individual change in the post-concussion symptom scale (PCSS) from baseline to 2 months. Decreasing scores indicate improvement in self-reported symptoms. **(B)** The individual change in ImPACT visual memory scores from baseline to 2 months. Increasing scores indicate improvement in tested visual memory. Serum ketosis levels were determined by peak measured serum BHB. Different line types indicate the month which peak ketosis was reached, a solid line indicating both month 1 and 2, a dashed line indicating month 1, and a dotted line indicating month 2. One participant (*) was considered not compliant with the KD and did not produce urine ketones as indicated by the urine ketone record nor had elevated serum BHB at any study visits. This participant's symptom score slightly worsened and verbal memory score slightly improved from at the end of the study. The other two participants that did not register elevated BHB at study visits recorded trace ketone production via urine ketone records during the course of the study.

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Ketogenesis in Psychiatry

frontiers in Psychiatry
REVIEW
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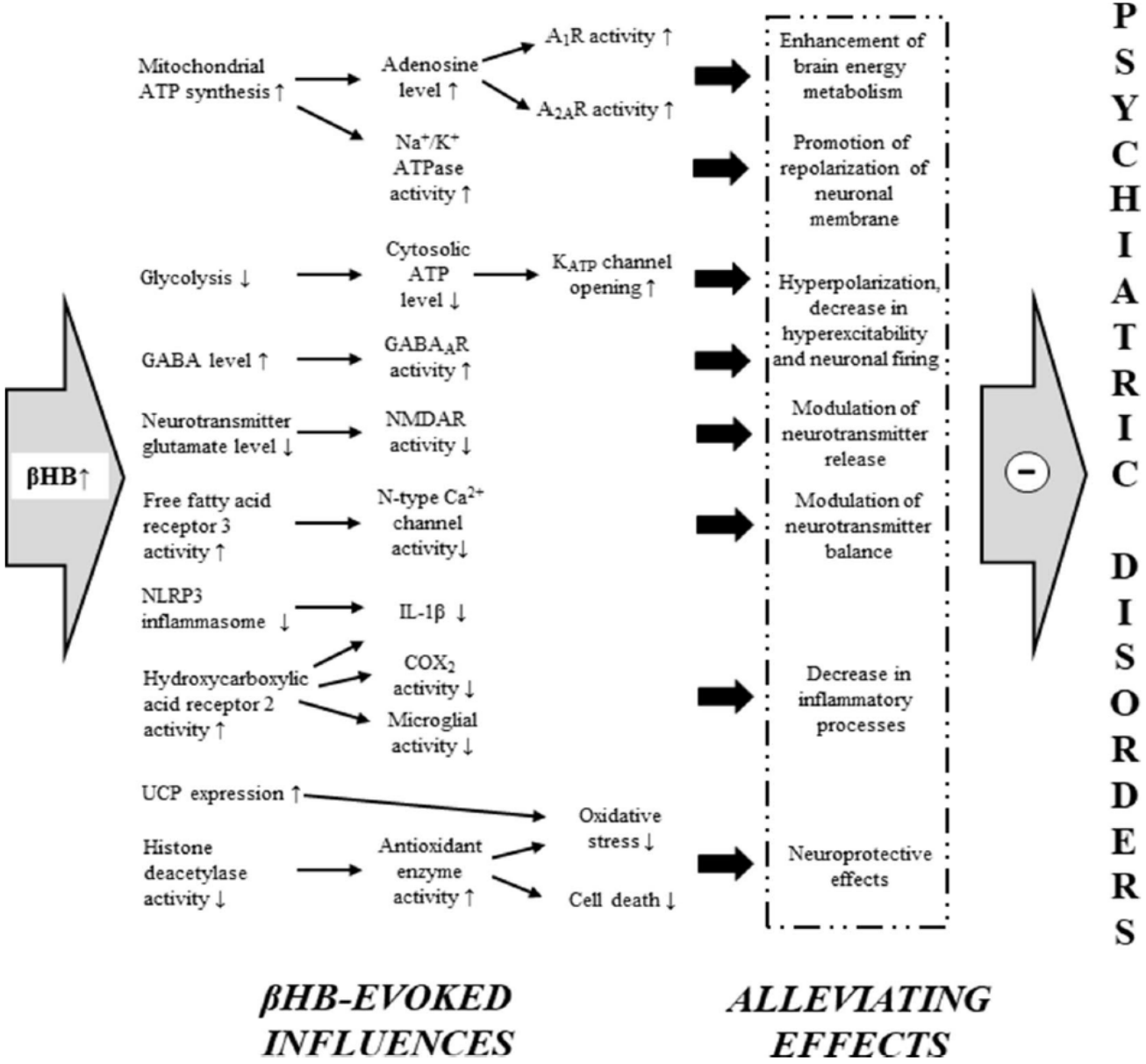
Therapeutic Potential of Exogenous Ketone Supplement Induced Ketosis in the Treatment of Psychiatric Disorders: Review of Current Literature

Zsolt Kovács[1], Dominic P. D'Agostino[2,3], David Diamond[2,4], Mark S. Kindy[5,6,7], Christopher Rogers[2] and Csilla Ari[4*]

Abbreviations: A, acetone; A_1R and $A_{2A}R$, different types of adenosine receptors; AcAc, acetoacetate; ATP, adenosine triphosphate; BBB, blood–brain barrier; βHB, D-beta-hydroxybutyrate (R-3-hydroxybutyrate); β-OHBD, βHB dehydrogenase; COX-2, cyclooxygenase-2; ETC, electron transport chain; GABA, gamma-aminobutyric acid; HMGL, hydroxymethylglutaryl-CoA-lyase; HMGS, hydroxymethylglutaryl-CoA-synthase; IL-1β, interleukin-1β; NADH/$FADH_2$, nicotinamide adenine dinucleotide/flavin adenine dinucleotide; NLRP3, NOD-like receptor pyrin domain 3; NMDAR, N-methyl-D-aspartate receptor; SCOT, succinyl-CoA:3-ketoacid CoA transferase; thiolase, acetoacetyl-CoA-thiolase; UCP, uncoupling proteins.



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Ketogenic diet and bipolar disorder

1. The **ketogenic diet** for type II **bipolar** disorder.
   Phelps JR, Siemers SV, El-Mallakh RS.
   Neurocase. 2013;19(5):423-6. doi: 10.1080/13554794.2012.690421. Epub 2012 Oct 3.
   PMID: 23030231
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2. **Ketogenic diet** in **bipolar** illness.
   Yaroslavsky Y, Stahl Z, Belmaker RH.
   Bipolar Disord. 2002 Feb;4(1):75. No abstract available.
   PMID: 12047499
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3. The **ketogenic diet** may have mood-stabilizing properties.
   El-Mallakh RS, Paskitti ME.
   Med Hypotheses. 2001 Dec;57(6):724-6.
   PMID: 11918434
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Ketogenic diet and Schizofrenia

1. **Schizophrenia**, gluten, and low-carbohydrate, **ketogenic** diets: a case report and review of the literature.
   Kraft BD, Westman EC.
   Nutr Metab (Lond). 2009 Feb 26;6:10. doi: 10.1186/1743-7075-6-10.
   PMID: 19245705 **Free PMC Article**
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2. A PILOT STUDY OF THE **KETOGENIC DIET** IN **SCHIZOPHRENIA**.
   PACHECO A, EASTERLING WS, PRYER MW.
   Am J Psychiatry. 1965 May;121:1110-1. No abstract available.
   PMID: 14283310
   Similar articles

The Current Status of the Ketogenic Diet in Psychiatry

Emmanuelle C. S. Bostock[1], Kenneth C. Kirkby[2] and Bruce V. M. Taylor[3]*

[1]Psychology, School of Medicine, University of Tasmania, Hobart, TAS, Australia, [2]Psychiatry, School of Medicine, University of Tasmania, Hobart, TAS, Australia, [3]Menzies Institute for Medical Research, Tasmania, Hobart, TAS, Australia

TABLE 2 | Summary of findings in human studies.

Reference	Condition	Subjects (*n*)	Mode of administration of diet	Duration of diet	Ketone*	Result
(46)	BD	Human women (2)	Ratio not mentioned in first but in second (70% fat, 22% protein, and 8% carbohydrate)	2 and 3 years	✓	Mood stabilization
(47)	BD	Human woman (1)	4:1 lipid:non-lipid ratio	1 month	No urinary ketones detected	No clinical improvement
(48)	SZ	Human women (10)	Not listed	2 weeks	Not listed	Statistically significant decrease in symptomatology
(49)	SZ	Human woman (1)	Not listed	12 months	Not listed	No recurrence of auditory or visual hallucinations
(50)	ASD	Human children (30)	30% MCT, 30% fresh cream, 11% saturated fat, 19% carbohydrate, and 10% protein	6 months (intervals of 4 weeks with 2 diet-free weeks)	✓	40% non-compliance. Two children showed significant improvements on Childhood Autism Rating Scale, while the rest showed mild-to-moderate improvements
(51)	ASD	Human child (1)	1.5:1 lipid:non-lipid ratio	Several years	✓	Score on the Childhood Autism Rating Scale decreased from 49 to 17 (severe autism to non-autistic)

*DEP, depression; BD, bipolar disorder; SZ, schizophrenia; *, ketone levels reported; MCT, medium-chain triglyceride; ASD, autism spectrum disorder.*

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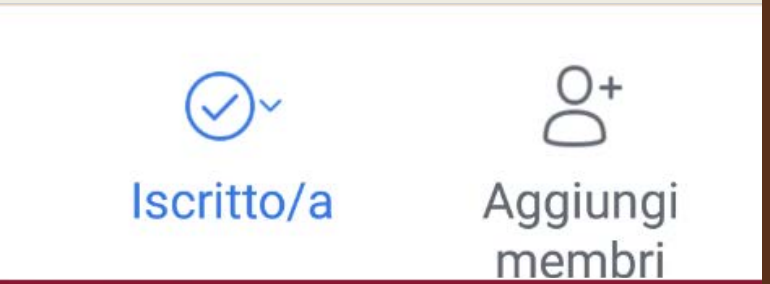

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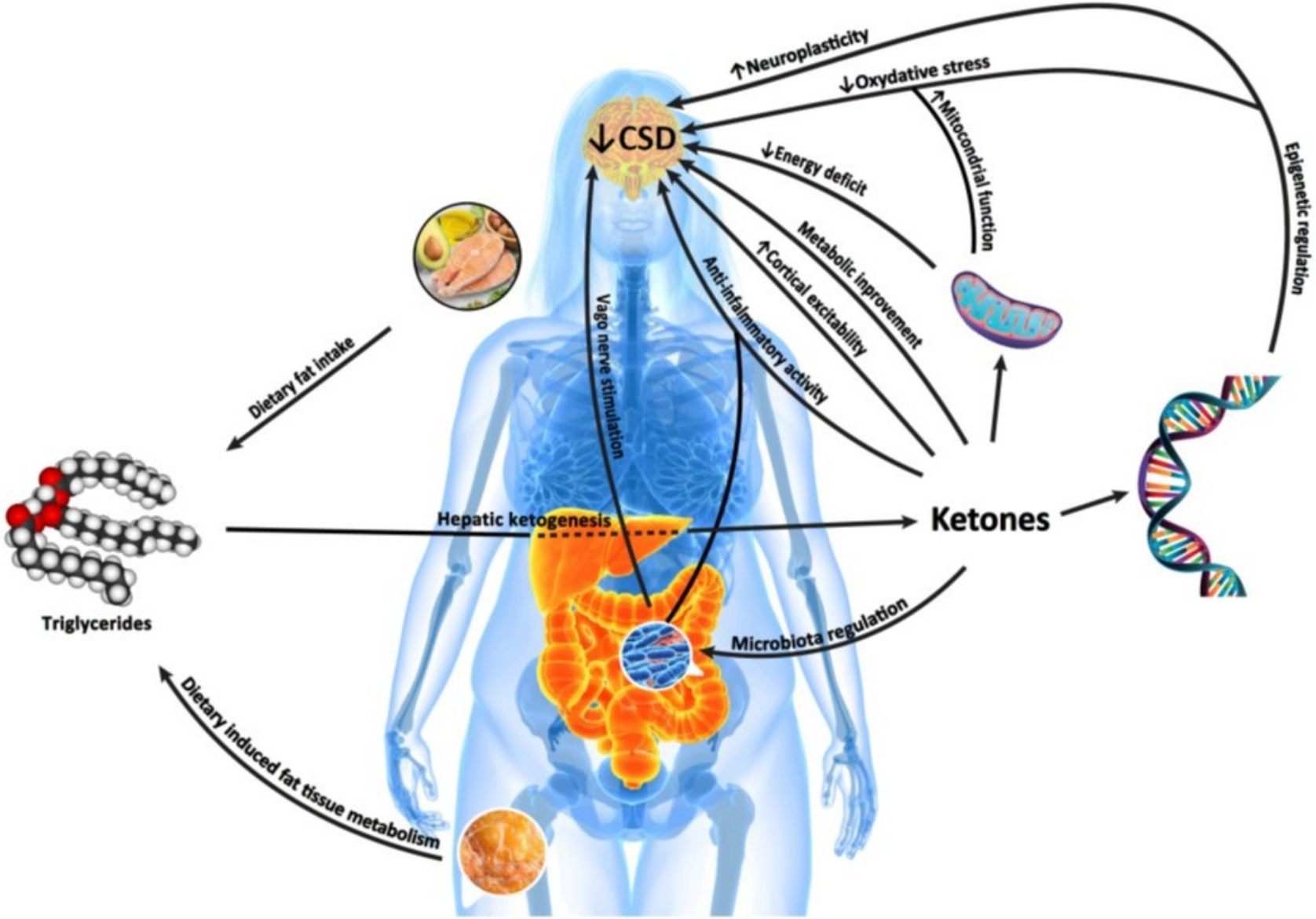

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