La Dieta Chetogenica nel Paziente Neurologico Adulto

Cherubino Di Lorenzo

Dipartimento di Scienze medico-chirurgiche e Biotecnologie, Università La Sapienza Roma - Fondazione Don Gnocchi Onlus

SINut
Società Italiana di Nutraceutica

SAPIENZA
UNIVERSITÀ DI ROMA

Ketogenic
Diet
Academy

Fondazione
Don Carlo Gnocchi
Onlus

Ketogenic Diets in Neurology

Drug resistant epilepsies

- Dravet syndrome
- Infantile spasms
- Myoclonic-astatic epilepsy
- Tuberous sclerosis complex

Metabolic diseases

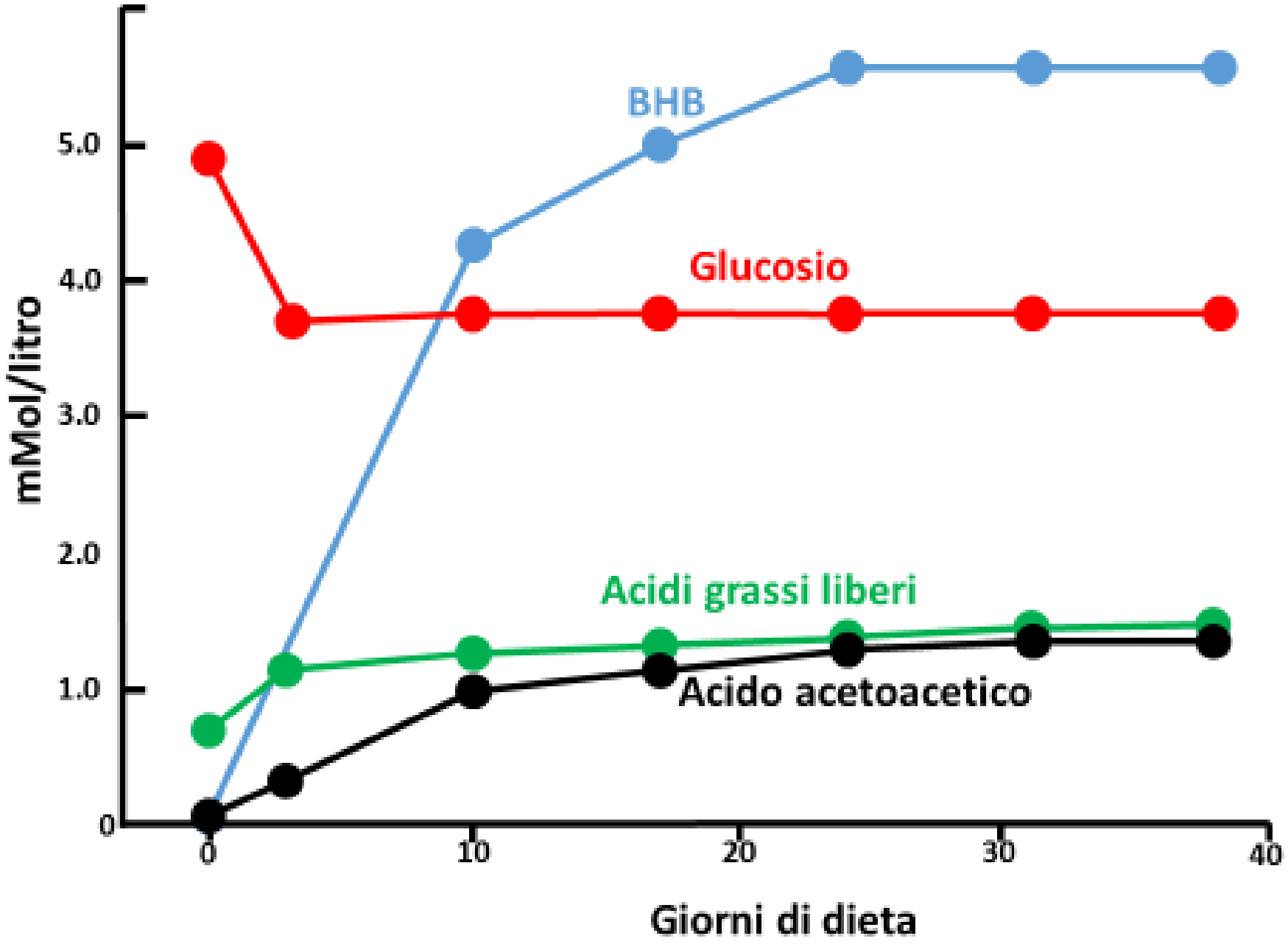
- Pyruvate dehydrogenase (E1) deficiency
- Glucose transporter 1 deficiency syndrome

Other Conditions

- Autism
- Depression
- Migraine
- Amyotrophic lateral sclerosis
- Alzheimer's disease
- Parkinson's disease
- TBI and Stroke
- Brain cancers?

Contra-indications

- Pyruvate carboxylase deficiency
- Porphyria
- Fat metabolism disorders


BHB
Glucosio
Acidi grassi liberi
Acido acetoacetico
mMol/litro
5.0
4.0
3.0
2.0
1.0
0
0
10
20
30
40
Giorni di dieta

Epilepsia, **48**(1):43–58, 2007
Blackwell Publishing, Inc.
© 2007 International League Against Epilepsy

Anticonvulsant Mechanisms of the Ketogenic Diet

*Kristopher J. Bough and †Jong M. Rho

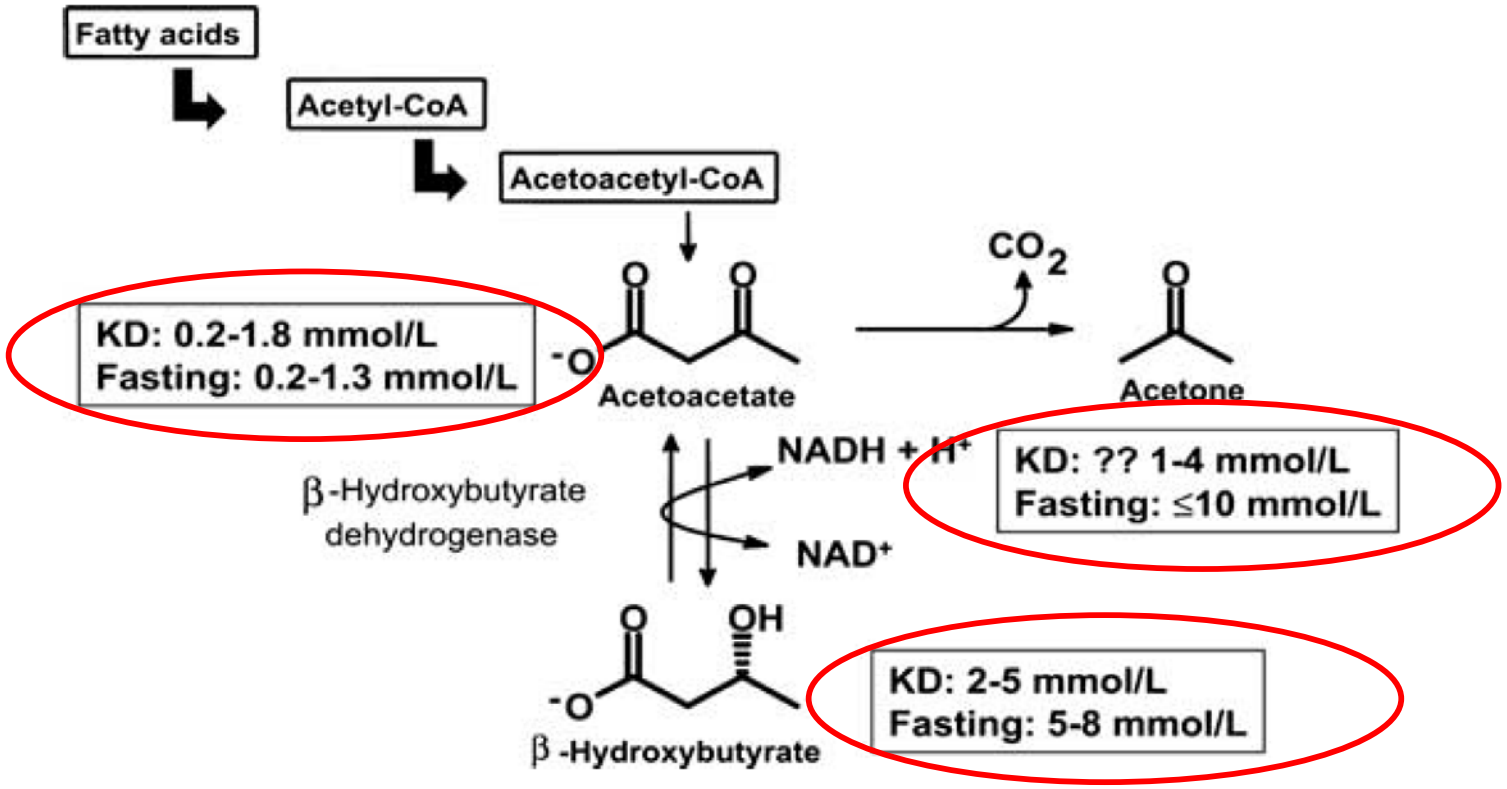
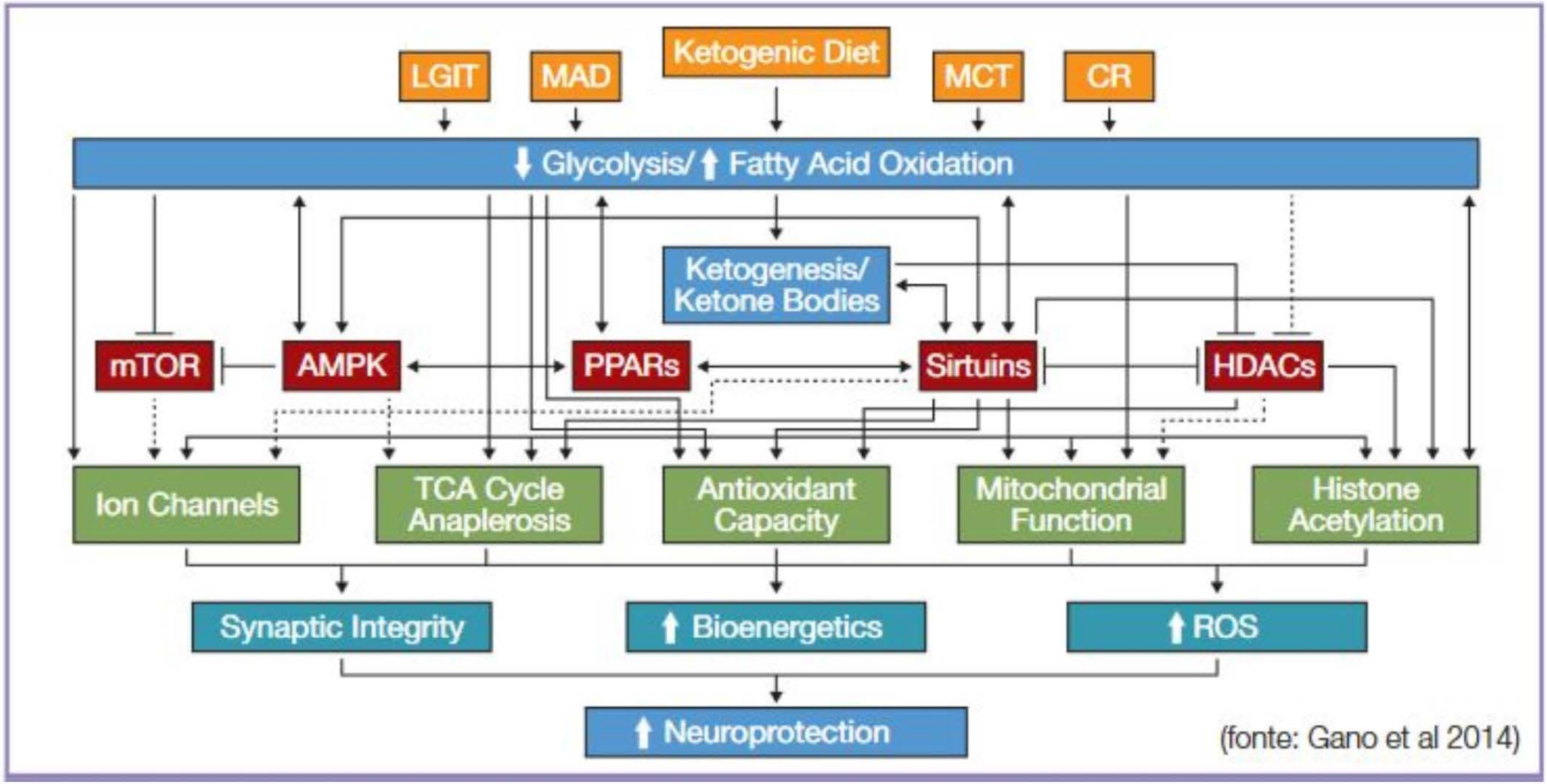


FIG. 1. Metabolic pathways highlighting the production of ketone bodies fatty acids during fasting or treatment with the ketogenic diet (KD). Estimated fasting- or KD-induced concentrations of beta-hydroxybutyrate, acetoacetate, and acetone in blood are listed (large boxes). Measures of beta-hydroxybutyrate levels in blood are most commonly used as the clinical indicator of successful KD treatment. From Likhodii and Burnham (2004).



(fonte: Gano et al 2014)

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)

Copyright © 2012, Michael A Rogawski, Antonio V Delgado-Escueta, Jeffrey L Noebels, Massimo Avoli and Richard W Olsen

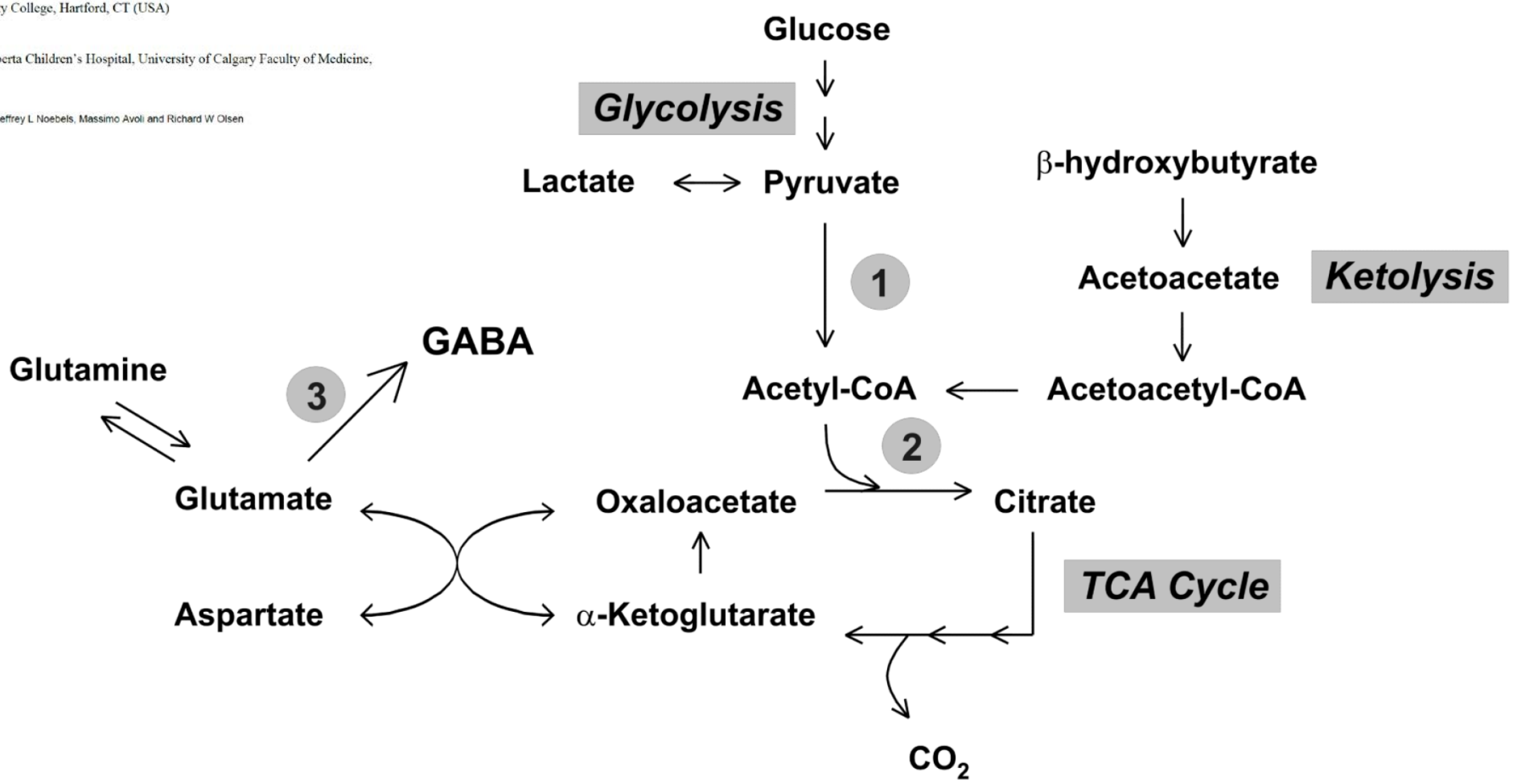
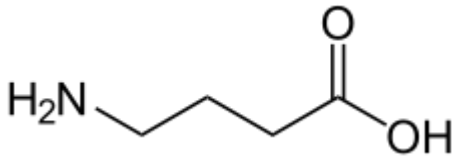


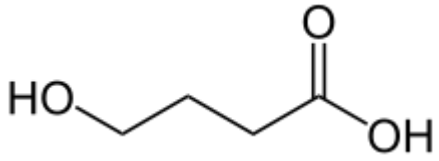
Figure 2. The metabolic inter-relationships between brain metabolism of glutamate, ketone bodies and glucose

GABAergic effect of ketone bodies

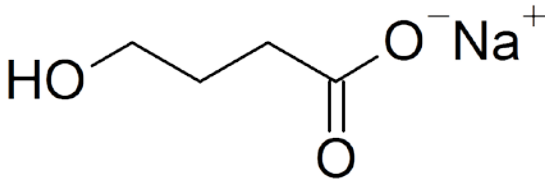
- Gamma-aminobutyric acid (GABA)



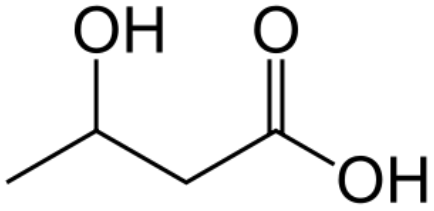
- Gamma-hydroxybutyric acid (GHB)



- Sodium Oxybate

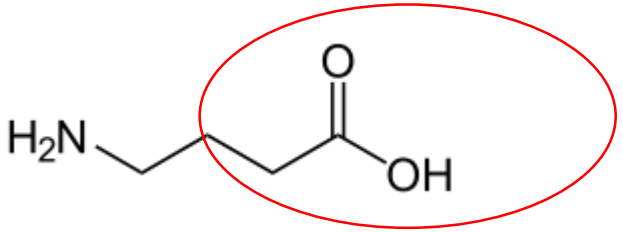


- Beta-hydroxybutyric acid (BHB)

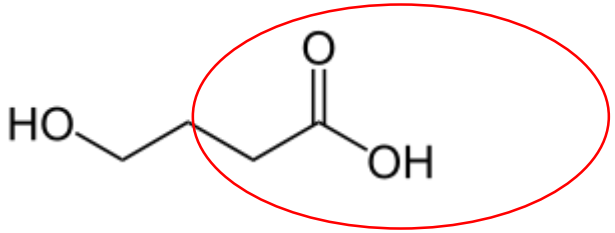


GABAergic effect of ketone bodies

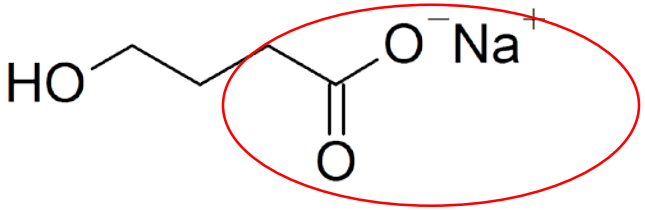
- Gamma-aminobutyric acid (GABA)



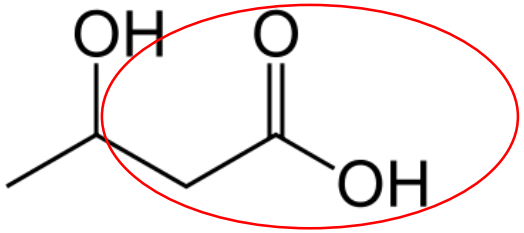
- Gamma-hydroxybutyric acid (GHB)



- Sodium Oxybate



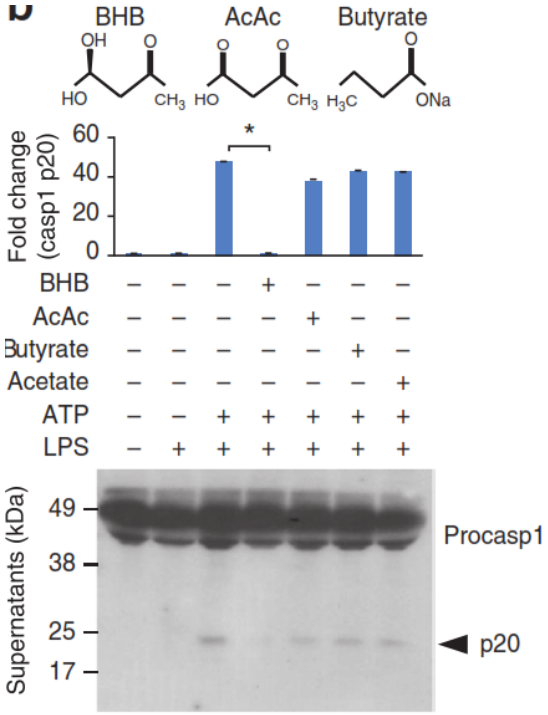
- Beta-hydroxybutyric acid (BHB)



nature medicine

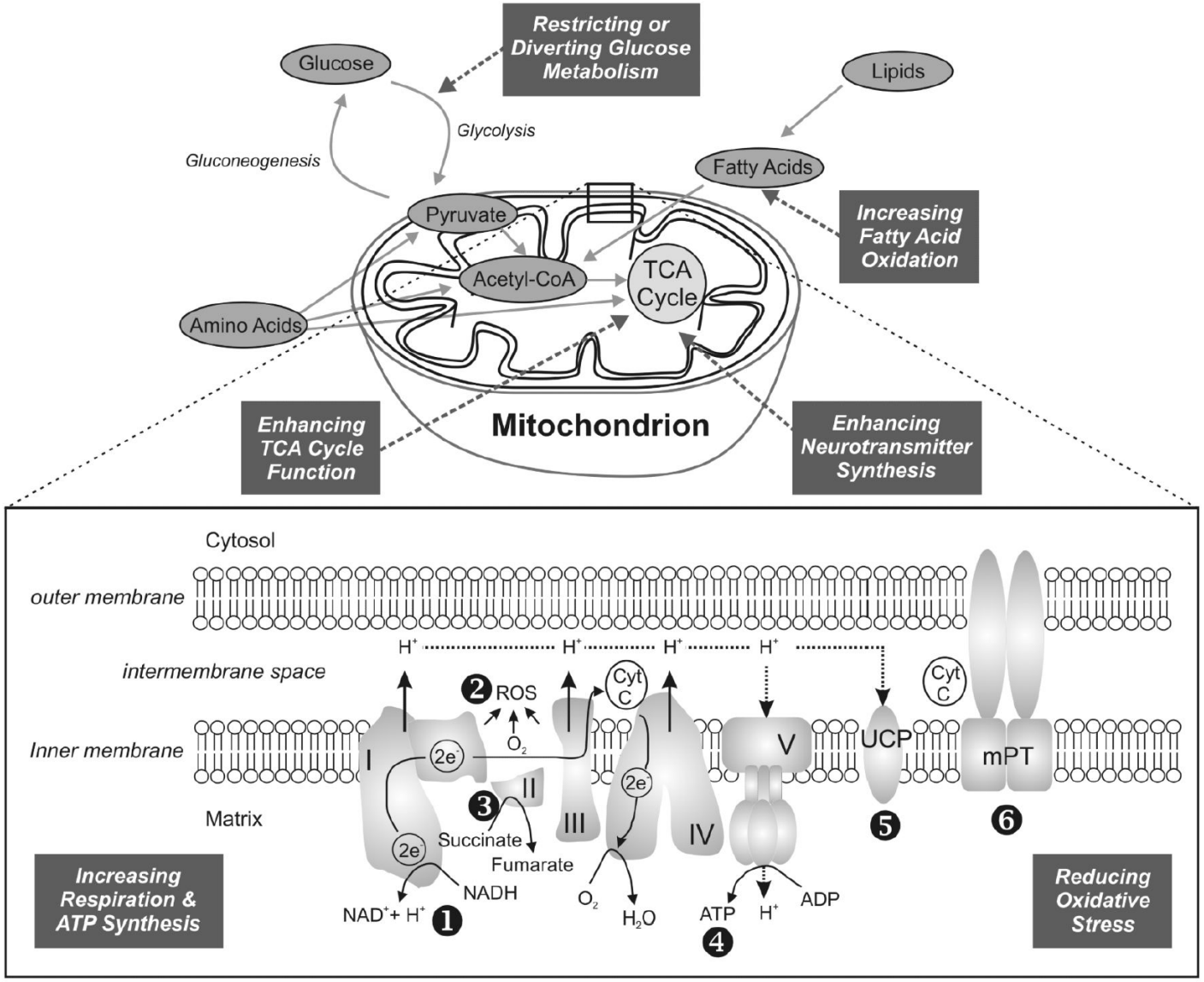
The ketone metabolite β-hydroxybutyrate blocks NLRP3 inflammasome–mediated inflammatory disease

Yun-Hee Youm[1,11], Kim Y Nguyen[1,11], Ryan W Grant[2], Emily L Goldberg[1], Monica Bodogai[3], Dongin Kim[4], Dominic D'Agostino[5], Noah Planavsky[6], Christopher Lupfer[7], Thirumala D Kanneganti[7], Seokwon Kang[8], Tamas L Horvath[1], Tarek M Fahmy[4], Peter A Crawford[9], Arya Biragyn[3], Emad Alnemri[8] & Vishwa Deep Dixit[1,10]



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

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,*]

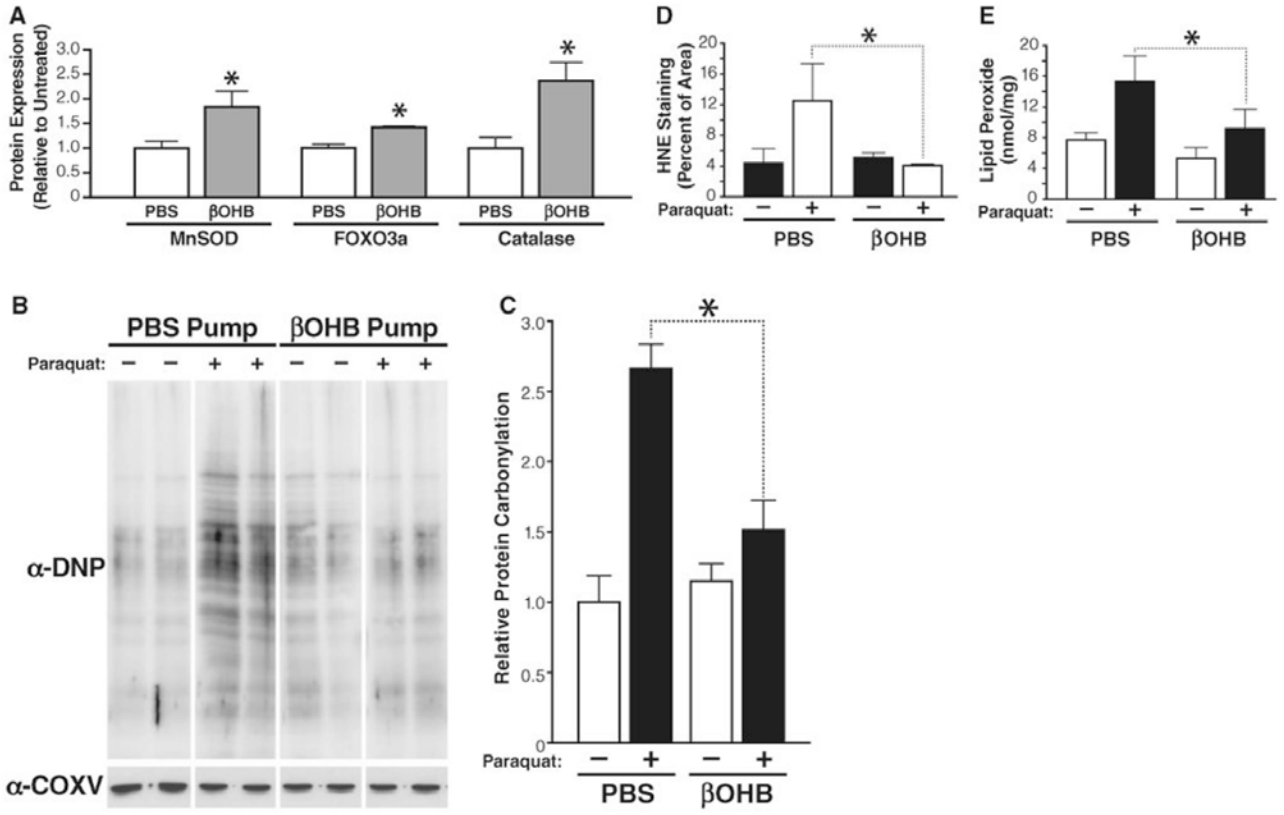


Fig. 4.

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.

CLINICS REVIEW

Neurobiochemical mechanisms of a ketogenic diet in refractory epilepsy

Patricia Azevedo de Lima,[I] Leticia Pereira de Brito Sampaio,[II] Nágila Raquel Teixeira Damasceno[III*]

CLINICS 2014;69(10):699-705

Table 1 - Neuroprotective effects of ketone bodies.

Species	Injury models	Intervention times	Treatments	Effect on seizures	Mechanisms	References
Rats	Maximal electroshock or subcutaneous pentylenetetrazol or amygdala kindling or AY-9944	1- 6 days	Acetone injection	↓	Anticonvulsant effect of acetone[a]	27
Mice	Pentylenetetrazol, 4-aminopyridine	15-240 min	Acetone injection	↓	Anticonvulsant effect of acetone[a]	26
Mice	-	3 days	KD	Not rated	↑ GABA	32
Rats (cultured astrocytes)	-	5 days	β-hydroxybutyrate	Not rated	↓ GABA transaminase mRNA	33
Humans (children with refractory epilepsy)	-	3-6 months	KD	↓	↑ GABA	30
Rats (hippocampal slices)	Antidromic stimulation	40 min	β-hydroxybutyrate	↓	↑ K_{ATP} channels	34
Rats	-	3 weeks	KD	↓	↑ Brain KBs and ↓ glucose uptake	29
In vitro (proteoliposomes)	-	n.d.	Acetoacetate	Not rated	↓ Glutamate	36
Mice (norepinephrine transporter knockouts)	Maximal electroshock	n.d.	KD	↓	↑ Norepinephrine[b]	38
Humans (children with refractory epilepsy)	-	3 months	KD	↓	↓ Dopamine and serotonin	19
Mice (with adenosine deficiency)	Kainic acid	4-6 weeks	No therapy	↑	↓ Adenosine	40
Mice (transgenic models)	-	3 weeks	KD	↓	↑ A_1R	41
Mice (hippocampal slices)	-	3 weeks	KD	↓	↑ Number of mitochondria	43
Mice (hippocampal mitochondria)	-	10-12 days	KD	Not rated	↑ UCP levels and ↓ ROS	44
Rats (hippocampal mitochondria)	-	3 weeks	KD	Not rated	↑ GSH and ↓ mitochondrial H_2O_2	45

GSH: glutathione; KD: ketogenic diet, ROS: reactive oxygen species; UCP: uncoupling protein; -: without seizure-inducing substance; n.d.: not described; [a]: very high doses of acetone may have contributed to motor impairment; [b]: norepinephrine transporter knockout mice and mice fed the KD showed similar reductions in seizure severity.

KD in GLUT1 and Pyruvate dehydrogenase deficit

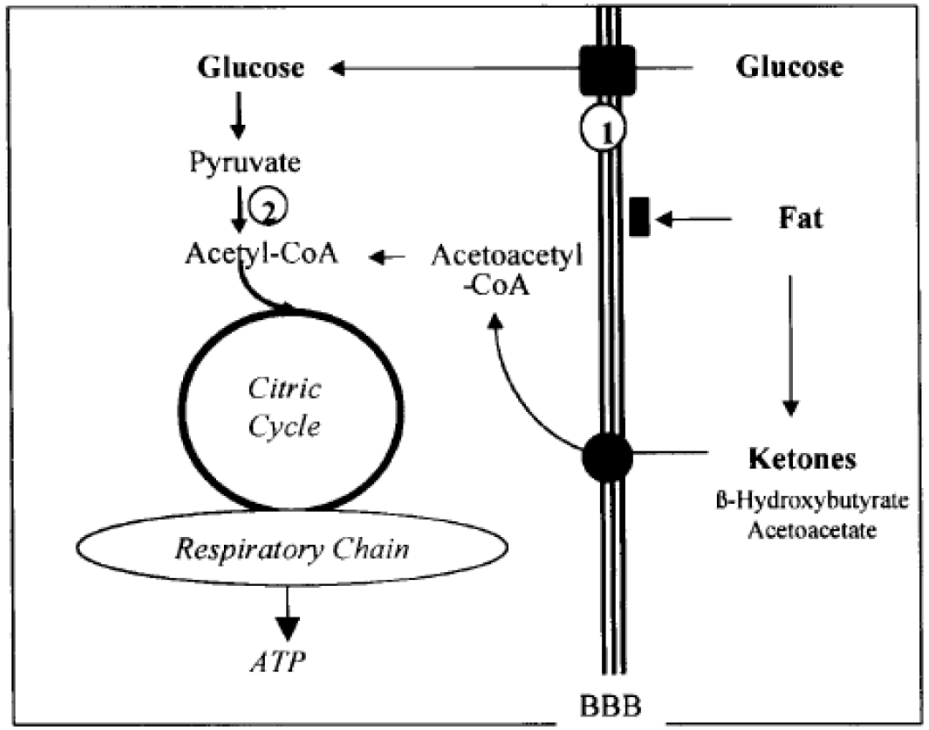
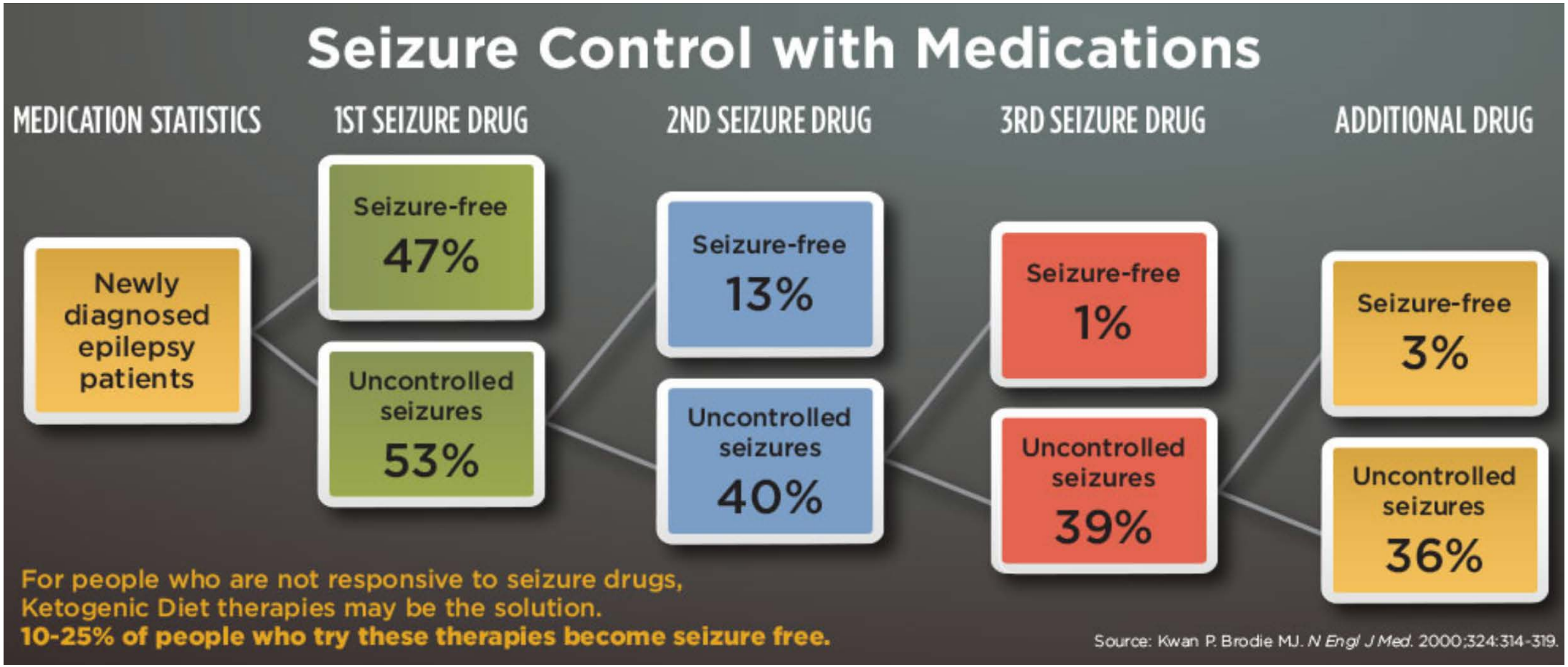


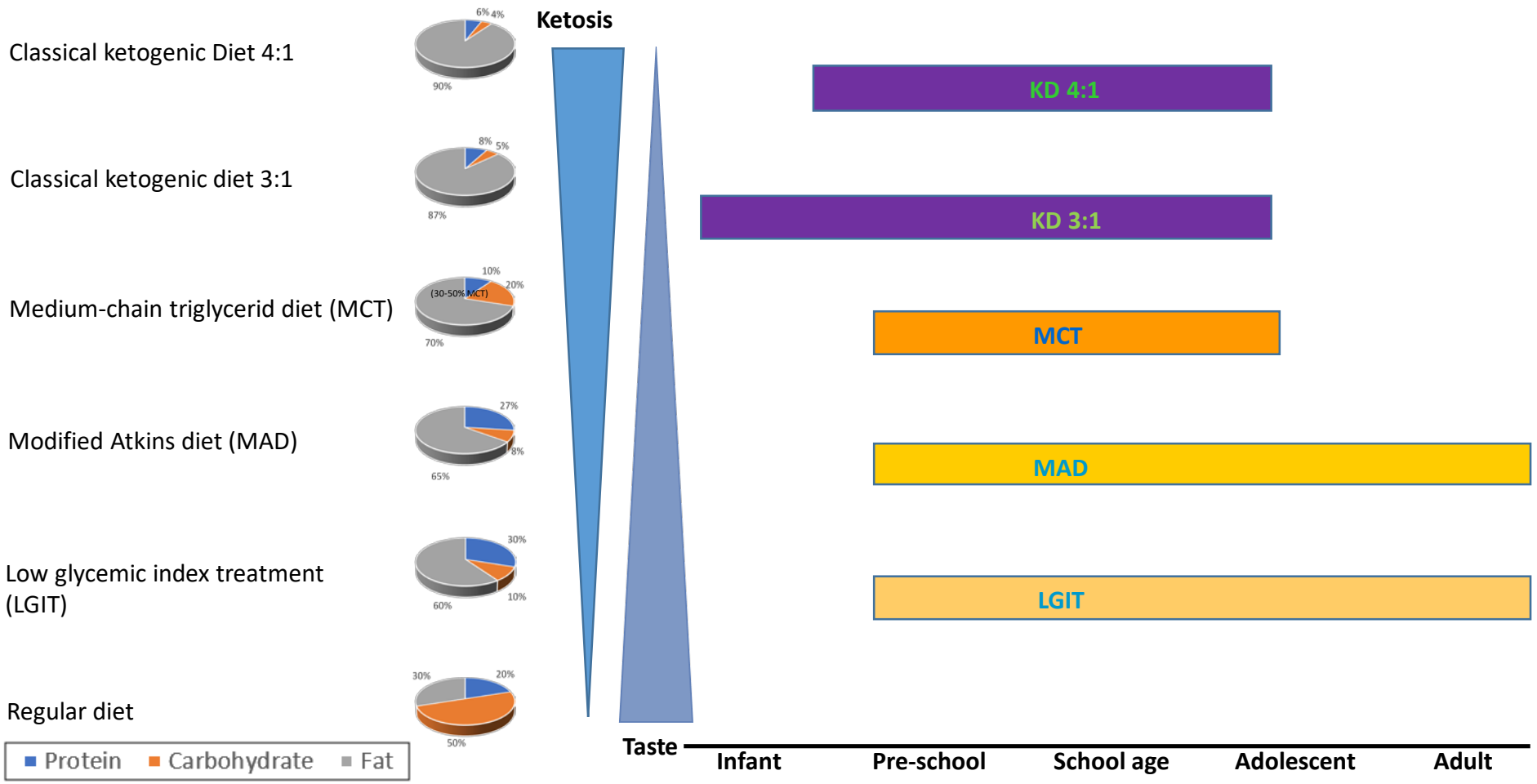
Figure 1 Ketosis and brain energy metabolism. Glucose enters the brain via the facilitated glucose transporter GLUT1 (■); ketones penetrate the blood–brain barrier (BBB) via the MCT1-transporter (●). Both substrates enter the citric acid cycle as acetyl-CoA for energy production. ① GLUT1 DS is caused 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.

Ketogenesis and Epilepsy

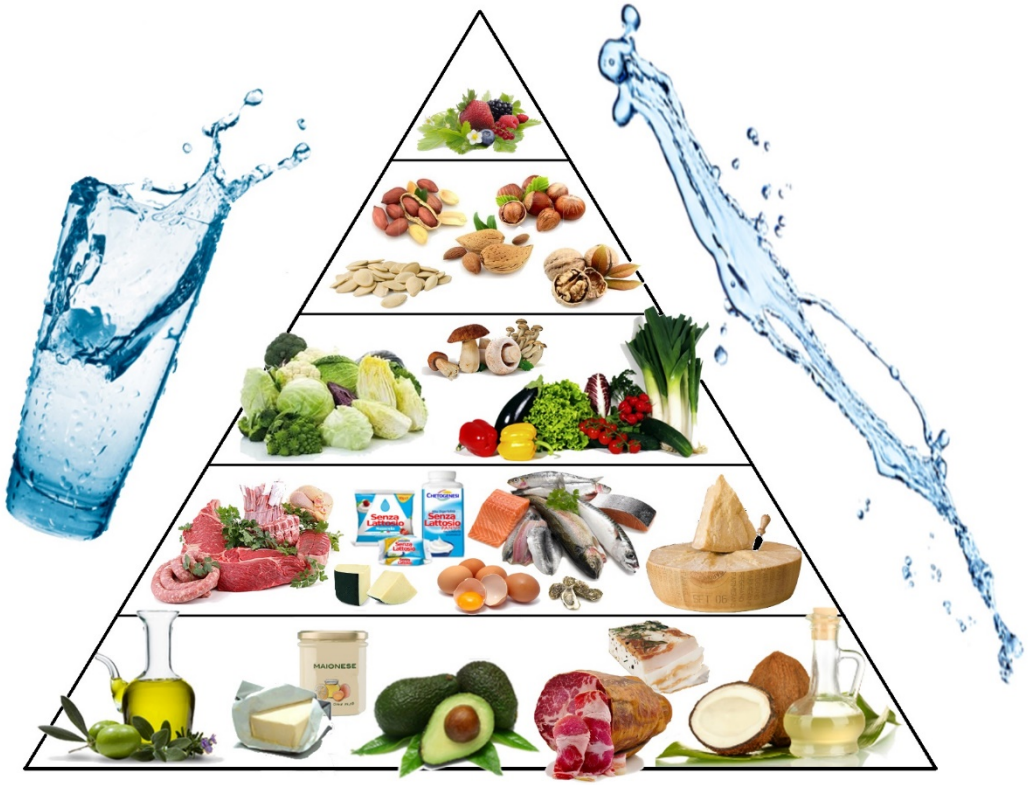
Ketogenic diet and Epilepsy

Why?




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

The Ketogenic Food Pyramid



Omnivore vs Vegan

Table 1. Epilepsy syndromes and conditions in which the KD has been reported as particularly beneficial
Probable benefit (at least two publications)
Glucose transporter protein 1 (GLUT-1) deficiency
Pyruvate dehydrogenase deficiency (PDHD)
Myoclonic-astatic epilepsy (Doose syndrome)
Tuberous sclerosis complex
Rett syndrome
Severe myoclonic epilepsy of infancy (Dravet syndrome)
Infantile spasms
Children receiving only formula (infants or enterally fed patients)
Suggestion of benefit (one case report or series)
Selected mitochondrial disorders
Glycogenosis type V
Landau-Kleffner syndrome
Lafora body disease
Subacute sclerosing panencephalitis (SSPE)

What are the minimum requirements for ketogenic diet services in resource-limited regions? Recommendations from the International League Against Epilepsy Task Force for Dietary Therapy

*Eric H. Kossoff, †Nabil Al-Macki, *Mackenzie C. Cervenka, ‡Heung D. Kim, §Jianxiang Liao, ¶Katherine Megaw, #Janak K. Nathan, **Ximena Raimann, ††Rocio Rivera, ‡‡Adelheid Wiemer-Kruel, §§Emma Williams, and ¶¶Beth A. Zupec-Kania

Epilepsia, 56(9):1337–1342, 2015

Table 1. Baseline and follow-up information, and diagnostic and laboratory studies for children and adults receiving the ketogenic diet

	Baseline (pre-KD)	Follow-up (at clinic visits)
Mandatory	Basic counseling, weight and height, history of food allergies and intolerances, food availability/preferences Labs: sodium, potassium, bicarbonate (CO_2), chloride, BUN, creatinine, glucose Metabolic testing to identify etiology, especially when suspected high risk based on presentation and family history	Weight and height Labs: sodium, potassium, bicarbonate (CO_2), chloride, BUN, creatinine, glucose, lipid profile, urinalysis Urine ketone testing (no consensus – 10 Task Force members voted "mandatory", and 2 voted "advised"); mandatory if patient is not doing well on the diet and considering stopping. Recommendations are also highly dependent on which diet patient is on, e.g., for LGIT no ketone testing may be required
Advised	Calorie count (e.g., three-day food record) Labs: hematocrit, white blood cell count, platelets (recommended especially in countries where nutritional anemia rates are high), calcium, vitamin D level (especially on first-generation anticonvulsants), fasting lipid profile (strongly recommended if history of personal or familial hyperlipidemia, cardiovascular risk factors), liver function tests (mandatory if on hepatically metabolized anticonvulsants)	Labs: liver function tests (if patients is receiving hepatically metabolized anticonvulsants; some discussion about whether this should be mandatory instead), vitamin D level, complete blood count, calcium, free carnitine (strongly recommended if receiving anticonvulsants such as valproate that deplete carnitine)
Optional, but not required	Free carnitine, selenium, magnesium, phosphorus, urinalysis, anticonvulsant levels	Selenium, magnesium, phosphorus, anticonvulsant levels, renal ultrasound, urine calcium and creatinine ratios (especially if not on citrates), DEXA scans CO_2 = bicarbonate; BUN = blood urea nitrogen; LGIT = low glycemic index treatment; DEXA = dual-energy X-ray absorptiometry

Ketogenic diet and child epilepsy around the World

Ketogenic diet and child epilepsy around the World

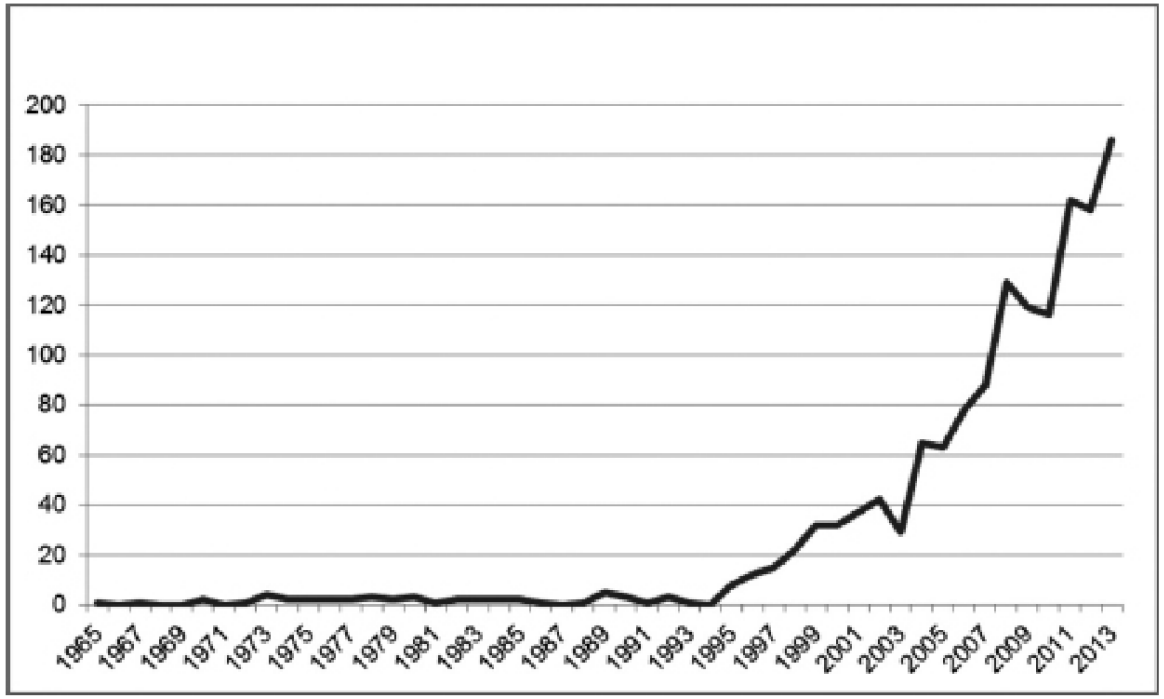


Figure 4.3. Publications over the years on the ketogenic diet, 1965 to 2014.

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

TABLE 5.3

The Effect of Age on Outcomes of the Ketogenic Diet

AGE AT START OF DIET	NO. INITIATING DIET	>50% CONTROL AT 12 MONTHS
<2 years	*N* = 27	59% (1 seizure free)
2–5 years	*N* = 50	56% (4 seizure free)
5–8 years	*N* = 32	50% (4 seizure free)
8–12 years	*N* = 25	40% (1 seizure free)
>12 years	*N* = 16	31% (1 seizure free)
Total	*N* = 150	50% (11 seizure free)

Source: **Adapted 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.**

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, Chen

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%)
Schiff	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%)

[a]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 in Multiple Sclerosis

OPEN ACCESS Freely available online

PLoS one

Inflammation-Mediated Memory Dysfunction and Effects of a Ketogenic Diet in a Murine Model of Multiple Sclerosis

Do Young Kim[1], Junwei Hao[1,2], Ruolan Liu[1], Gregory Turner[3], Fu-Dong Shi[1,2]*, Jong M. Rho[1,4]*

1 Barrow Neurological Institute, Medical Center, St. Joseph's Hospital, Phoenix, Arizona, United States of America, **2** Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China, **3** Keller Center for Imaging Innovation, Barrow Neurological Institute, Phoenix, Arizona, United States of America, **4** Departments of Pediatrics and Clinical Neurosciences, University of Calgary, Alberta Children's Hospital, Calgary, Alberta, Canada

Abstract

A prominent clinical symptom in multiple sclerosis (MS), a progressive disorder of the central nervous system (CNS) due to heightened neuro-inflammation, is learning and memory dysfunction. Here, we investigated the effects of a ketogenic diet (KD) on memory impairment and CNS-inflammation in a murine model of experimental autoimmune encephalomyelitis (EAE), using electrophysiological, behavioral, biochemical and *in vivo* imaging approaches. Behavioral spatial learning deficits were associated with motor disability in EAE mice, and were observed concurrently with brain inflammation. The KD improved motor disability in the EAE model, as well as CA1 hippocampal synaptic plasticity (long-term potentiation) and spatial learning and memory (assessed with the Morris Water Maze). Moreover, hippocampal atrophy and periventricular lesions in EAE mice were reversed in KD-treated EAE mice. Finally, we found that the increased expression of inflammatory cytokines and chemokines, as well as the production of reactive oxygen species (ROS), in our EAE model were both suppressed by the KD. Collectively, our findings indicate that brain inflammation in EAE mice is associated with impaired spatial learning and memory function, and that KD treatment can exert protective effects, likely via attenuation of the robust immune response and increased oxidative stress seen in these animals.

Citation: Kim DY, Hao J, Liu R, Turner G, Shi F-D, et al. (2012) Inflammation-Mediated Memory Dysfunction and Effects of a Ketogenic Diet in a Murine Model of Multiple Sclerosis. PLoS ONE 7(5): e35476. doi:10.1371/journal.pone.0035476

Hindawi Publishing Corporation
Multiple Sclerosis International
Volume 2015, Article ID 681289, 9 pages
http://dx.doi.org/10.1155/2015/681289

Review Article

The Therapeutic Potential of the Ketogenic Diet in Treating Progressive Multiple Sclerosis

Mithu Storoni and Gordon T. Plant

The ketogenic diet has the potential to treat the neurodegenerative component of progressive MS on the basis of the following observations obtained from in vitro and in vivo studies,

(1) Neurodegeneration is thought to underlie the pathogenesis of progressive MS.

(2) Mitochondrial dysfunction may result in reduced ATP availability. This may promote axonal atrophy, leading to degeneration. There is evidence of mitochondrial dysfunction within "normal appearing" grey matter and mitochondrial function appears to correlate with axonal survival.

(3) According to in vitro and animal studies, the ketogenic diet increases ATP production, promotes mitochondrial biogenesis, and bypasses dysfunctional steps within the mitochondrial bioenergetic process, increases antioxidant levels and reduces oxidative damage. Since an increase in ATP and overall improvement in mitochondrial functioning correlates with axonal survival, the ketogenic diet may offer a therapeutic benefit for the neurodegenerative component of MS.

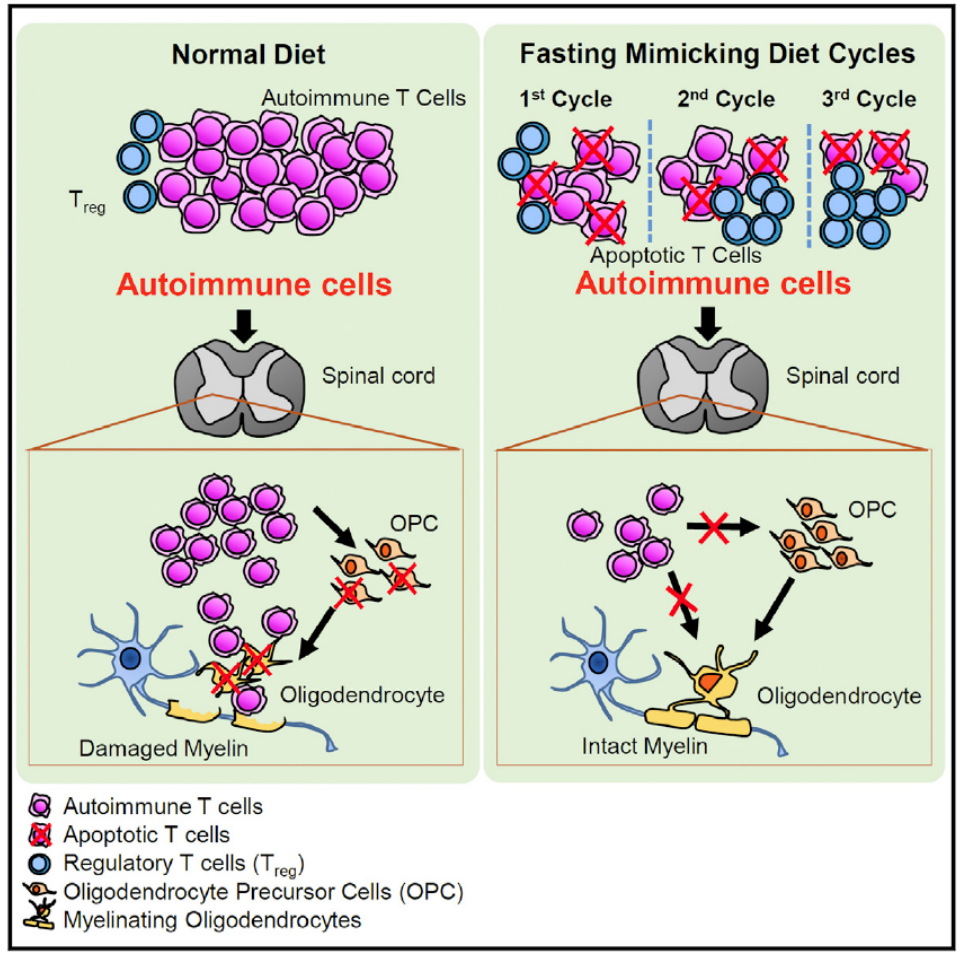
Report

Cell Reports

A Diet Mimicking Fasting Promotes Regeneration and Reduces Autoimmunity and Multiple Sclerosis Symptoms

CellPress

Graphical Abstract



Authors

In Young Choi, Laura Piccio, Patra Childress, ..., Friedemann Paul, Markus Bock, Valter D. Longo

Correspondence

vlongo@usc.edu

In Brief

Choi et al. show that cycles of a fasting mimicking diet (FMD) ameliorate disease severity by suppressing autoimmunity and stimulating remyelination via oligodendrocyte regeneration in multiple sclerosis (MS) mouse models. They also show that a similar FMD is a safe, feasible, and possibly a potentially effective treatment for patients with relapsing-remitting MS.

Highlights

- FMD reduces pro-inflammatory cytokines and increases corticosterone levels
- FMD suppresses autoimmunity by inducing lymphocyte apoptosis
- FMD promotes regeneration of oligodendrocyte in multiple MS models
- FMD is a safe, feasible, and potentially effective treatment for MS patients

Choi et al., 2016, Cell Reports *15*, 2136–2146
June 7, 2016 © 2016 The Author(s).
http://dx.doi.org/10.1016/j.celrep.2016.05.009

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.

Ketogenesis
and Muscular disorders

Ketogenic Diet and Glycogenoses III

JIMD Reports
DOI 10.1007/8904_2014_343

CASE REPORT

Improvement of Cardiomyopathy After High-Fat Diet in Two Siblings with Glycogen Storage Disease Type III

Alessandra Brambilla • Savina Mannarino • Roberta Pretese • Serena Gasperini • Cinzia Galimberti • Rossella Parini

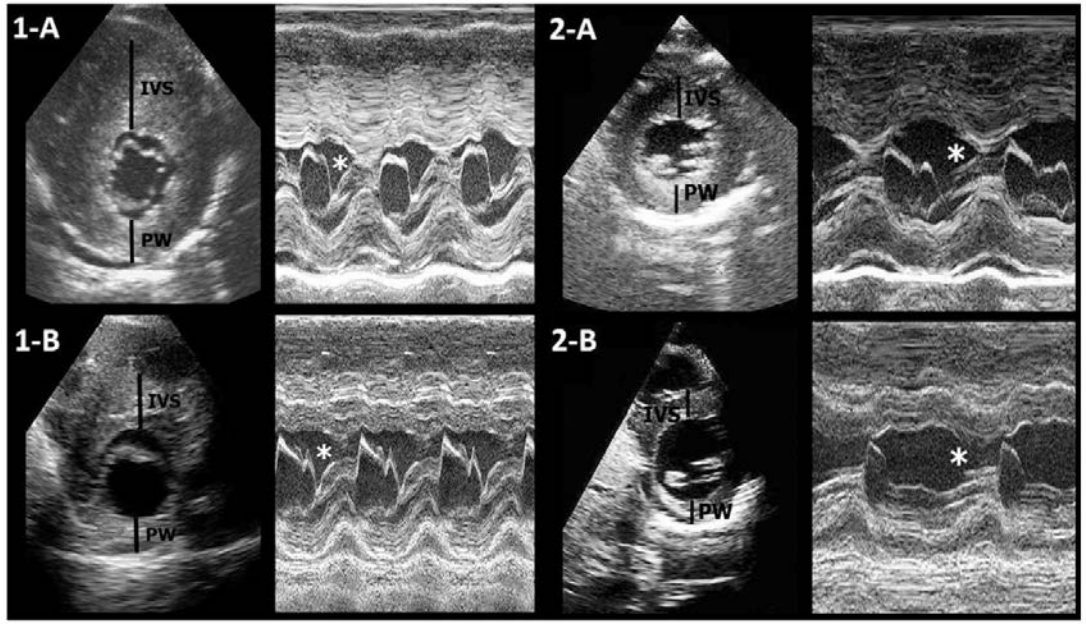


Fig. 1 2D and M-mode echocardiography of girl (1-A and 2-A) and boy (1-B and 2-B) before and after the diet manipulation. *IVS* interventricular septum, *PW* posterior wall of the left ventricle. Note the typical systolic anterior motion of the mitral valve (SAM), responsible of outflow obstruction (*asterisk*) and the reduction of the thickness and the amplitude of SAM after the diet

Table 1 Biochemical and clinical data of the two siblings before and after 1 year of high-fat diet

	Girl		Boy	
	Before	12 months later	Before	12 months later
Clinical data				
Age (years)	7	8	5	6
Weight (kg), centile	24.4, 75–90th	25.3, 50–75th	18.5, 50th	18.3, 25th
Height (cm), centile	115.8, 50th	119, 25th	101, 10th	107, 10th
Hepatomegaly (cm from rib cage)	6	6	8	8
Diet				
Row cornstarch (g/kg ideal body weight/day)	6	0	5	0
Glucose (mg/kg ideal body weight/min)	6.5	1.9	4.8	1.9
Proteins (% total energy; g/kg ideal body weight)	24; 3.5	26; 3.3	33; 5	25; 4.2
Lipids (% total energy)	12	59	16	60
Carbohydrates (% total energy)	64	15	52	15
Kcal/day (kcal/kg ideal body weight)	1,100; 59	1,120; 51	1,025; 60	1,050; 70
Biochemical data				
Preprandial glucose levels (mg/dL)	90–100	80–100	80–90	87–94
1 h postprandial glucose levels (mg/dL)	70–90	70–90	120–125	70–90
Lactate (normal range 0.44–2.22 mmol/L)	1.9–2.1	0.8–2.2	0.6–1.1	0.4–0.8
Triglycerides (normal range 50–200 mg/dL)	117–179	127–161	155–224	246–273
Cholesterol (normal range 130–200 mg/dL)	114–176	170–171	170–204	164–175
Creatine kinase (normal range 20–180 U/L)	3,439–4,473	324–698	1,304–1,868	581–1,006
Aspartate transaminase (normal range <32 U/L)	303–413	264–303	557–1,583	286–324
Alanine transaminase (normal range <33 U/L)	444–544	280–653	521–1,298	447–693
NT–pro-brain natriuretic peptide (normal range <125 pg/mL)	1,907–2,262	206	649–917	135
Troponin T (normal range 0–14 ng/L)	25	21	49	21
Myoglobin (normal range 28–72 ng/mL)	172	39	153	61
Echocardiogram				
Maximum thickness of the septum (mm)	30	16	16	11
Maximum thickness of the posterior wall (mm)	18	7	13	8
Outflow tract obstruction (max/medium Doppler gradient at rest, mmHg)	90–70/30–25	50/21	32–23/10–7	No gradient

Ketogenic Diet and Glycogenoses V

Treatment of Glycogenosis Type V with Ketogenic Diet

Verena Busch, MD,[1] Klaus Gempel, MD,[2] Alexandra Hack ,[1] Klaus Müller, PhD,[3] Matthias Vorgerd, MD,[3] Hanns Lochmüller, MD,[4] and Friedrich A. M. Baumeister, MD[1]

© 2005 American Neurological Association

Published by Wiley-Liss, Inc., through Wiley Subscription Services

Table. Increase of Exercise Tolerance before and with KD

Exertion Level (without interruption to the onset of myalgias)	Before KD	With KD (1 mo 6 mo 1 year)	Increase (n-fold)
Moderate (walking)	200m	2km 6km 12km	10–60
Medium (stepper training in 10 minutes)	20 steps	1 × 100 steps 2 × 100 steps 3 × 100 steps	5–15
High (cycling)	3km	10km 20km 60km	3–20
Maximal duration of ergometer exercise[a]	70 sec	240s	>3

[a]Standard protocol for phosphorous NMR: rhythmic plantar flexion for a defined distance with 10% of the maximal voluntary strength (F_{max}); F_{max} raised by 9% from 750N to 820N.

KD = Ketogenic diet.

Acta Myologica • 2007; XXVI: p. 61-63

Treatment of glycogenosys type V (McArdle disease) with creatine and ketogenic diet with clinical scores and with ^{31}P-MRS on working leg muscle

M. Vorgerd[1], J. Zange[2]

[1] Department of Neurology, Neuromuscular Centre Ruhrgebiet, Ruhr-University Bochum, Germany;
[2] Institute of Aerospace Medicine, Deutsches Zentrum für Luft- und Raumfahrt, DLR e.V., Cologne, Germany;
Faculty of Medicine, University of Cologne, Germany

Case Report

iMedPub Journals
http://www.imedpub.com/

DOI: 10.21767/2380-7245.100054

Journal of Rare Disorders: Diagnosis & Therapy
ISSN 2380-7245

2017
Vol. 3 No. 1: 1

Can a Low-Carbohydrate Diet Improve Exercise Tolerance in Mcardle Disease?

Reason SL[1], Westman EC[2], Godfrey R[3] and Maguire E[3]

Table 2 Clinical response: Not in ketosis and while in ketosis.

Case	Not in Ketosis		In Ketosis	
	CK	Exercise Tolerance	CK	Exercise Tolerance
1	1648 U/L	From childhood, would have to stop due to muscle pain, especially early in any activity or if there was an incline. Walking or cycling uphill was always a challenge, with pain starting in the legs and progressing to the upper body until there would be no alternative but to stop and rest. After resting, could then carry on slowly. As a result of exercise intolerance, walking, running or cycling with friends was avoided. At school, would try anything to get out of having to run or participate in cross-country events.		Exercise intolerance is distinctly less. Can start walking at a faster pace in ketosis. Am able to jog and exercise on a completely different level. Before LCKD, lifetime personal best for a 50-minute treadmill session was average speed of 4.5 mph, that is now a bad day. On LCKD, new personal best is an average speed 5.5 mph. Limits are now more down to basic fitness level, rather than due to McArdles. There is no question a LCKD has improved both aerobic and anaerobic activity tolerance.
2	22.271 U/L	Upon diagnosis, was advised to begin a high carbohydrate diet. Within a few months, exercise intolerance worsened. Was only able to walk for 20 minutes @ 0.75-1.1 mph. Could climb approximately 20 steps. Began to have problems in daily activities, like walking, eating, bathing and playing. After a few months needed to use a wheelchair four days/week due to muscle damage of the leg muscles.	494 U/L	Exercise tolerance dramatically improved once in ketosis. However due to prolonged inactivity while on a high carbohydrate diet, it has taken a few months to regain aerobic fitness. Personal care, playing with other kids, attendance at school have been dramatically improved on a LCKD. Use of a wheelchair is no longer required, therefore PE classes have been restarted. Aerobic function has improved to the level of being able to walk 3.1 mph for 3 miles.
3	10,744 U/L	Experienced muscle failure, muscle spasm and flu-like symptoms regularly. With age, muscle pain was more prevalent. ADLs would cause fatigue and muscle cramps. Exercise seemed to get harder and harder to maintain with age.	150 U/L*	Overall CK is much lower while on a LCKD. No longer experience flu-like symptoms. Aerobically, can run on the treadmill from the start at about 5.5-6.0 mph for 2-3 minutes at a time, and then slower for prolonged periods. There is no need to wait until 'second wind'. Anaerobically, weight training is easier, no longer suffering from muscle aches and pain afterwards.

Reference Range: Males >18 years: 52-336 U/L; Females 8-14 years: 91-391 U/L & >18 years: 38-176 U/L; *within normal reference range

Ketogenesis and other neurological disorders

Lack of consistent clinical data…

- ALS
- Multiple sclerosis

At least one clinical trial has been terminated but no study results were posted

- Autistic spectrum disorder
- Tourette syndrome
- Dystonia
- Various mitochondriopathy

Anecdotal experiences

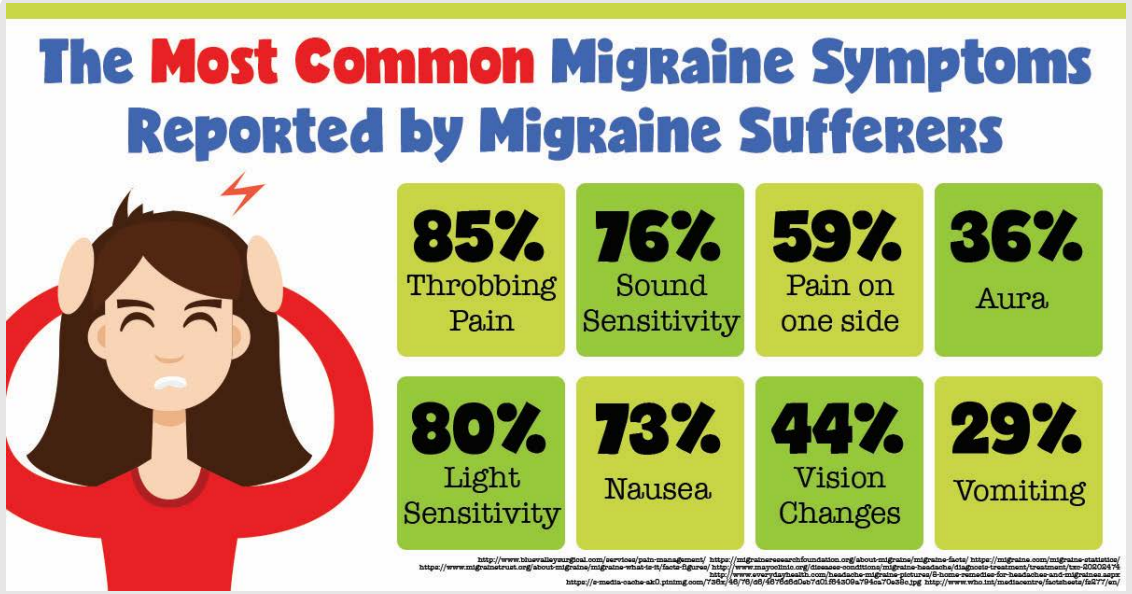
Ketogenesis and Migranie

Migraine

Prevalence

Migraine is the third most common disease in the world (behind dental caries and tension-type headache) with an estimated global prevalence of 14.7% (that's around 1 in 7 people).

Chronic migraine (>15 days/month) affects approximately 2% of the world population.

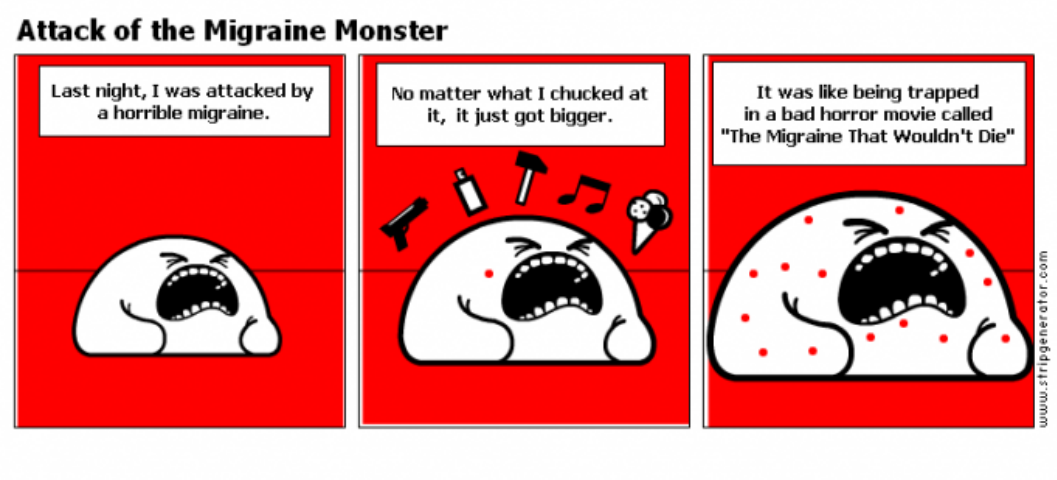


Migraine

Prevalence

Research suggests that 3,000 migraine attacks occur every day for each million of the general population **(>180,000 per day only in Italy**.)

More than three quarters of migraineurs experience at least one attack each month, and more than half experience severe impairment during attacks (all activities are precluded).

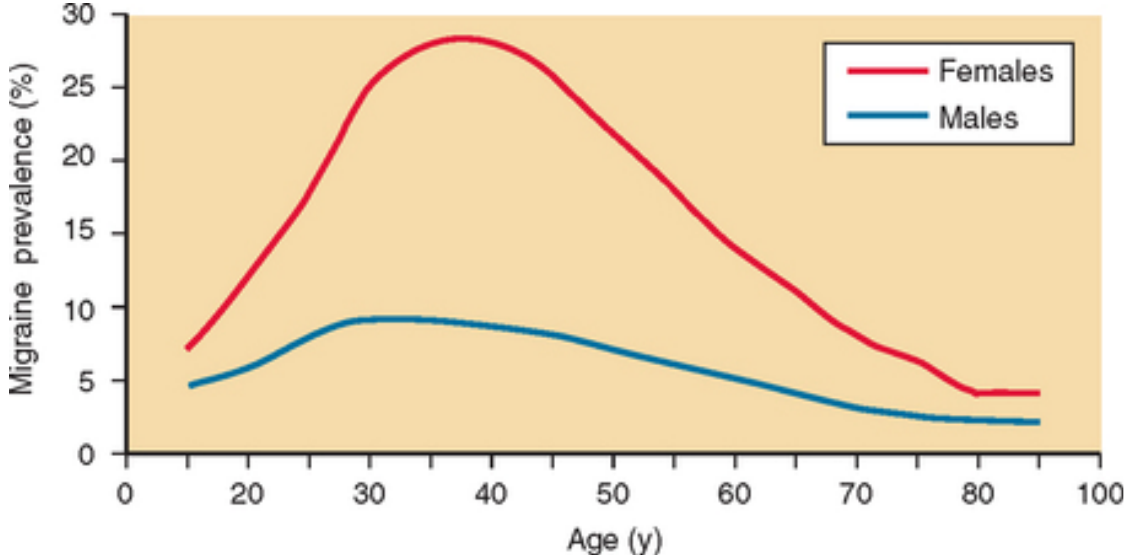


Migraine

Prevalence

Migraine often starts at puberty and most affects those aged between 35 and 45 years, but it can trouble much younger people including children.

About 4% of boys and girls in pre pubertal age suffer from migraine. As children get older there is a predominance among girls.



Migraine

Burden – impact and disability

Migraine is ranked globally as the seventh most disabling disease among all diseases (responsible for 2.9% of all years of life lost to disability/YLDs) and the leading cause of disability among all neurological disorders.

The estimated proportion of time spent with migraine (i.e. experiencing an attack) during an average person's life is 5.3%.

The top 20 leading causes of YLDs in GBD2013	YLDs
1. Low back pain	72,318,000
2. Major depression	51,784,000
3. Iron-deficiency anaemia	36,663,000
4. Neck pain	34,348,000
5. Other hearing loss	32,580,000
6. Migraine	**28,898,000**
7. Diabetes	29,518,000
8. Chronic obstructive pulmonary disease	26,131,000
9. Anxiety disorders	24,356,000
10. Other musculoskeletal disorders	22,644,000
11. Schizophrenia	15,204,000
12. Falls	12,818,000
13. Osteoarthritis	12,811,000
14. Refraction and accommodation errors (of the eye)	11,257,000
15. Asthma	10,596,000
16. Dysthymia	9,849,000
17. Bipolar disorder	9,911,000
18. Medication overuse headache	**9,846,000**
19. Other mental and substance use disorders	9,257,000
20. Dermatitis	9,278,000

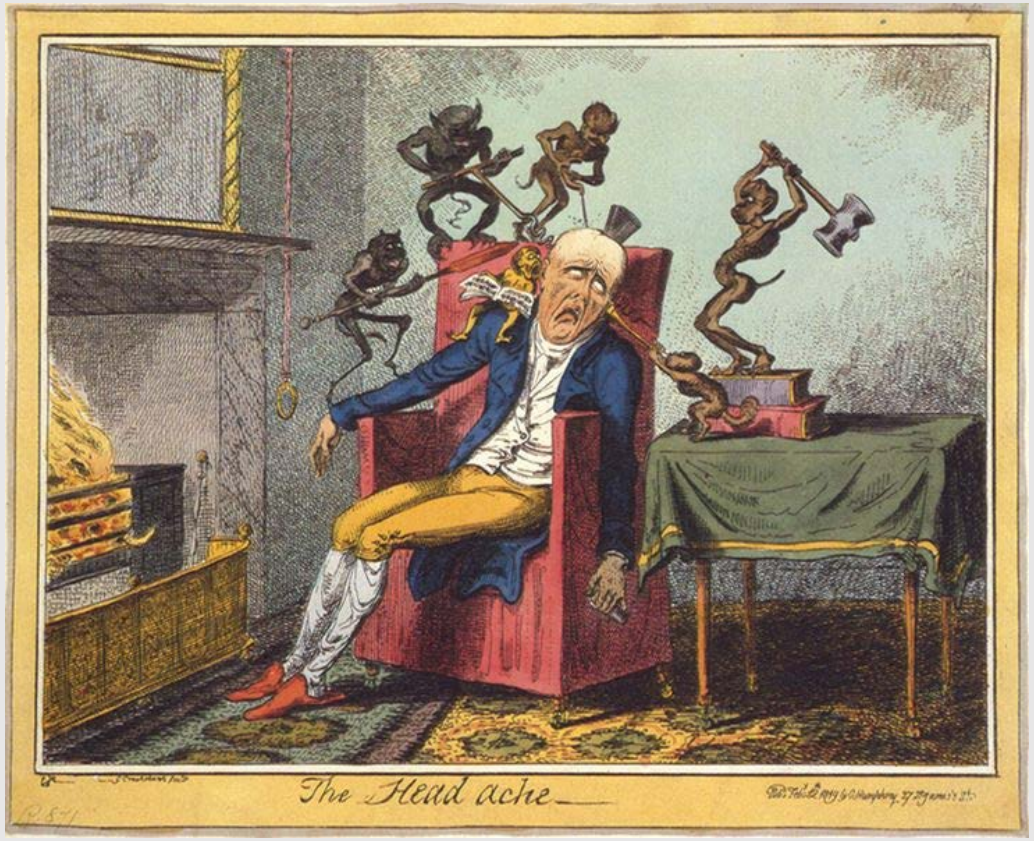
Migraine (6th) and medication-overuse headache (18th) together account for 38,744,000 YLDs, putting headache disorders collectively in 3rd place.

Migraine

Burden – impact and disability

Severe migraine attacks are classified by the World Health Organization as **among the most disabling illnesses**, comparable to dementia, quadriplegia and active psychosis.

Migraine/chronic headache was found to be the second most frequently identified cause of short-term absence (47%) for non-manual employees.

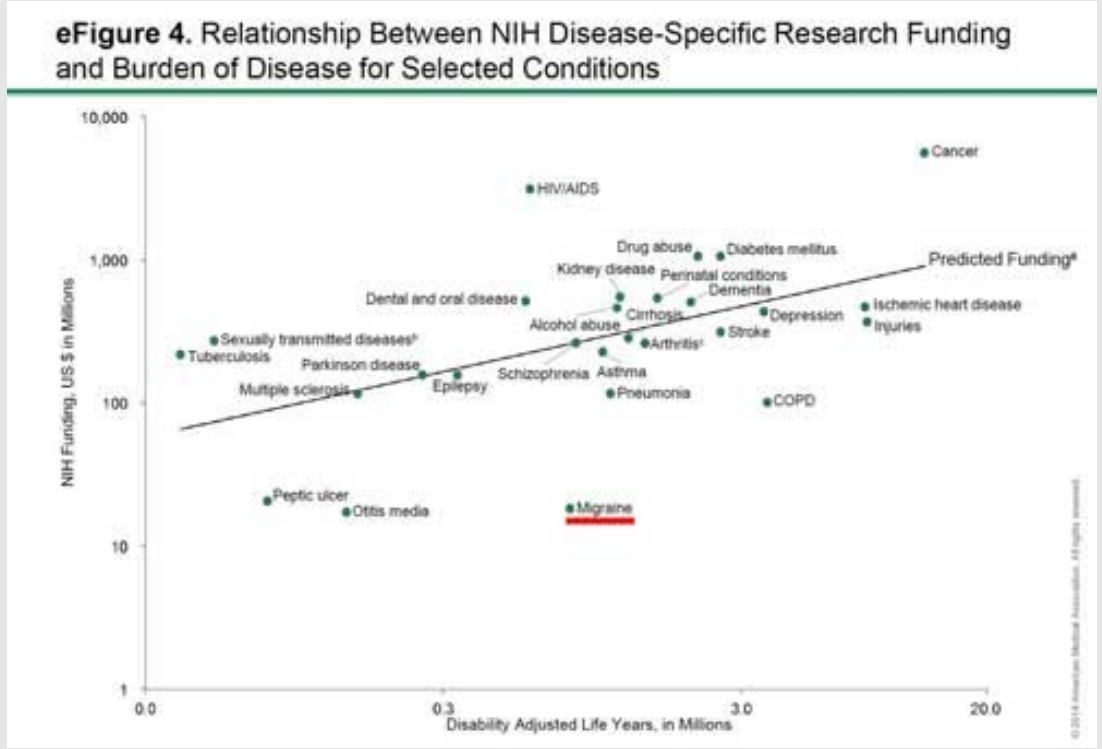


Migraine

Burden – impact and disability

Migraine is the least publicly funded of all neurological illnesses relative to its economic impact.

Depression is three times more common in people with migraine or severe headaches than in healthy individuals.



Migraine and metabolic syndrome

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Screening for the metabolic syndrome in subjects with migraine

Cephalalgia
0(0) 1–9
© International Headache Society 2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0333102416672494
cep.sagepub.com
SAGE

Sylvie Streel[1], Anne-Françoise Donneau[1], Nadia Dardenne[1], Axelle Hoge[1], Adelin Albert[1], Jean Schoenen[2,*] and Michèle Guillaume[1,*]

Article highlights

- The risk of MetS is significantly higher in MA subjects compared to non-migraineurs, while it is not in MO subjects.
- When considering MetS components separately, MA was positively associated with low HDL-cholesterol, hyperglycemia and abdominal obesity.
- A systematic screening of MetS in migraineurs with aura should be advised.

IASP

PAIN® 154 (2013) 1305–1311

PAIN®

www.elsevier.com/locate/pain

Migraine, headache and development of metabolic syndrome: An 11-year follow-up in the Nord-Trøndelag Health Study (HUNT)

Bendik Slagsvold Winsvold [a,b,*], Irene Sandven [c], Knut Hagen [d,e], Mattias Linde [d,e], Kristian Midthjell [f], John-Anker Zwart [a,b,g]

[a] Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[b] Department of Neurology, Oslo University Hospital, Oslo, Norway
[c] Department of Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway
[d] Department of Neuroscience, Faculty of Medicine, Norwegian University of Science and Technology, Trondheim, Norway
[e] Section of Neurology, Norwegian National Headache Centre, St. Olav's Hospital, Trondheim, Norway
[f] Department of Public Health, Norwegian University of Science and Technology, Trondheim, Norway
[g] Communication- and Research Unit for Musculoskeletal Disorders (FORMI), Oslo University Hospital, Oslo, Norway

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 25 September 2012
Received in revised form 11 March 2013
Accepted 2 April 2013

Keywords:
Migraine
Headache
Cardiovascular disease
Metabolic syndrome
Cohort study

ABSTRACT

Migraine with aura is associated with an increased incidence of stroke and cardiovascular disease, but the biological mechanisms are poorly understood. This study examined the incidence of metabolic syndrome and its relationship to migraine with and without aura and to nonmigraine headache. In the population-based the Nord-Trøndelag Health Study (HUNT), 19,895 individuals were followed for the development of metabolic syndrome, with a median follow-up time of 11.3 years. Headache diagnoses were based on a validated headache questionnaire, and metabolic syndrome was based on a modified version of the National Cholesterol Education Program's Adult Treatment Panel (ATP) III criteria, using objective anthropometric measurements and blood biochemistry. Using the Poisson regression model, migraine with aura was associated with an increased risk for developing metabolic syndrome. The effect was modified by smoking, with an adjusted incident risk ratio (IRR) among smokers of 2.10 (95% CI 1.53-2.89) and among nonsmokers of 1.39 (95% CI 1.03-1.86), when compared to headache-free controls. A moderate risk increase was seen for migraine without aura (IRR 1.26, 95% CI 1.12-1.42) and nonmigraine headache (IRR 1.22, 95% CI 1.13-1.32), not modified by smoking. The results suggest that traditional risk factors may be one of the mechanisms through which migraine with aura is linked to an increased risk for cardiovascular disease. A heightened vigilance concerning cardiovascular risk factors in this patient group may be warranted.

© 2013 International Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Insulin sensitivity is impaired in patients with migraine

I Rainero[1], P Limone[2], M Ferrero[1], W Valfrè[1], C Pelissetto[2], E Rubino[1], S Gentile[1], R Lo Giudice[1] & L Pinessi[1]
[1]*Neurology III – Headache Centre, Department of Neuroscience and* [2]*Division of Endocrinology, Department of Internal Medicine, University of Turin, Italy*

Cephalalgia

Rainero I, Limone P, Ferrero M, Valfrè W, Pelissetto C, Rubino E, Gentile S, Lo Giudice R & Pinessi L. Insulin sensitivity is impaired in patients with migraine. Cephalagia 2005; 25:593–597. London. ISSN 0333-1024

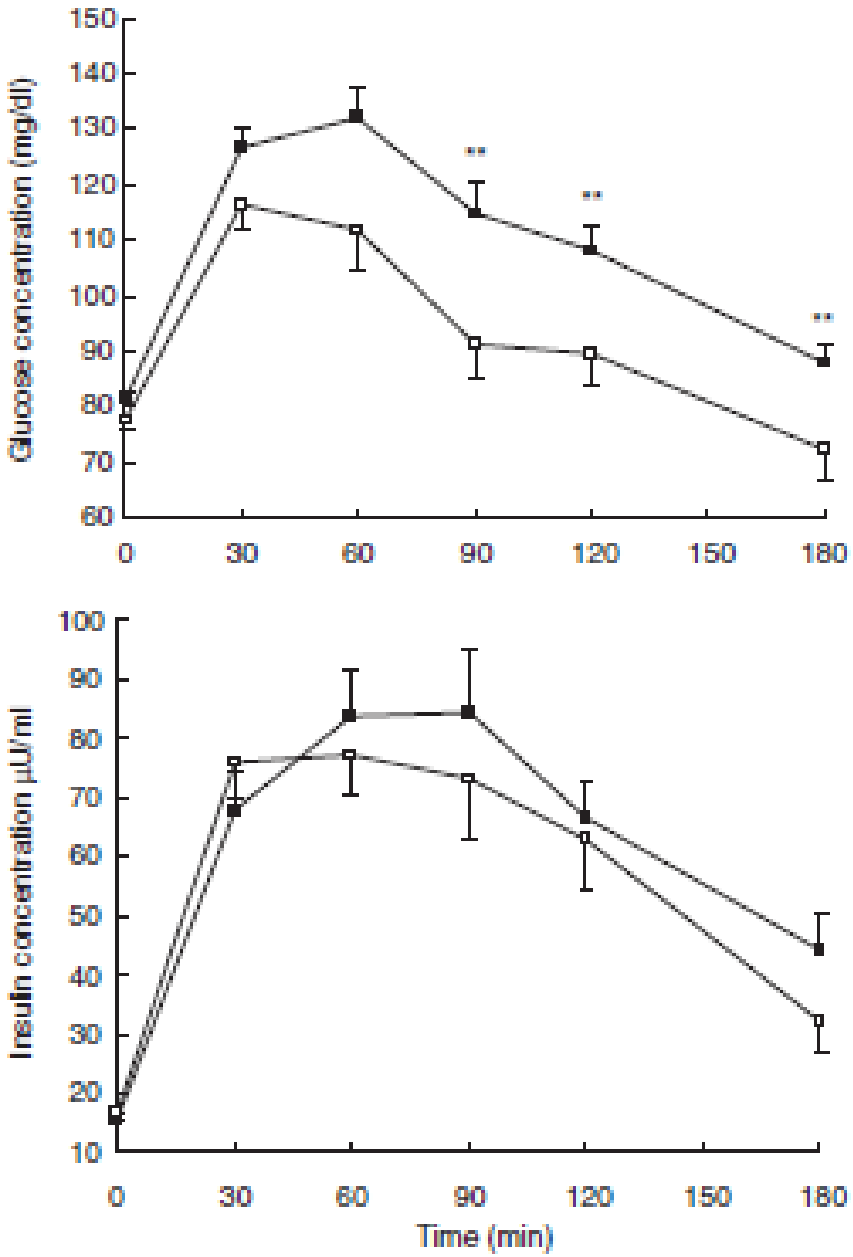
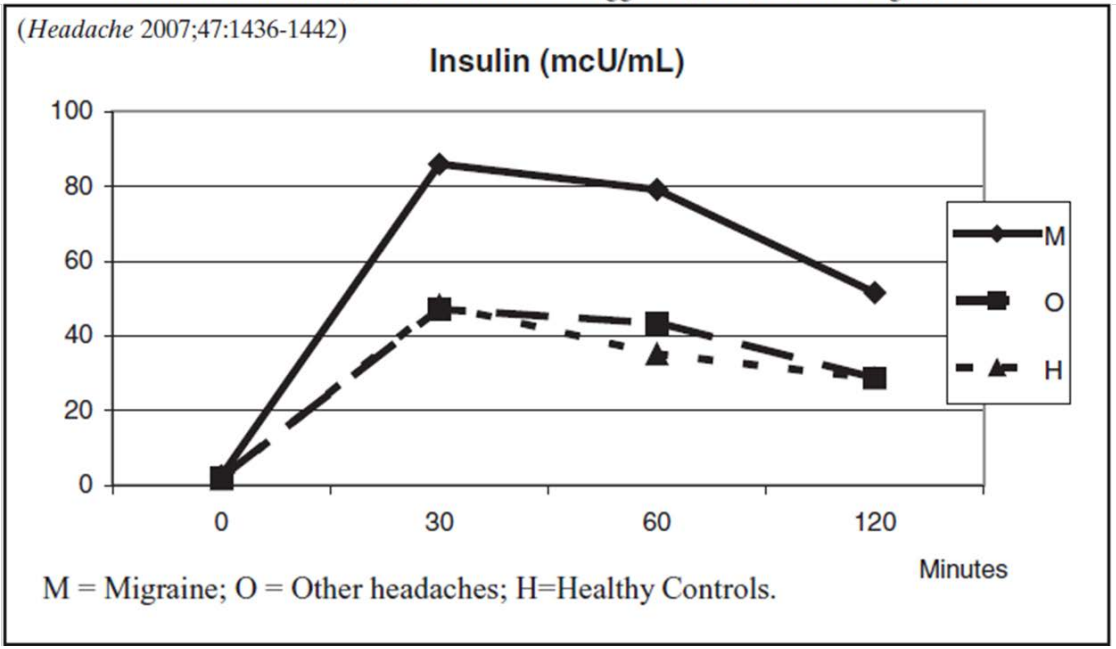


Figure 1 Oral glucose tolerance test (OGTT) in patients with migraine and controls. ■ Migraine patients, □ Controls. Values are mean ± SE.

Insulin Metabolism is Altered in Migraineurs: A New Pathogenic Mechanism for Migraine?

Cinzia Cavestro, MD; Annalisa Rosatello, MD; GianMatteo Micca, MD; Marisa Ravotto; Maria Pia Marino, MD; Giovanni Asteggiano, MD; Ettore Beghi, MD

(*Headache* 2007;47:1436-1442)



M = Migraine; O = Other headaches; H=Healthy Controls.

Original Article

Cephalalgia
An International Journal of Headache

International Headache Society

Cephalalgia
0(0) 1–7
© International Headache Society 2016
Reprints and permissions:
sagepub.co.uk/journalsPermissions.nav
DOI: 10.1177/0333102416665871
cep.sagepub.com
SAGE

Investigating the role of adipokines in chronic migraine

Elisa Rubino[1], Alessandro Vacca[1], Flora Govone[1], Annalisa Gai[1], Silvia Boschi[1], Milena Zucca[1], Paola De Martino[1], Salvatore Gentile[2], Lorenzo Pinessi[1,2] and Innocenzo Rainero[1,2]

Abstract

Background and aims: Adiponectin, leptin, and resistin are adipocyte-derived secretory factors involved in endothelial function, weight, inflammation, and insulin resistance. Recent studies suggested a role for adipokines in episodic migraine as mediators of inflammatory processes. The aim of this study was to investigate plasma concentrations of adiponectin, leptin, and resistin in patients with chronic migraine.

Materials and methods: Twenty-seven chronic migraineurs (20 females, 7 males; mean age 49.0 ± 9.0 yrs) and 37 healthy controls (23 females, 14 males; mean age 49.8 ± 15.0 yrs) were selected for the study. Fasting plasmatic levels of total adiponectin, leptin, and resistin were measured using ELISA kits during a pain-free period. Fasting glucose, insulin, total and HDL-cholesterol, triglycerides, and ESR were also determined.

Results: Serum levels of adiponectin and resistin were significantly increased in chronic migraineurs in comparison with controls ($p = 0.001$ and $p = 0.032$, respectively). After correction for BMI, sex and age, leptin levels were significantly increased in chronic migraineurs ($p = 0.007$). A positive correlation between leptin concentrations and both indices of insulin resistance and markers of inflammation was found.

Discussion: Our data suggest that adiponectin and resistin are altered in non-obese chronic migraineurs. Further studies are needed to elucidate the neurobiological mechanisms underlying adipokine dysfunction in migraine.

Insulin resistance
- ↑ Adiponectin
- ↑ Resistin
- ↑ Leptin resistance

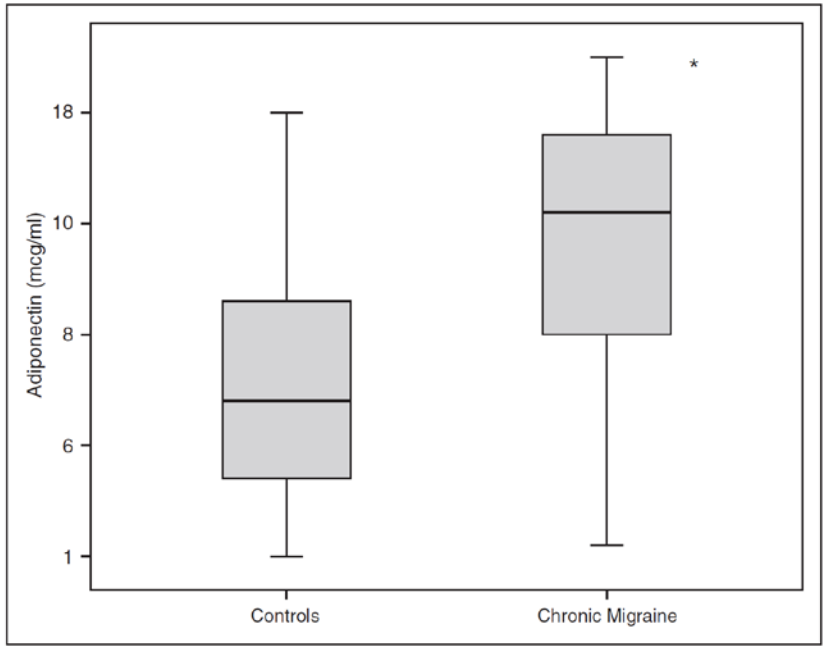


Figure 1. Adiponectin concentration in controls and patients with chronic migraine. Data are presented as a box plot. Adiponectin levels were significantly higher in patients with chronic migraine when compared with controls.
*$p = 0.001$.

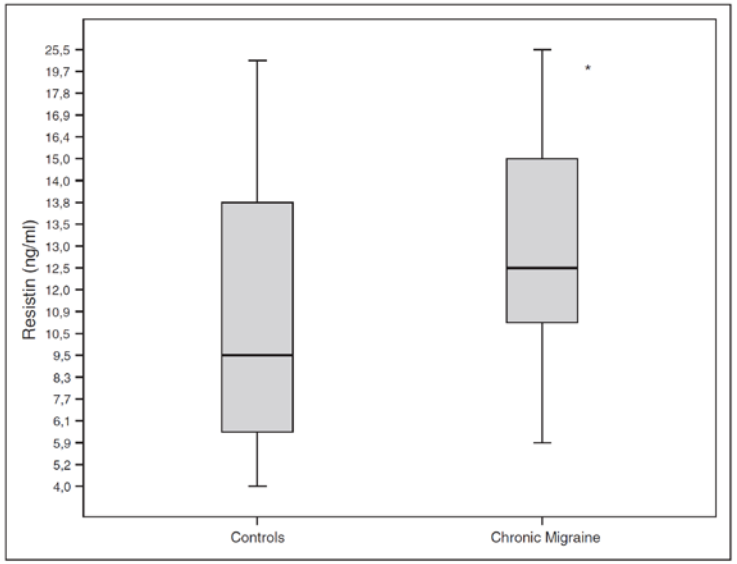


Figure 2. Resistin concentration in controls and patients with chronic migraine. Data are presented as a box plot. Resistin levels were significantly higher in patients with chronic migraine when compared with controls.
*$p < 0.05$.

Migraine and cardiovascular disease

Marcelo E. Bigal[1]

Arq Neuropsiquiatr 2011;69(1):122-129

Cardiovascular events

Cardiovascular Risk factors

Migraine with Aura

Migraine without Aura

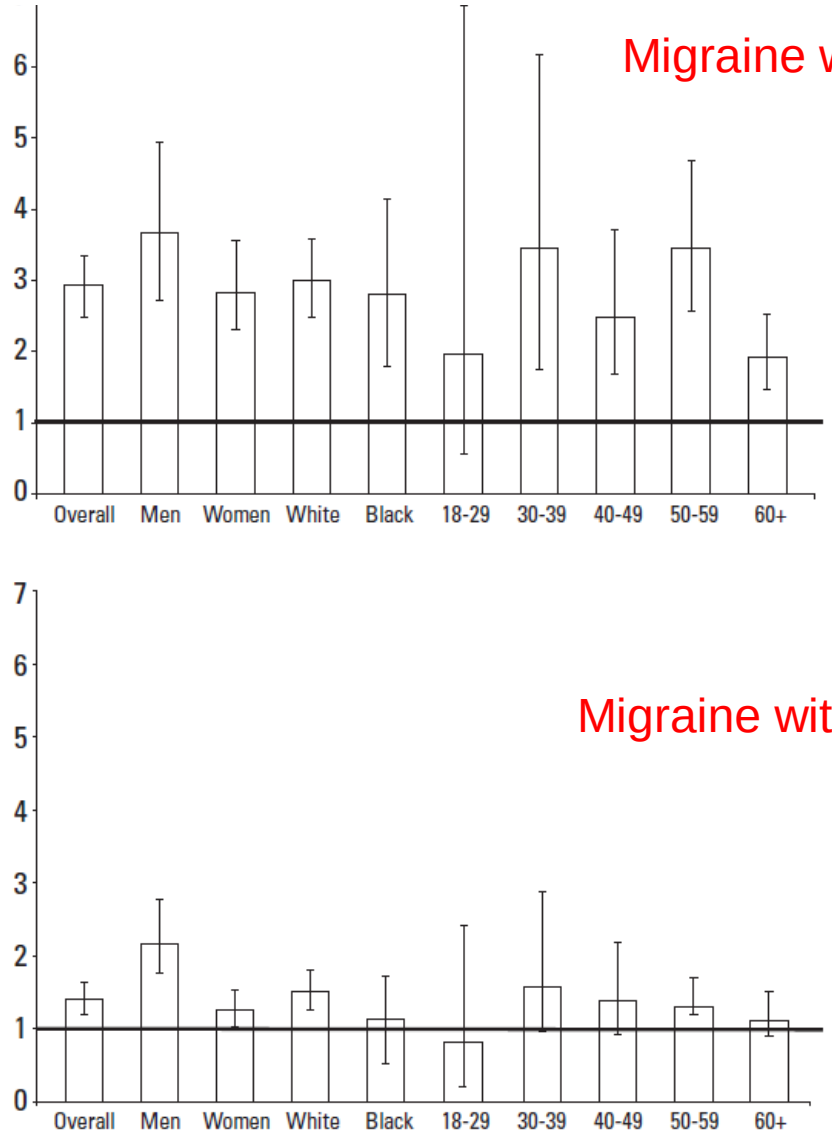


Fig 1. Odds ratio of reporting any cardiovascular event in individuals with migraine with aura (top graphic) and migraine without aura (bottom graphic) (based on[56]). Bars represent the odds ration and whiskers represent the confidence intervals.

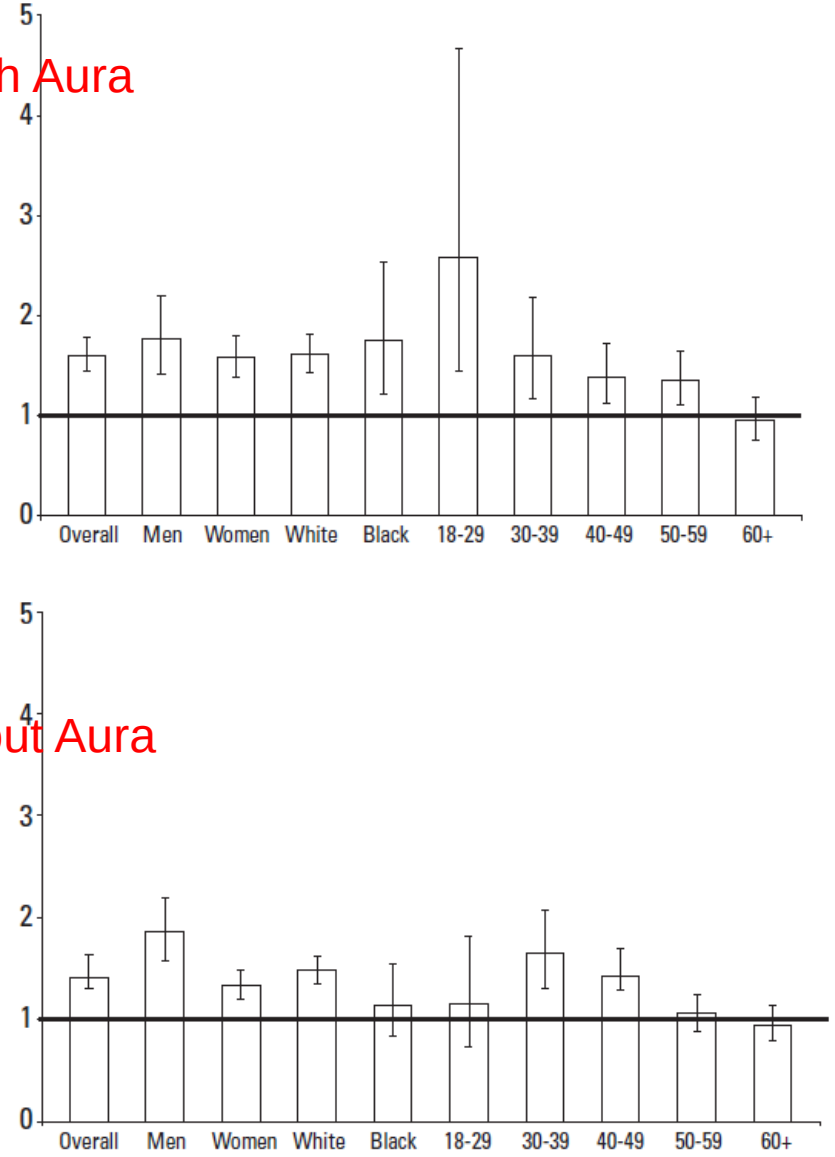


Fig 2. Odds ratio of reporting at least two risk factors for cardiovascular events in individuals with migraine with aura (top graphic) and migraine without aura (bottom graphic) (based on[56]). Bars represent the odds ration and whiskers represent the confidence intervals.

Migraine and cardiovascular disease

Marcelo E. Bigal[1]
Arq Neuropsiquiatr 2011;69(1):122-129

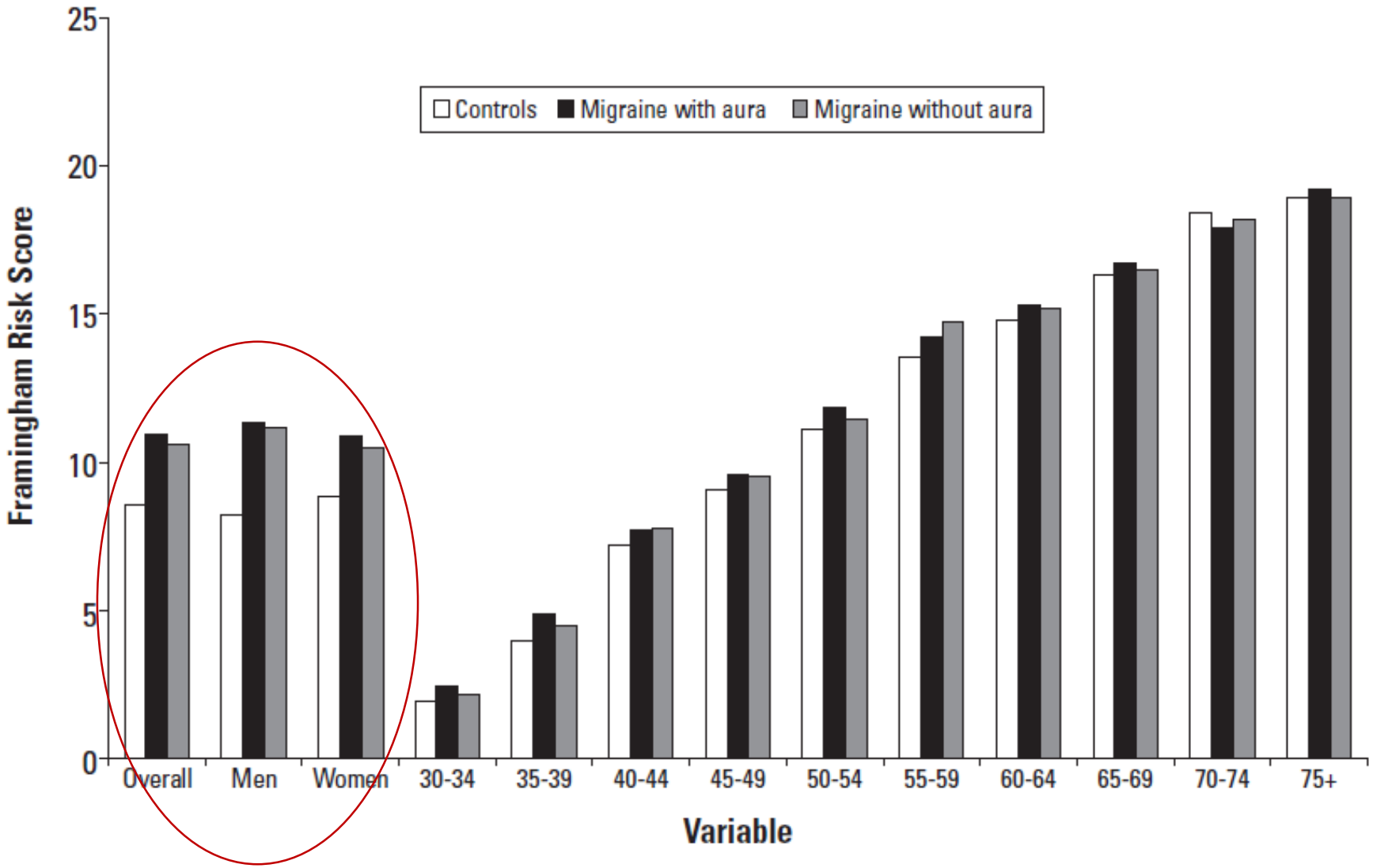


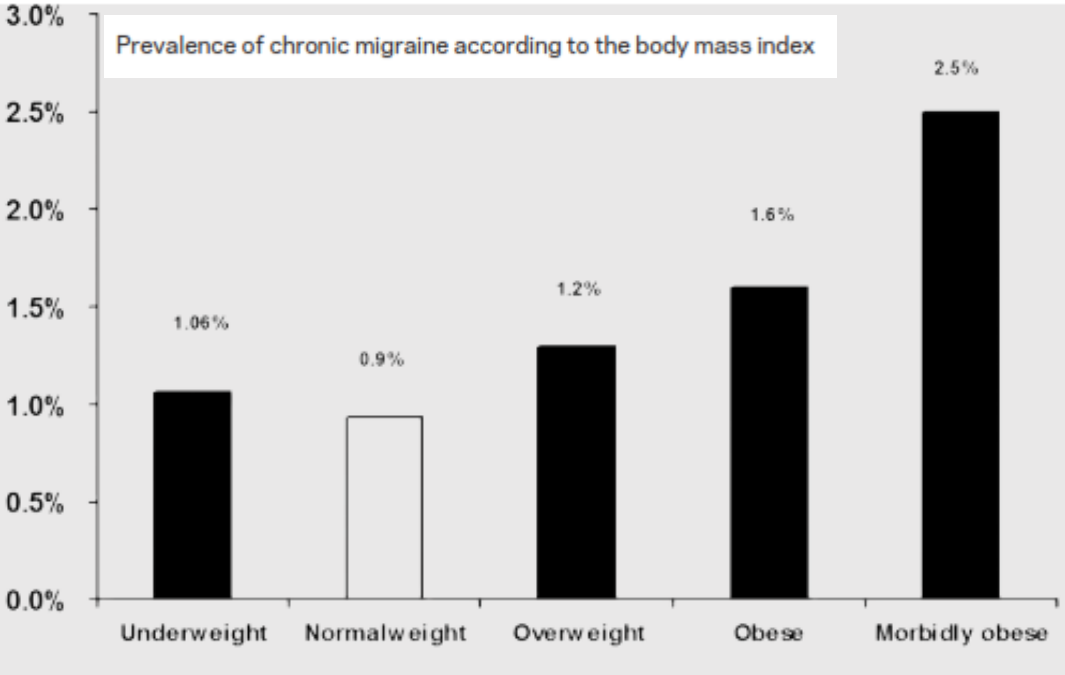
Fig 3. Mean Framingham scores of participants as a function of their headache status and of demographics (based on[56]). Stratification is by age in years.

Obesity, migraine, and chronic migraine

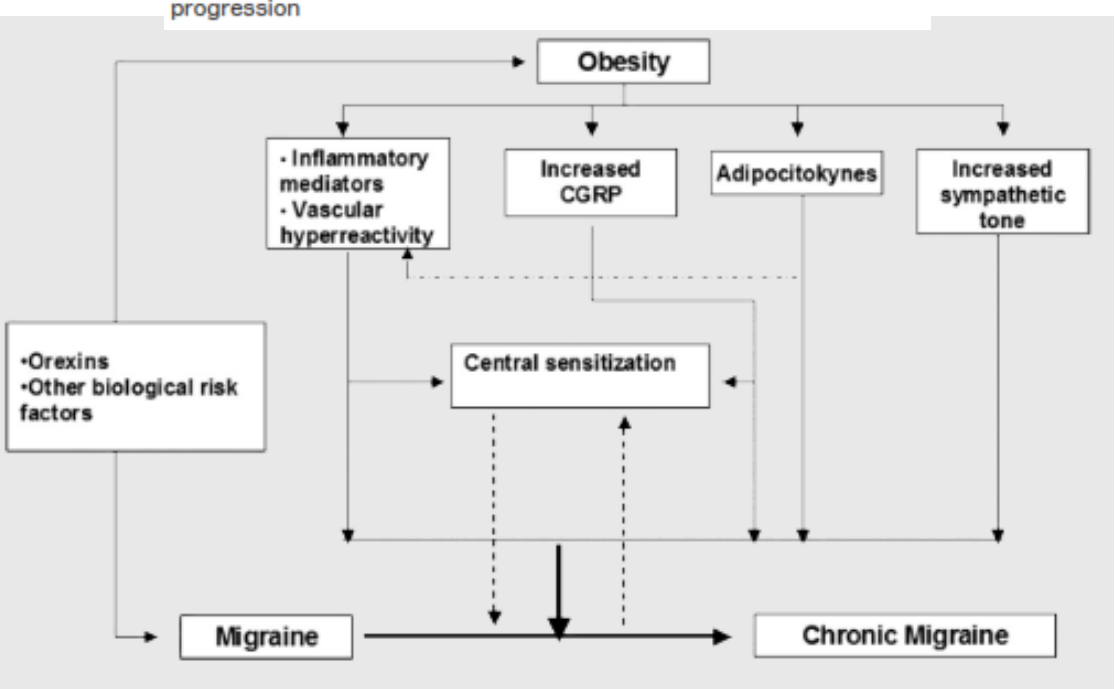
Possible mechanisms of interaction

Neurology, 2007 May 22;68(21):1851-61.

Marcelo E. Bigal, MD, PhD
Richard B. Lipton, MD
Philip R. Holland, PhD
Peter J. Goadsby, MD, PhD



Algorithm summarizing the relationship between obesity and migraine progression



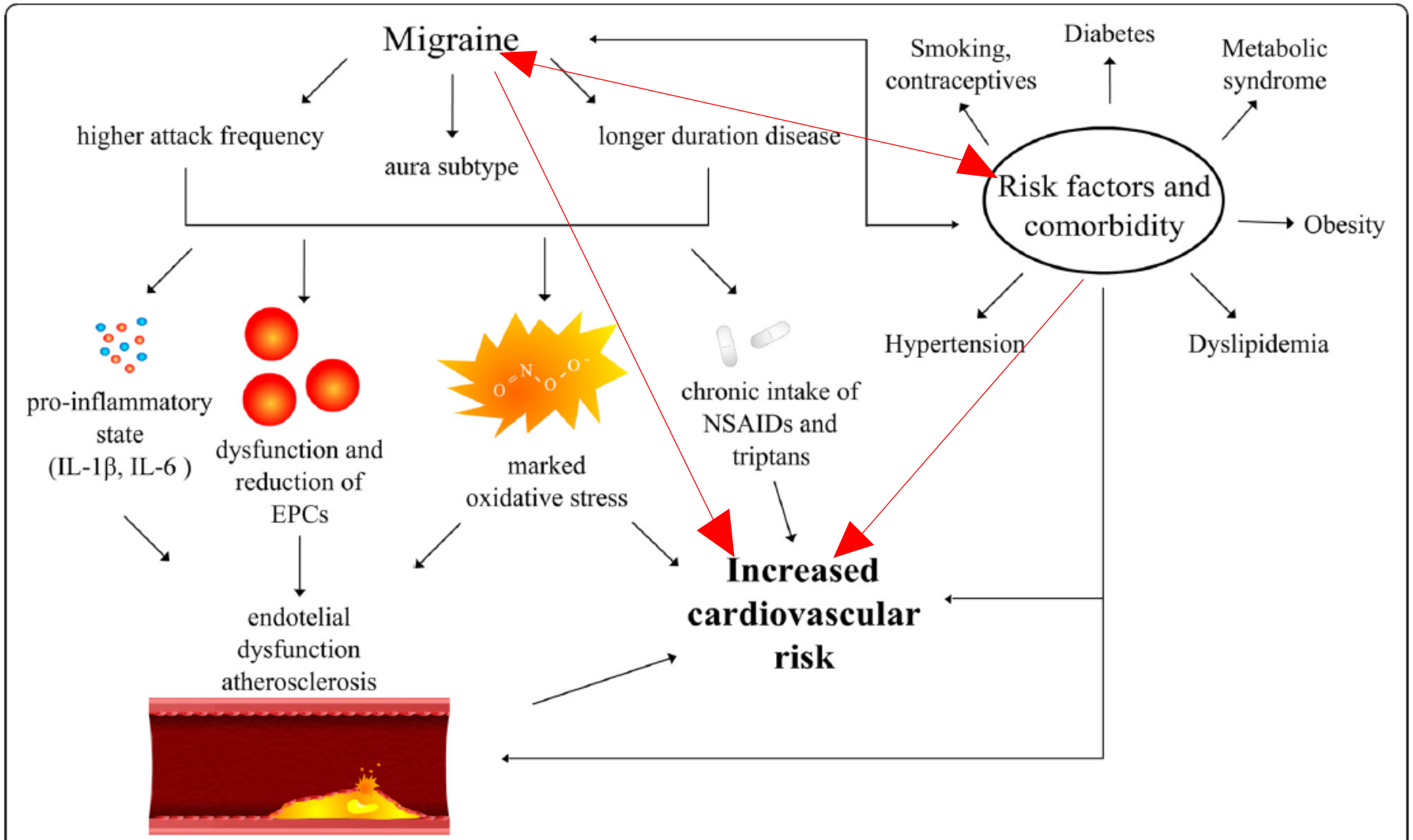


Figure 1 Putative mechanisms which may increase the risk of vascular events in patients with migraine. EPCs Endothelial Progenitor Cells; NSAIDs Non-steroidal anti-inflammatory drugs.

Warning!!!

It is noteworthy that weight increase is a common side effect of the most of preventive treatments for migraine. In particular, flunarizine and amitriptyline induces a weight increase related to higher levels of insulin, leptin and C-peptide [Berilgen et al., 2005], together with changes in the levels of hypothalamic orexinergic peptides [Caproni et al., 2010].

The increase of weight, insulin and leptin (leptin resistance?), although induced by migraine preventive drugs, could counteract the treatment and explain why in some cases these prophylactic therapies lose their efficacy, and potentially, on a long lasting, could worsen the preexisting migraine if the weight does not remain under control (the “prophylactic paradox”).

Questions…

- Migraine is the most prevalent inheritable disease that affects people during the reproductive life. Why?
- Is migraine a prodromic feature of metabolic syndrome?
- Type 3 (or, Brain-) diabetes?

Nutrition 31 (2015) 1–13

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Critical Review

Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base

Highlihgts

- We present major evidence for low-carbohydrate diets as first approach for diabetes.
- Such diets reliably reduce high blood glucose, the most salient feature of diabetes.
- Benefits do not require weight loss although nothing is better for weight reduction.
- Carbohydrate-restricted diets reduce or eliminate need for medication.
- There are no side effects comparable with those seen in intensive pharmacologic treatment.

Nutrition 31 (2015) 1–13

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Critical Review

Dietary carbohydrate restriction as the first approach in obese migraineurs management: Critical review and evidence base

Highlihgts

- We present major evidence for low-carbohydrate diets as first approach for obese migraineurs
- Such diets reliably reduce high blood glucose, the most salient feature of obese migraineurs
- Benefits do not require weight loss although nothing is better for weight reduction.
- Carbohydrate-restricted diets reduce or eliminate need for medication.
- There are no side effects comparable with those seen in intensive pharmacologic treatment.

MANGIA SANO CHE TI PASSA

Nutrizione e Mal di Testa

Pagine: 544
Anno di pubblicazione: 2016
Copertina: brossurata
Formato: 17x24
ISBN: 978-99-7141-991-6
Pagine: 544

Prezzo: € 23.00
Online: € 19.55

1928

An Experience with a Ketogenic Dietary in Migraine*

By Truman G. Schnabel, M.D., *Philadelphia, Pa.*

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 omitted them from their dietary often with satisfactory results. The practice has been further extended by physicians who interdict for their patients as nearly as feasibility permits some one of the three great food groups. Even this course has undoubtedly been suggested by patients themselves when they have offered the observation that an increased intake of either carbohydrates, proteins, or fats has been followed by sick headaches and that restriction in one of these three types of food has seemingly been of some benefit. Here and there, either on their own initiative or under direction, individuals have practiced either prolonged or periodic fasting for bilious headaches not without some good effect as it would seem at least to those who have gone through this experience. Up to the present time various explanations have been offered for the apparent effectivity of either complete or partial dietary restriction in the control of migraine, but many of these explanations are largely theoretical and are open to justifiable adverse criticism.

With a knowledge that diet would seem to have a relationship to the migraine attacks of some individuals it must have occurred to many that the starvation treatment as advocated in epilepsy by Guelpa and Marie (1) abroad and by Geylin in this country must have some reasonable logic in its application. When Wilder (2) in 1921 suggested a high fat diet for the treatment of epilepsy on the hypothesis that the ketone bodies are responsible for the favorable effect of starvation in epilepsy, the conviction of the logic of a ketogenic diet must also have been born home to those who had been observing migraine in relationship to diet. It was only when Peterman (3) in 1925 reported results in the treatment of epilepsy by ketogenic diet that the applicability of this type of diet in migraine suggested itself to me.

There seemed, however, at the time

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

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 to the use of large doses of calcium lactate in an effort to lessen the irritability of the nerves.

The suggestion that migraine is sometimes a phenomenon of protein sensitization is not new. Pagniez[8] and his associates assumed that migraine is an anaphylactic manifestation. Miller and Raulston[9] continued the work in this country. Vaughan,[10] Rowe,[11] and many others have considered migraine from the standpoint of an allergic manifestation. Curtis-Brown[12] proposed the theory of inherited impaired metabolism with intolerance of nitrogenous foods, a protein-poison theory. They advocated various forms of treatment from the use of peptone to the restriction of certain proteins.

Chiray,[13] Duval,[14] Diamond,[15] Hetinyi,[16] McClure and Huntsinger,[17] and others have approached the problem from the standpoint of dysfunction of the liver and duodenum. They have called attention to biliary stasis as an etiologic factor. The French literature has emphasized duodenal migraine; in it evidence is presented of disturbed hepatic function as estimated

Table 1.—*Observations on Patients Whose Conditions Had Been Controlled*

Case	Age	Sex*	Attacks Before Treatment	Disease, Years	On Diet, Months	Ketosis	Comment
1	28	♀	About once a week, lasting two to three days	13	23	Always present	Attacks disappeared after two months
2	26	♀	Twice a week, lasting about two days.....	19	7	Always present	Headaches frequent first six weeks on diet; none since
3	29	♀	Two to three time a week, lasting twelve to eighteen hours	19	20	Periodic	Controlled after first two months
4	37	♀	Once a week, lasting twelve to thirty-six hours	27	9	Always present	First month on diet less severe headache every week; then entirely free since
5	33	♀	Two to three a month, lasting two to three days	8	23	Periodic	After first two months free from attacks
6	44	♀	At least two a month.....	32	16	Periodic	Attacks disappeared after two months
7	21	♀	One to two a week, lasting several hours...	4	14	Always present	After two months some relief; after three months arrested
8	52	♀	One to two a week, lasting one to two days, menopause at thirty-eight; no alteration in attacks	25	16	Always present	After two months no headaches
9	23	♀	Cyclic vomiting beginning at age of two years; migraine at 14; attacks about every five to six weeks	21	15	Always present	Controlled since ketosis developed
10	31	..	Once and sometimes twice a week.....	21	18	Almost always present	No headaches after first three weeks
11	30	♀	Three to six weeks.....	17	13	Always present	Attacks controlled since being on diet
12	27	♀	One to three a week lasting about twelve hours	16	9	Periodic	Attacks controlled since fourth week on diet
13	54	♂	Cephalic migraine thirty-eight years; abdominal migraine last two years	38	36	Present one year, periodic since	Both abdominal and cephalic migraine disappeared after six weeks
14	25	♀	Every two to four weeks.....	8	9	Almost always present	One attack in first three months; none since

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

Serendipity!

Can Ketosis Help Migraine Sufferers? A Case Report

2006

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

Which kind of diet?

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 Fioricet. 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 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.

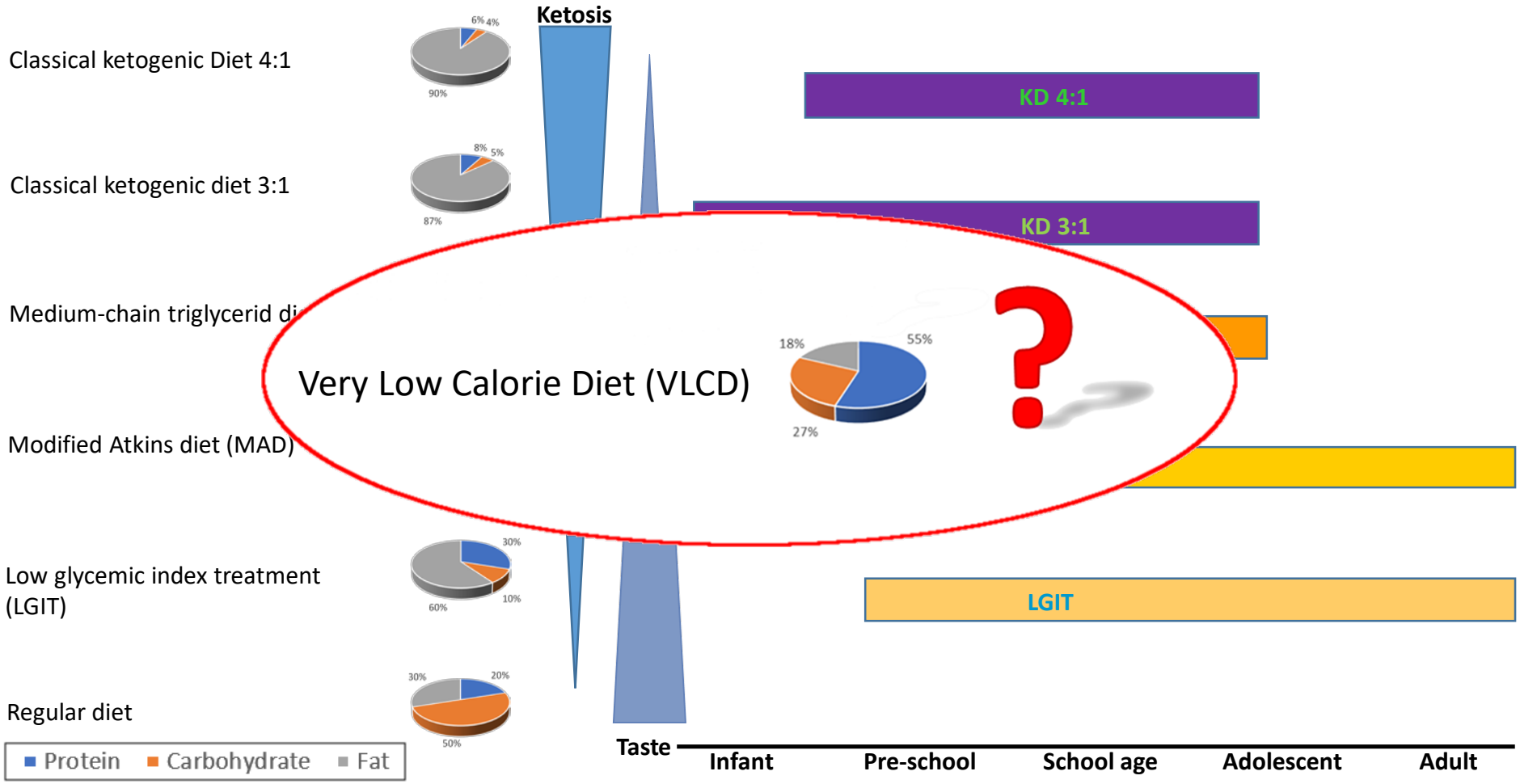
In conclusion, ketosis appears to have cured my wife's migraines. Other refractory migraine sufferers might be willing to enter a period of ketosis to rid them of their headaches.

Baltimore, MD, 21205

REFERENCES

1. Sinha SR, Kossoff EH. The ketogenic diet. *Neurologist*. 2005;11:161-170.
2. Mady MA, et al. The ketogenic diet: adolescents can do it, too. *Epilepsia*. 2003;44:847-851.
3. Sirven J, et al. The ketogenic diet for intractable epilepsy in adults: preliminary results. *Epilepsia*. 1999;40:1721-726.
4. Kossoff EH, Krauss GL, McGrogan JR, Freeman JM. Efficacy of the Atkins diet as therapy for intractable epilepsy. *Neurology*. 2003;61:1789-1791.
5. Murphy P, Likhodii S, Nylen K, Burnham WM. The antidepressant properties of the ketogenic diet. *Biol Psychiatry*. 2004;56:981-983.

Which kind of diet?



Very low calorie diet (VLCD)

- 400 – 800 Kcal/day
- Low carbohydrate: Ketogenic (**VLCKD**)
- Hihg carbohydrate: non-Ketogenic (**VLCnKD**)
- The vantages of KD + prolonged fasting
- Limits: duration

Very Low Calorie Ketogenic Diet (VLCKD)

Is it a difficult diet?
No!

Water (2 lit./day)

Protein supplement (≅15 gr X4)

Up to 200 gr X2 (well dressed)

100-200 gr/day

- 1.2-1.4 gr/Kg protein/day
- <50 gr carbohydrate/day
- 10-20 gr lipids/day
- Vitamin and mineral (K^+, Mg^+, Na^+, Se^+) supplementation

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

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

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

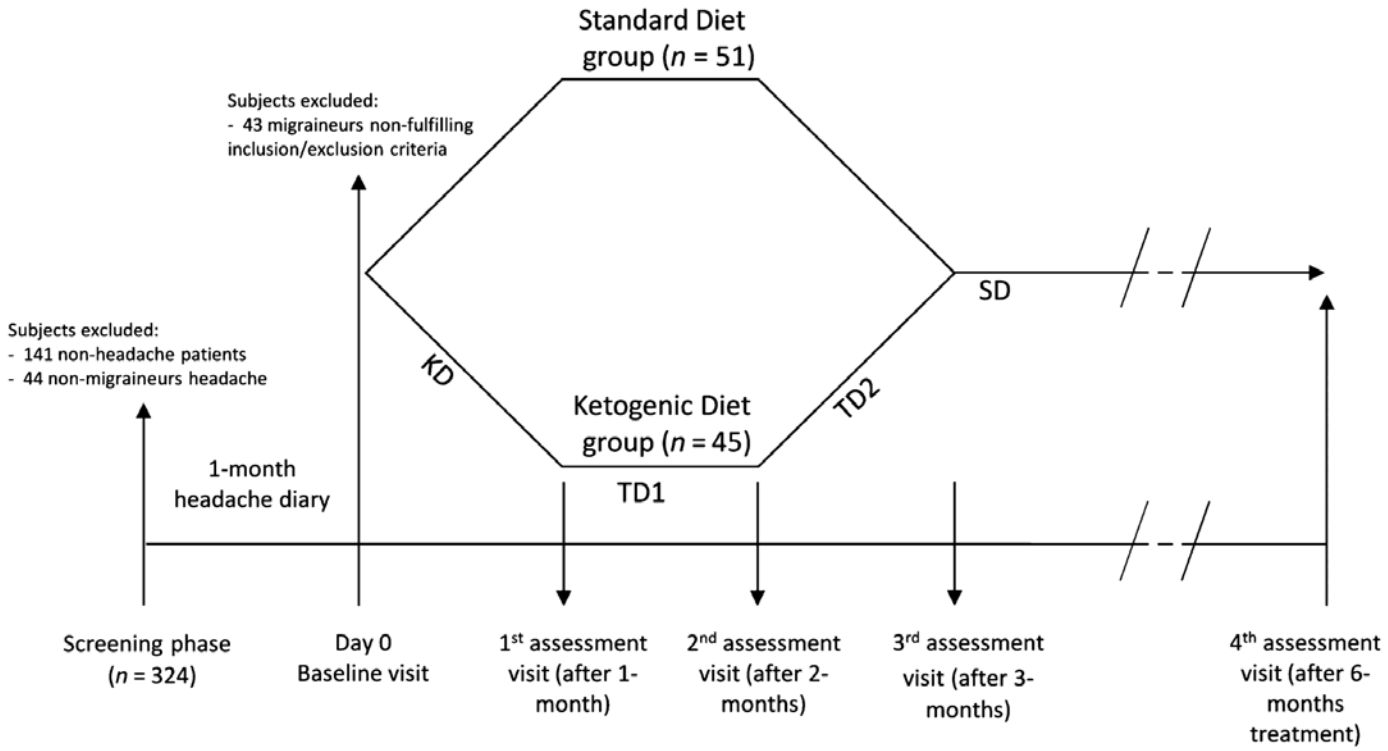


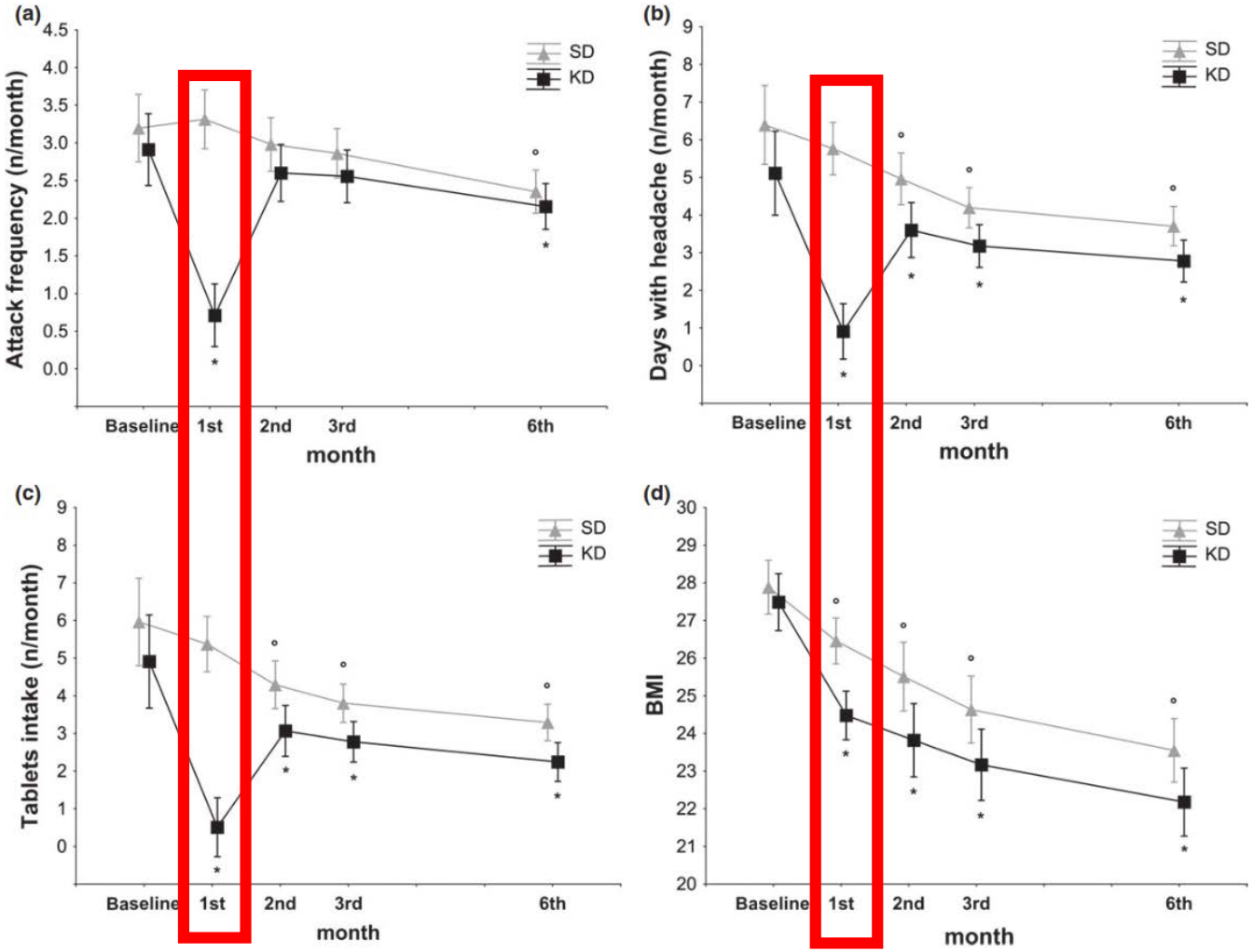
Figure 1 Outline of the study design. SD, standard low-calorie diet; KD, ketogenic very-low-calorie diet, supplemented by nutraceutical integrators; TD1, transitional diet supplemented by nutraceutical integrators; TD2, transitional diet without nutraceutical integrators.

ORIGINAL ARTICLE

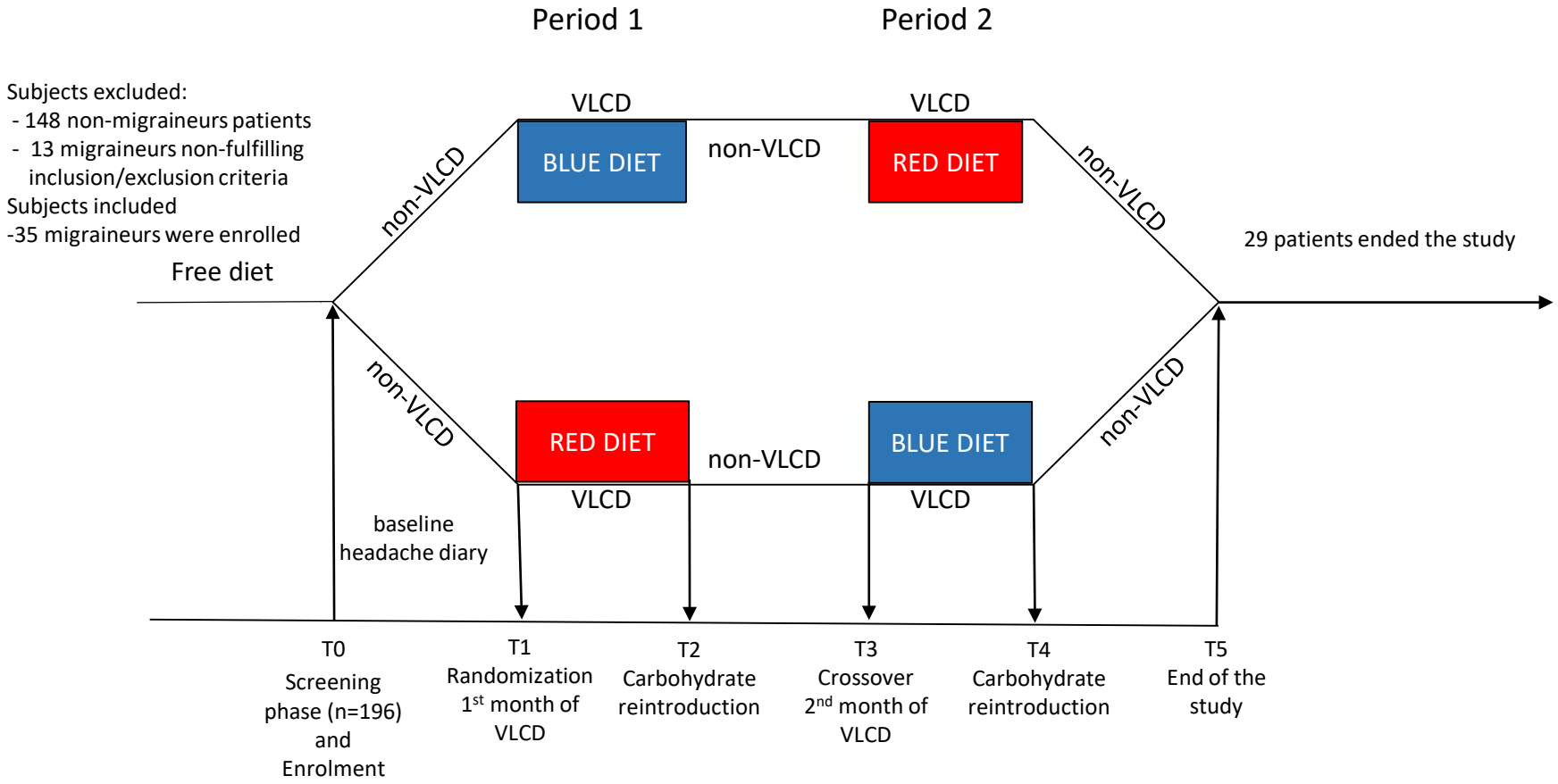
European Journal of Neurology 2015, **22:** 170–177

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]



Double blind vs. sham crossover study: study design



Baseline values

	Whole sample	R = > B	B => R	Statistics
Gender (women / men)	29 / 6	15 / 3	14 / 3	X_1^2 = 0.006, p = 1.000
Age (years)	43.43 (10.17)	40.72 (11.93)	46.29 (7.19)	t_{33} = -1.661, p = 0.106
Headache days/months	6.97 (3.47)	6.28 (2.89)	7.71 (3.95)	t_{33} = -1.227, p = 0.229
Attacks/months	5.37 (2.29)	4.83 (2.01)	5.94 (2.49)	t_{33} = -1.454, p = 0.155
Symptomatic /months	4.63 (3.77)	3.94 (3.59)	5.35 (3.94)	t_{33} = -1.107, p = 0.276
BMI (Kg/m^2)	35.40 (6.25)	34.89 (5.40)	35.94 (7.18)	t_{33} = -0.491, p = 0.627

Double blind vs. sham crossover study: Completed

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”.

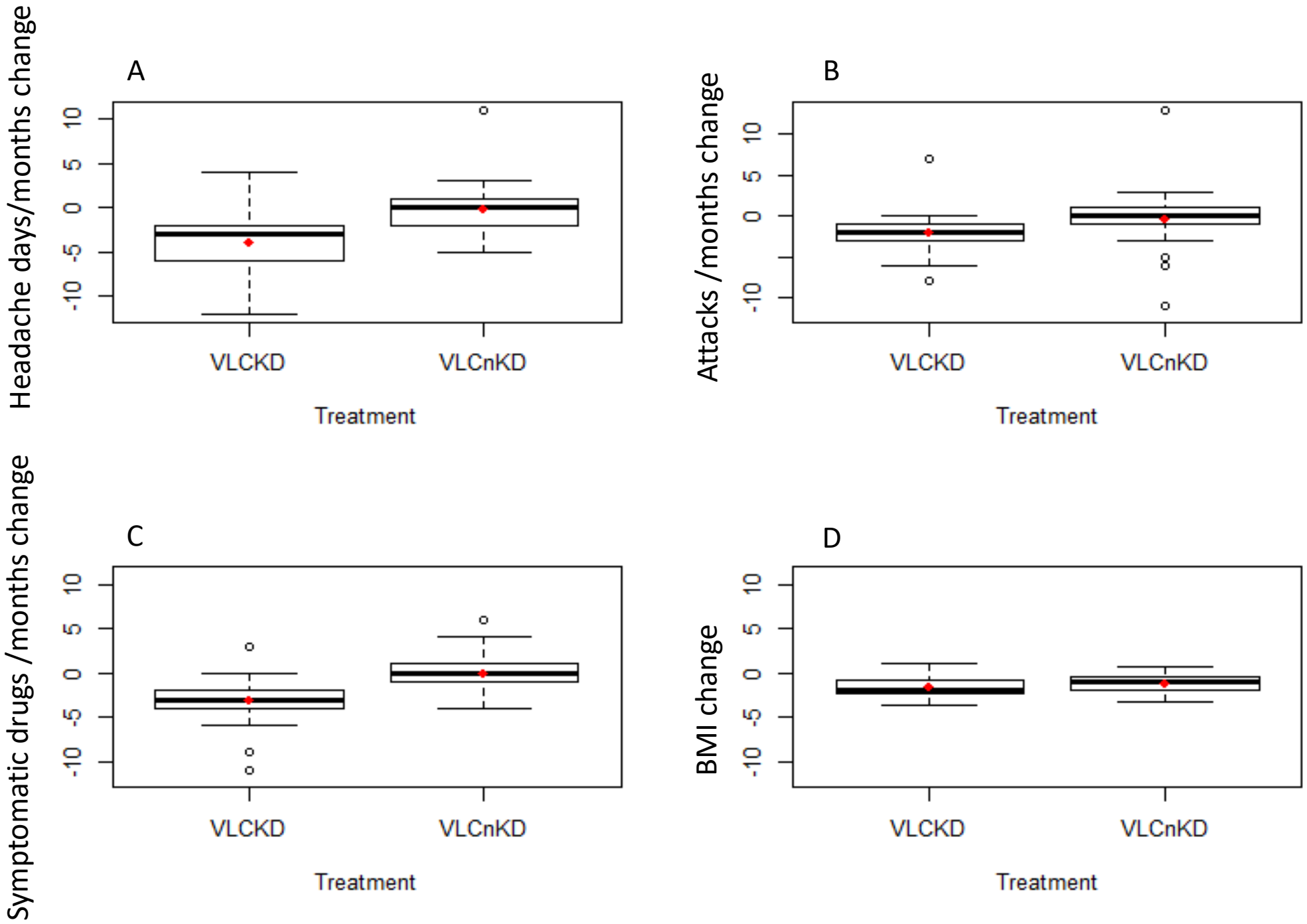
Double blind vs. sham crossover study: Completed

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”.

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


A
Headache days/months change
10
5
0
-5
-10
VLCKD
VLCnKD
Treatment
B
Attacks /months change
10
5
0
-10
VLCKD
VLCnKD
Treatment
C
Symptomatic drugs /months change
10
5
0
-5
-10
VLCKD
VLCnKD
Treatment
D
BMI change
10
5
0
-5
-10
VLCKD
VLCnKD
Treatment

Ketogenesis and Cluster Headache (CH)

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!

☐ Efficiency of **sodium oxybate** in episodic **cluster headache**.

1. Hidalgo H, Uhl V, Gantenbein AR, Sándor PS, Kallweit U.
Headache. 2013 Oct;53(9):1490-1. doi: 10.1111/head.12068. Epub 2013 Mar 6.
PMID: 23463909
Similar articles

☐ Targeting sleep disruption using **sodium oxybate** in chronic **cluster headache** prophylaxis.

2. Silberstein SD, Robbins MS.
Neurology. 2011 Jul 5;77(1):16-7. doi: 10.1212/WNL.0b013e3182231445. Epub 2011 May 25. No abstract available.
PMID: 21613603
Similar articles

☐ Long-term efficacy of **sodium oxybate** in 4 patients with chronic **cluster headache**.

3. Khatami R, Tartarotti S, Siccoli MM, Bassetti CL, Sándor PS.
Neurology. 2011 Jul 5;77(1):67-70. doi: 10.1212/WNL.0b013e31822313c6. Epub 2011 May 25.
PMID: 21613599
Similar articles

Looking for information out of conventional channels…

Herbert Markley · 24.63 · 83.41 · University of Massachusetts Medical School

I have followed 4 patients with chronic cluster headache who became headache free as long as they could maintain a strict Atkins diet. They monitored their urinary ketosis with test strips. They all found that the headaches returned when they stopped spilling ketones, improved when they got ketotic again. All three gave up on this management because it was too taxing to follow the diet protocol. All three have done much better now with Botox.

Methods

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

- Food low in carbohydrates were allowed
- Protein intake was about 0.7-1 gr/Kg/day
- Carbohydrate intake was about 10-50 gr/day
- KD ratio (fat:non-fat) about 1:1
- Lipid supplementation with specific products

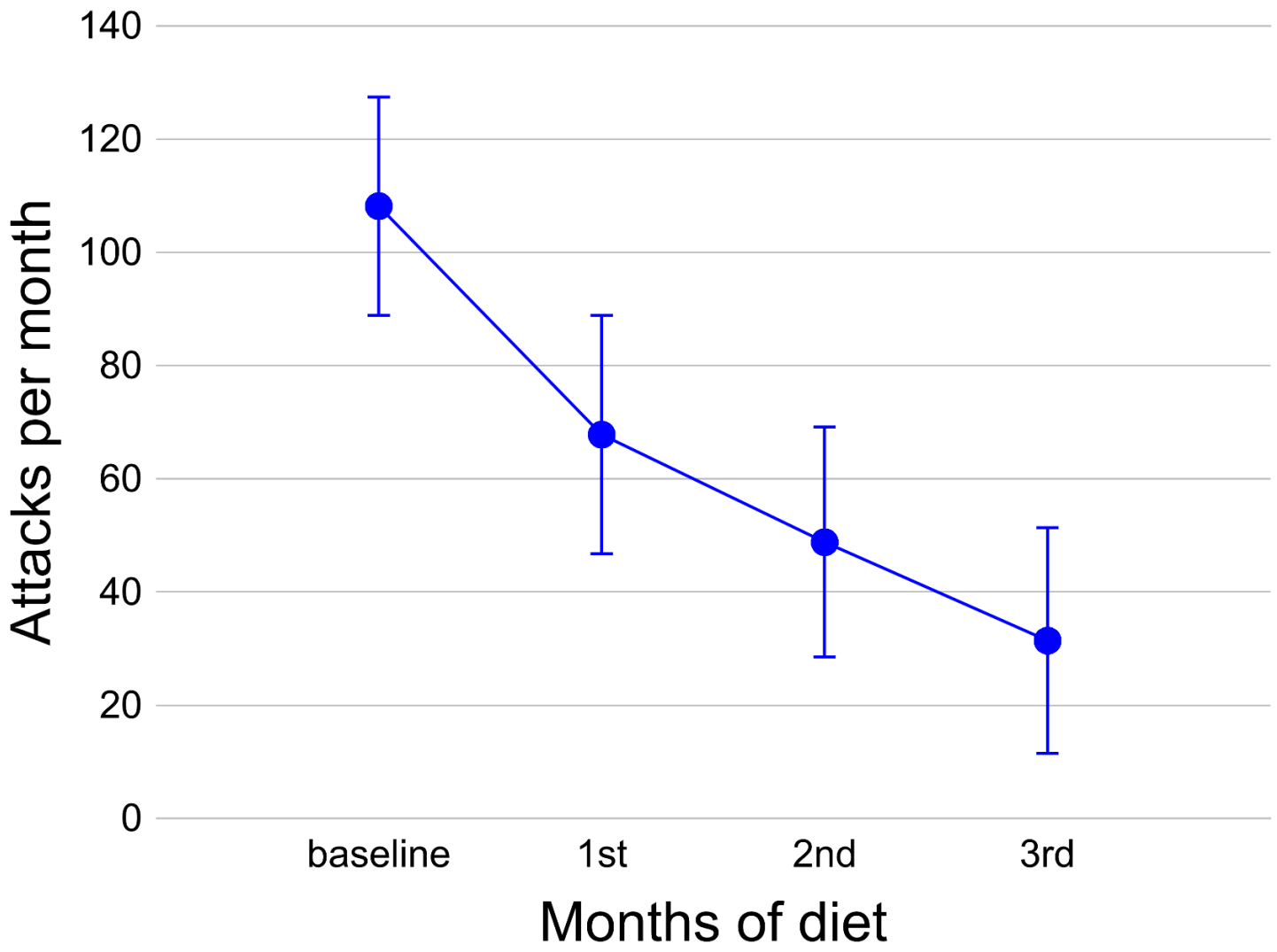
frontiers in Neurology

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

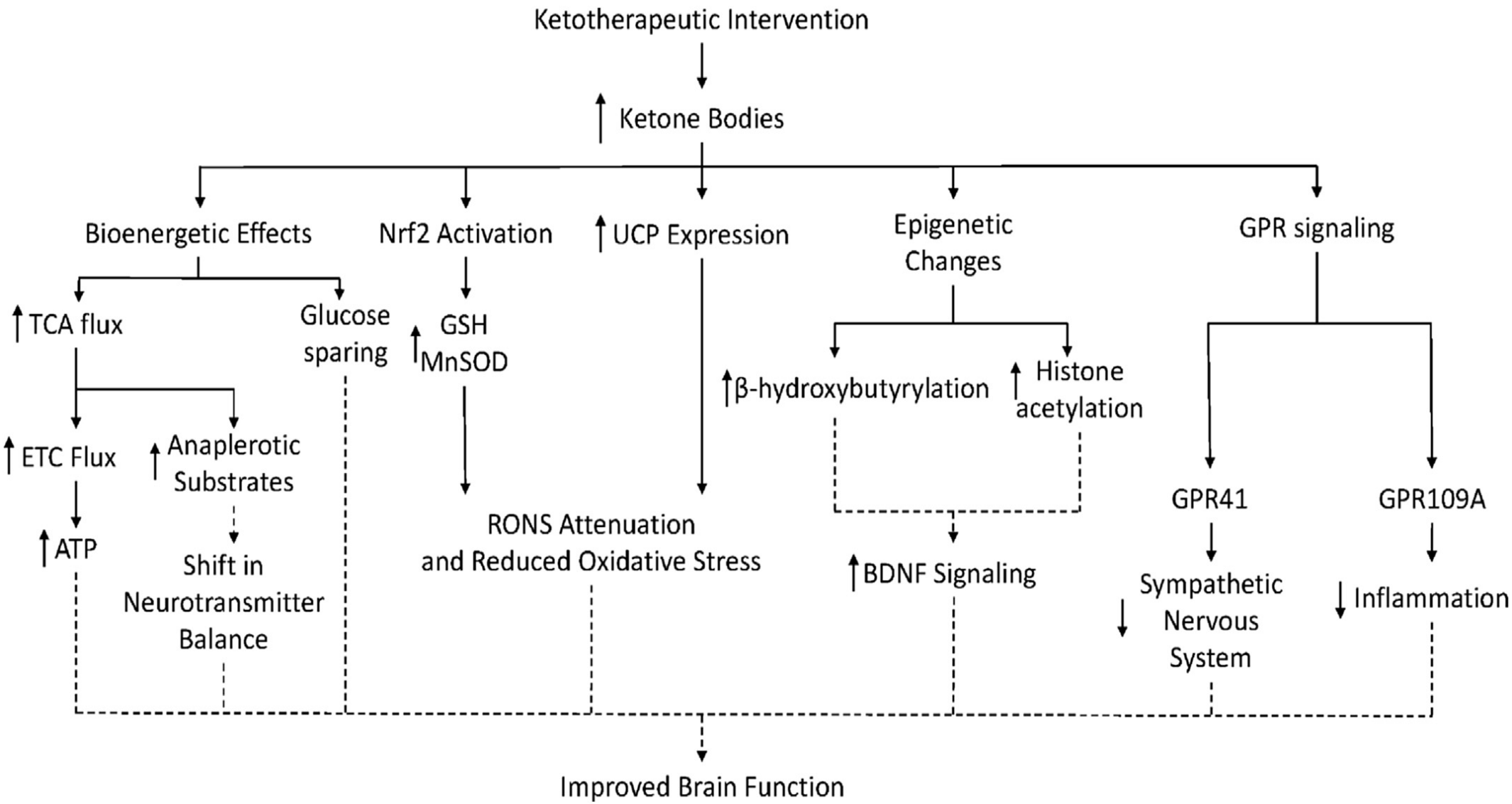
Efficacy of Modified Atkins Ketogenic Diet in Chronic Cluster Headache: An Open-Label, Single-Arm, Clinical Trial

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]*

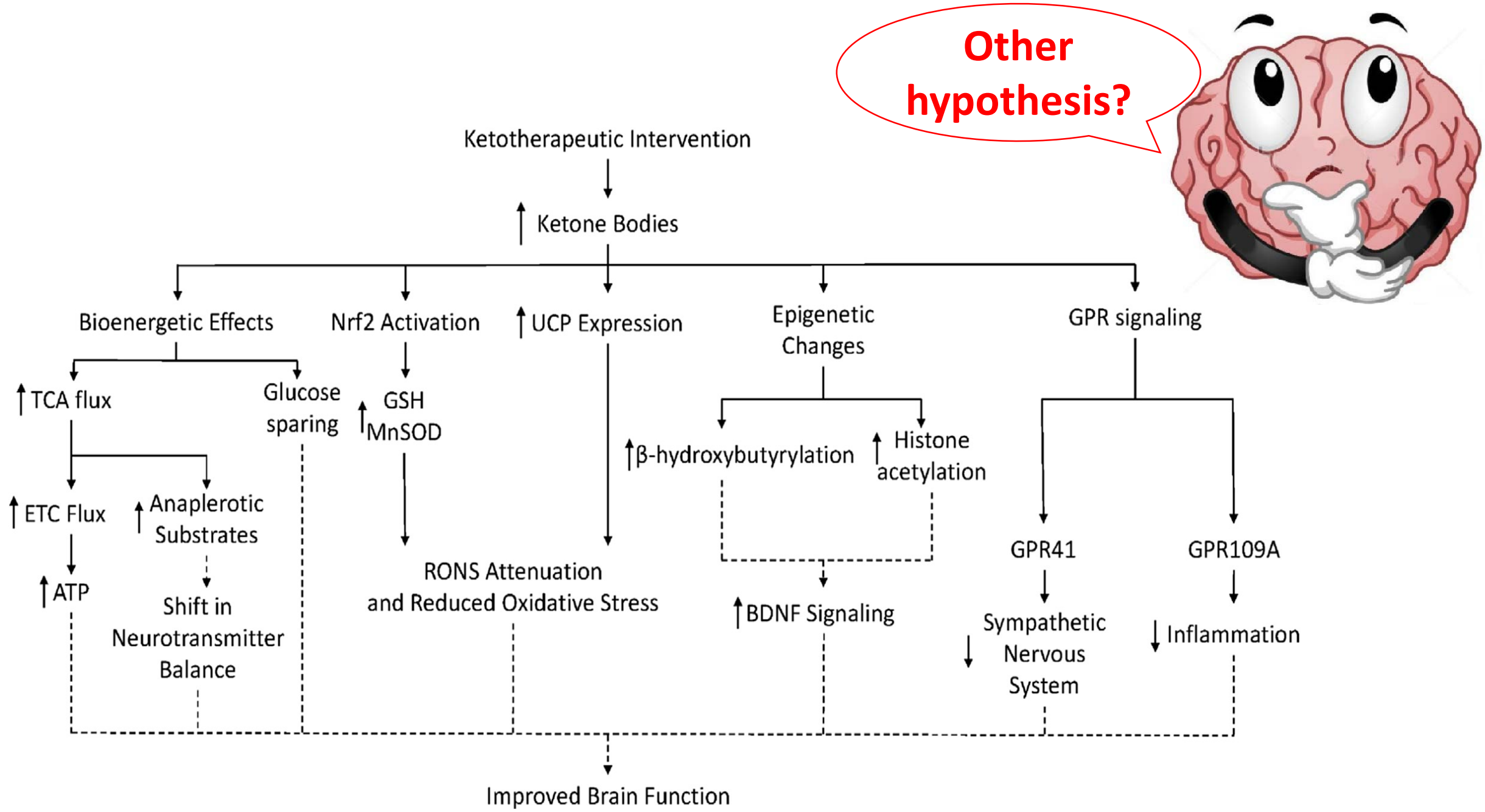
We enrolled 30 consecutive drug resistant (or not compliant) patients with cluster headache and propose them to follow a KD for at least 12 weeks.



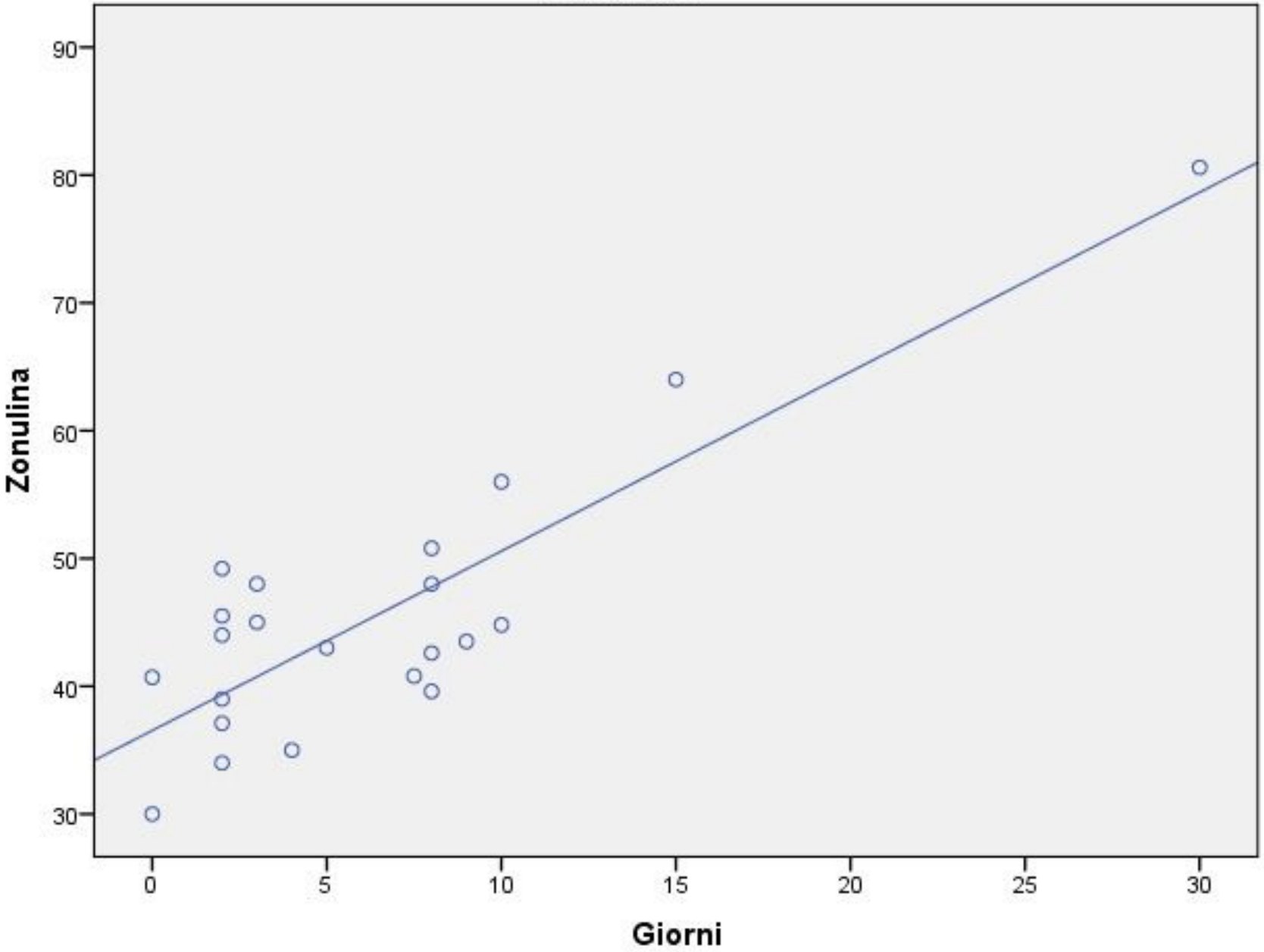
Why KD does act in Migraine and Cluster Headache?



Efficacia della dieta chetogenica come terapia di profilassi dei pazienti emicranici: studio randomizzato controllato in doppio cieco


Other hypothesis?
Ketotherapeutic Intervention
↑ Ketone Bodies
Bioenergetic Effects
Nrf2 Activation
↑ UCP Expression
Epigenetic Changes
GPR signaling
↑ TCA flux
Glucose sparing
GSH
↑ MnSOD
↑ β-hydroxybutyrylation
↑ Histone acetylation
↑ ETC Flux
↑ Anaplerotic Substrates
↑ ATP
Shift in Neurotransmitter Balance
RONS Attenuation and Reduced Oxidative Stress
↑ BDNF Signaling
GPR41
GPR109A
↓ Sympathetic Nervous System
↓ Inflammation
Improved Brain Function

Gut-Brain Axis?



Which kind of diet in adult patients?

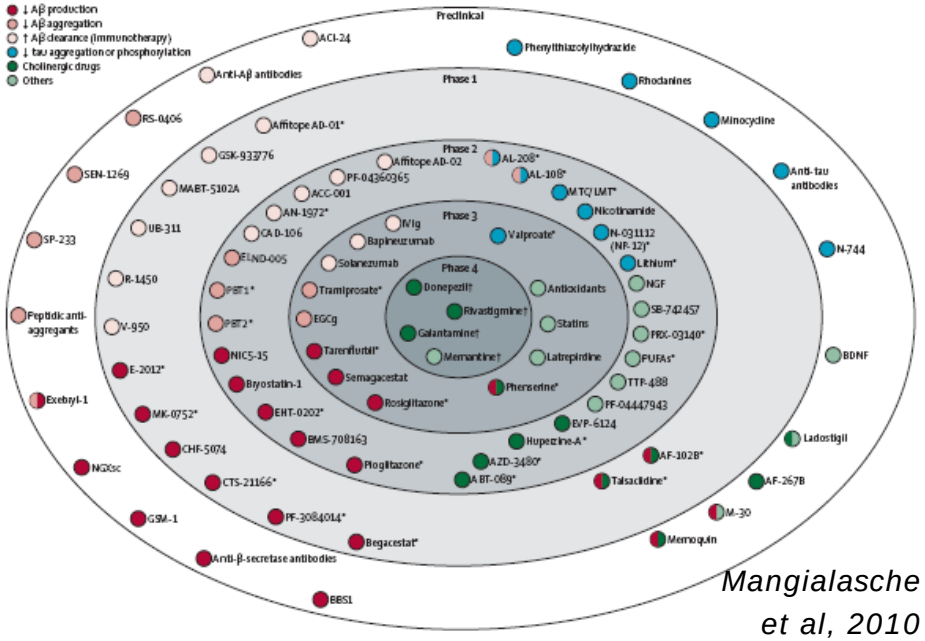
Very low calorie ketogenic diet (VLCKD)
VS.
Classic or Modified ketogenic diet

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

Ketogenesis in Elderly

DISEASE MODIFYING TREATMENTS?



Mangialasche et al, 2010

PREVENTION

Counteracts the risk factors and the transition from MCI to AD

The prevention

Prevention of sporadic Alzheimer's disease: lessons learned from clinical trials and future directions

Sandrine Andrieu*, Nicola Coley*, Simon Lovestone, Paul S Aisen, Bruno Vellas

The projected effects of preventive interventions with even quite modest effects at the individual level are impressive, dramatically reducing the future burden of dementia. For example, an intervention that delays disease onset and progression by 1 year, or a reduction in the prevalence of several modifiable lifestyle risk factors of 10% per decade, could potentially reduce the number of Alzheimer's disease dementia cases worldwide in 2050 by around 9 million.[5,6]

Andrieu et al, 2015

Potential for primary prevention of Alzheimer's disease: an analysis of population-based data

Sam Norton, Fiona E Matthews, Deborah E Barnes, Kristine Yaffe, Carol Brayne

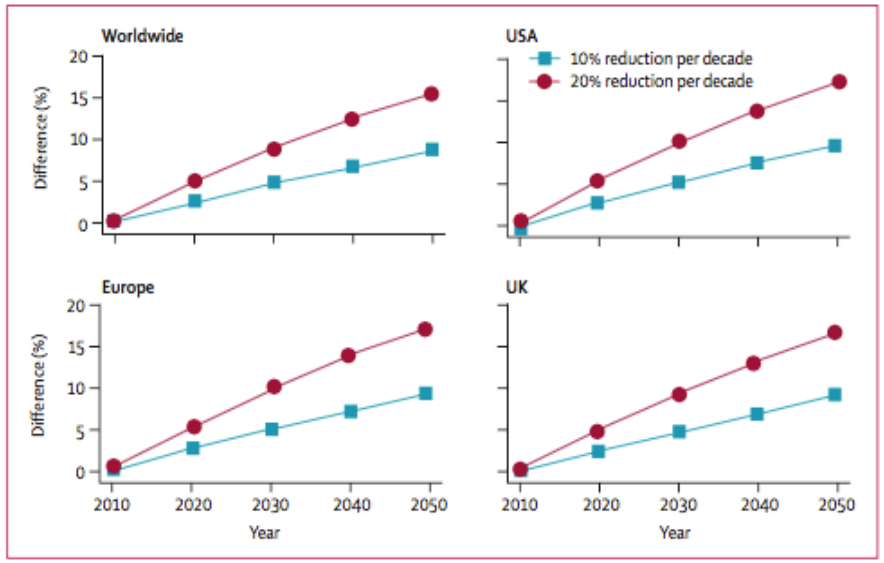


Figure: Projected percentages of Alzheimer's disease cases that could be prevented, with 10% or 20% reductions per decade in each risk factor

Norton S et al, 2014

Epidemiology of AD

(nature or nurture?)

GBD region	Population >60 years of age (millions 2010)	Crude estimated prevalence (%, 2010)	Number of people with dementia (millions)			Proportionate increases (%)	
			2010	2030	2050	2010–2030	2010–2050
Asia	406.6	3.9	15.9	33.0	60.9	107.0	282.0
Europe	160.2	6.2	10.0	14.0	18.7	40.0	87.0
The Americas	120.7	6.5	7.8	14.8	27.1	89.0	246.0
Africa	71.1	2.6	1.9	3.9	8.7	111.0	370.0
World	758.5	4.7	35.6	65.7	115.4	85.0	225.0

	1990		2010	
	Alzheimer's disease	Dementia	Alzheimer's disease	Dementia
55–59 years	0·0014 (0·0000–0·8378)	0·0047 (0·0000–0·6702)	0·0023 (0·0000–0·7227)	0·0068 (0·0000–0·5451)
60–64 years	0·0033 (0·0000–0·6410)	0·0094 (0·0000–0·5266)	0·0055 (0·0000–0·4982)	0·0135 (0·0000–0·3830)
65–69 years	0·0076 (0·0000–0·5304)	0·0180 (0·0000–0·4438)	0·0127 (0·0000–0·3612)	0·0258 (0·0000–0·2816)
70–74 years	0·0164 (0·0000–0·4946)	0·0332 (0·0000–0·4170)	0·0273 (0·0000–0·3178)	0·0476 (0·0000–0·2460)
75–79 years	0·0330 (0·0000–0·5040)	0·0592 (0·0000–0·4323)	0·0552 (0·0000–0·3391)	0·0850 (0·0000–0·2639)
80–84 years	0·0625 (0·0000–0·5337)	0·1019 (0·0000–0·4782)	0·1044 (0·0000–0·3862)	0·1463 (0·0000–0·3137)
85–89 years	0·1109 (0·0000–0·5785)	0·1694 (0·0000–0·5564)	0·1854 (0·0000–0·4500)	0·2432 (0·927–0·3937)
90–94 years	0·1847 (0·0000–0·6549)	0·2720 (0·0000–0·6840)	0·3086 (0·0595–0·5578)	0·3903 (0·2416–0·5389)
95–99 years	0·2884 (0·0000–0·7974)	0·4214 (0·0000–0·8892)	0·4819 (0·1904–0·7735)	0·6047 (0·3967–0·8128)

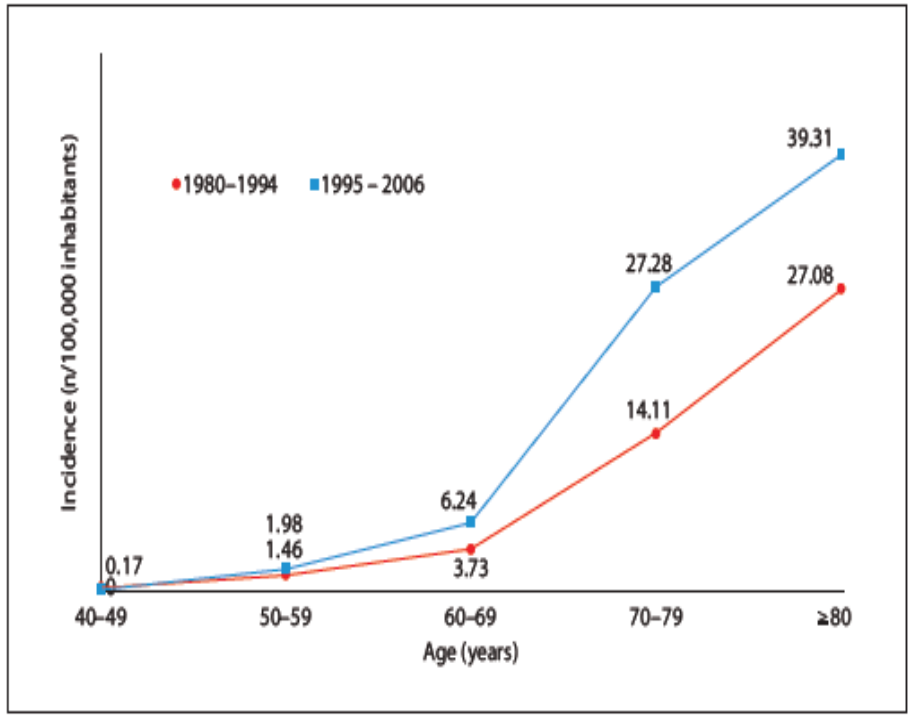
Data are prevalence (95% CI).

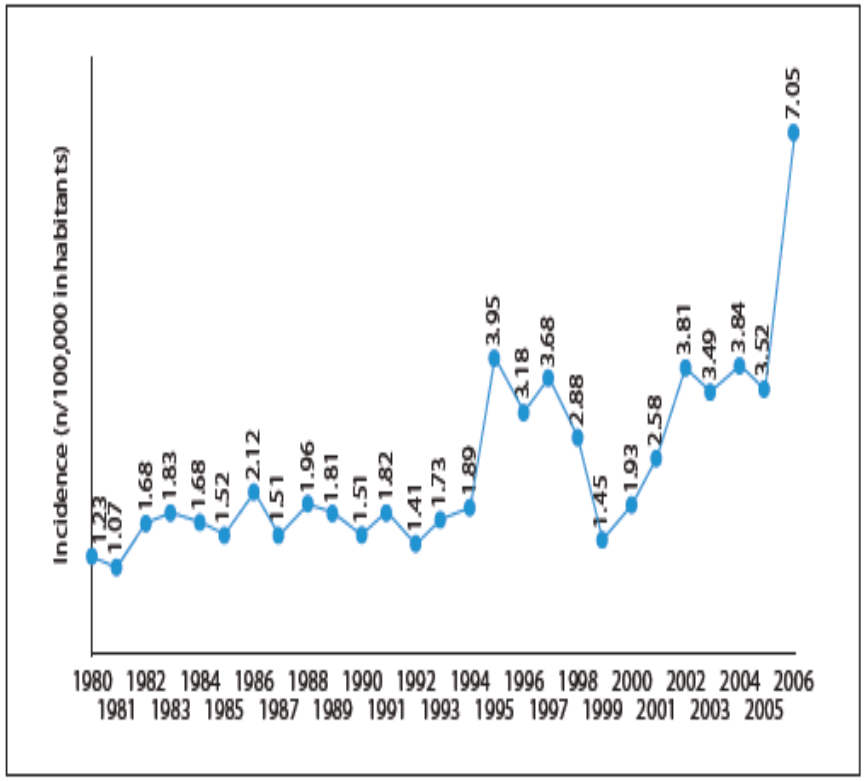
CHINA

Nature and Nurture: the case of Romania

AD Incidence in Romania between 1980 and 2006:

Stable levels untill 1994, than significant increase

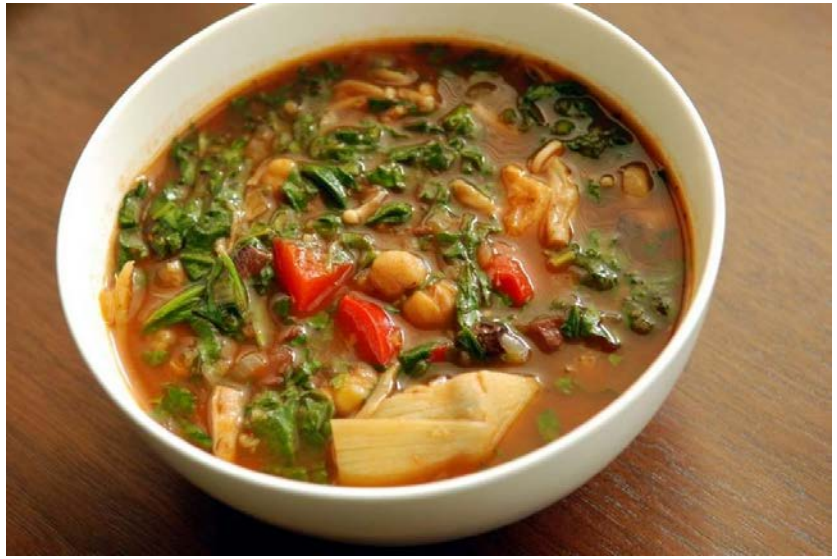




WHY?

G. Cornutiu, Neurodegenerative Dis., 2011

Nature and Nurture: the case of Romania



Nature and Nurture: the case of Romania

Western diet and junk foods availability

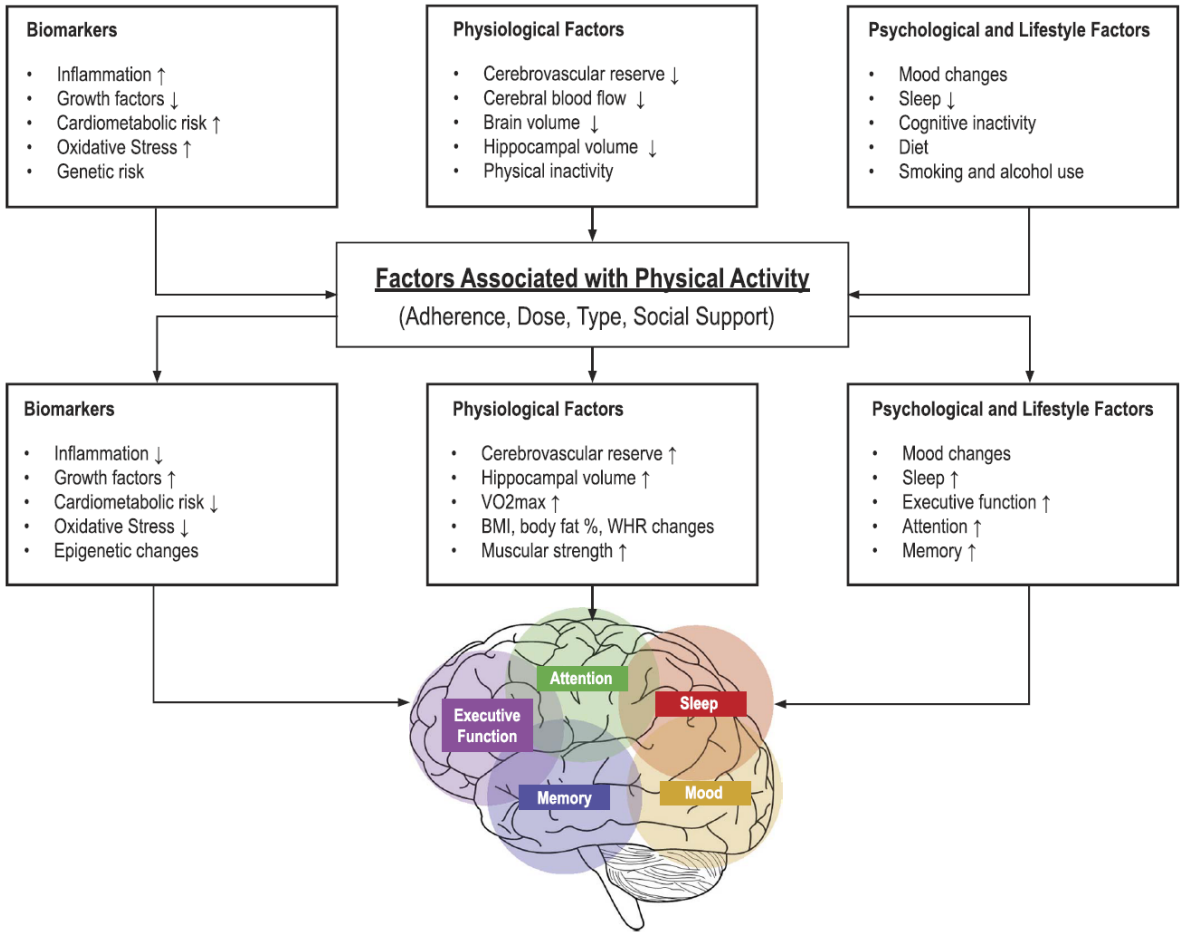
(rich in refined sugars, unhealty fats and calories)

ARTICLE

Protective Effects of Exercise on Cognition and Brain Health in Older Adults

Amanda V. Tyndall[1,2], Cameron M. Clark[1,2], Todd J. Anderson[3,4], David B. Hogan[2,5,6,7], Michael D. Hill[2,5,6], R.S. Longman[2,8,9], and Marc J. Poulin[1,2,4,5,10,11]

Proposed Mechanisms Underlying Cognitive Decline with Aging

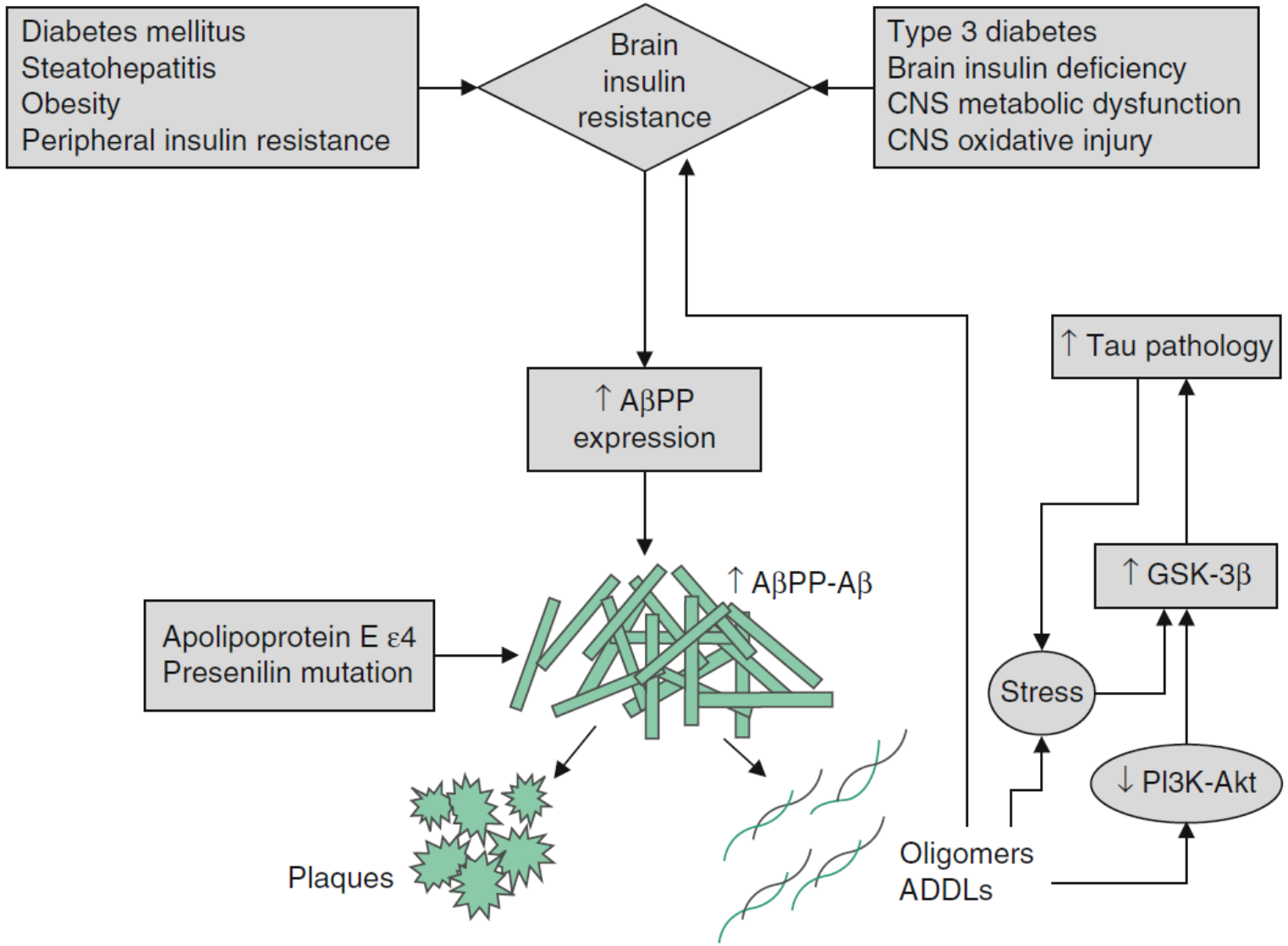


Exercise and Sport Sciences Reviews
DOI: 10.1249/JES.0000000000000161

Drugs 2012; 72 (1): 49-66
0012-6667/12/0001-0049/$55.55/0

Contributions of Brain Insulin Resistance and Deficiency in Amyloid-Related Neurodegeneration in Alzheimer's Disease

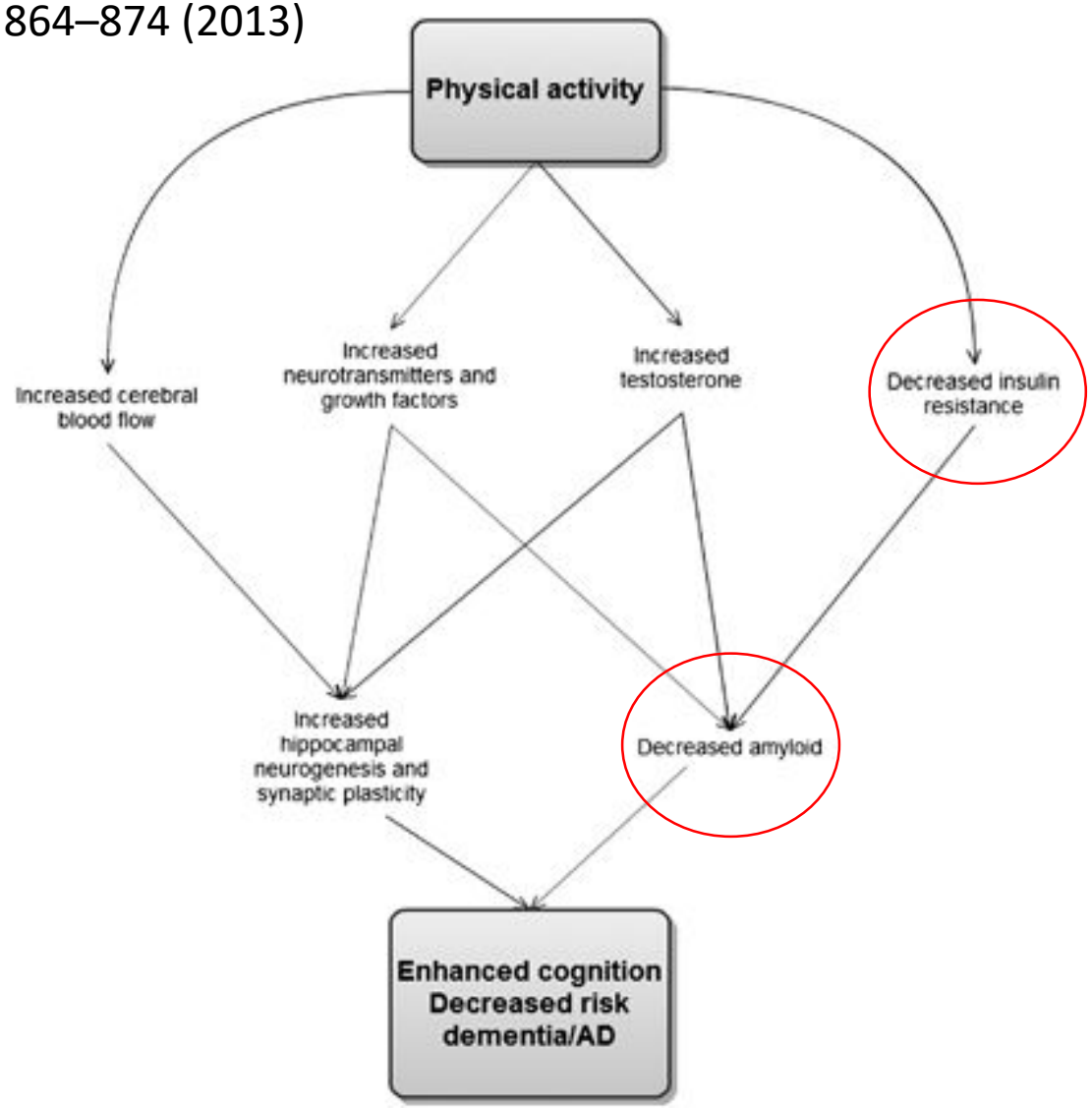
Suzanne M. de la Monte



Multiple effects of physical activity on molecular and cognitive signs of brain aging: can exercise slow neurodegeneration and delay Alzheimer's disease?

B M Brown, J J Peiffer, R N Martins

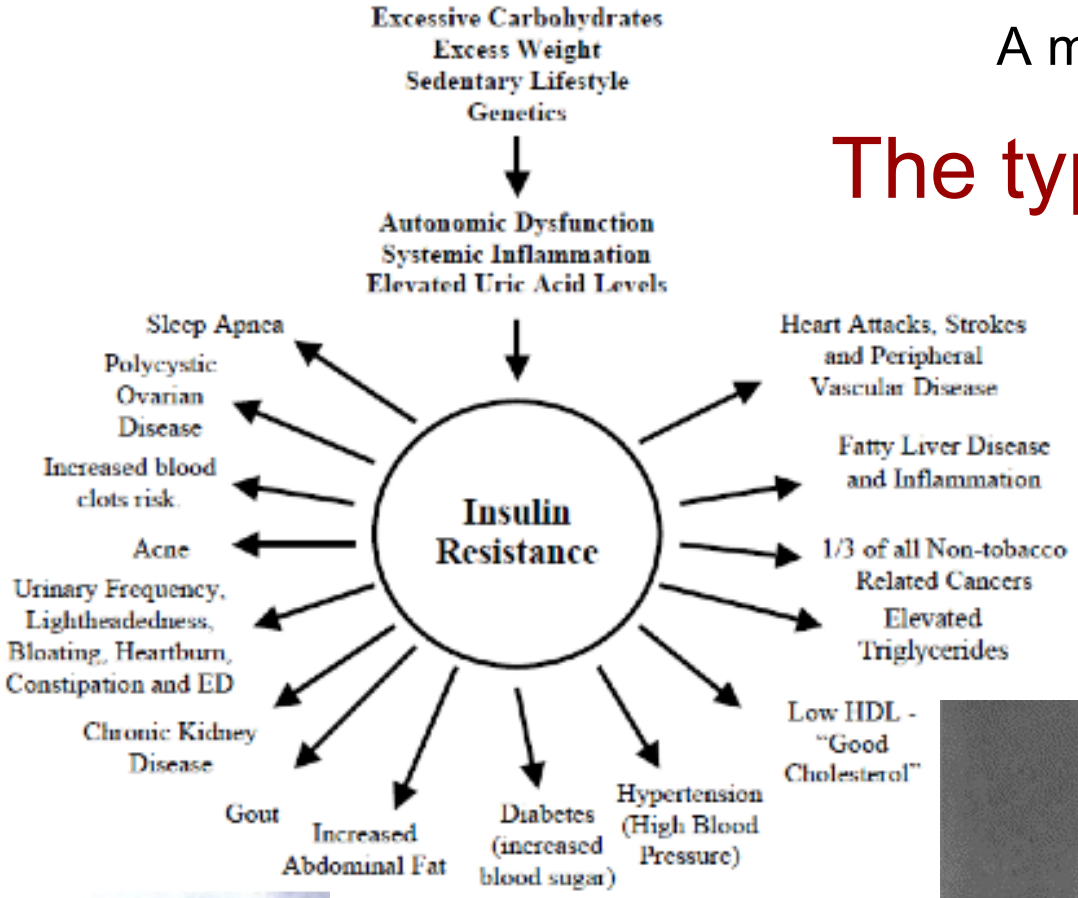
Molecular Psychiatry volume 18, pages 864–874 (2013)



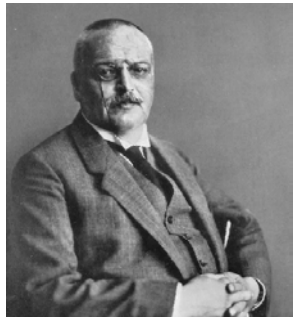
Alzheimer's disease

A modern disease?

The type 3 diabetes?

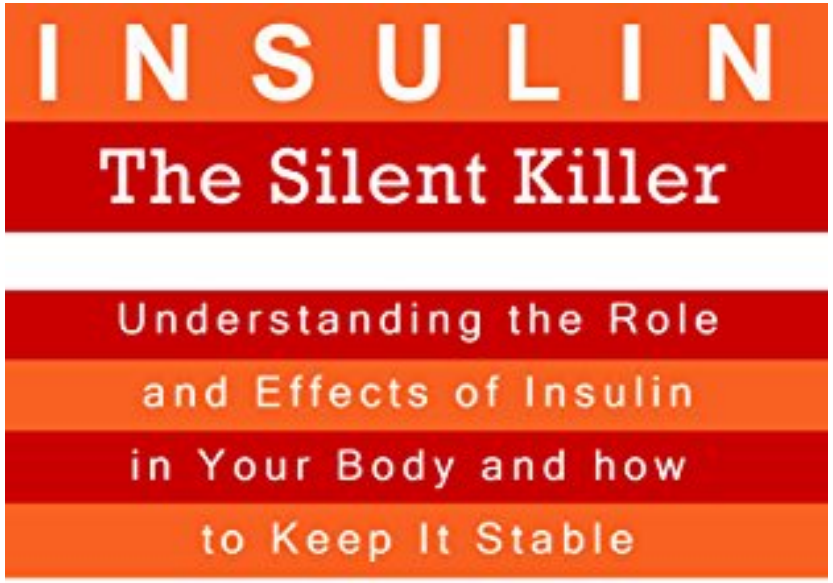


GaetanoPerusini
(*1879-1915*)



Alois Alzheimer
(*1863-1915*)

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



Diet under an evolutionary pint of view? The Paleo diet!

(a fashionable diet: myth or reality?)

E. Bufill et al., Journal of Anthropological Sciences 2013

Low glicemic index foods, no grains, no legumes, no diary, wild fruits

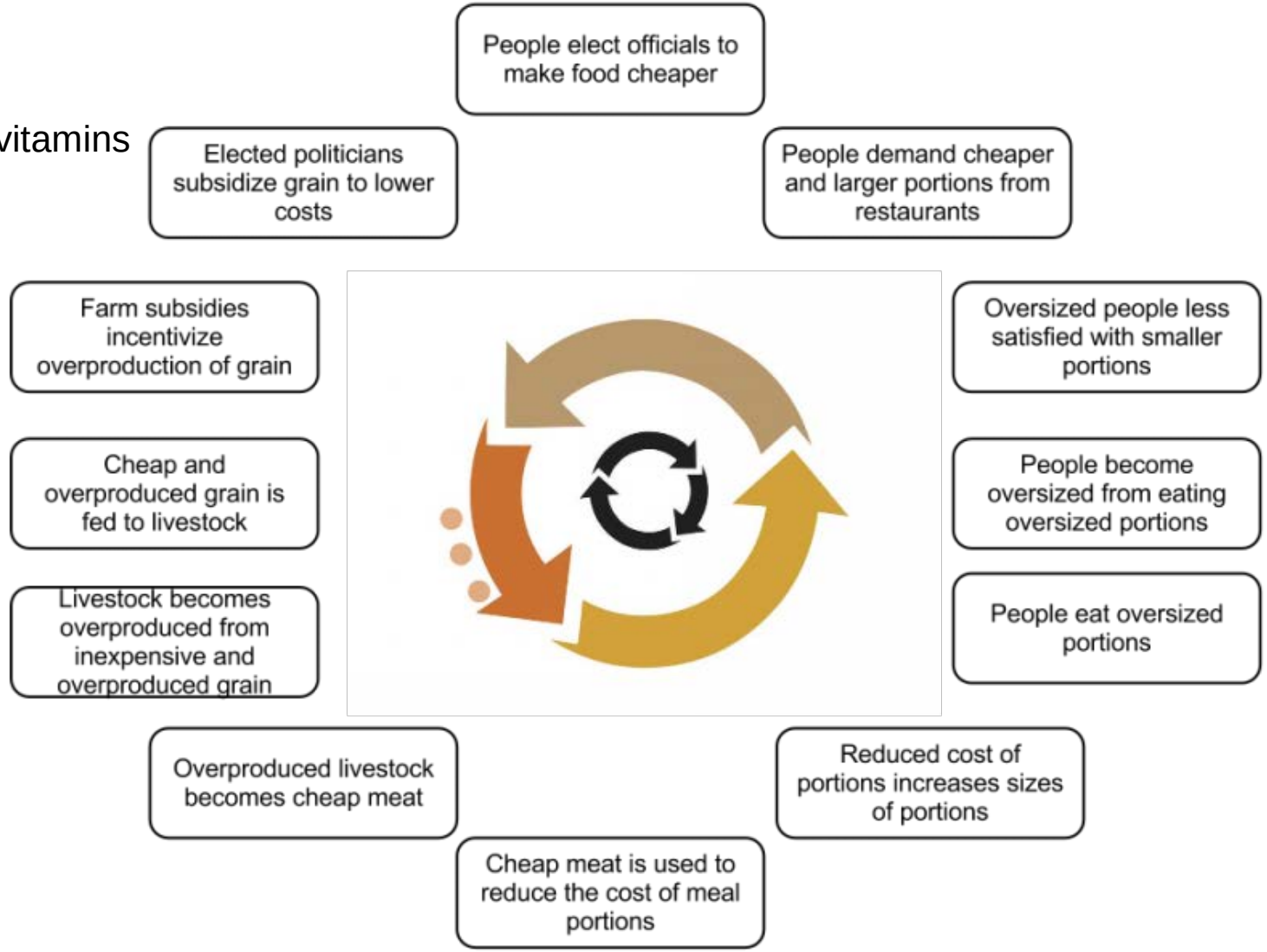
DIET IN PALEOLITHIC AGE: **Grass-feed beef**
Meat lean but rich in omega-3, low calories, high fibers, vitamins minerals

MODERN DIET: **Meat from factory farming**
Low fibers, low vitamins, low minerals, high calories, rich in non-healthy fats.
(saturated and mono-insaturateded fatty acids)

Ratios of (n-6) to (n-3) fatty acids in various populations

Population	(n-6):(n-3)
Paleolithic	0.79
Greece before 1960	1.00–2.00
Current United States	16.74
Current United Kingdom and northern Europe	15.00
Current Japan	4.00

Simopoulos et al , 2001



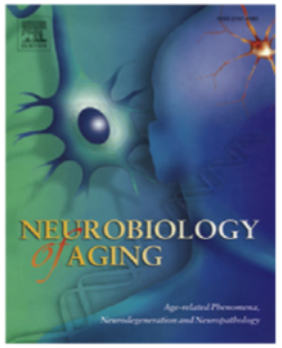
Is Alzheimer a specific disorder of Humans? Not, also in apes, but only in captivity

Neurobiology of Aging 59 (2017) 107–120

Contents lists available at ScienceDirect

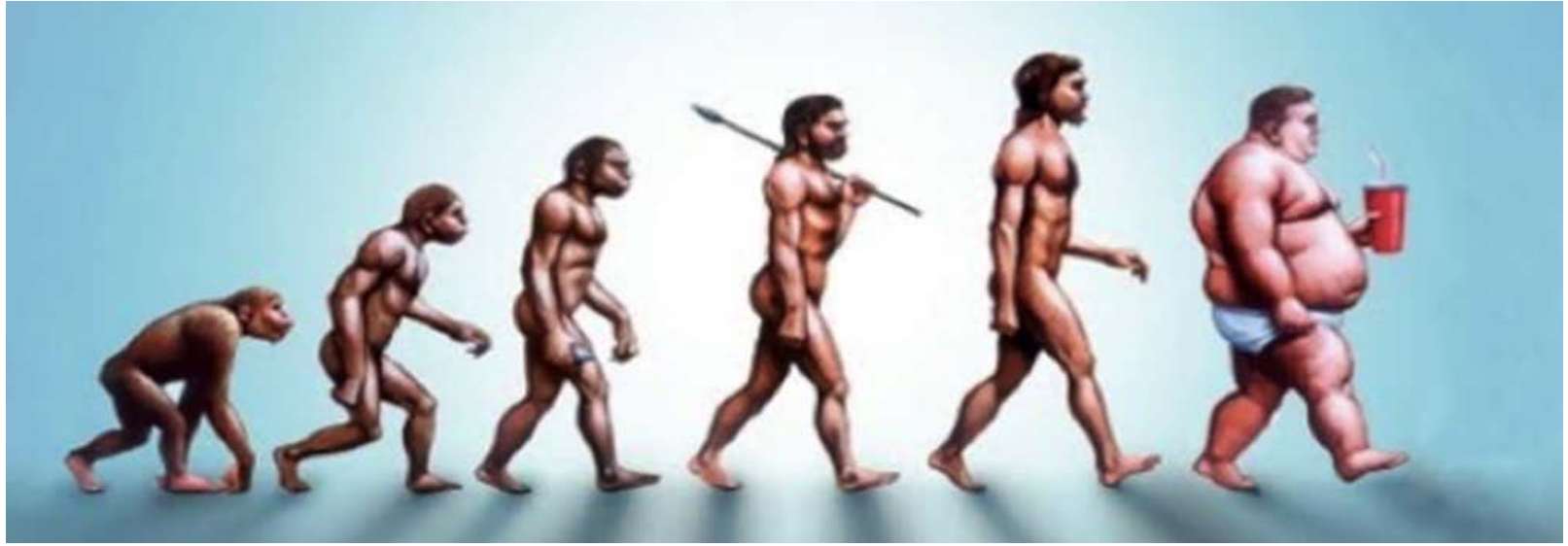
Neurobiology of Aging

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



Aged chimpanzees exhibit pathologic hallmarks of Alzheimer's disease

Melissa K. Edler [a,b,*], Chet C. Sherwood [c], Richard S. Meindl [d], William D. Hopkins [e,f], John J. Ely [g], Joseph M. Erwin [c], Elliott J. Mufson [h], Patrick R. Hof [i,j], Mary Ann Raghanti [a,d]



Macronutrient	Percent of Energy
Polyunsaturated fat	<2%
Saturated and monounsaturated fat	58%
Carbs (ex fiber)	15.9%
Protein	24.4%

Species	Large Intestine	Small Intestine	Stomach
Gorilla	60%	14%	25%
Chimpanzee	57%	23%	20%
Human	17%	67%	17%

Organ	Percent of Body Weight, Humans	Percent of Body Weight, Other Primates (Scaled for Body Size)
Brain	2.0%	0.7%
Liver	2.2%	2.5%
Gut	1.7%	2.9%

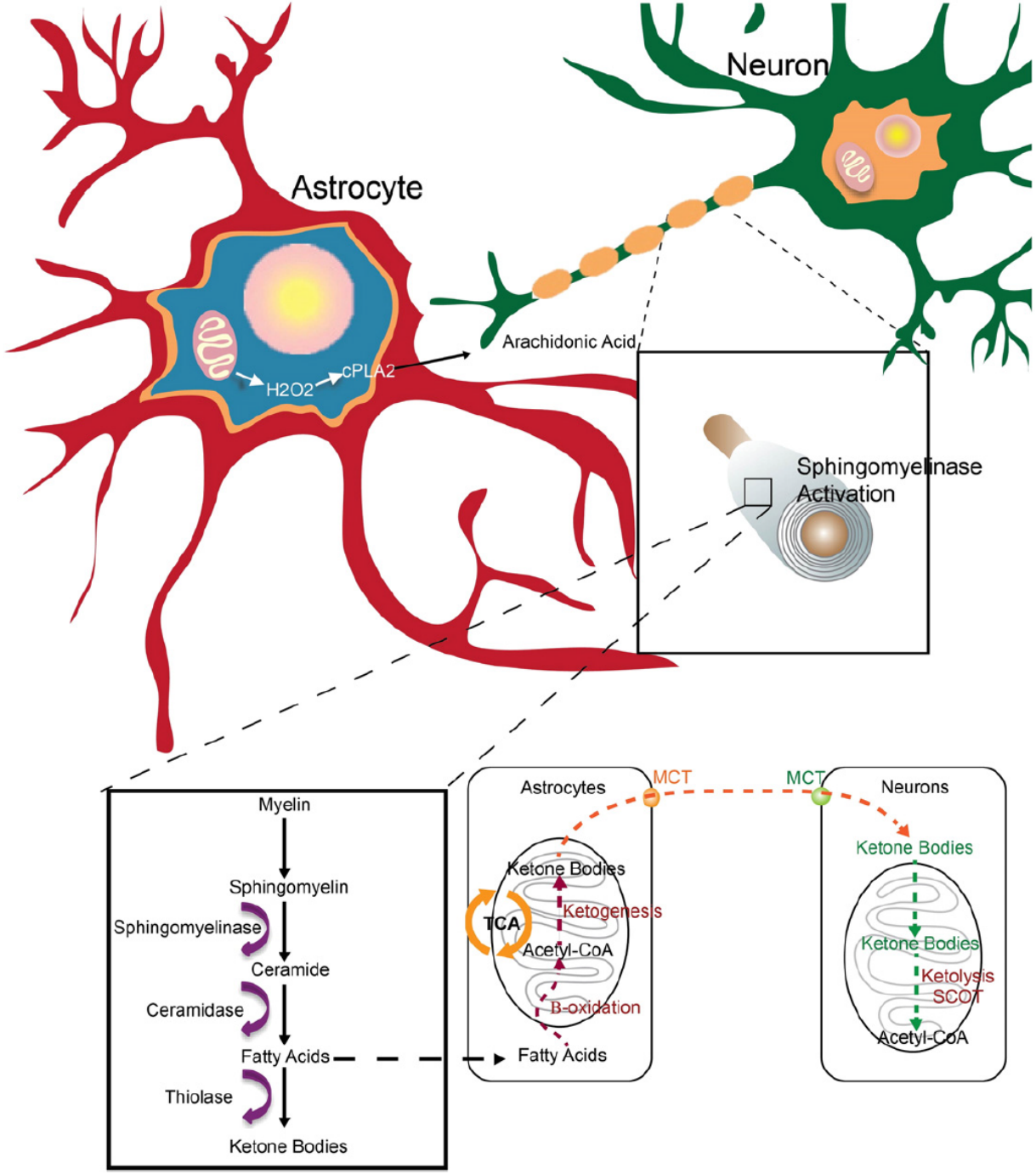
Brain energy expenditure:

Mammalians	2-8%
Monkeys	11-13%
Humans	20-25%

Ketogenesis in Dementia

Ketones and AD: why?

- When standard energetic sources are falling behind, the AD brain is forced to rely on alternative energy substrates. In this view, ketone bodies may play an important role (Iadecola, 2015; VanItallie, 2015).
- Ketones are produced by the catabolism of fatty acids, a process operated by liver mitochondria. Interestingly, functional deficits in hepatic mitochondrial and/or peroxisomal fatty acids metabolism have been indicated as potential contributors to AD and related cognitive impairment (Astarita and Piomelli, 2011). Moreover, in aging rats, decreased hepatic peroxisomal fatty acid beta-oxidation (FAO) has been linked to the development of alterations in the lipid composition of the brain (Yang et al., 2014).
- Alterations of hepatic FAO can affect brain functioning. In that regard, ketones are substrates that, in elderly subjects, may become an energetic source to be used, for brain functioning, as alternative to glucose.
  This concept is supported by findings indicating that healthy elderly brains increase consumption of energy substrates that are alternative to glucose when glucose utilization decreases, thereby suggesting a compensatory role played by these metabolites in coping with brain energy demand (Hoyer et al., 1991).

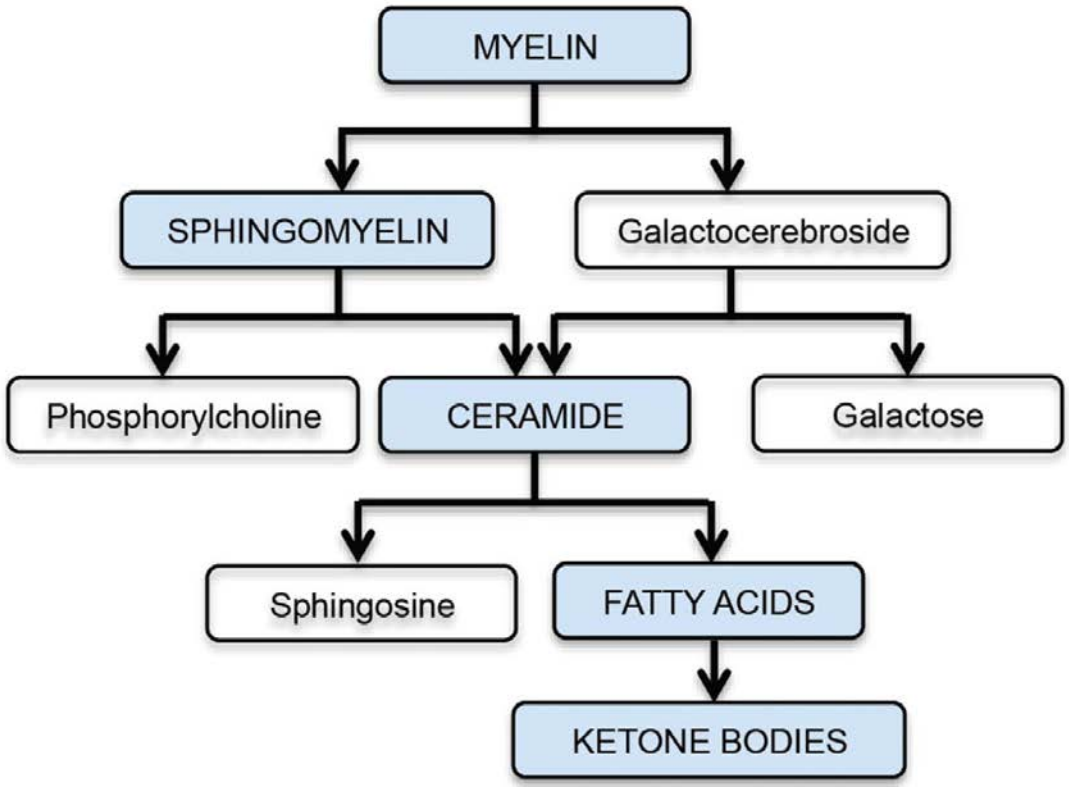


Research Article

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



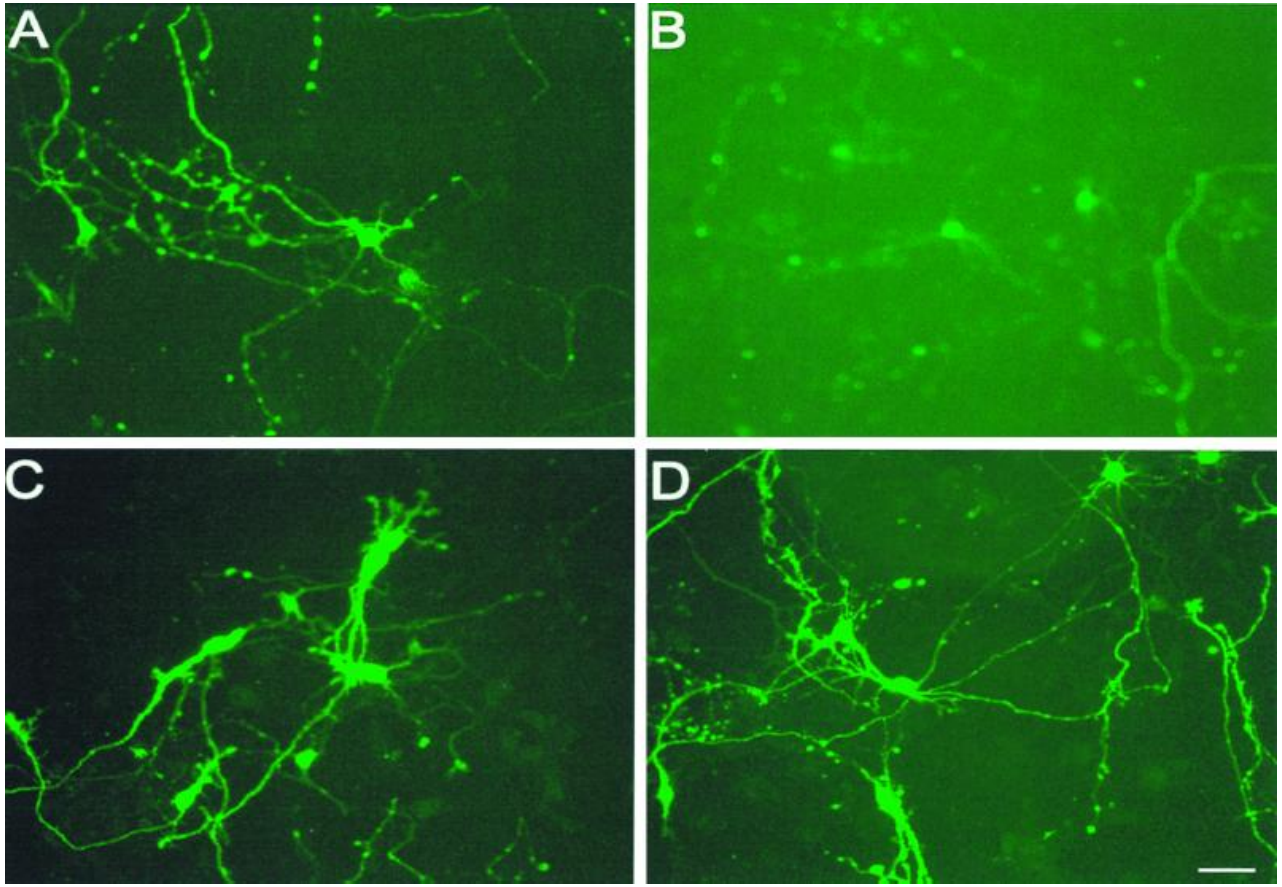
The putative neuroprotective effects of ketone bodies have been associated with the following mechanisms:

- increasing intracellular adenosine triphosphate (ATP) availability;
- reducing ROS generation by mitochondrial complex I;
- inhibiting mitochondrial permeability transition;
- stimulating mitochondrial biogenesis, resulting in stabilized synaptic function;
- altering metabolism of neurotransmitters such as glutamate and gamma-amino butyric acid (GABA);
- activating energy-sensing signaling pathways such as the peroxisome proliferator activated receptor (PPAR), mammalian target of rapamycin (mTOR), and adenosine monophosphate- (AMP)-activated kinase (AMPK) pathways.

Antioxidants **2018**, *7*, 63; doi:10.3390/antiox7050063

β-Hydroxybutyrate protects neurons in models of Alzheimer's disease

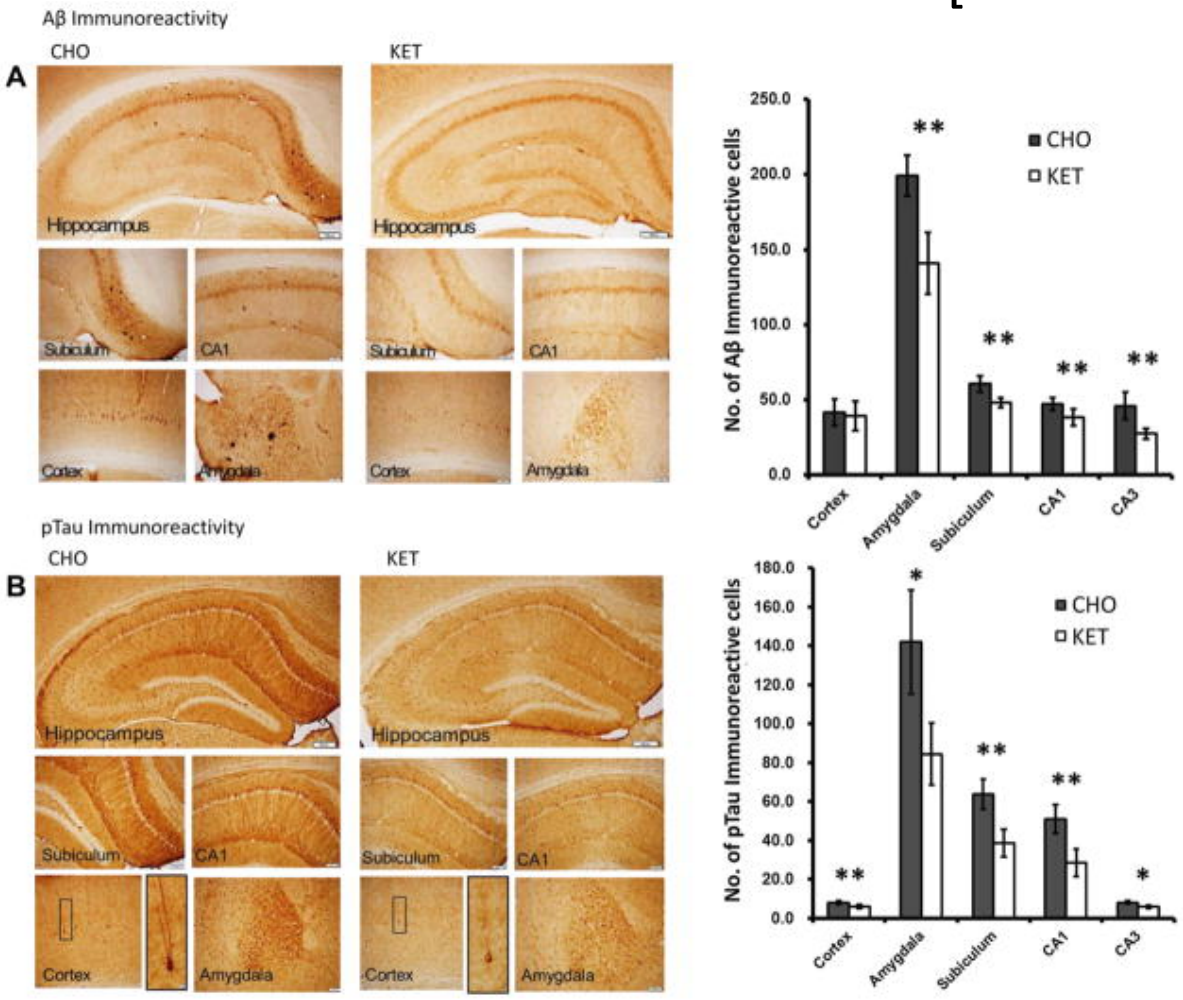
[Kashiwaya et al., 2000]



The effects on cultured rat hippocampal cells of $A\beta_{1-42}$, ketones, or the combination. (*A*) The 6-day control cultures of 18-day embryonic rat hippocampal tissue; (*B*) after 14 h exposure to 5 µM $A\beta_{1-42}$, (*C*) after exposure to both $A\beta_{1-42}$ and 4 mM d-β-hydroxybutyrate, and (*D*) the effects of ketone bodies alone. Addition of $A\beta_{1-42}$ resulted in a decrease in neuronal number and number of neurites (*B* versus *A*). Addition of ketones to cells exposed to $A\beta_{1-42}$ showed no decrease in neuron or neurite number, indicating that ketones act as neuroprotective agents against the toxicity of $A\beta_{1-42}$ on cultured hippocampal neurons (*C* versus *B*).

A ketone ester diet exhibits anxiolytic and cognition-sparing properties, and lessens amyloid and tau pathologies in a mouse model of Alzheimer's disease

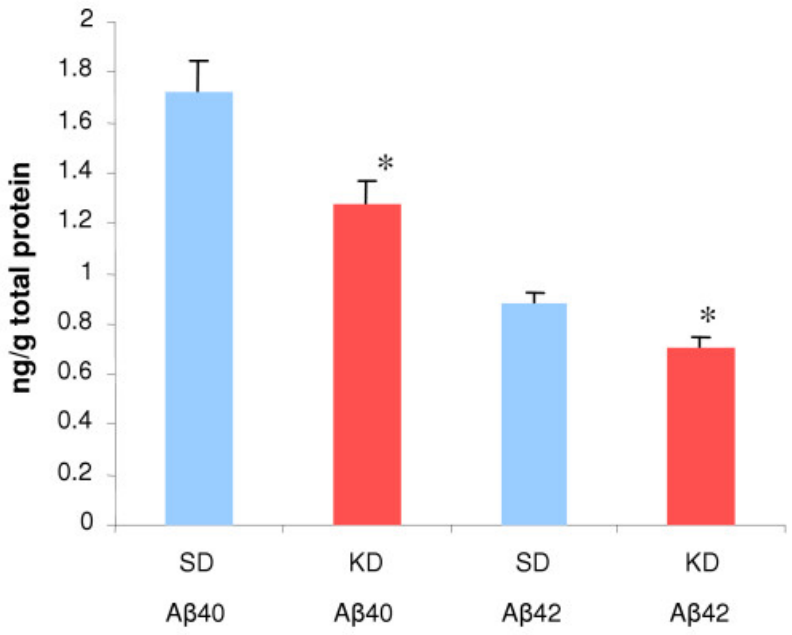
[Kashiwaya et al., 2013]



Ketone ester feeding reduces intracellular accumulations of amyloid β (Aβ) and phosphorylated tau (pTau) in the subiculum, CA1 and CA3 area of hippocampus, amygdala, and cerebral cortex of 3xTgAD mice. (A) Aβ immunoreactivity in brain sections from mice in the carbohydrate-enriched (CHO; left) and ketone ester (KET; right) diet groups. The upper panels are low magnification images of the regions of the hippocampus and the lower panels are high magnification images of the regions of the subiculum, CA1, cerebral cortex, and amygdala. The graph on the right shows the results of counts of Aβ immunoreactive cells in the indicated brain regions. (B) pTau immunoreactivity in brain sections from mice in the CHO (left) and KET (right) diet groups. The upper panels are low magnification images of the regions of the hippocampus and the lower panels are high magnification images of the regions of the subiculum, CA1, cerebral cortex, and amygdala respectively. The graph on the right shows the results of counts of pTau immunoreactive cells in the indicated brain regions. Scale bars: lower magnification images, 200 µm; high magnification images, 100 µm. Values are the mean ± SEM (n = 6–9 mice per group). $*p < 0.05$ and $**p < 0.001$ by the Student *t* test.

In a mouse model of Alzheimer's disease, Ketogenic diet reduces amyloid beta 40 and 42 peptides

[Van der Auwera et al., 2005]



Ketogenic diet reduces Aβ40 and Aβ42. Aβ levels as ng/g of brain tissue. Standard diet (SD) group shown in blue, ketogenic diet (KD) group shown in red, error bars represent standard error of the mean. SD chow Aβ40 1.72 ± 0.12 ng/g vs. KD chow Aβ40 1.28 ± 0.09 ng/g, p= 0.012. SD chow Aβ42 0.88 ± 0.05 ng/g vs. KD chow Aβ42 0.71 ± 0.0.4 ng/g, p = 0.016.

Christa M. Studzinski , William A. MacKay , Tina L. Beckett , Samuel T. Henderson , M. Paul Murphy , Patrick G. Su...

Induction of ketosis may improve mitochondrial function and decrease steady-state amyloid-β precursor protein (APP) levels in the aged dog

Brain Research, Volume 1226, 2008, 209 - 217

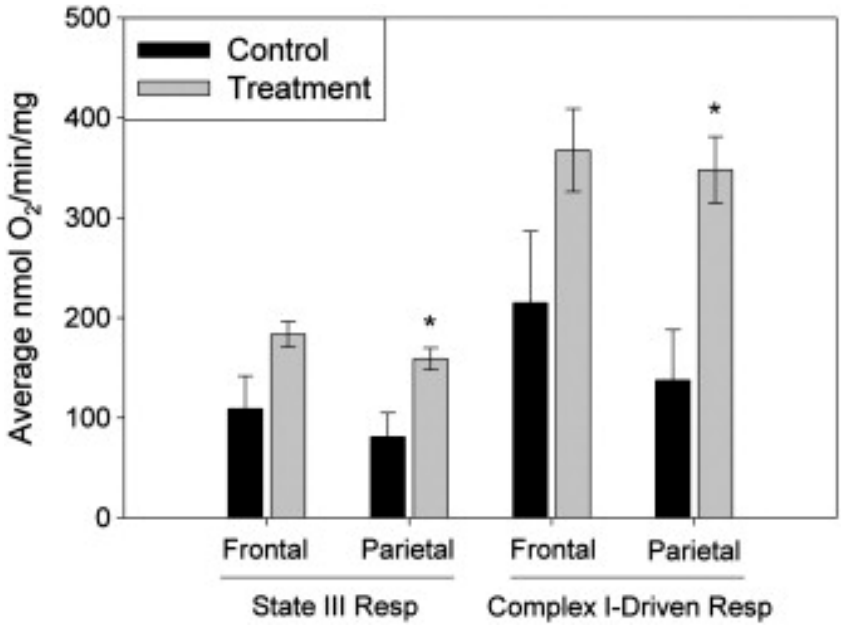


Fig. 2 Mitochondrial respiration. The treatment animals had larger rates of state III respiration in the parietal lobes, as compared to controls (*t* -test, *P* = 0.025). The treatment animals also had an increa...

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

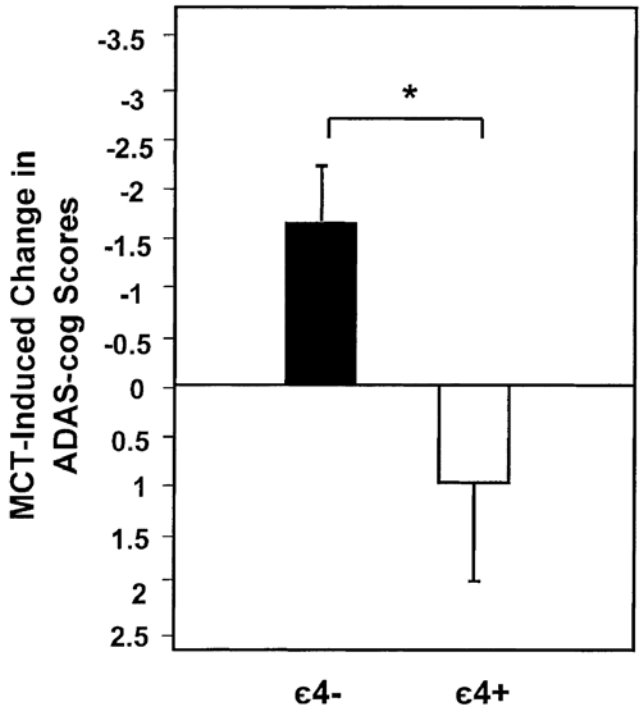


Fig. 1. ADAS-cog mean change with MCT treatment; benefits of treatment depended on $\varepsilon 4$ status ($^*P = 0.039$). Note: negative scores indicate improvement on the ADAS-cog.

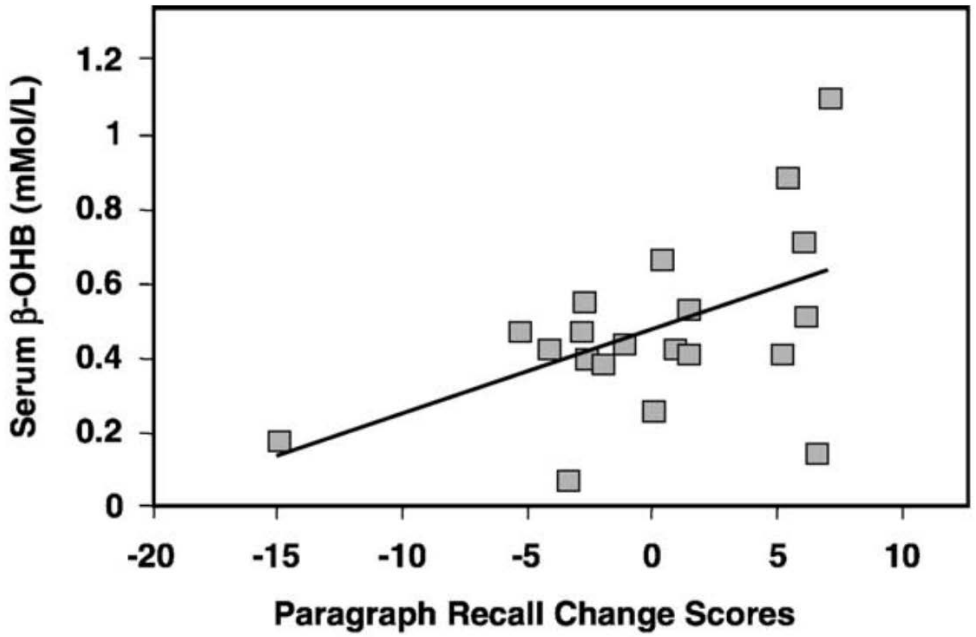
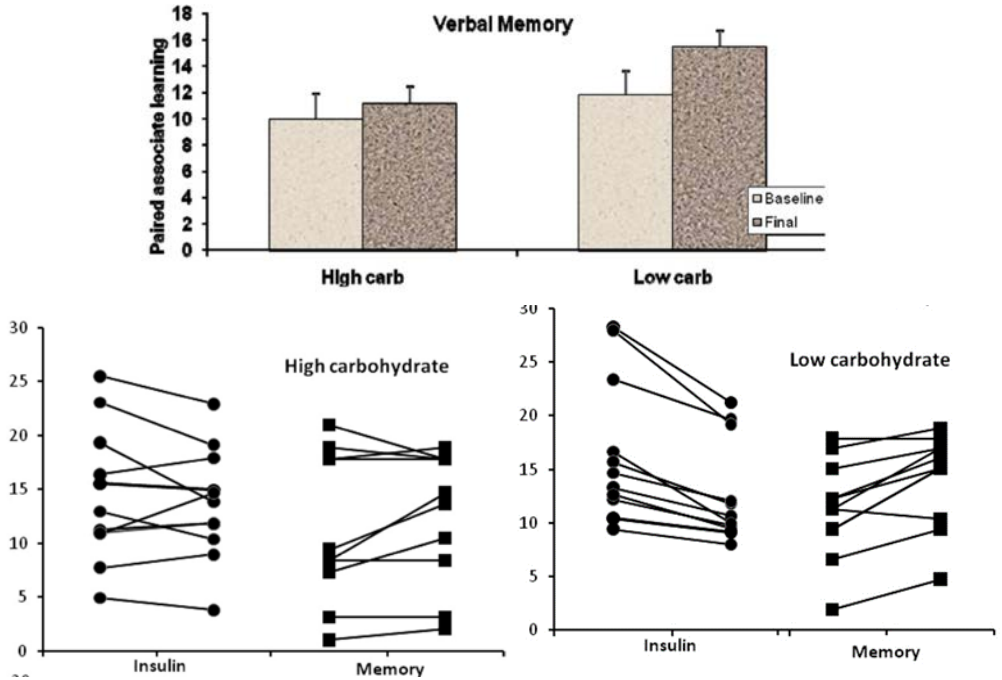


Fig. 2. Relationship between β-OHB levels at the time of cognitive testing and the change in paragraph recall following MCT treatment; $r = 0.50$, $P = 0.02$.

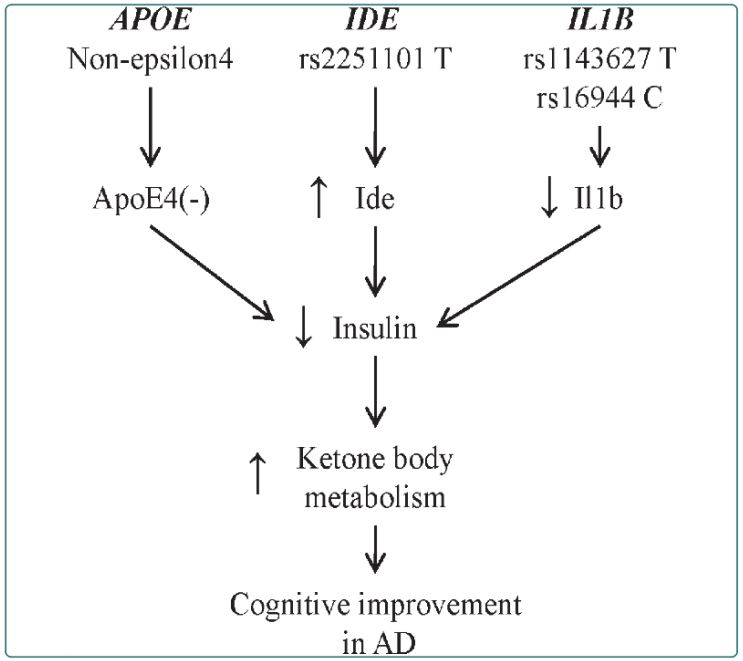
Ketogenesis and Cognition

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)

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,*]

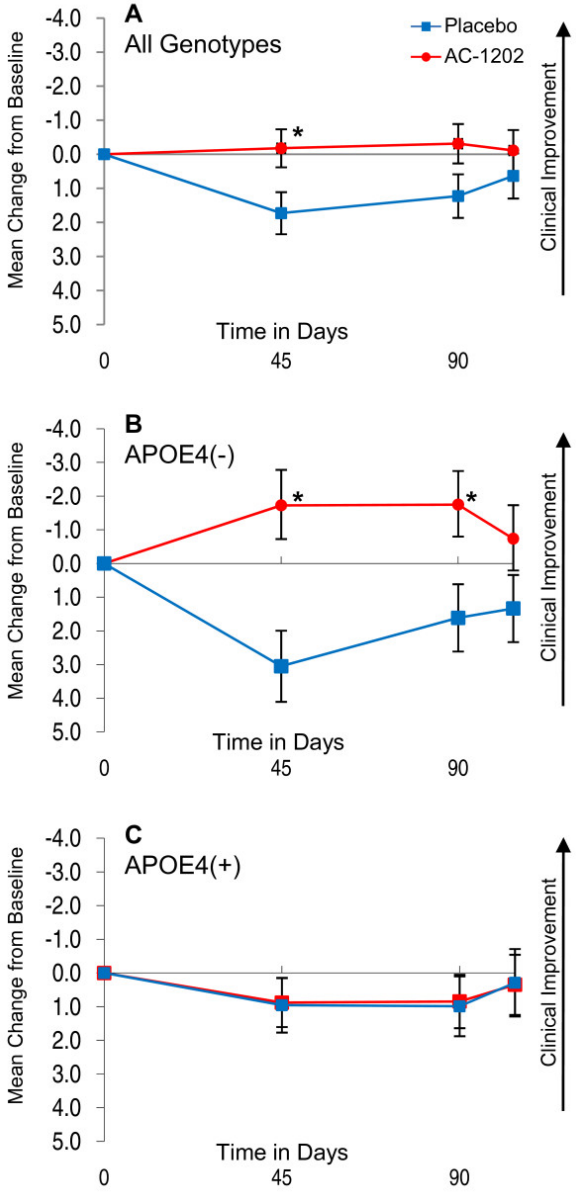
[a] Pennington Biomedical Research Center, Louisiana State University System, 6400 Perkins Road, Baton Rouge, United States
[b] School of Nutrition and Food Sciences, Louisiana State University, Baton Rouge, United States

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.

Ketogenesis in Parkinson Disease

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.

Realtà Sannita

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

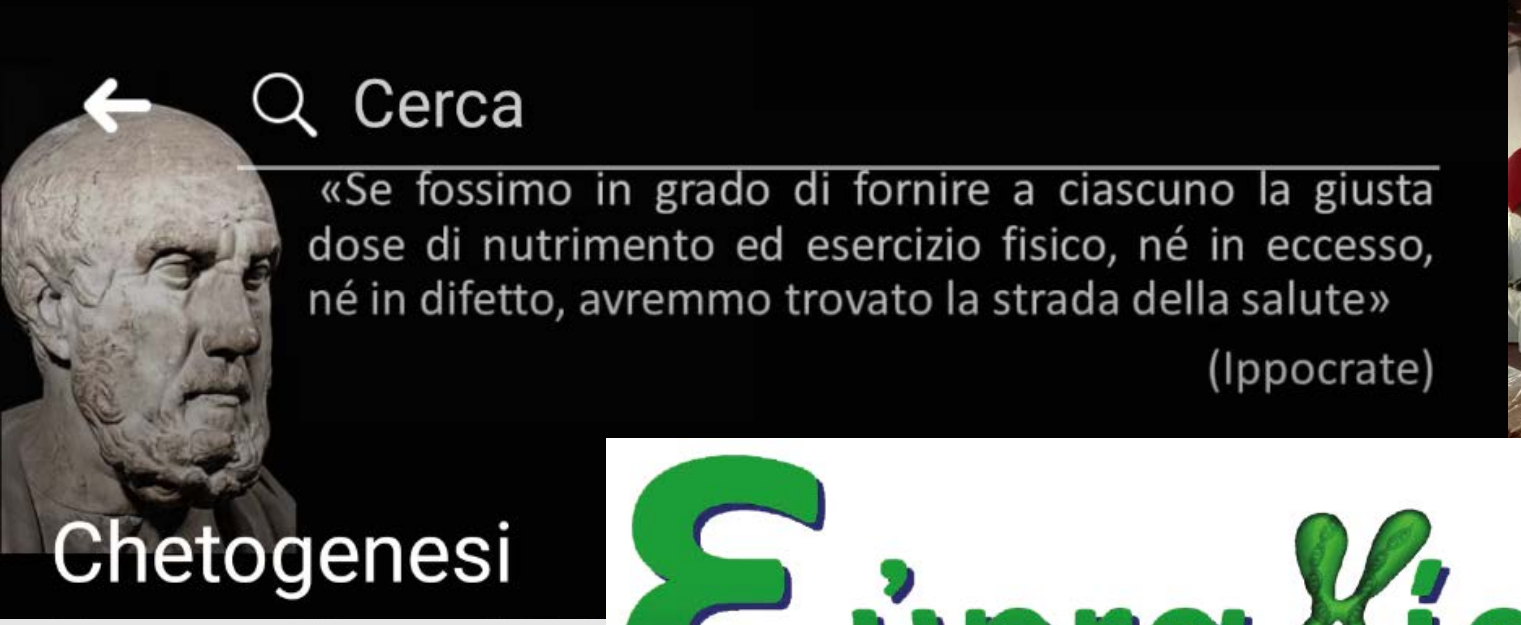
Abstract

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

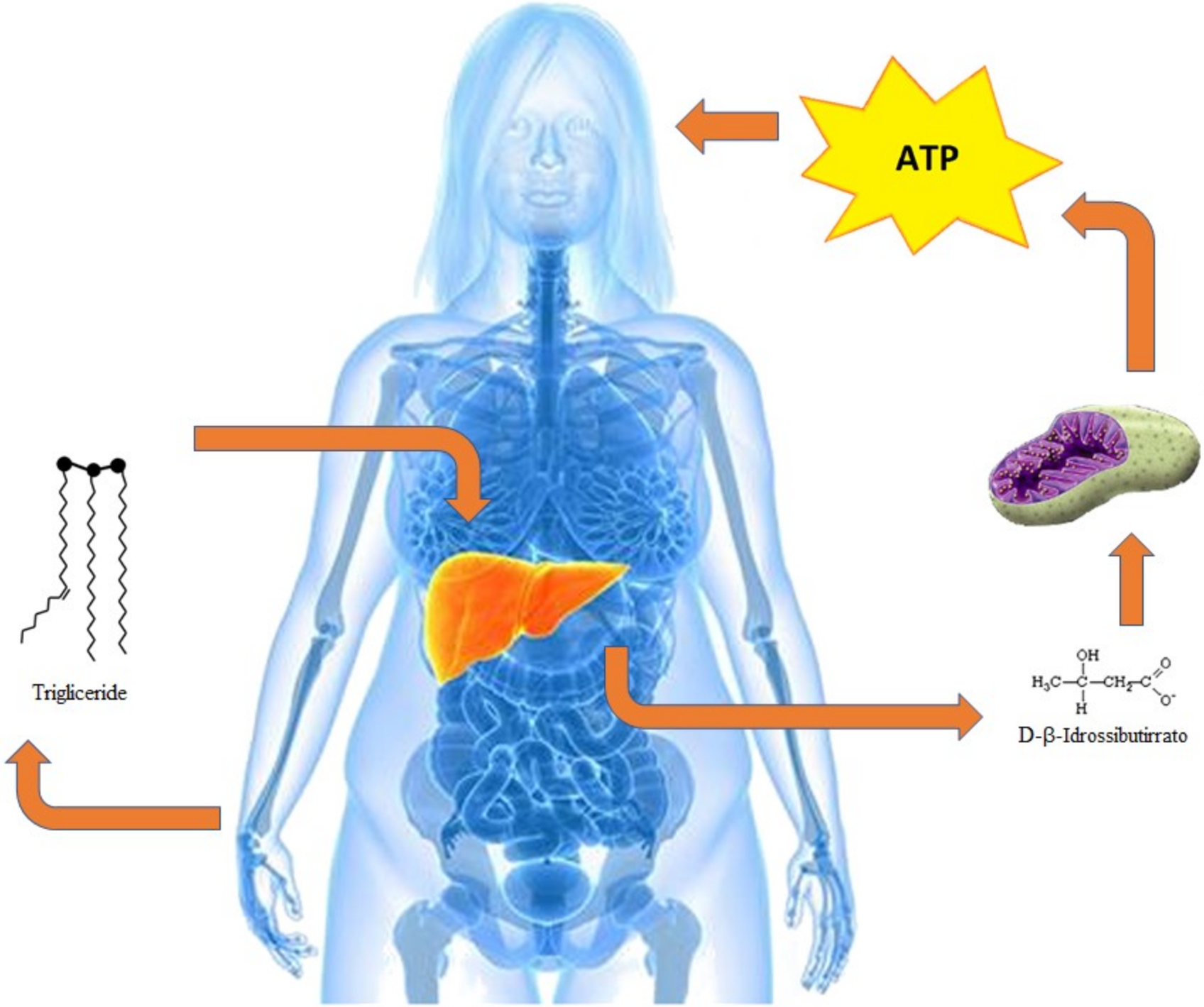
HPLC, ketogenic diet, L-Dopa, Parkinsonism, pharmacokinetics, validation

Alone at home?



Εὐpraxía

Membri 17.000


ATP
Trigliceride
D-β-Idrossibutirrato

IRCCS FONDAZIONE STELLA MARIS

Filippo M Santorelli

NEUROMED I.R.C.C.S. ISTITUTO NEUROLOGICO MEDITERRANEO

Anna Ambrosini

Armando Perrota

G.B.Bietti Foundation

Gianluca Coppola

INI

Paolo Rossi

Sapienza University of Rome

Fondazione Don Carlo Gnocchi Onlus

Cherubino Di Lorenzo

Sapienza University of Rome

Francesco Pierelli

Rita Businaro

Grazia Semeraro

DIPARTIMENTO DI MEDICINA SPERIMENTALE

Alessandro Pinto

Roberta Ienca

UNIVERSITA' degli STUDI di ROMA TOR VERGATA

Giorgio Di Lorenzo

Thank you for your kind attention

cherub@inwind.it