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Società Italiana di Nutraceutica

Ketogenic
Diet
Academy

INDICAZIONI DELLA KETOGENIC DIET

EVIDENZE

Giovanni De Pergola

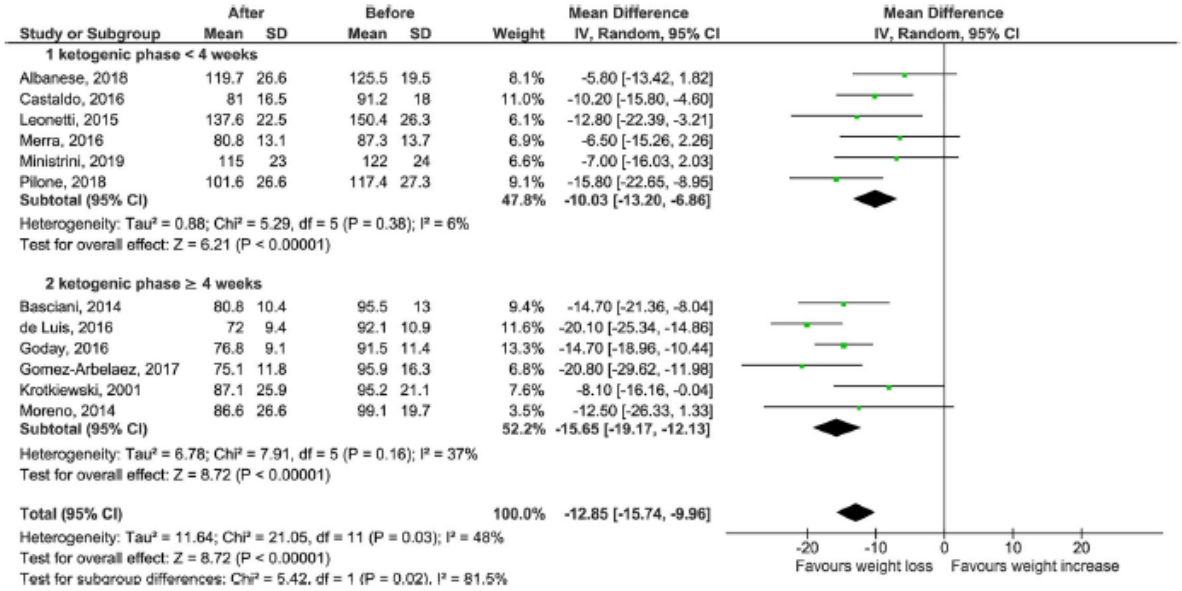
09 Febbraio 2020

THE KETOGENIC DIET: ONE NAME MANY DIETS

- Calorie Unrestricted High Fat Ketogenic
- Low Calorie High Fat Ketogenic
- Very Low Calorie Ketogenic
- (Low Carbohydrate)
- Very Low Carbohydrate)

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

VLCKD was associated with weight losses of –10.0 kg and – 15.6 kg in studies with a ketogenic phase up to and of at least four weeks, respectively.



Forest plot of meta-analysis for change in body weight from baseline to the last available follow-up on VLCKD

The overall **prevalence** of patients **discontinuing VLCKD** was **7.5%** and this was similar to patients undergoing a low calorie diet.

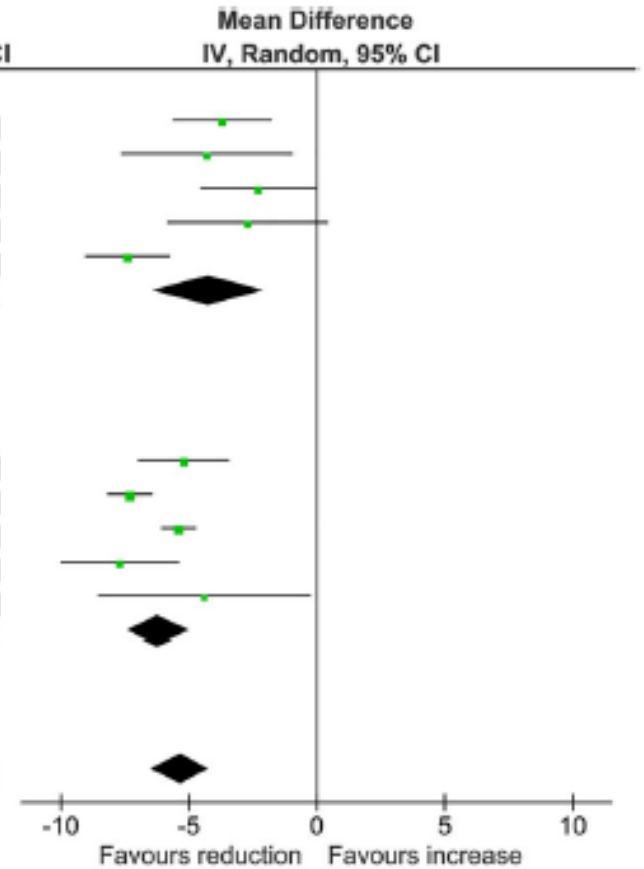
The weight lost during the ketogenic phase was stable in the subsequent follow-up up to two years

The present review supports the use of VLCKD as an **effective strategy for the management of overweight and obesity**.

Castellana M et al, Rev Endocr Metab Dis, 2019

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Study or Subgroup	After Mean	After SD	Before Mean	Before SD	Weight	Mean Difference IV, Random, 95% CI
1 ketogenic phase < 4 weeks						
Castaldo, 2016	29.7	5.5	33.4	6.3	10.7%	-3.70 [-5.62, -1.78]
Leonetti, 2015	49.2	8.7	53.5	8.4	6.5%	-4.30 [-7.65, -0.95]
Merra, 2016	29.1	3.5	31.4	3.4	9.5%	-2.30 [-4.55, -0.05]
Ministrini, 2019	42	8	44.7	8.3	7.0%	-2.70 [-5.83, 0.43]
Pilone, 2018	34.1	5.2	41.5	7.6	11.7%	-7.40 [-9.05, -5.75]
Subtotal (95% CI)					**45.4%**	**-4.20 [-6.36, -2.04]**
Heterogeneity: Tau² = 4.50; Chi² = 17.25, df = 4 (P = 0.002); I² = 77%						
Test for overall effect: Z = 3.81 (P = 0.0001)						
2 ketogenic phase ≥ 4 weeks						
Basciani, 2014	28.6	3.1	33.8	3.2	11.2%	-5.20 [-6.98, -3.42]
de Luis, 2016	25.9	1.7	33.2	1.7	14.3%	-7.30 [-8.18, -6.42]
Goday, 2016	27.9	1.8	33.3	1.5	14.8%	-5.40 [-6.08, -4.72]
Gomez-Arbelaez, 2017	27.8	2.9	35.5	4.4	9.4%	-7.70 [-10.01, -5.39]
Moreno, 2014	30.8	8.7	35.2	4.8	4.9%	-4.40 [-8.55, -0.25]
Subtotal (95% CI)					**54.6%**	**-6.18 [-7.40, -4.96]**
Heterogeneity: Tau² = 1.16; Chi² = 14.71, df = 4 (P = 0.005); I² = 73%						
Test for overall effect: Z = 9.94 (P < 0.00001)						
Total (95% CI)					**100.0%**	**-5.31 [-6.42, -4.20]**
Heterogeneity: Tau² = 2.04; Chi² = 38.05, df = 9 (P < 0.0001); I² = 76%						
Test for overall effect: Z = 9.37 (P < 0.00001)						
Test for subgroup differences: Chi² = 2.46, df = 1 (P = 0.12), I² = 59.4%						

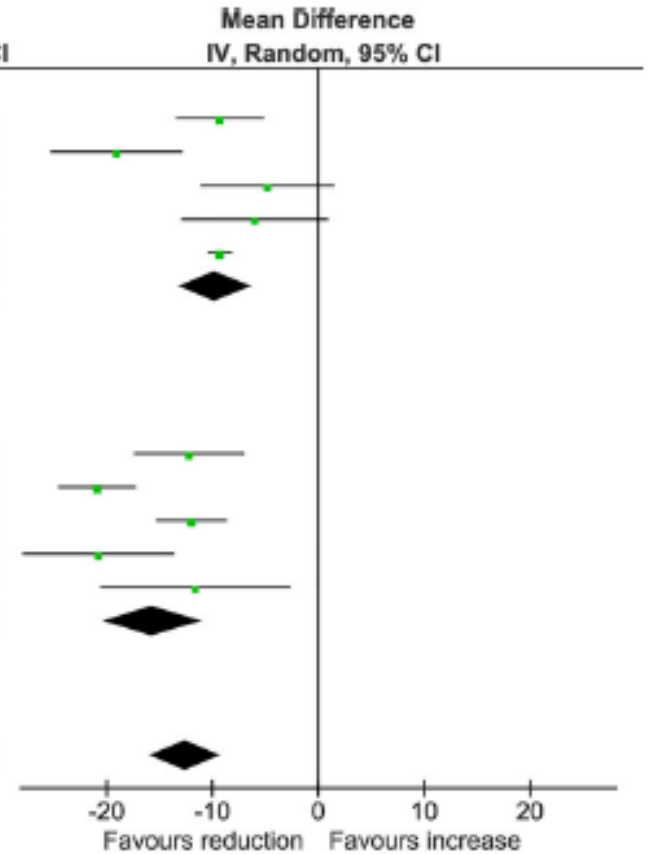


Forest plot of meta-analysis for change in body mass index from baseline to the last available follow-up on VLCKD

Castellana M et al, Rev Endocr Metab Dis, 2019

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Study or Subgroup	After Mean	After SD	Before Mean	Before SD	Weight	Mean Difference IV, Random, 95% CI
1 ketogenic phase < 4 weeks						
Castaldo, 2016	97.6	12.5	106.9	13.2	11.2%	-9.30 [-13.47, -5.13]
Leonetti, 2015	125.9	16.3	145	15.6	9.1%	-19.10 [-25.35, -12.85]
Merra, 2016	89.5	8.5	94.3	10.8	9.0%	-4.80 [-11.15, 1.55]
Ministrini, 2019	124	17	130	19	8.5%	-6.00 [-12.93, 0.93]
Pilone, 2018	107	3.9	116.3	5	13.4%	-9.30 [-10.44, -8.16]
Subtotal (95% CI)					**51.2%**	**-9.68 [-13.11, -6.26]**
Heterogeneity: Tau² = 9.16; Chi² = 12.21, df = 4 (P = 0.02); I² = 67%						
Test for overall effect: Z = 5.54 (P < 0.00001)						
2 ketogenic phase ≥ 4 weeks						
Basciani, 2014	88.9	7.9	101.1	10.3	10.2%	-12.20 [-17.39, -7.01]
de Luis, 2016	88.2	6.4	109.1	7.8	11.6%	-20.90 [-24.57, -17.23]
Goday, 2016	96.1	7.6	108.1	8.6	11.9%	-12.00 [-15.35, -8.65]
Gomez-Arbelaez, 2017	88.6	10.1	109.4	12.8	8.3%	-20.80 [-27.95, -13.65]
Moreno, 2014	100.9	16.3	112.5	14	6.8%	-11.60 [-20.58, -2.62]
Subtotal (95% CI)					**48.8%**	**-15.61 [-20.27, -10.94]**
Heterogeneity: Tau² = 20.17; Chi² = 16.87, df = 4 (P = 0.002); I² = 76%						
Test for overall effect: Z = 6.56 (P < 0.00001)						
Total (95% CI)					**100.0%**	**-12.58 [-15.89, -9.28]**
Heterogeneity: Tau² = 21.00; Chi² = 56.49, df = 9 (P < 0.00001); I² = 84%						
Test for overall effect: Z = 7.46 (P < 0.00001)						
Test for subgroup differences: Chi² = 4.02, df = 1 (P = 0.04), I² = 75.1%						

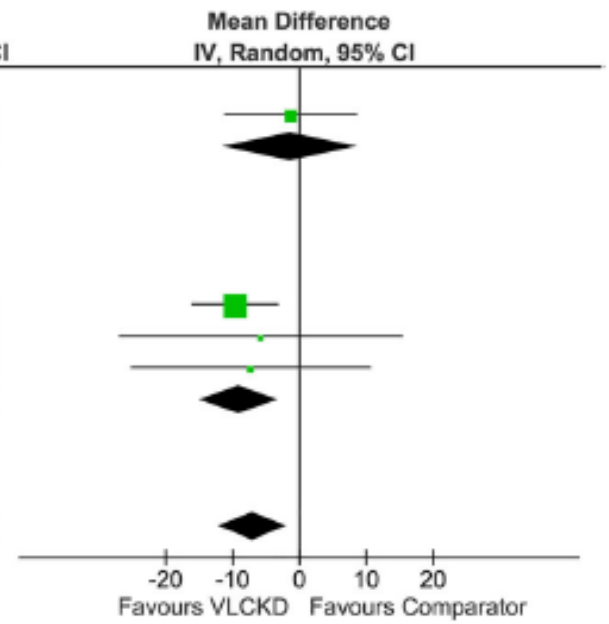


Forest plot of meta-analysis for change in waist circumference from baseline to the last available follow-up on VLCKD

Castellana M et al, Rev Endocr Metab Dis, 2019

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Study or Subgroup	VLCKD Mean	VLCKD SD	Comparator Mean	Comparator SD	Weight	Mean Difference IV, Random, 95% CI
1 VLCKD versus VLCD						
Albanese, 2018	-5.8	32.4	-4.5	34.3	25.8%	-1.30 [-11.23, 8.63]
Subtotal (95% CI)					**25.8%**	**-1.30 [-11.23, 8.63]**
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
2 VLCD versus LCD						
Goday, 2016	-14.7	13.9	-5.1	17.1	60.6%	-9.60 [-16.08, -3.12]
Leonetti, 2015	-12.8	33.7	-7	53.3	5.6%	-5.80 [-27.04, 15.44]
Moreno, 2014	-12.5	31.2	-5.2	30.3	7.9%	-7.30 [-25.28, 10.68]
Subtotal (95% CI)					**74.2%**	**-9.07 [-14.93, -3.20]**
Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)					**100.0%**	**-7.06 [-12.11, -2.01]**
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.74 (P = 0.006)						
Test for subgroup differences: Chi² = 1.74, df = 1 (P = 0.19), I² = 42.6%						



Forest plot of meta-analysis for differences in body weight changes from baseline to the last available follow-up on VLCKD versus other diets

Castellana M et al, Rev Endocr Metab Dis, 2019

Efficacy and safety of very low calorie ketogenic diet (VLCKD) in patients with overweight and obesity: A systematic review and meta-analysis

Also, VLCKD was associated with reductions of
HbA1c (–0.7%)
total cholesterol (–28 mg/dl)
triglycerides (–30 mg/dl)
AST (–7 U/l), ALT (–8 U/l) e γGT (–8 U/l),
systolic and diastolic blood pressure
(–8 and–7 mmHg, respectively)

No changes in LDL cholesterol, HDL cholesterol, serum creatinine, serum uric acid and serum potassium were found.

Serum sodium increased during VLCKD (+1.6 mEq/l)

Castellana M et al, Rev Endocr Metab Dis, 2019

nutrients

MDPI

Uric Acid and Potassium Serum Levels Are Independent Predictors of Blood Pressure Non-Dipping in Overweight or Obese Subjects

Roberta Zupo [1], Fabio Castellana [1], Barbara Boninfante [2], Luisa Lampignano [1], Antonio Lattanzio [3], Rodolfo Sardone [1], Gianluigi Giannelli [4] and Giovanni De Pergola [3,*]

Abstract:
….. Methods: A sample of 100 consecutive healthy overweight/obese subjects, aged 20–69 years and never treated with antihypertensive drugs was examined. Results: Hypertension was demonstrated in 69% (n = 69) and 27% of the sample (n = 27) had a non-dipping profile.
Conclusions:
This study shows, for the first time, that
1) an unexpectedly high percentage (69%) of overweight/obese subjects is affected by hypertension;
2) early hypertensive subjects have an increased eGFR and higher FT4 serum levels;
3) **lower potassium** and **uric acid levels** are **independent predictors of** pathological **nocturnal non-dipping**

Nutrients, 2019

Effect of A Very Low-Calorie Ketogenic Diet on Food and Alcohol Cravings, Physical and Sexual Activity, Sleep Disturbances, and Quality of Life in Obese Patients

……. twenty obese patients (12 females, 47.2 ± 10.2 year and BMI of 35.5 ± 4.4) through the course of a 4-month VLCK diet …….. Each subject acted as their own control.

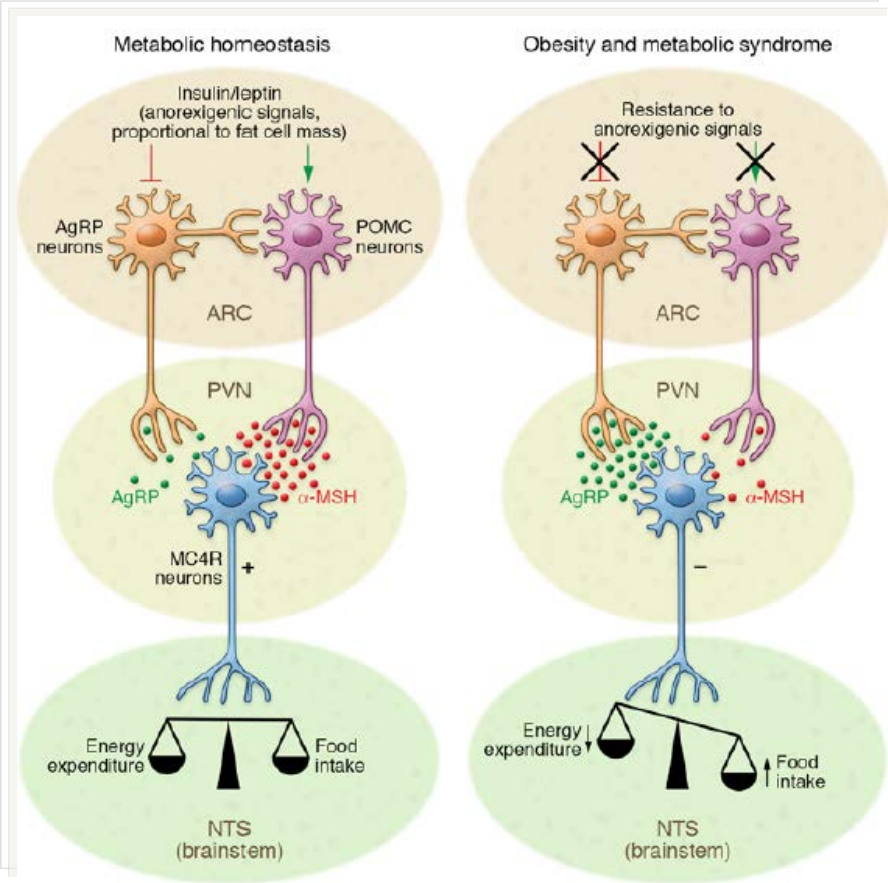
Relevantly, the dietary-induced changes in body composition (7.7 units of BMI lost, 18 kg of fat mass (1.2 kg of visceral fat mass) were associated with a statistically **significant improvement** in **food craving scores**, **physical activity**, **sleepiness**, and **female sexual function**.
Overall, these results also translated in a notable **enhancement in QoL** of the treated obese patients.

……. which could contribute to the long-term success of this therapy.

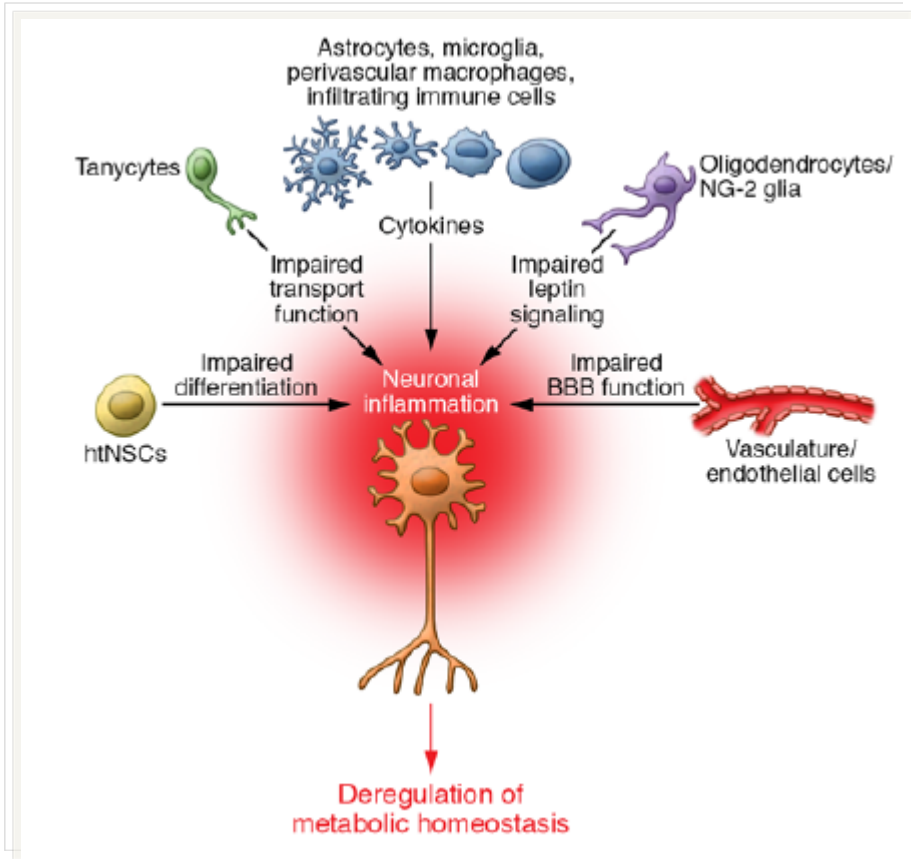
Castro AI et al, Nutrients, 2018

Hypothalamic inflammation in obesity and metabolic disease

HYPOTHALAMIC CONTROL OF ENERGY HOMEOSTASIS



CELLULAR NETWORK OF HYPOTHALAMIC INFLAMMATION



Jais A e Bruning JC, *J Clin Invest*, 2017

Original Article

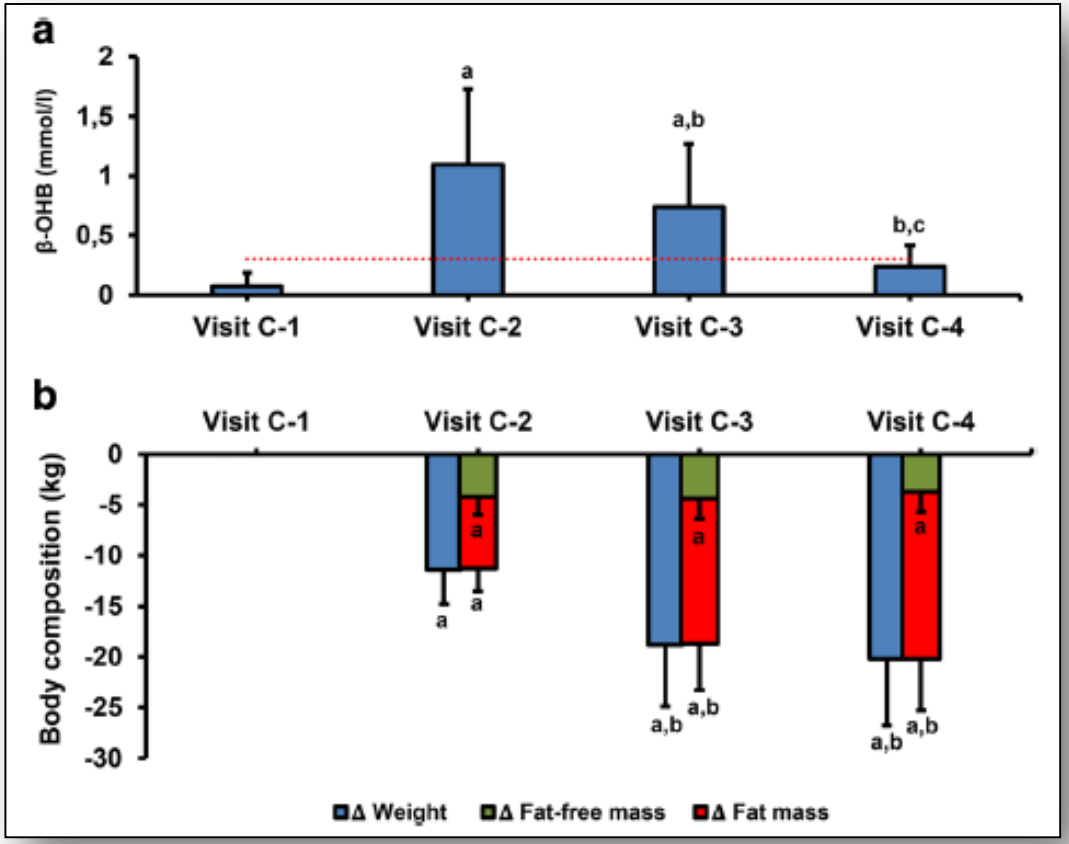
MOLECULAR METABOLISM

Dietary sugars, not lipids, drive hypothalamic inflammation

Yuanqing Gao[1,2,12], Maximilian Bielohuby[3,12], Thomas Fleming[4], Gernot F. Grabner[5], Ewout Foppen[2], Wagner Bernhard[6], Mara Guzmán-Ruiz[7], Clarita Layritz[1], Beata Legutko[1], Erwin Zinser[6], Cristina García-Cáceres[1], Ruud M. Buijs[7], Stephen C. Woods[8], Andries Kalsbeek[2,9], Randy J. Seeley[10], Peter P. Nawroth[4], Martin Bidlingmaier[3,***], Matthias H. Tschöp[1,11,**], Chun-Xia Yi[2,*]

2017

Resting metabolic rate of obese patients under very low calorie ketogenic diet

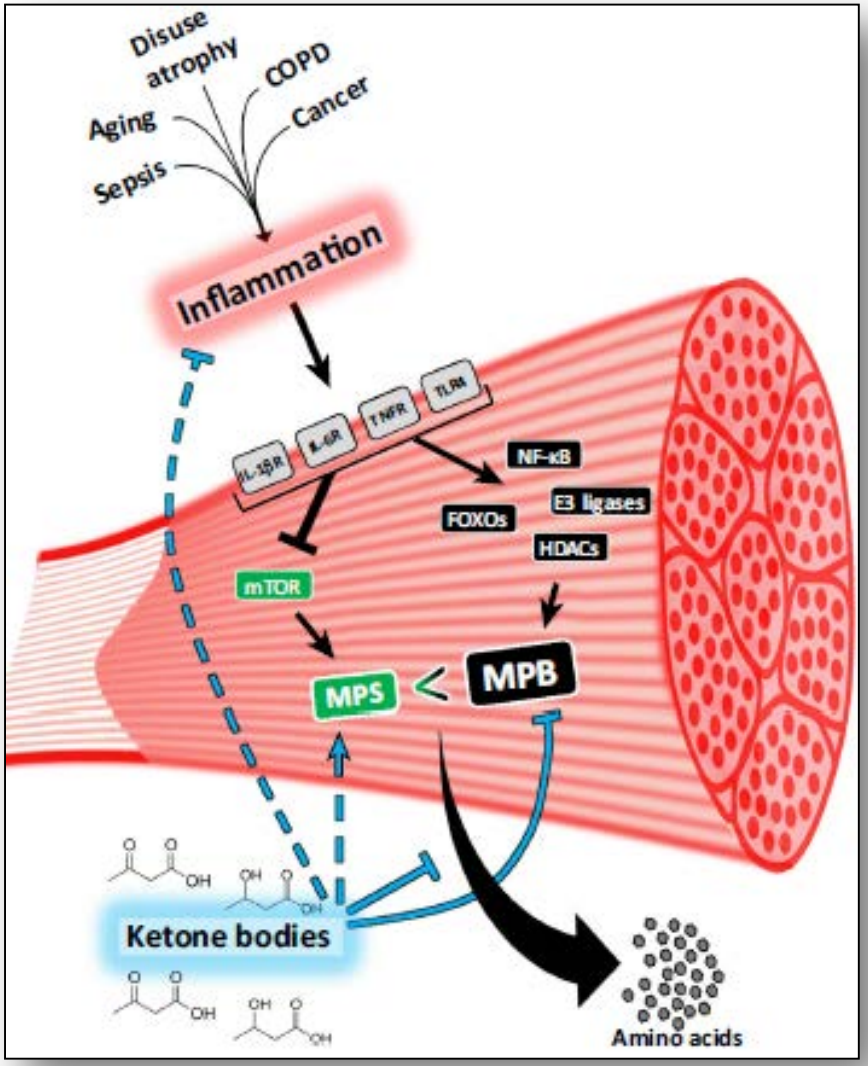


La rapida e importante perdita del peso e della massa grassa indotta dalla VLCKD non ha indotto la prevista riduzione della RMR, probabilmente per **preservazione della FFM**

Gomez-Arbealez D et al, Nutr Metab, 2018

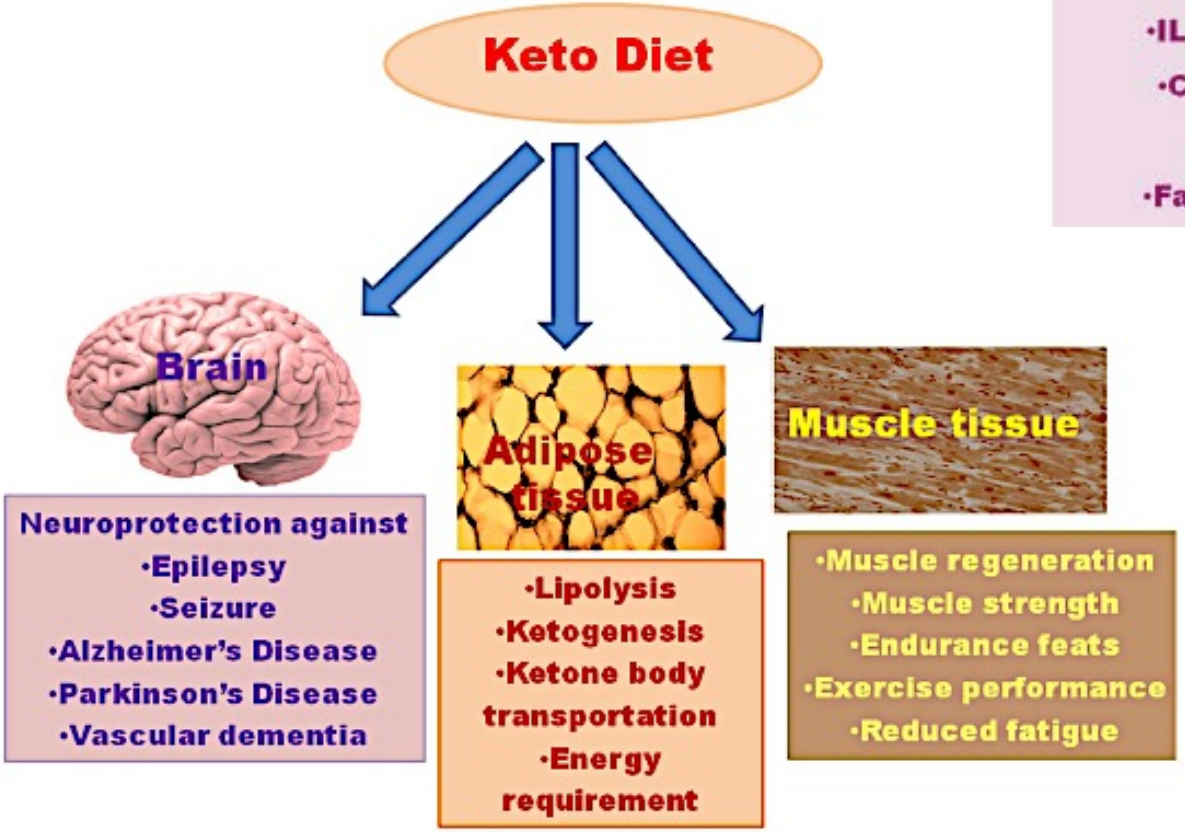
Anticatabolic Effects of Ketone Bodies in Skeletal Muscle

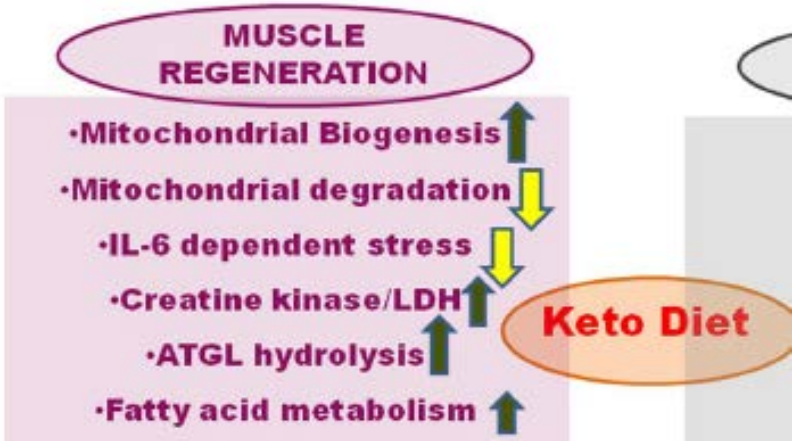
MPB, muscle protein breakdown
MPS, muscle protein synthesis



Koutnik AP et al, Cell Press Rev, 2019

KETOGENIC DIET and MUSCLE





Li RJ et al, Journal of Food Biochemistry 2020

Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations
Severe obesity
Management of severe obesity before bariatric surgery
Sarcopenic obesity
Obesity associated with type 2 diabetes (preserved beta cell function)
Obesity associated with hypertriglyceridemia
Obesity associated with hypertension
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet

Caprio M et al, J Endocrinol Invest, 2019

Medical News & Perspectives

Interest in the Ketogenic Diet Grows for Weight Loss and Type 2 Diabetes

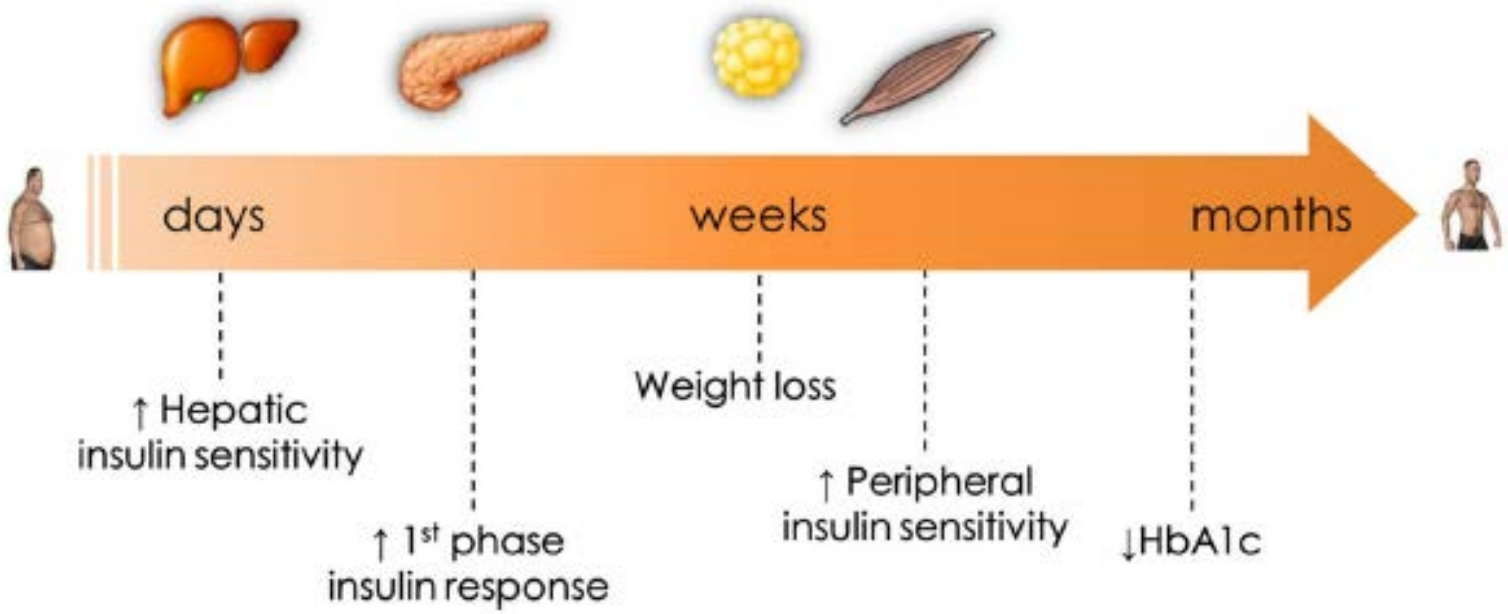
Jennifer Abbasi

Remissione del diabete:

- unica alternativa medica alla chirurgia metabolica
- opzione terapeutica da proporre al paziente motivato al cambiamento.

JAMA January 16, 2018 Volume 319, Number 3 215

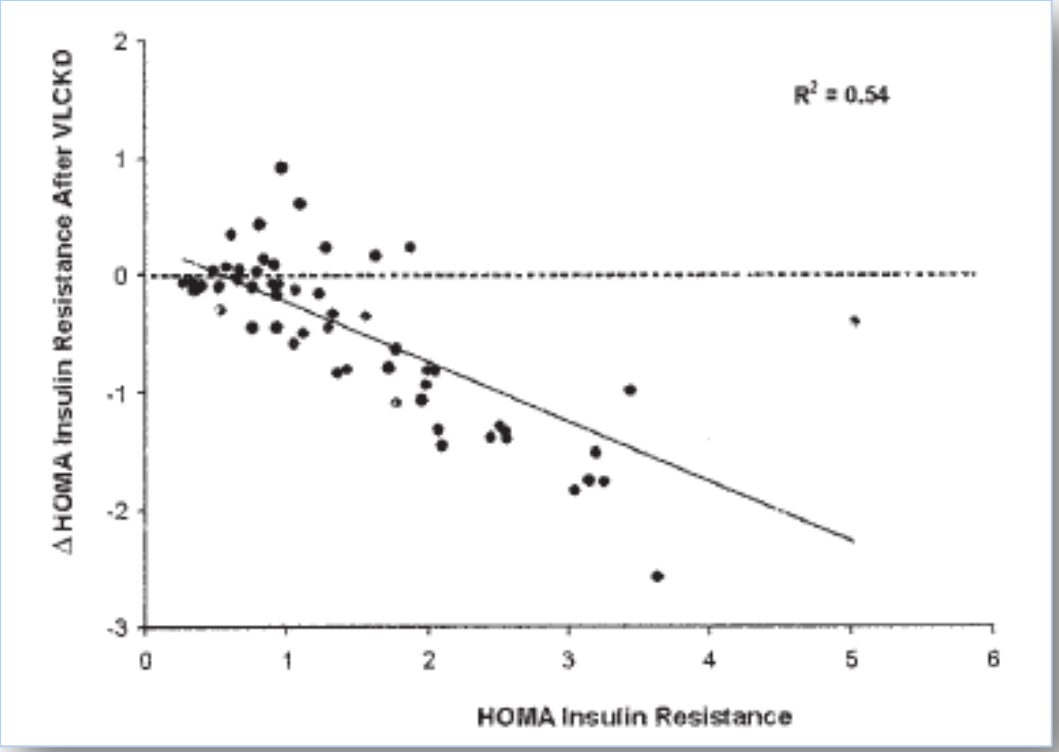
Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)



Caprio M et al, J Endocrinol Invest, 2019

Cardiovascular and Hormonal Aspects of Very-Low-Carbohydrate Ketogenic Diets

Relazione tra il livello d'insulino-resistenza di base e la entità della sua riduzione in risposta alla VLCKD



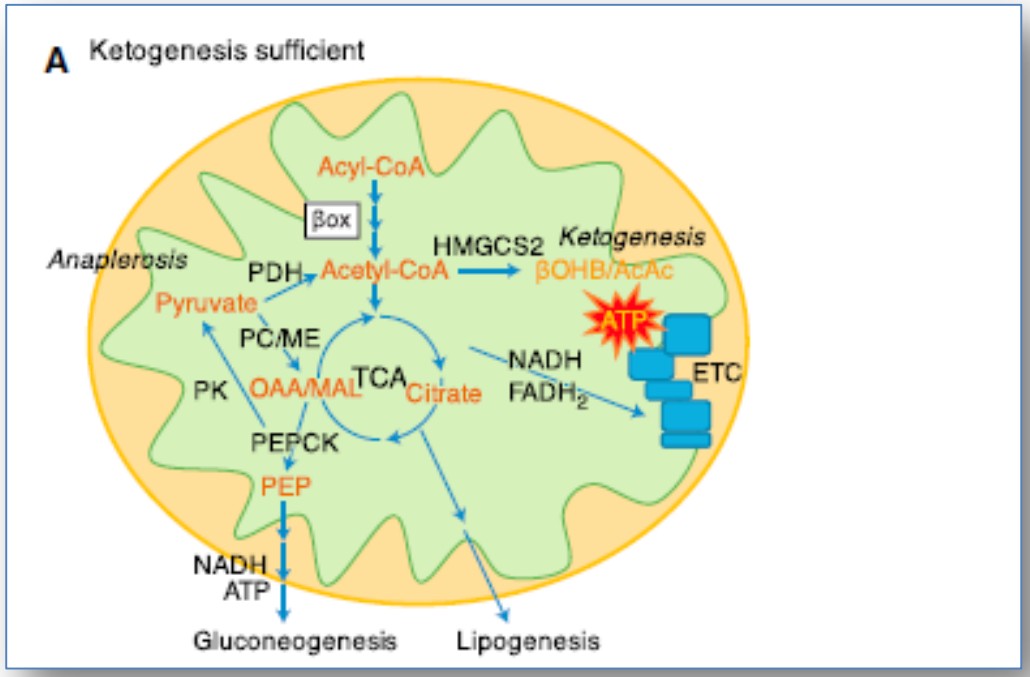
Volek e Sharman, Obes Res, 12: 115S-123S, 2004

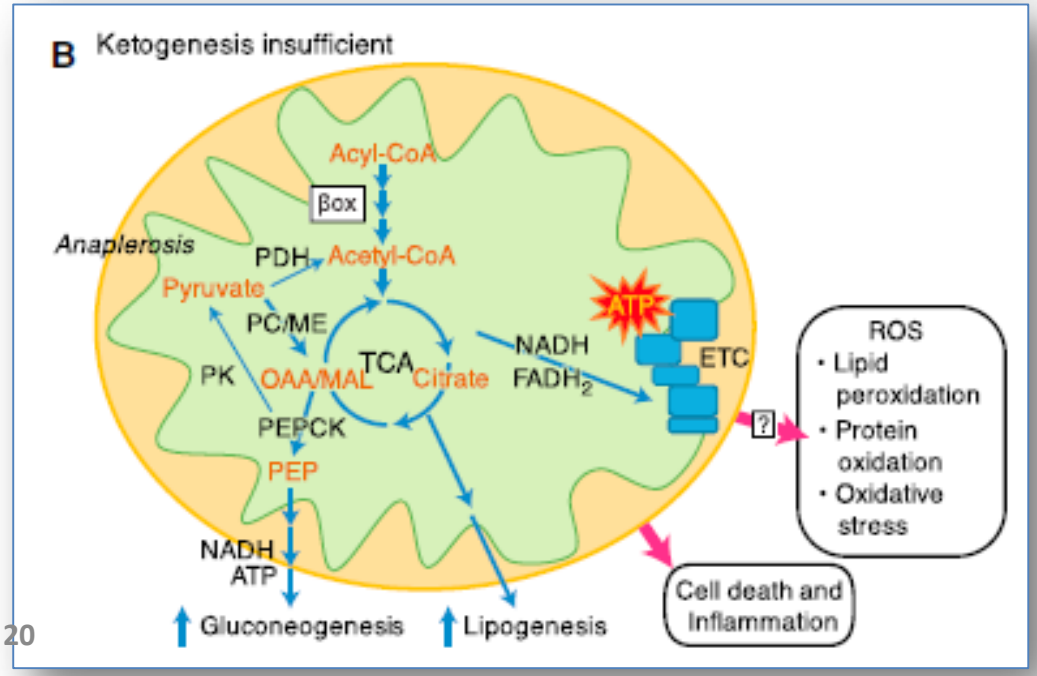
Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 2 Indications for the use of VLCKD in metabolic diseases

Weak recommendations
Obesity associated with dysbiosis of the gut microbiota
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol
Obesity associated with non-alcoholic fatty liver disease (NAFLD)
Obesity associated with heart failure (NYHA I–II)
Obesity associated with atherosclerosis
Male obesity secondary hypogonadism
Obesity associated with polycystic ovary syndrome (PCOS)
Menopausal transition-related obesity

Caprio M et al, J Endocrinol Invest, 2019

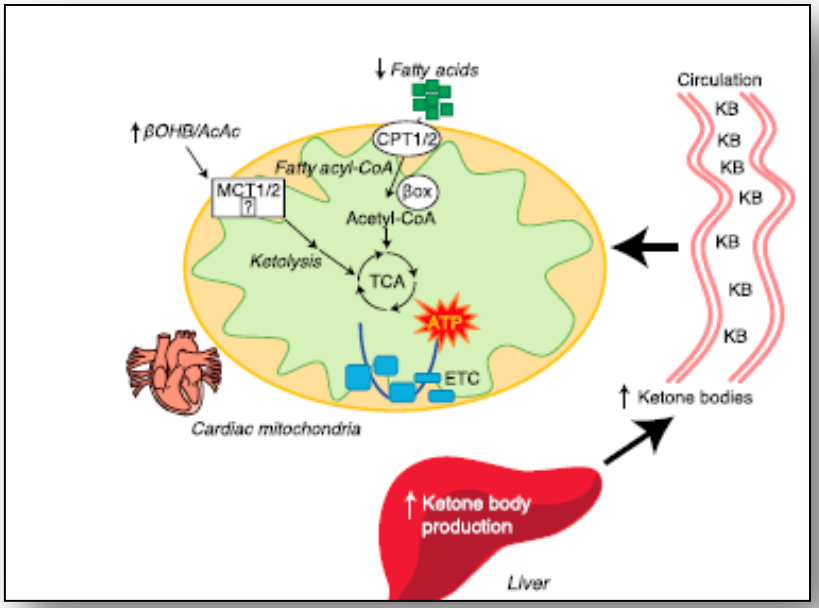

A
Ketogenesis sufficient
Acyl-CoA
βox
HMGCS2
Ketogenesis
Anaplerosis
PDH
Acetyl-CoA
βOHB/AcAc
Pyruvate
ATP
PC/ME
NADH
ETC
PK
OAA/MAL
TCA
Citrate
FADH2
PEPCK
PEP
NADH
ATP
Gluconeogenesis
Lipogenesis


B
Ketogenesis insufficient
Acyl-CoA
βox
Anaplerosis
PDH
Acetyl-CoA
Pyruvate
ATP
PC/ME
NADH
ETC
PK
OAA/MAL
TCA
Citrate
FADH2
?
PEPCK
PEP
ROS
• Lipid peroxidation
• Protein oxidation
• Oxidative stress
NADH
ATP
Cell death and Inflammation
Gluconeogenesis
Lipogenesis

NASH

Multi-dimensional Roles of Ketone Bodies in Fuel Metabolism, Signaling, and Therapeutics.

EFFETTO CARDIOPROTETTIVO DEI CORPI CHETONICI



Il cuore **normale** preferisce gli acidi grassi tra i diversi substrati energetici, ma ossida i corpi chetonici in maniera proporzionale alla concentrazione nel sangue.

Il cuore scompensato è riprogrammato e riduce la ossidazione degli acidi grassi. Il cuore scompensato **predilige la ossidazione dei corpi chetonici**

Puchalska C et al, Cell Metab Rev, 25: 261-284, 2017

Biomarkers and prediction of myocardial triglyceride content in non-diabetic men

Table 2 Biomarkers across tertiles of myocardial triglyceride (TG) content.

	Myocardial TG content low 0.32 (0.14–0.45) (n = 25)	Myocardial TG content moderate 0.74 (0.46–0.87) (n = 26)	Myocardial TG content high 1.29 (0.88–2.33) (n = 25)	P
S-Adiponectin (ug/mL)	2.54 (0.56–6.83)	1.80 (0.20–5.56)	1.12 (0.59–3.85)[b]	0.125[a]
S-Leptin (ng/mL)	1.26 (0.01–25.65)	6.38 (1.07–30.54)	8.70 (0.01–30.23)	0.092
S-A-FABP 4 (ng/mL)	7.73 (4.72–21.27)	16.28 (7.48–30.81)[b]	17.22 (7.23–52.33)[b]	<0.001[a]
S-β-OHB (mg/dL)	1.02 (0.51–4.56)	0.67 (0.46–3.98)[b]	0.68 (0.27–4.89)[b]	0.003[a]
S-Resistin (ng/mL)	3.03 ± 0.87	3.14 ± 0.86	2.76 ± 0.72	0.200
S-Lipocalin-2 (ng/mL)	60.66 ± 15.88	64.25 ± 13.67	58.02 ± 14.44	0.112[a]

Table 3 Results of stepwise multivariable regression analyses.

Independent variables	Myocardial TG content (log)		
	Unstandardized coefficients		
	β	Std. Error	p
Constant	−8.468	1.759	<0.001
Age (log)	0.765	0.296	0.012
Body mass index (log)	0.493	0.446	0.273
Triglyceride (log)	−0.095	0.117	0.423
fP-glucose (log)	1.711	0.561	0.003
Smoking status	0.258	0.122	0.039
S-Adiponectin (log)	−0.169	0.081	0.042
S-Adipocyte fatty-acid binding protein 4 (log)	0.268	0.140	0.060
B-hydroxy buturate (log)	−0.256	0.080	0.002
Adjusted R^2		0.588	<0.001

Graner M et al, Nutr Metab Cardiovasc Dis, 26: 134-140, 2016

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DOI: 10.1111/andr.12754

ORIGINAL ARTICLE

ANDROLOGY WILEY

Weight loss more than glycemic control may improve testosterone in obese type 2 diabetes mellitus men with hypogonadism

Vito Angelo Giagulli[1,2] | Marco Castellana[3] | Matteo Domenico Carbone[4] | Carla Pelusi[5] | Maria Isabella Ramunni[2] | Giovanni De Pergola[6] | Edoardo Guastamacchia[1] | Vincenzo Triggiani[1]

Current Perspectives On The Role Of The Ketogenic Diet In Epilepsy Management

Table 2 Probable Anti-Seizure Mechanisms Of KD

Primary Physiological Change	Probable Hypothesized Mechanism Of Seizure Reduction
(a) Ketosis	(i) Hyperpolarization of neurons by Potassium channel activation
	(ii) Slow energy production (compared to pathway wherein energy is derived primarily from glucose) which leads to anti-seizure effects
	(iii) Potentiation of inhibitory neurotransmitters (eg, GABA)
	(iv) Augmented neuronal function through cellular
	(v) Chronic ketosis is postulated to stabilize and reduce synaptic hyperexcitability in order to conserve energy, thereby increasing seizure threshold
(b) Increased levels of Polyunsaturated Fatty Acids (PUFA)	(i) Activation of e peroxisome proliferator-activated receptors (PPARs)
	(ii) Hyperpolarization of neurons
(c) Alteration of gut microbiome	Possible role in increasing seizure threshold due to putative microorganisms (eg, Akkermansiamuciniphila and Parabacteroides) which has been noted in murine models as well as human studies of gut microbiome
(d) Alteration of proinflammatory and anti-inflammatory mediators	Reduced levels of Interleukin 1b and other proinflammatory cytokines in mice treated with KD supports the role of modulation of these inflammatory mediators in combating epilepsy

Note: Data from.[85–86]

Goswami JN e Sharma S, NDT, 2019

Ketogenic diets and tumour hypoxia – kulturkampf and 'the insurgency'

Table 1. Possible modes of action of the ketogenic diet in treatment of epilepsy

Hypothetic modes of action	Comments
Ketones act directly as anti-seizure agents	Demonstrated in animals and humans but no plausible mediating mechanism
Increased flux of acetyl-CoA with reduced glycolysis leads to less conversion of glutamate to aspartate, with beneficial effects on synthesis of GABA and neurotransmission	Based mainly on changes in concentration of intracellular metabolites
Improved cellular bioenergetics and mitochondrial function	May be mediated through Nrf2, a protective transcription factor that is activated by cellular stress
Restriction in glycolysis flux and diversion of metabolites into the pentose phosphate shunt substrate (fructose-1,6-bisphosphate)	Reduction in $NADH:NAD^+$ ratio modulates histone acetylation
Fatty acids act directly as anti-seizure agents	Pleiotypic increase in plasma concentrations of all accessory molecules for fat metabolism (including PUFA). Some evidence that PUFA supplementation reduces seizures
Reduced oxidative stress	May be mediated through Nrf2, a protective transcription factor that is activated by cellular stress
Increased efficiency of the TCA cycle function through supplementation with 'anaplerotic' substrates	Experimentally, the KD increases neuronal ATP concentration. It is postulated that the increased presentation of acetyl-CoA from ketones increases TCA cycle flux through 'anaplerosis' (Greek: 'filling up') but this is a fundamental misunderstanding. Aspartate and glutamate feed this process as the metabolites oxaloacetate and α-ketoglutarate. Ketones feed in acetyl-CoA which will be oxidized and cannot therefore fill up the TCA cycle

Grimble G e Ryall J, Curr Opin Clin Nutr Metab Care, 2019

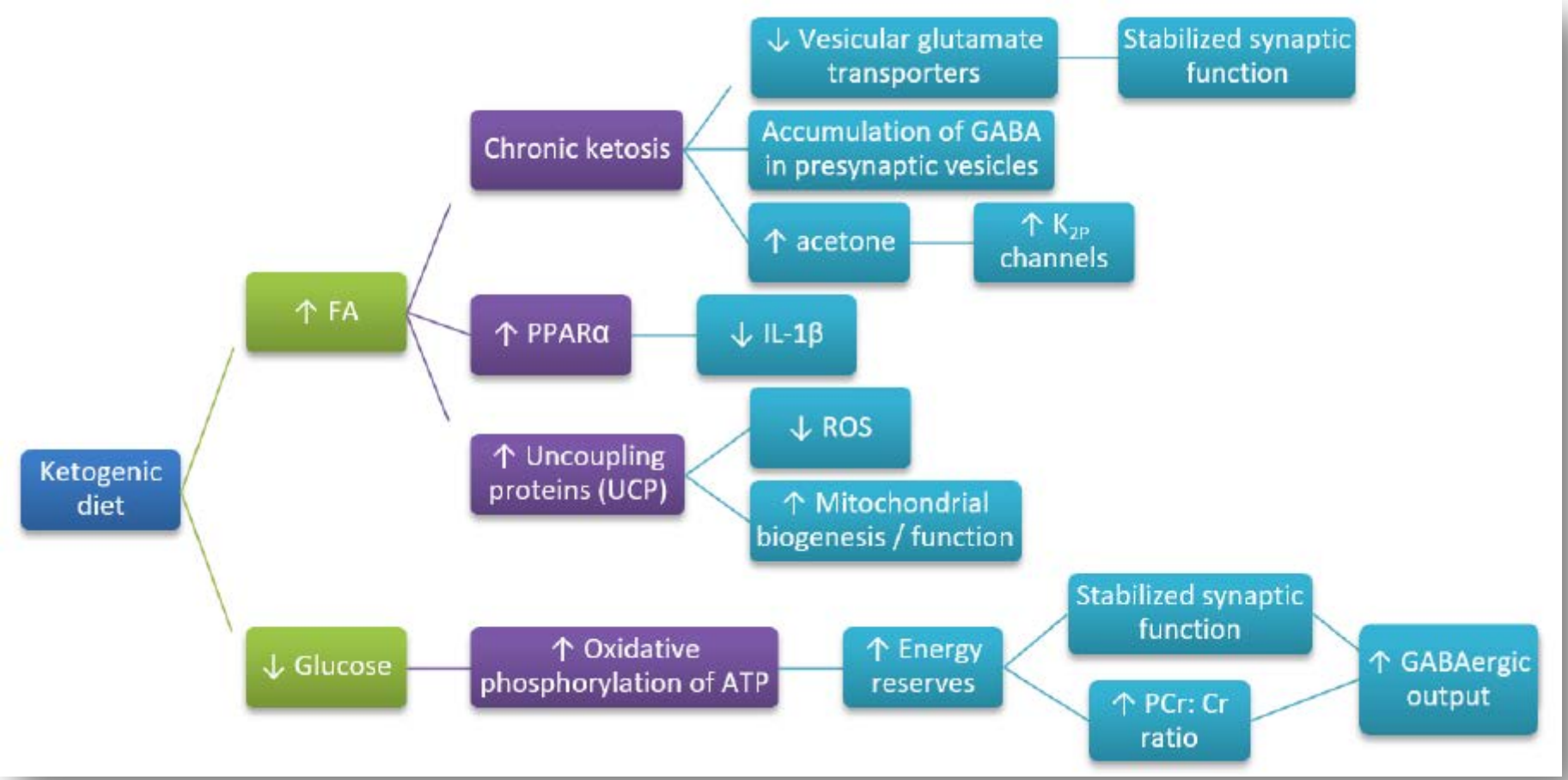
TABLE 1 | Epilepsy syndromes and some conditions in which the KD therapies has been reported probable benefit*.

Angelman syndrome
Complex 1 mitochondrial disorders
Dravet syndrome
Epilepsy with myoclonic–atonic seizures (Doose syndrome)
Glucose transporter protein 1 (Glut-1) deficiency syndrome (Glut1DS)
Febrile infection–related epilepsy syndrome (FIRES)
Formula-fed (solely) children or infants
Infantile spasms
Ohtahara syndrome
Pyruvate dehydrogenase deficiency (PDHD)
Super-refractory status epilepticus
Tuberous sclerosis complex

**Adapted from Kossoff et al. (2018). Optimal clinical management of children receiving dietary therapies for epilepsy: Updated recommendations of the International Ketogenic Diet Study Group (Kossoff et al., 2018).*

Review

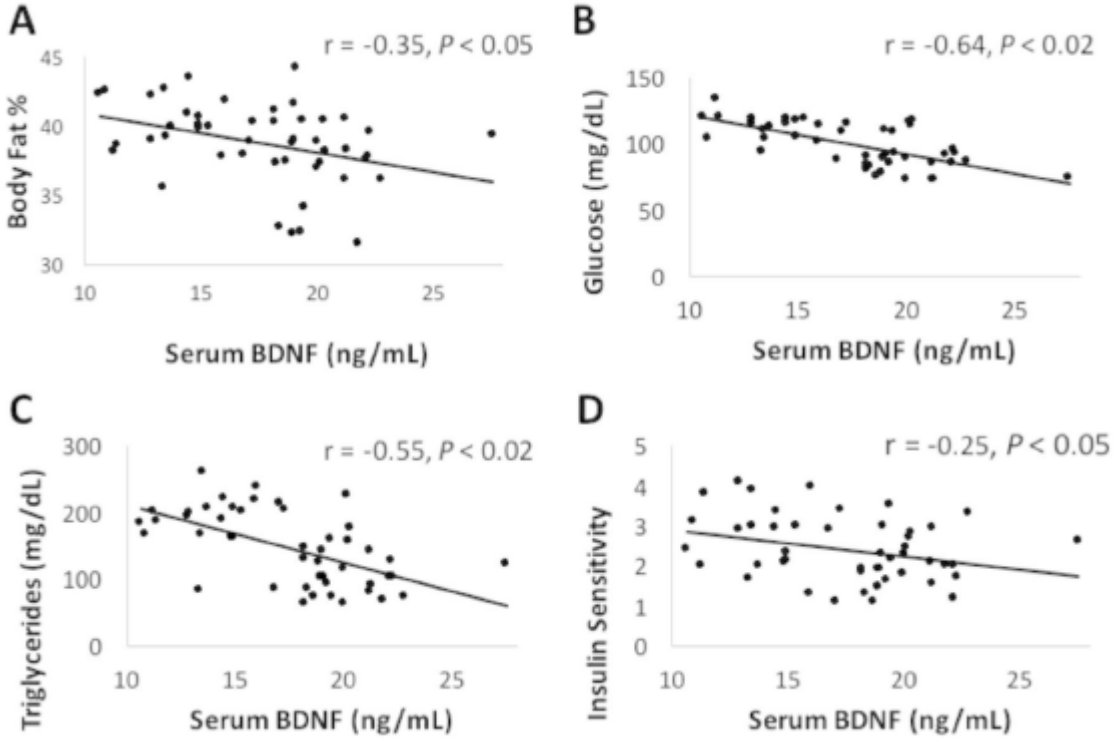
Ketogenic Diet in Alzheimer's Disease



Rusek M et al, Int J Mol Scu, 2019

Carbohydrate-restricted Diet and Exercise Increase Brain-derived Neurotrophic Factor and Cognitive Function: A Randomized Crossover Trial

This study shows the **short-term beneficial effects of carbohydrate-restricted diet on serum BDNF** and executive function in those **individuals** characterized **with MetS**. We have shown that the addition of **exercise can further improve neuroprotection and cognitive function** beyond the results of diet alone.



Gyorkos A et al, Cureus, 2019

Review

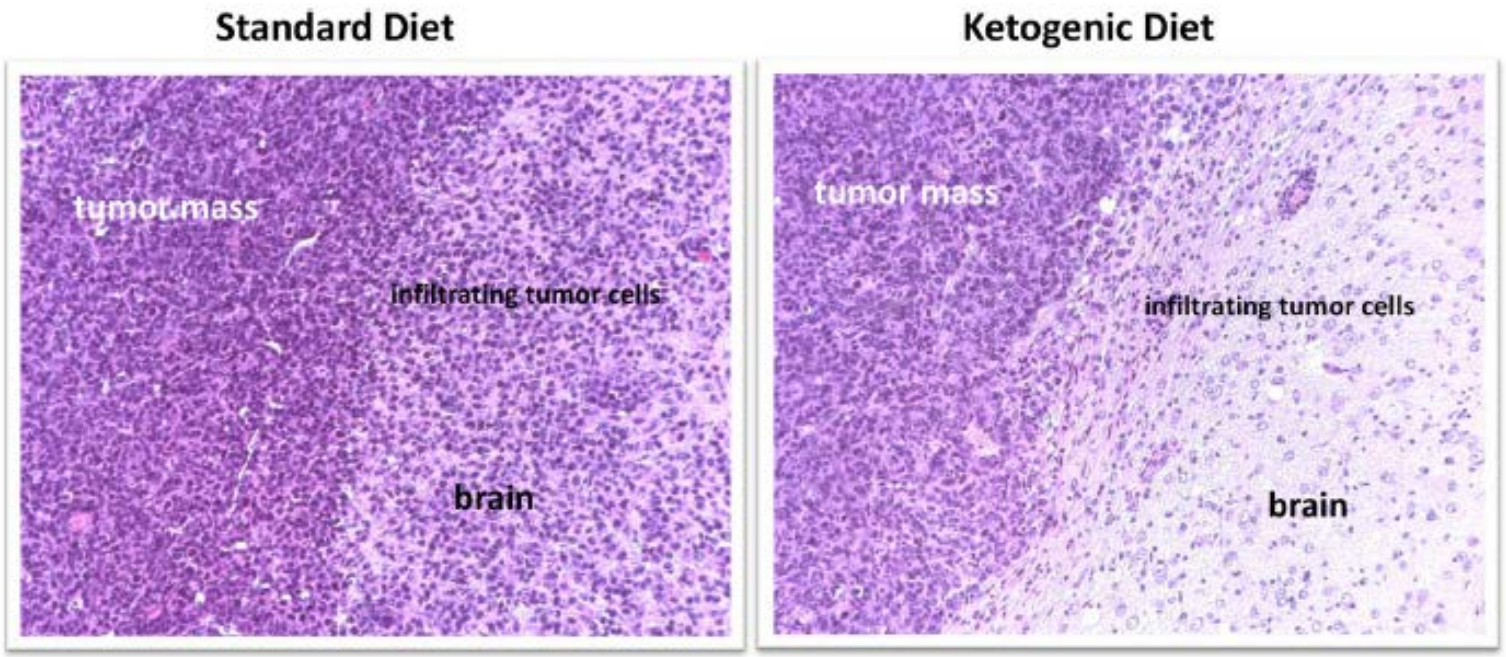
The Expanding Role of Ketogenic Diets in Adult Neurological Disorders

Table 1. Hypothesized mechanisms through which ketogenic therapies influence neurological disease.

Ketogenic Mechanisms	Epilepsy	Malignant Glioma	Alzheimer's Disease
Metabolic Regulation			
↓Glucose uptake & glycolysis	+	+	
↓Insulin, IGF1 signaling		+	+
↑Ketones/ketone metabolism	+		+
Altered gut microbiota	+		
Neurotransmission			
Altered balance of excitatory/inhibitory neurotransmitters	+		
Inhibition of AMPA receptors	+		
↓mTOR activation & signaling	+	+	
Modulation of ATP-sensitive potassium channels	+		
Oxidative Stress			
↓Production of reactive oxygen species	+	+	
↑Mitochondrial biogenesis/function	+		+
Inflammation/Neuroprotection			
↓Inflammatory cytokines	+	+	
NLRP3 inflammasome inhibition	+	+	
↑cytotoxic T cell function		+	
↓peritumoral edema		+	
↓amyloid-β levels			+
Genomic Effects			
Inhibition of HDACs	+	+	
↑PPARγ	+		
↓Expression of angiogenic factors in tumor cells		+	

McDonald TJW et al, Brain Sci, 8: 148, 2018

Provocative Question: Should Ketogenic Metabolic Therapy Become the Standard of Care for Glioblastoma?

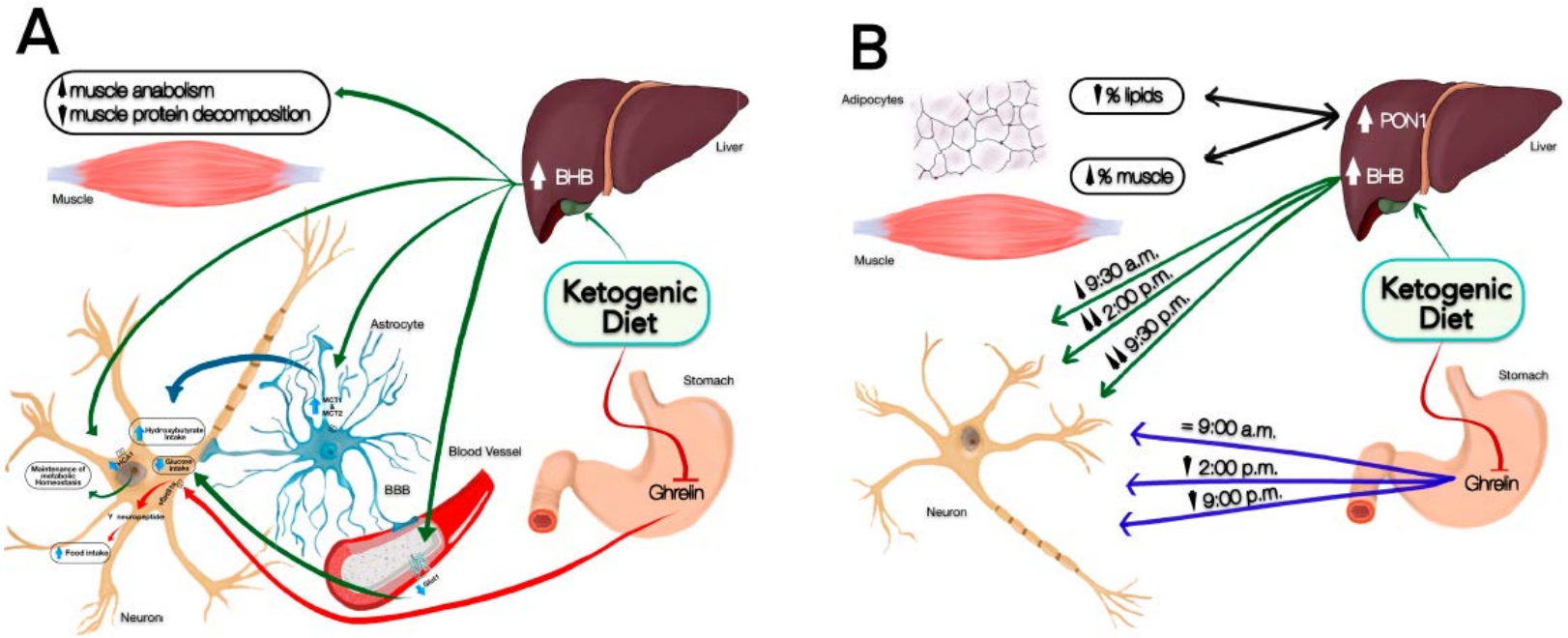


100x

Seyfried TN et al, Neurochem Res, 2019

Satiating Effect of a Ketogenic Diet and Its Impact on Muscle Improvement and Oxidation State in Multiple Sclerosis Patients

Measure	Pre-Test		Post-Test		Z	p
	Mean	SD	Mean	SD		
Muscle %	39.39	2.88	40.22	2.86	–2.955	0.003 *



this is the first study addressing improvements in body composition, oxidation state and metabolism in MS patients

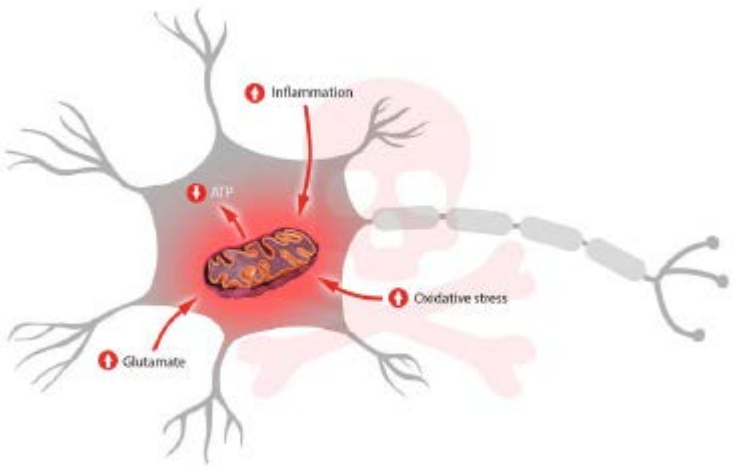
Benlloch M et al, Nutrients, 2019

REVIEW

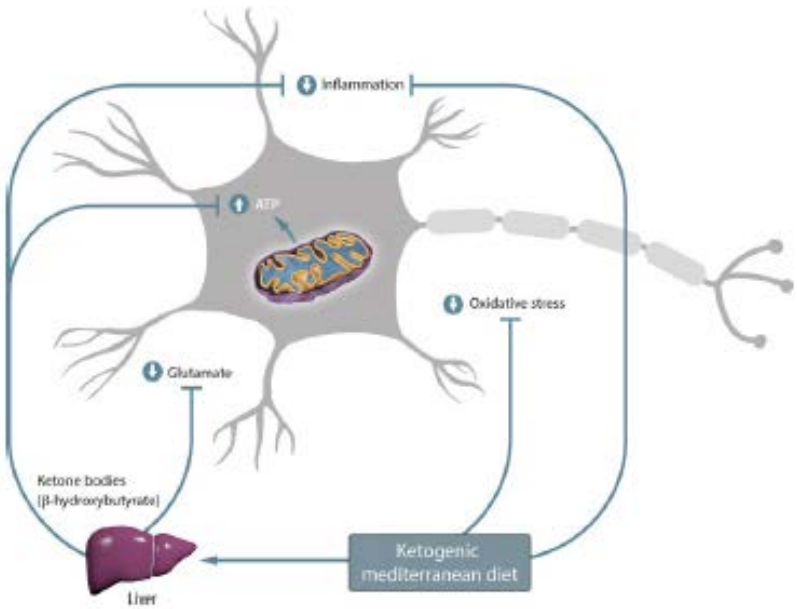
Food Science & Nutrition Open Access WILEY

Therapeutic alternative of the ketogenic Mediterranean diet to improve mitochondrial activity in Amyotrophic Lateral Sclerosis (ALS): A Comprehensive Review

Pathogenesis of ALS after the genetic mutation in the SOD1 gene, which causes the death of the motor neuron by damaging mitochondrial activity

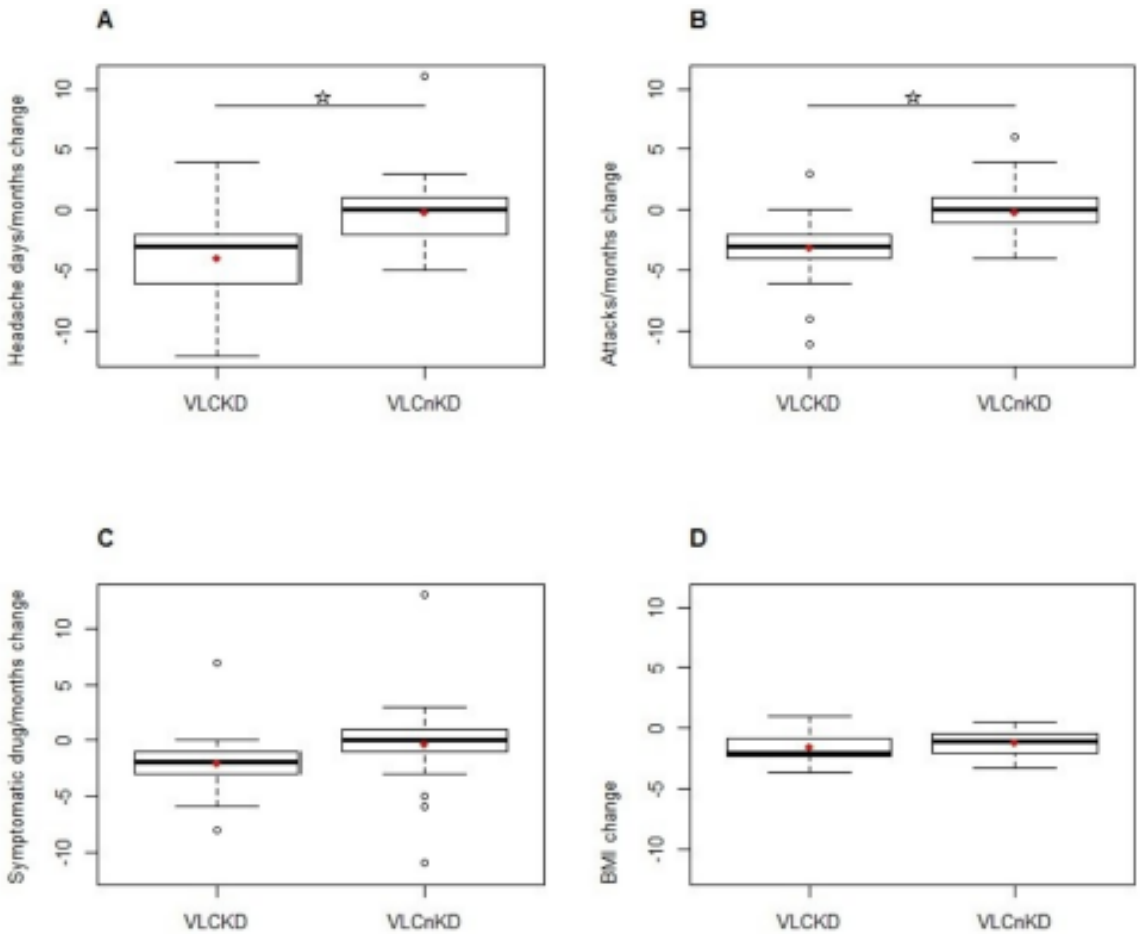


Activity proposal of the Mediterranean ketogenic diet on the different pathogenic mechanisms of ALS



Cappliure-Llopis J et al, Food Sci Nutr, 2020

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

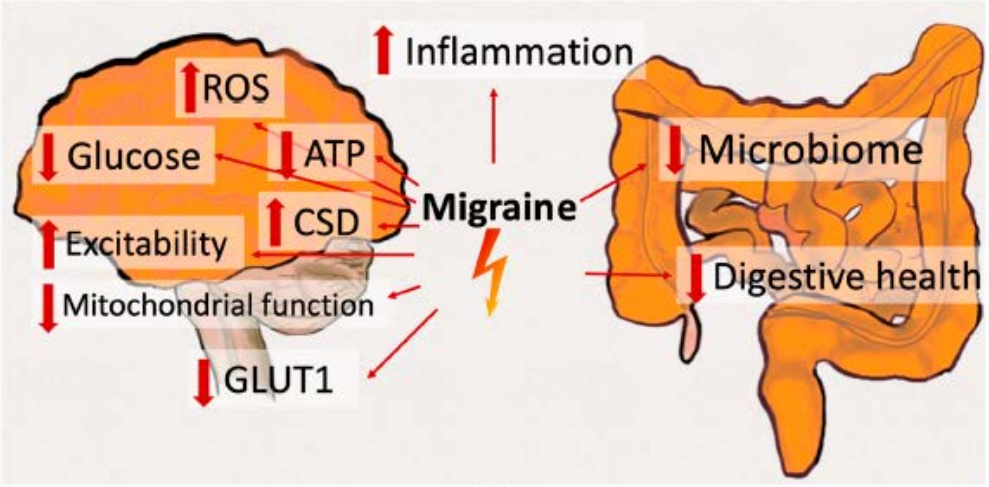


Our results confirm, in a double-blind design, that VLCKD is selective for rapid, short-term improvement of migraines in overweight patients, while VLCnKD is not.

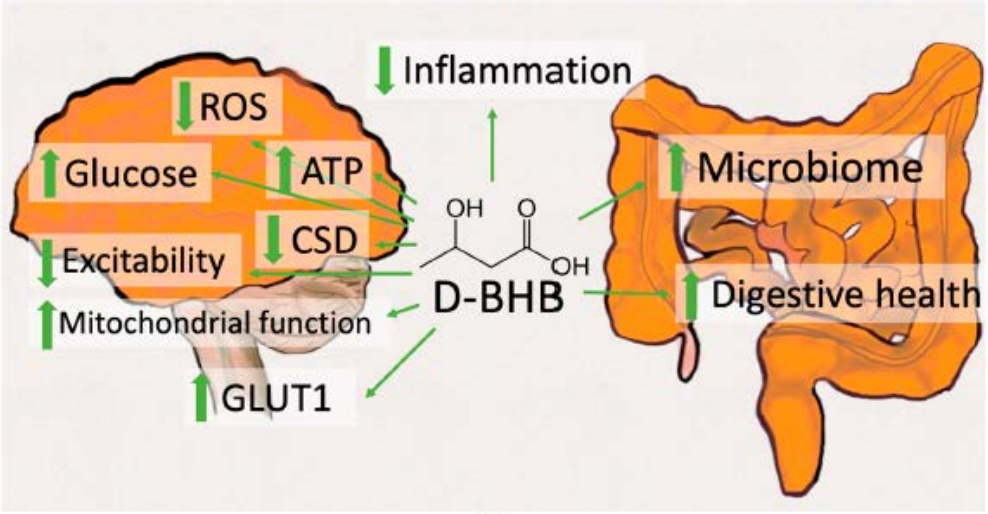
Di Lorenzo C et al, Nutrients, 2019

Review

Potential Protective Mechanisms of Ketone Bodies in Migraine Prevention



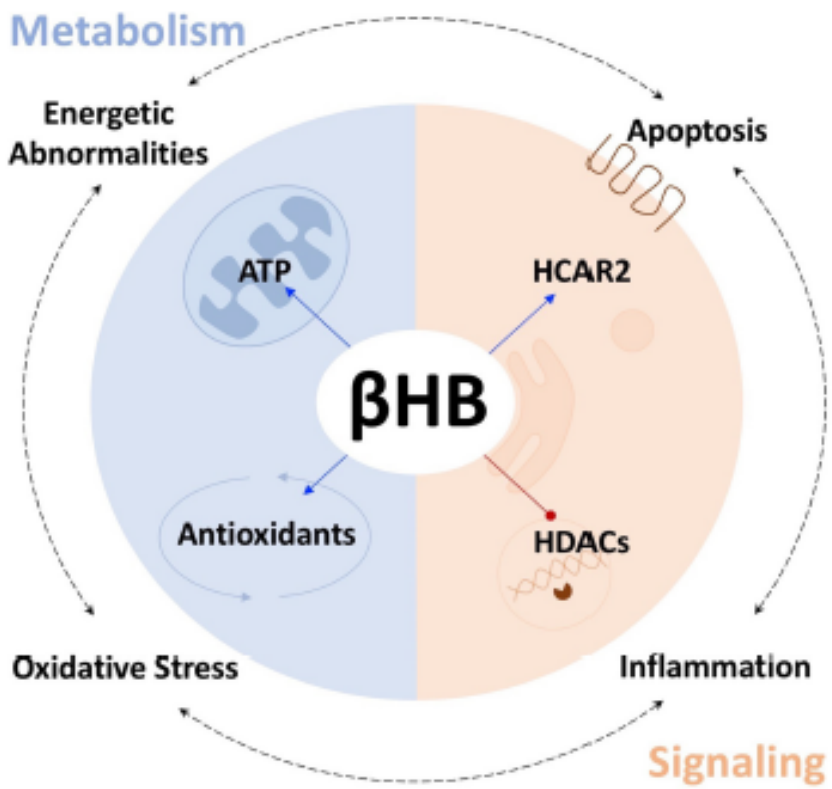
(a)

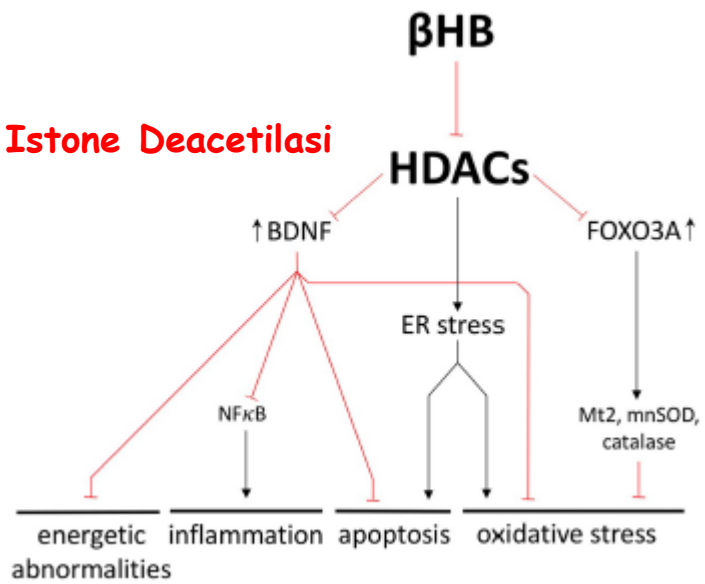


(b)

Gross EC et al, Nutrients, 2019

The Mechanisms by Which the Ketone Body D-β-Hydroxybutyrate May Improve the Multiple Cellular Pathologies of Parkinson's Disease





Norwitz NG et al, Front Nutr, 2019

Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

Table 2 Indications for the use of VLCKD in metabolic diseases

Strong recommendations
Severe obesity
Management of severe obesity before bariatric surgery
Sarcopenic obesity
Obesity associated with type 2 diabetes (preserved beta cell function)
Obesity associated with hypertriglyceridemia
Obesity associated with hypertension
Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet
Weak recommendations
Obesity associated with dysbiosis of the gut microbiota
Obesity associated with high levels of LDL-cholesterol and/or low levels of HDL-cholesterol
Obesity associated with non-alcoholic fatty liver disease (NAFLD)
Obesity associated with heart failure (NYHA I–II)
Obesity associated with atherosclerosis
Male obesity secondary hypogonadism
Obesity associated with polycystic ovary syndrome (PCOS)
Menopausal transition-related obesity
Neurodegenerative disorders associated with sarcopenic obesity

Caprio M et al, J Endocrinol Invest, 2019

The emerging role of ketogenic diets in cancer treatment

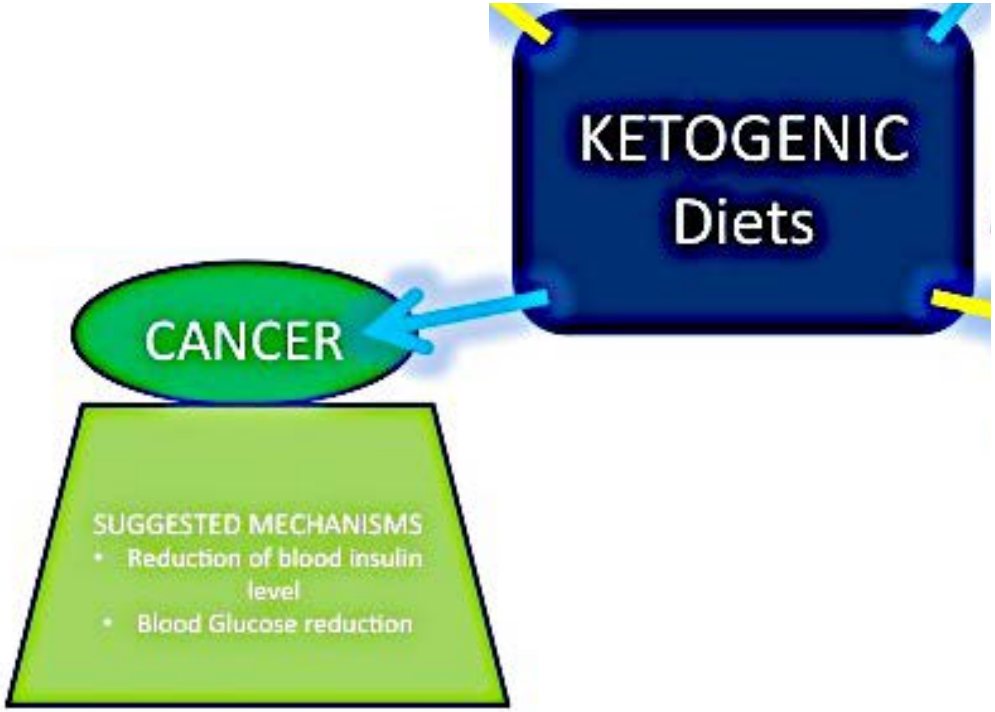
KEY POINTS

- Most animal studies provide evidence for anti-tumor effects of ketogenic diets, although more recently some tumor models not responding have been described.
- The available data support the use of ketogenic diets as adjuncts to other treatments rather than as stand-alone therapies.
- Ketogenic diets in cancer treatment are safe, but prone to compliance problems, making appropriate patient selection important
- The most recent case and cohort studies have shown promising results for the KD concerning anti-tumor effects, body composition, physical functioning and metabolic parameters.
- However, robust correlations with clinical endpoints such as overall survival have not yet been demonstrated.

Klement RJ et al, Current Opinion, 2018

DIETA CHETOGENICA: USO TERAPEUTICO

Nelle cellule tumorali prevale la glicolisi aerobica (***effetto Warburg***): queste cellule possono presentare livelli di attività glicolitica fino a 200 volte superiori a quelli dei tessuti sani



Utilizzando la dieta chetogenica, la sostituzione del glucosio con i corpi chetonici pone "a dieta" il tumore, poiché la maggior parte delle cellule tumorali **è incapace di utilizzare i corpi chetonici** a scopo energetico (per disfunzione mitocondriale)

I corpi chetonici esercitano un effetto antinfiammatorio, anti-angiogenico e pro-apoptotico nelle cellule tumorali

Paoli et al, Eur J Clin Nutr, 2013

The emerging role of ketogenic diets in cancer treatment

Table 1. Mechanisms for antitumor effects of the ketogenic diet

Physiological change	Mechanisms for antitumor effect
Blood glucose ↓ (in particular, when combined with calorie restriction)	Tumor cells are metabolically inflexible and depend on steady glucose supply. Glucose restriction sensitizes tumor cells to radiotherapy and chemotherapy
Insulin ↓	Lower insulin levels lead to a downregulation of oncogenic signaling pathways downstream of the insulin receptor: PI3K-Akt-mTOR ↓, RAS-RAF-MAPK ↓
Fatty acids ↑, ketone bodies ↑	Inhibition of glycolysis through fatty acids and ketone bodies (Randle cycle) is problematic for tumor cells with dysfunctional mitochondria that rely on glycolysis for energy and antioxidant production
β-hydroxybutyrate ↑	β-hydroxybutyrate is an endogenous histone deacetylase inhibitor with the potential to epigenetically alter protein expression in tumors towards a less aggressive phenotype
Decanoic acid ↑ (if MCT oil is part of the ketogenic diet)	Decanoic acid is a PPARγ agonist and inhibits AMPA glutamate receptors, which are overexpressed by human glioblastoma cells

Klement RJ et al, Current Opinion, 2018

Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes

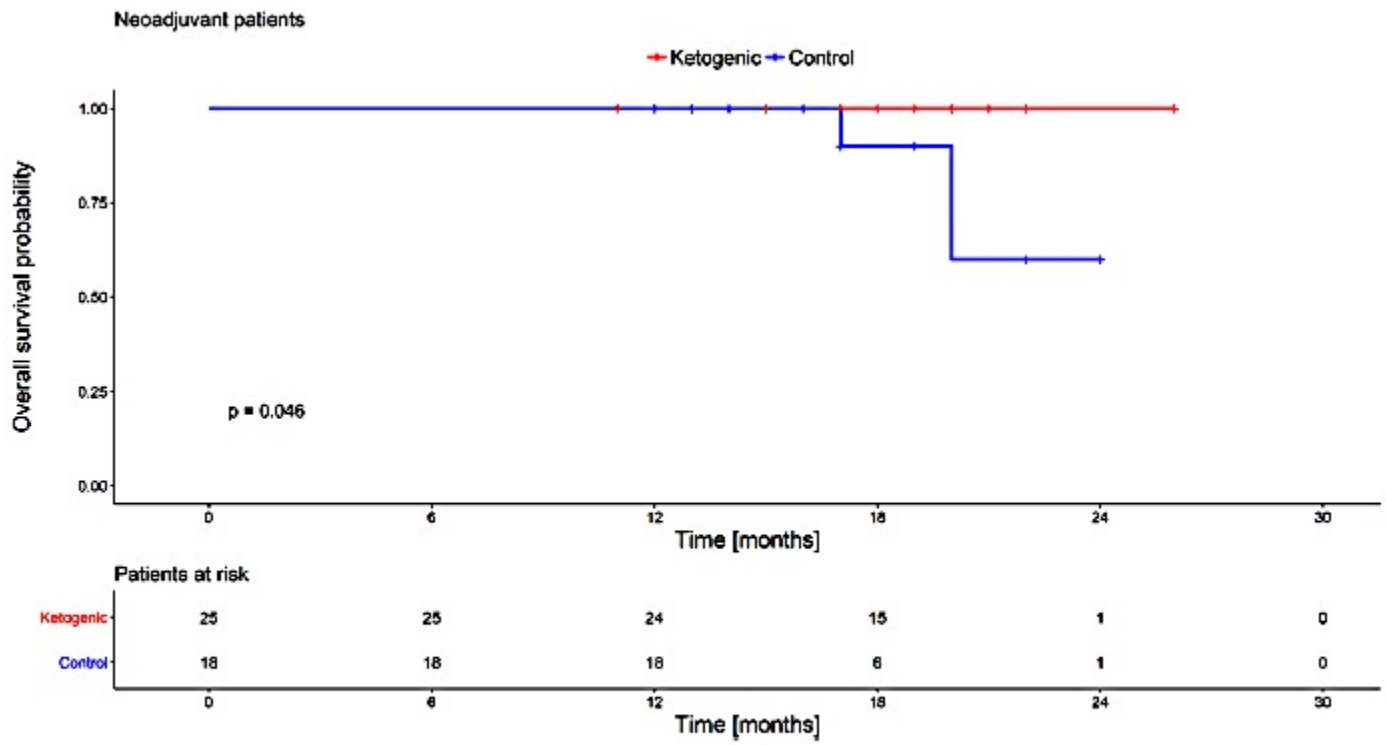


Fig. 2 Kaplan–Meier survival curves for breast cancer patients receiving neoadjuvant chemotherapy ± a ketogenic diet from the study by Khodabakhshi et al. [42]. Based on the individual patient data kindly provided by the authors

Klement RJ et al, Medical Oncology, 2019

Ketogenic diets in medical oncology: a systematic review with focus on clinical outcomes

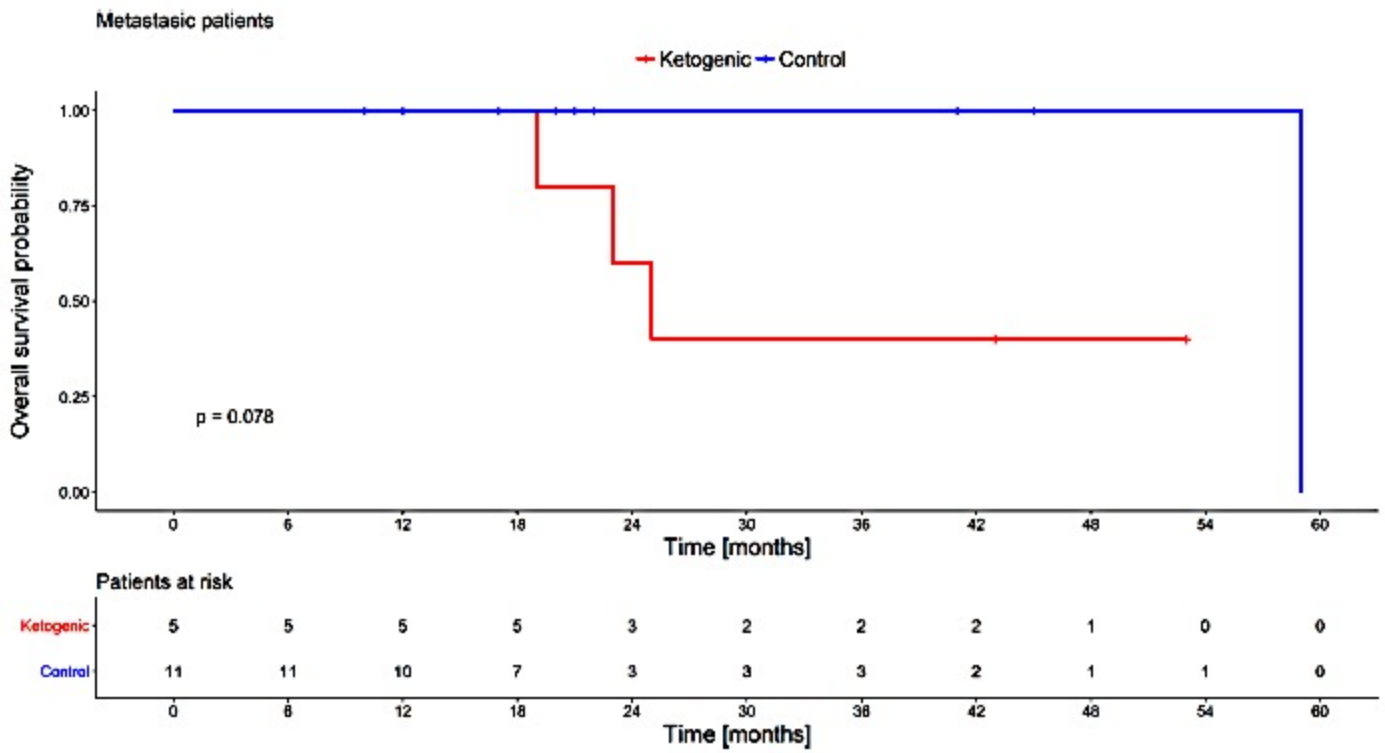
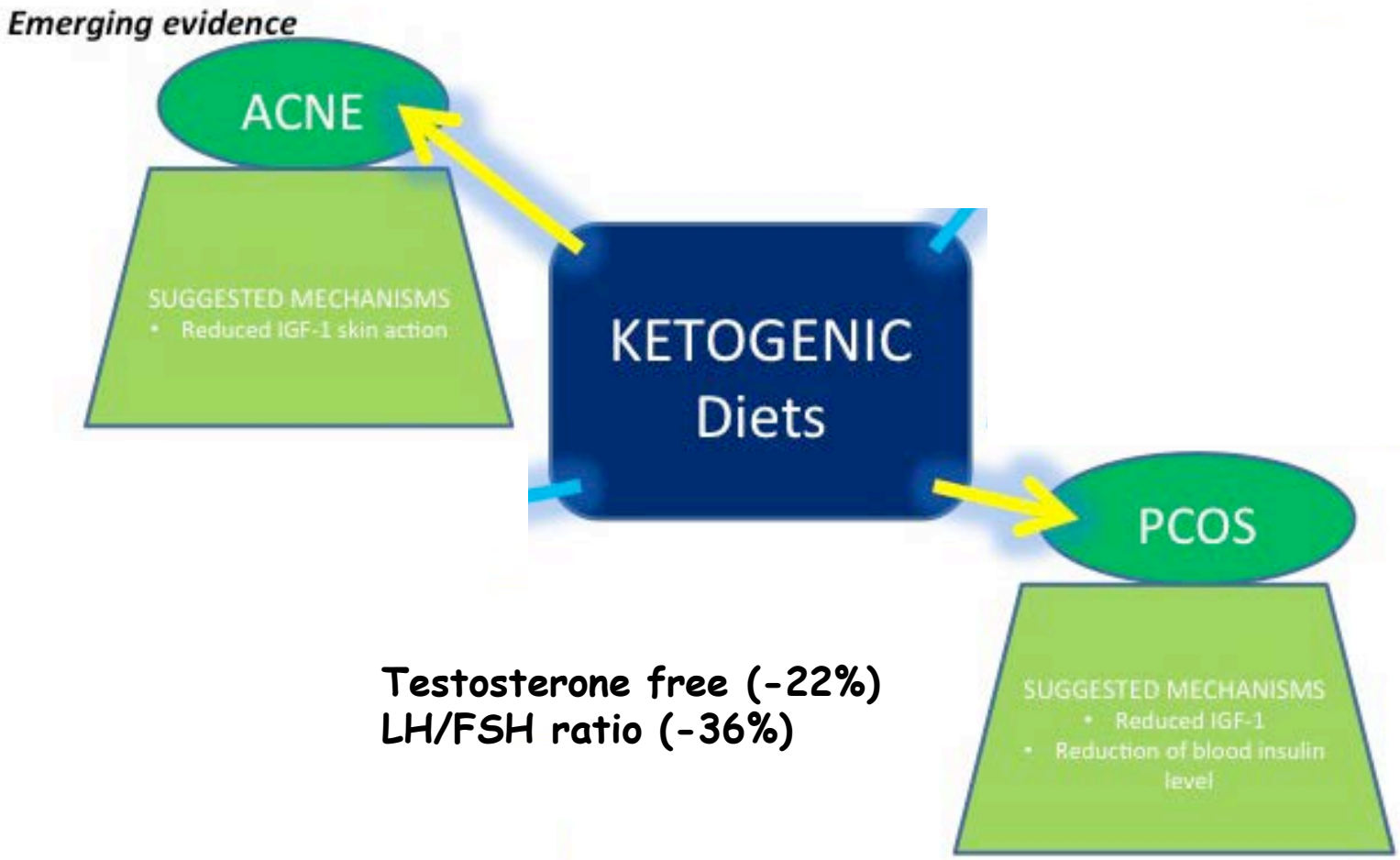


Fig. 3 Kaplan–Meier survival curves for metastasized breast cancer patients receiving chemotherapy ± a ketogenic diet from the study by Khodabakhshi et al. [42]. Based on the individual patient data kindly provided by the authors

Klement RJ et al, Medical Oncology, 2019

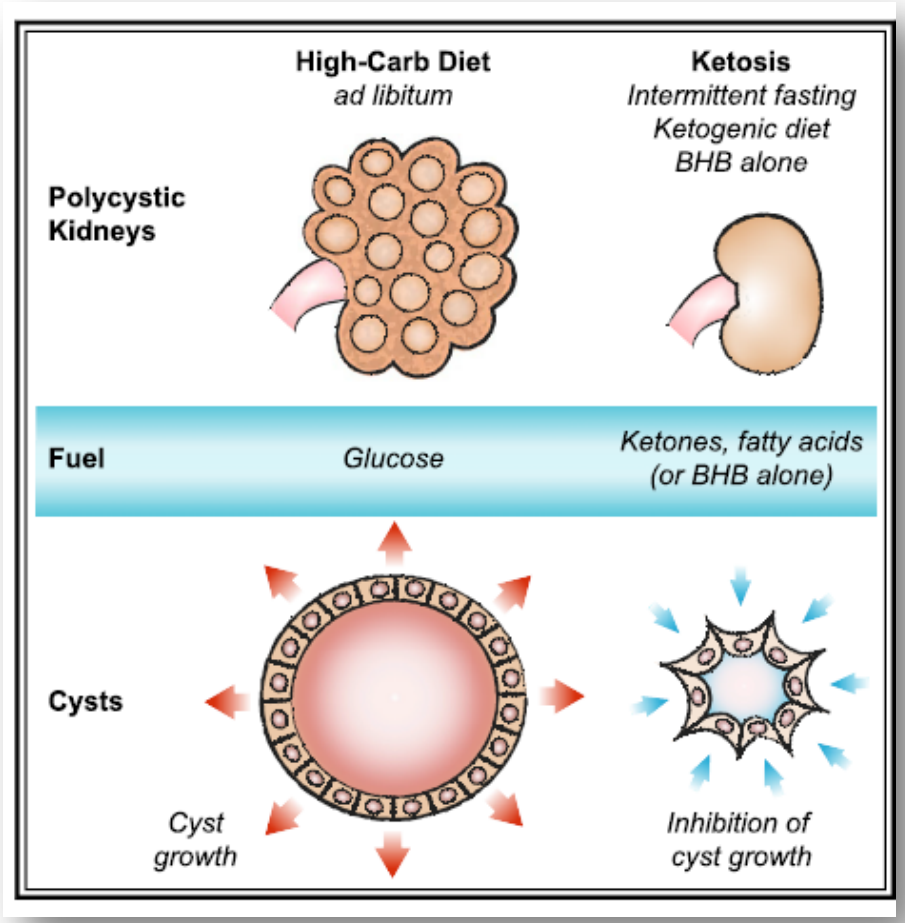
DIETA CHETOGENICA: USO TERAPEUTICO



Testosterone free (-22%)
LH/FSH ratio (-36%)

Paoli et al, Eur J Clin Nutr, 2013

Ketosis Ameliorates Renal Cyst Growth in Polycystic Kidney Disease



Highlights

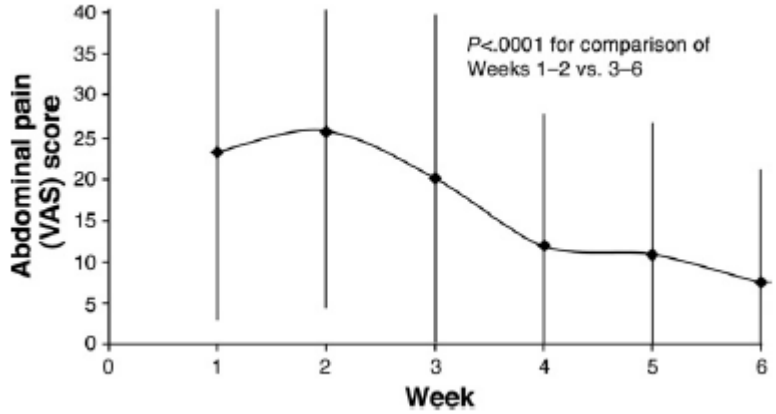
- Ketosis prevents or reverses PKD in animal models
- Dietary changes that induce ketosis prevent PKD
- Oral β-hydroxybutyrate supplementation alone inhibits PKD progression

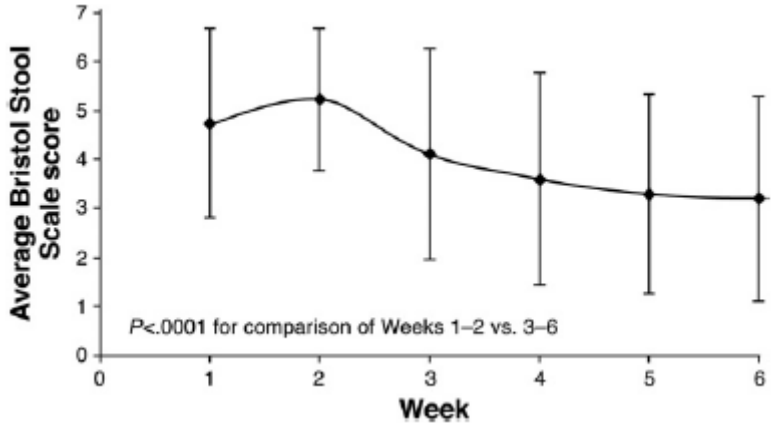
Torres JA et al, Cell Metab, 30: 1-17, 2019

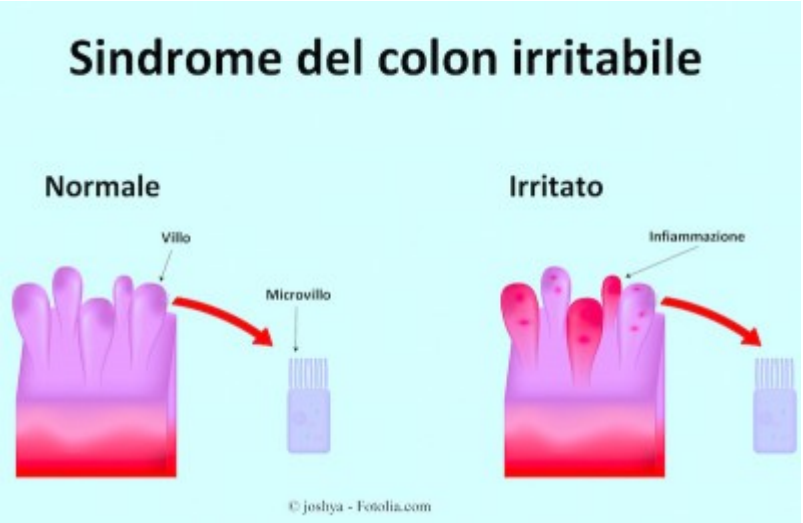
A Very Low-Carbohydrate Diet Improves Symptoms and Quality of Life in Diarrhea-Predominant Irritable Bowel Syndrome

Patients with diarrhea-predominant irritable bowel syndrome (IBS-D)

a 2-week standard diet, then 4 weeks of a VLCKD (20 g carbohydrates/d)







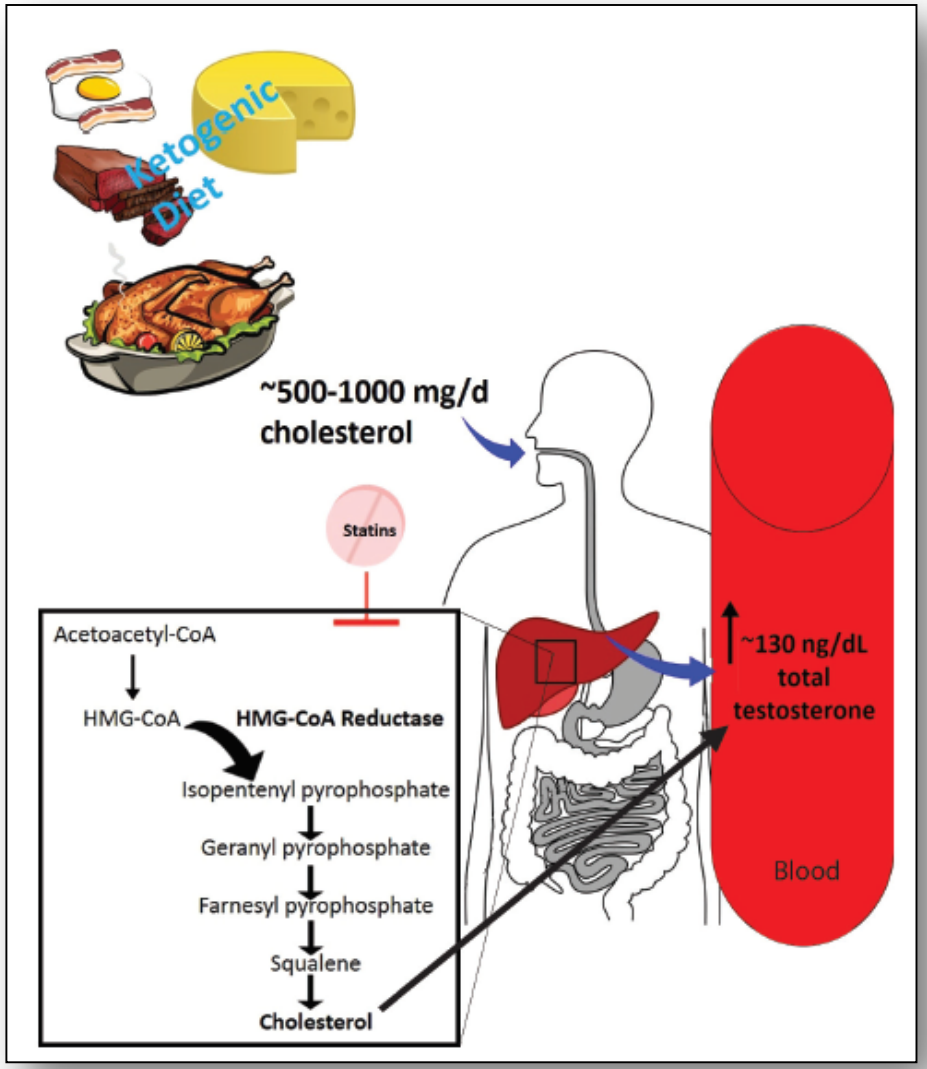
Austin GL, Clin Gastroenterol Hepatol, 7: 706-708, 2009

INDICAZIONI DELLE DIETE CHETOGENETICHE

- OBESITA'
- SINDROME METABOLICA
- DIABETE MELLITO TIPO 2
- EPILESSIA
- ALZHEIMER E PATOLOGIE COGNITIVE
- GLIOBLASTOMA
- SCLEROSI MULTIPLA E SCLEROSI LATERALE AMIOTROFICA
- EMICRANIA
- PARKINSON
- CANCRO
- OVAIO POLICISTICO ED ACNE
- IPOGONADISMO NEL MASCHIO
- MALATTIA POLICISTICA RENALE
- COLON IRRITABILE

THE END

Ketogenic diet and testosterone increase: Is the increased cholesterol intake responsible? To what extent and under what circumstances can there be benefits?



Santos HO et al, Hormones, 2017