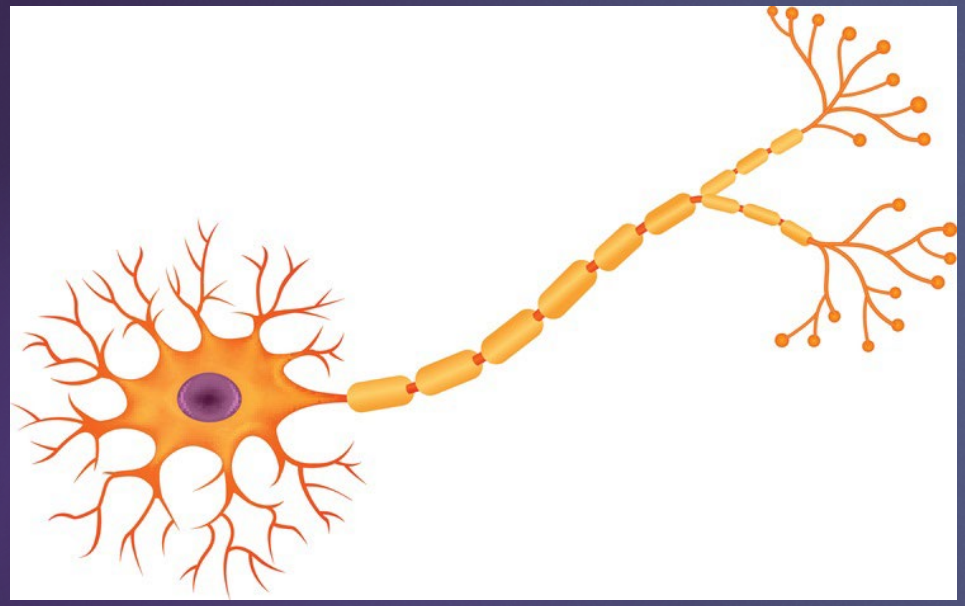
Ketogenic Therapies for Neurological & Neurodegenerative Disorders



Keto Salt Lake 2022

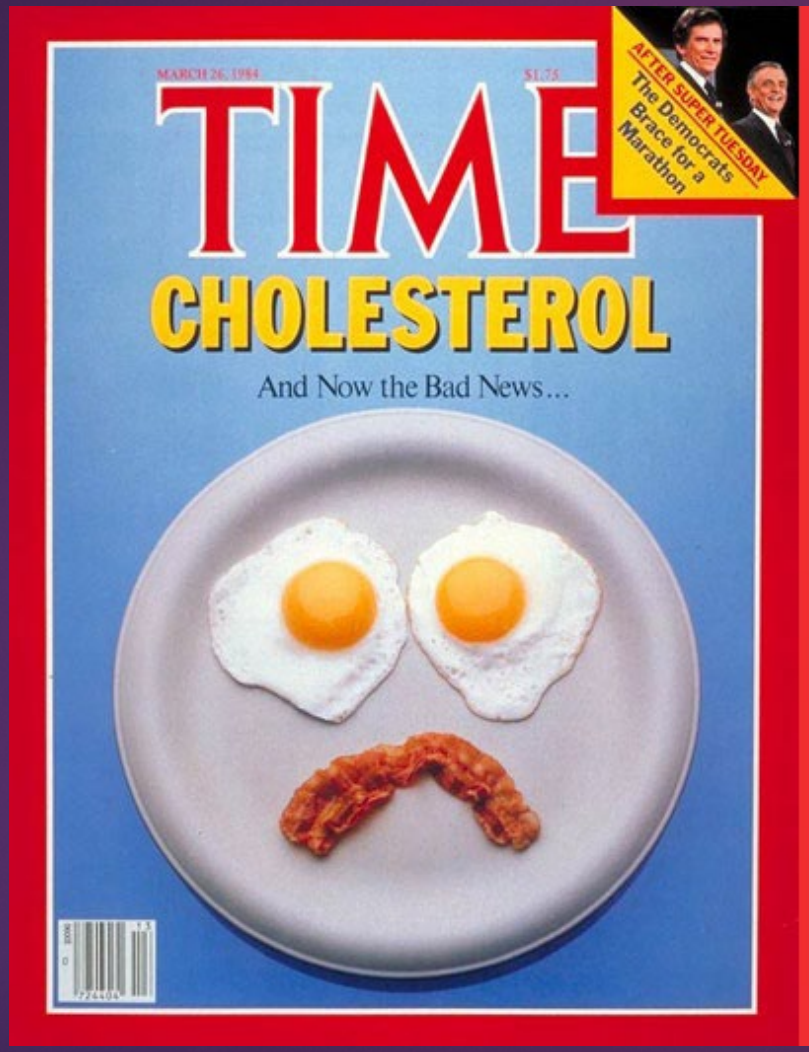
Amy Berger, MS, CNS

Why Look at New or Alternative Approaches?

Why Ketogenic Therapies ?

- ✓ Conventional treatments are lackluster
- ✓ Treatment-resistant cases
- ✓ Decline in efficacy of conventional treatment
- ✓ Pharmaceutical side-effects
- ✓ Commonalities in cellular energetics
- ✓ Address numerous factors with a single intervention
  - ➢ Address the root cause(s)

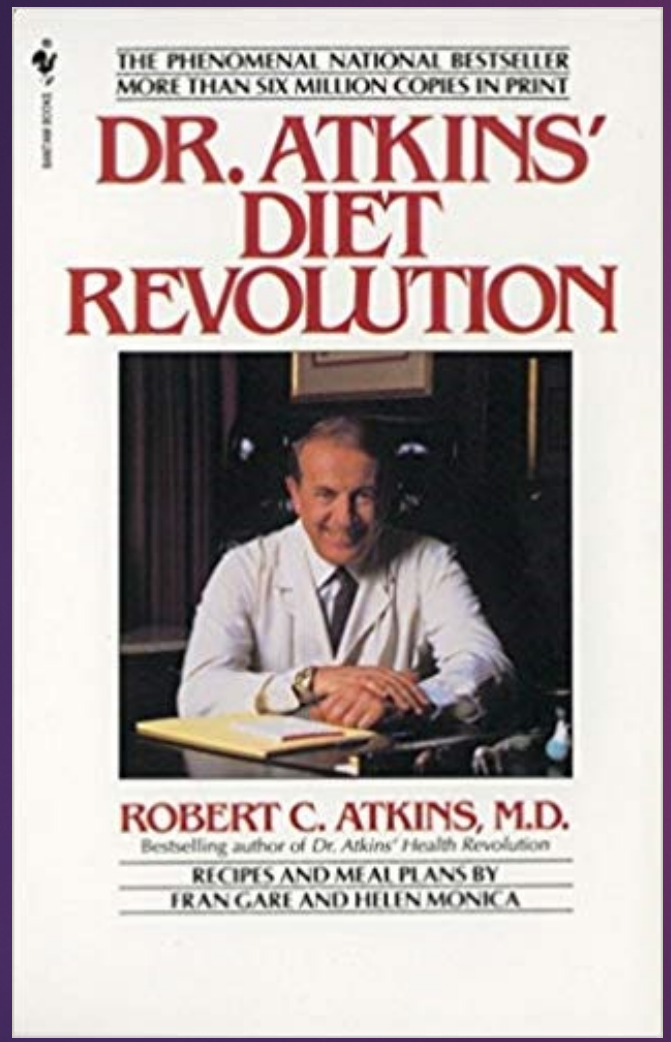
30 Years in the Making



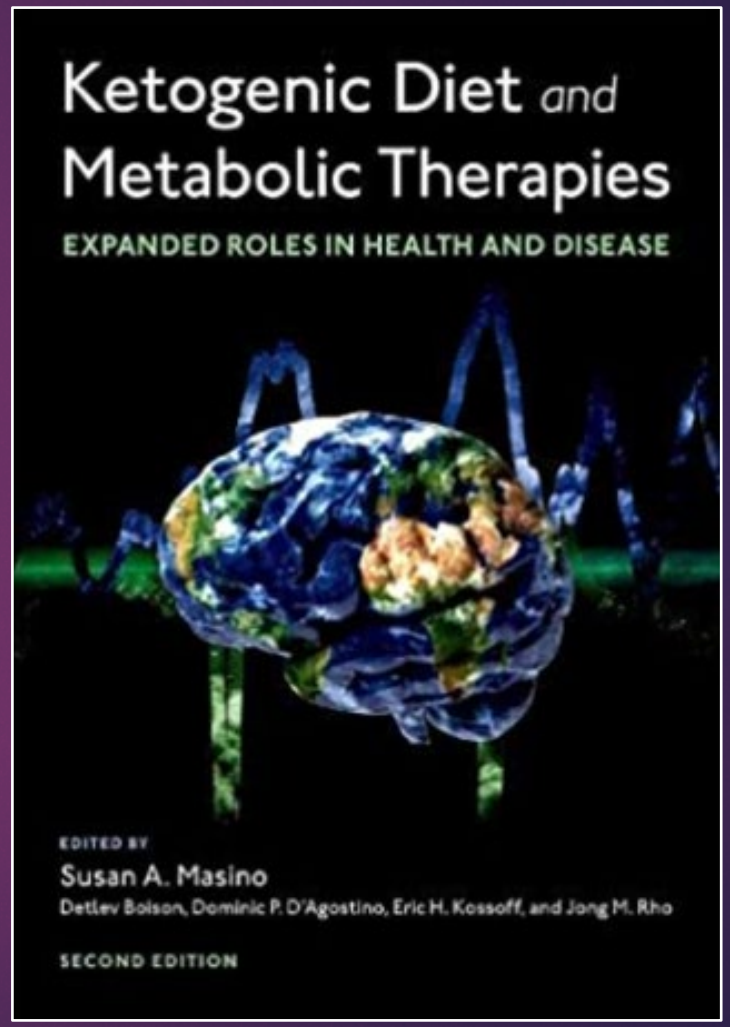
March 1984

June 2014

50 Years in the Making



1972



2022

…*100*+ Years in the Making

Epilepsy & seizure treatment

- Fasting (ancient times)

  "Fasting is the only therapeutic measure against epilepsy recorded in the Hippocratic collection."

- Ketogenic diet (1920s)
  - Mimics fasting while consuming food
  - ***There's something unique about carbohydrate restriction***

(Wheless JW. History of the ketogenic diet. Epilepsia. 2008 Nov;49 Suppl 8:3-5)

Substantiated Research on Ketogenic Diets for:

- Types 1 and 2 diabetes
- Obesity
- Metabolic syndrome
- PCOS
- NAFLD
- GERD/acid reflux
- Dyslipidemia (high trigs; low HDL, pattern B lipoproteins)

Emerging Evidence & Patient Anecdotes Support Ketogenic Diets for:

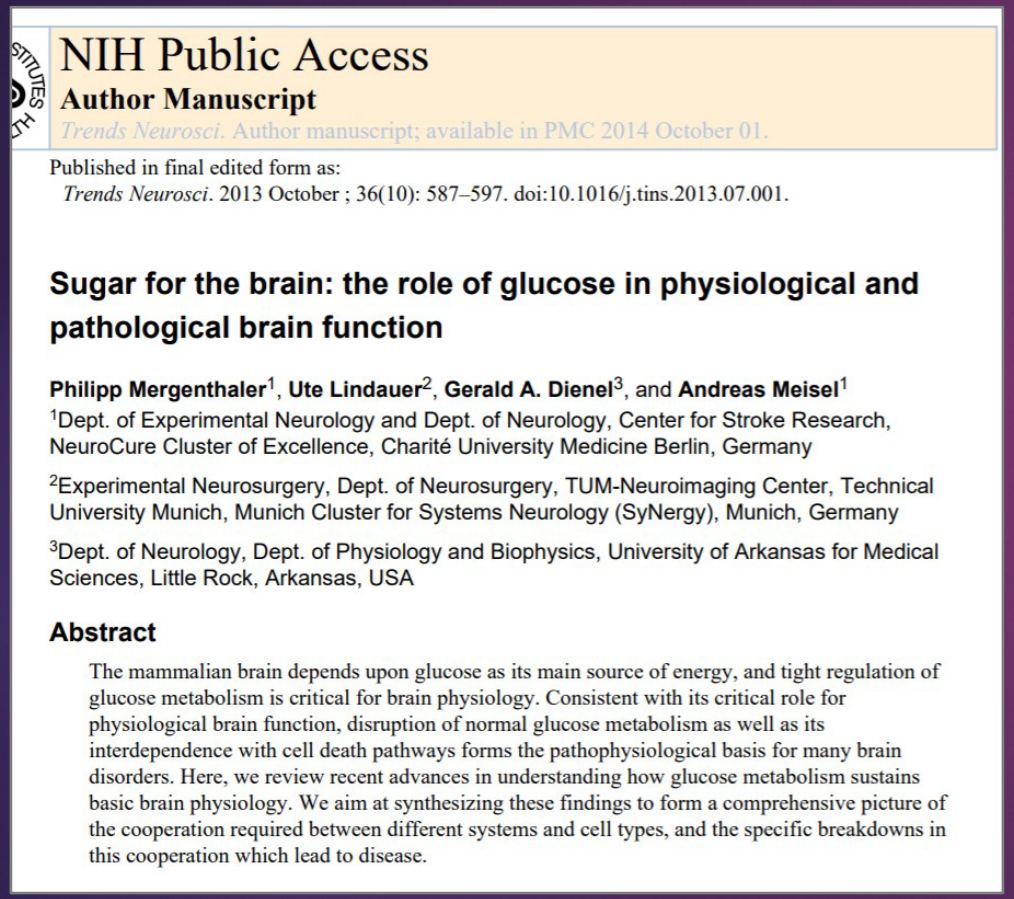
- Gout
- Migraine
- Anxiety
- Schizophrenia
- Bipolar disorder
- Rheumatoid arthritis
- Traumatic brain injury
- Ehlers-Danlos syndrome
- Lipedema
- Glycogen storage diseases

“Keto is a really big hammer, and there are a lot of little nails out there.”

– Jeff Volek, PhD, RD

Commonalities Among Diverse Neurological/Neurodegenerative Disorders

These are *Energy* Problems



NIH Public Access
Author Manuscript
Trends Neurosci. Author manuscript; available in PMC 2014 October 01.

Published in final edited form as:
Trends Neurosci. 2013 October ; 36(10): 587–597. doi:10.1016/j.tins.2013.07.001.

Sugar for the brain: the role of glucose in physiological and pathological brain function

Philipp Mergenthaler[1], **Ute Lindauer**[2], **Gerald A. Dienel**[3], and **Andreas Meisel**[1]
[1]Dept. of Experimental Neurology and Dept. of Neurology, Center for Stroke Research, NeuroCure Cluster of Excellence, Charité University Medicine Berlin, Germany
[2]Experimental Neurosurgery, Dept. of Neurosurgery, TUM-Neuroimaging Center, Technical University Munich, Munich Cluster for Systems Neurology (SyNergy), Munich, Germany
[3]Dept. of Neurology, Dept. of Physiology and Biophysics, University of Arkansas for Medical Sciences, Little Rock, Arkansas, USA

Abstract

The mammalian brain depends upon glucose as its main source of energy, and tight regulation of glucose metabolism is critical for brain physiology. Consistent with its critical role for physiological brain function, disruption of normal glucose metabolism as well as its interdependence with cell death pathways forms the pathophysiological basis for many brain disorders. Here, we review recent advances in understanding how glucose metabolism sustains basic brain physiology. We aim at synthesizing these findings to form a comprehensive picture of the cooperation required between different systems and cell types, and the specific breakdowns in this cooperation which lead to disease.

"Neurons are largely intolerant of inadequate energy supply, and thus the high energy demand of the brain predisposes it to a variety of diseases if energy supplies are disrupted. […] Although neurodegenerative diseases are not classically thought to be caused by disturbed metabolism, bioenergetic defects are emerging as important pathophysiological mechanisms in several disorders."

Alzheimer's Disease

"Type 3 Diabetes"

"Diabetes of the Brain"

"Brain Insulin Resistance"

Alzheimer's: a Metabolic Problem

"…the predominant abnormality in incipient late onset Alzheimer's disease was **a 45% reduction in cerebral glucose utilization…"**

"…**it is now widely acknowledged that brain hypometabolism accompanies AD**…"

"A prominent and well-characterized feature of AD is progressive, region-specific, declines in the cerebral metabolic rate of glucose."

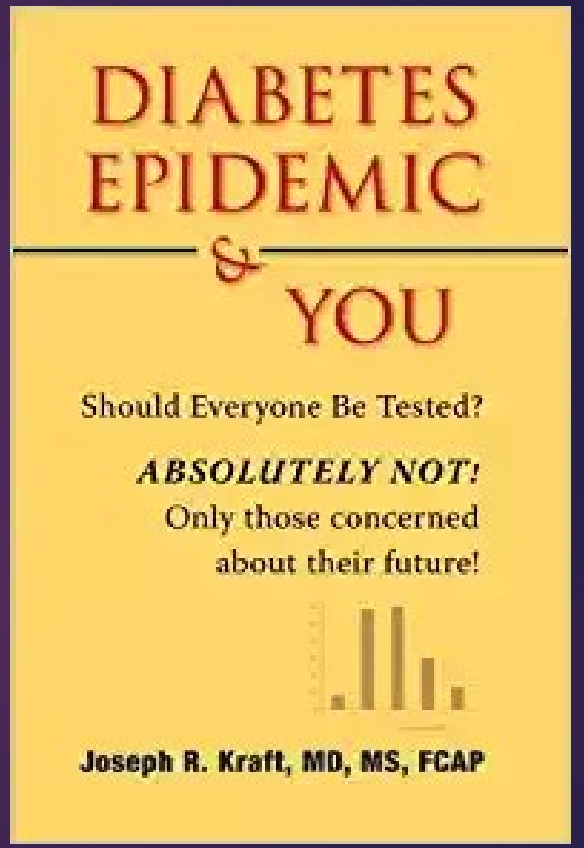
"Reductions in regional cerebral glucose metabolic rate […] ***can be observed years before dementia onset.*****"**

Fukuyama H. et al. Altered cerebral energy metabolism in Alzheimer's disease: a PET study. J Nucl Med. 1994 Jan;35(1):1-6.
Cunnane S et al. Brain fuel metabolism, aging, and Alzheimer's disease. Nutrition. 2011;27(1):3–20.
Henderson ST. Ketone bodies as a therapeutic for Alzheimer's disease. Neurotherapeutics. 2008;5(3):470–480.
Baker LD et al. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol. 2011;68(1):51–57.

Chronic Hyperinsulinemia

"The pathology of diabetes mellitus occurs in those with normal blood sugars. **There are far too many who are told 'Don't worry, your fasting blood sugars are normal.'"**

"Normal weight, normal BMI, normal fasting blood sugar, and normal fasting insulins do not exclude hyperinsulinemia/type 2 diabetes."



"It's the Insulin, Stupid"

"The risk of AD doubled in the 39% of the sample with hyperinsulinemia and was highest in people without diabetes."

"Insulin resistance may be a marker of AD risk that is associated with reduced CMRglu and subtle cognitive impairments at the earliest stage of disease, even before the onset of mild cognitive impairment."

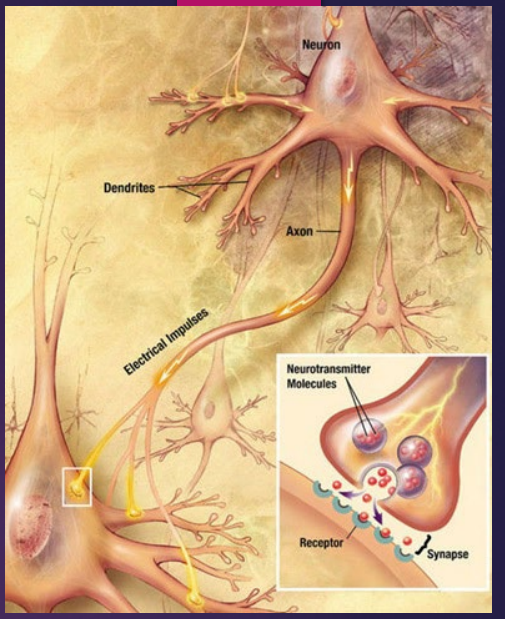
Luchsinger JA et al. Hyperinsulinemia and risk of Alzheimer disease. Neurology. 2004 Oct 12;63(7):1187-92.
Baker LD et al. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch Neurol. 2011;68(1):51–57.

“Metabolic-Cognitive Syndrome”

Commonalities Among Neurological & Neurodegenerative Disorders

- Neuronal hypometabolism – ***specific to glucose***
  - Decreased ATP
- Mitochondrial dysfunction – *or is it??*
- Increased oxidative stress (ROS)
- Chronic hyperinsulinemia (often)
- Neuronal atrophy
- Cellular malfunction
- Glutamate toxicity
- Neuronal death

Glucose in Brain & CNS Energy Metabolism



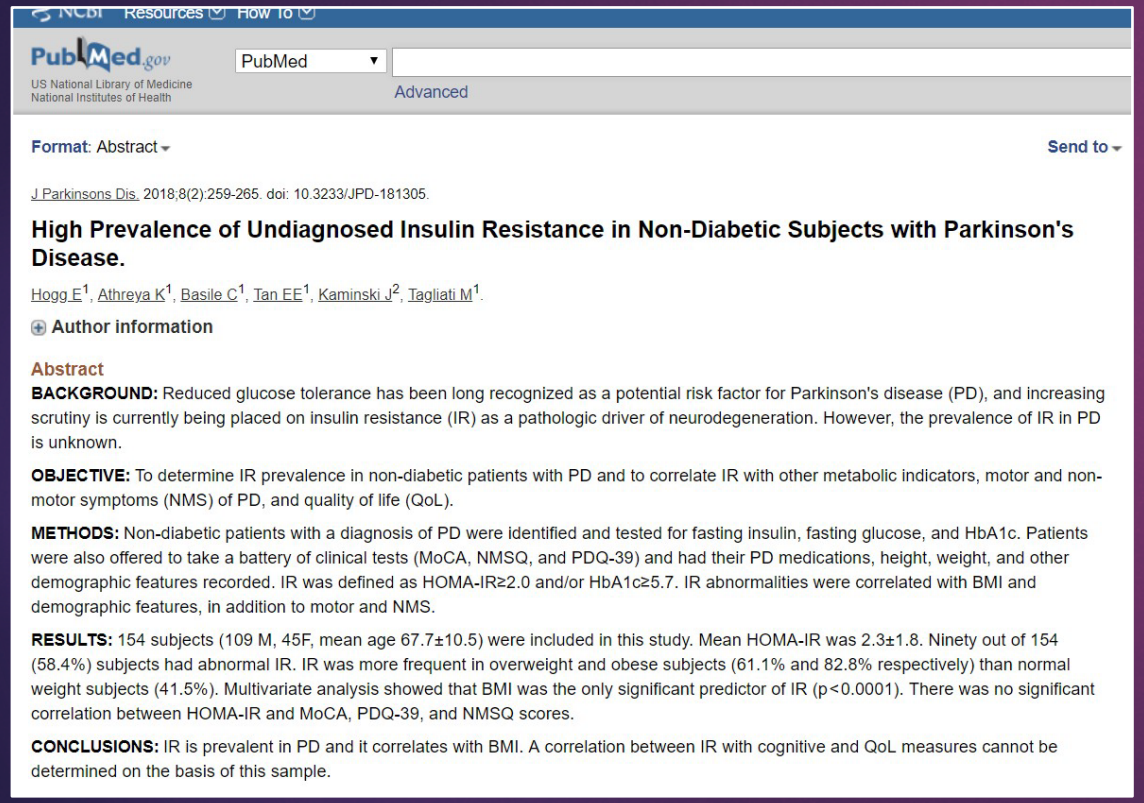
- Maintains axons and dendrites
- Nerve impulse transmission (action potentials and post-synaptic potentials)
- Maintains ion gradients & neuronal resting potential
- Synthesizes neurotransmitters
- Building block for select neuroactive compounds that don't cross the BBB and must be synthesized in the brain

Parkinson's Disease

"Nigrostriatal dopaminergic cell loss occurs in early PD, with more than 50% of putamen dopaminergic terminals having been lost before clinical diagnosis of disease."

Sterling NW, Lewis MM, Du G, Huang X. Structural Imaging and Parkinson's Disease: Moving Toward Quantitative Markers of Disease Progression. J Parkinsons Dis. 2016;6(3):557–567.

High Prevalence of Undiagnosed Insulin Resistance in Non-Diabetic Subjects with Parkinson's Disease



NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

J Parkinsons Dis. 2018;8(2):259-265. doi: 10.3233/JPD-181305.

High Prevalence of Undiagnosed Insulin Resistance in Non-Diabetic Subjects with Parkinson's Disease.

Hogg E[1], Athreya K[1], Basile C[1], Tan EE[1], Kaminski J[2], Tagliati M[1].

Author information

Abstract

BACKGROUND: Reduced glucose tolerance has been long recognized as a potential risk factor for Parkinson's disease (PD), and increasing scrutiny is currently being placed on insulin resistance (IR) as a pathologic driver of neurodegeneration. However, the prevalence of IR in PD is unknown.

OBJECTIVE: To determine IR prevalence in non-diabetic patients with PD and to correlate IR with other metabolic indicators, motor and non-motor symptoms (NMS) of PD, and quality of life (QoL).

METHODS: Non-diabetic patients with a diagnosis of PD were identified and tested for fasting insulin, fasting glucose, and HbA1c. Patients were also offered to take a battery of clinical tests (MoCA, NMSQ, and PDQ-39) and had their PD medications, height, weight, and other demographic features recorded. IR was defined as HOMA-IR≥2.0 and/or HbA1c≥5.7. IR abnormalities were correlated with BMI and demographic features, in addition to motor and NMS.

RESULTS: 154 subjects (109 M, 45F, mean age 67.7±10.5) were included in this study. Mean HOMA-IR was 2.3±1.8. Ninety out of 154 (58.4%) subjects had abnormal IR. IR was more frequent in overweight and obese subjects (61.1% and 82.8% respectively) than normal weight subjects (41.5%). Multivariate analysis showed that BMI was the only significant predictor of IR ($p<0.0001$). There was no significant correlation between HOMA-IR and MoCA, PDQ-39, and NMSQ scores.

CONCLUSIONS: IR is prevalent in PD and it correlates with BMI. A correlation between IR with cognitive and QoL measures cannot be determined on the basis of this sample.

N = 154 (109 male, 45 female; mean age 68)

58% had undiagnosed IR* – with *normal fasting glucose*

(IR defined as HOMA-IR ≥ 2.0 or HbA1c ≥ 5.7)

Overweight: 61% had undiagnosed IR

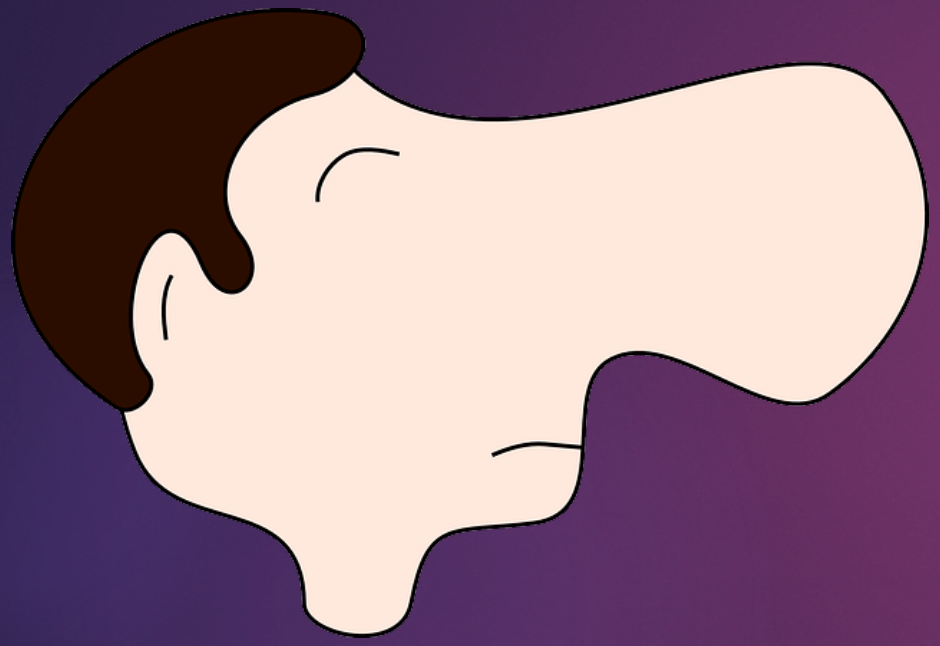
Obese: 83% had undiagnosed IR

Normal weight: 41% had undiagnosed IR

Mean HOMA-IR: 2.3 ± 1.8

*Only based on *fasting insulin*

The Nose Knows



"Insulin transport varies among brain regions. The olfactory bulb tends to have the fastest rate of transport, being about 2–6 times faster than the rate of uptake in the remaining brain. The olfactory bulb also has the highest concentration of insulin protein, the highest concentration of insulin receptors…"

"Insulin receptors are highly abundant in the neurons … cell bodies and synapses […] Brain IRs are highly enriched in the olfactory bulb…

Banks WA, Owen JB, Erickson MA. Insulin in the brain: there and back again. Pharmacol Ther. 2012;136(1):82–93.
Akintola AA, van Heemst D. Insulin, aging, and the brain: mechanisms and implications. Front Endocrinol. 2015;6:13.

Parkinson's Disease

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Prog Neurobiol. 2016 Oct - Nov;145-146:98-120. doi: 10.1016/j.pneurobio.2016.10.001. Epub 2016 Oct 3.

Insulin resistance and Parkinson's disease: A new target for disease modification?

Athauda D[1], Foltynie T[2].

Author information

Abstract

There is growing evidence that patients with Type 2 diabetes have an increased risk of developing Parkinson's disease and share similar dysregulated pathways suggesting common underlying pathological mechanisms. Historically insulin was thought solely to be a peripherally acting hormone responsible for glucose homeostasis and energy metabolism. However accumulating evidence indicates insulin can cross the blood-brain-barrier and influence a multitude of processes in the brain including regulating neuronal survival and growth, dopaminergic transmission, maintenance of synapses and pathways involved in cognition. In conjunction, there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of Parkinson's disease patients, even in those without diabetes. This raises the possibility that defective insulin signalling pathways may contribute to the development of the pathological features of Parkinson's disease, and thereby suggests that the insulin signalling pathway may potentially be a novel target for disease modification. Given these growing links between PD and Type 2 diabetes it is perhaps not unsurprising that drugs used the treatment of T2DM are amongst the most promising treatments currently being prioritised for repositioning as possible novel treatments for PD and several clinical trials are under way. In this review, we will examine the underlying cellular links between insulin resistance and the pathogenesis of PD and then we will assess current and future pharmacological strategies being developed to restore neuronal insulin signalling as a potential strategy for slowing neurodegeneration in Parkinson's disease.

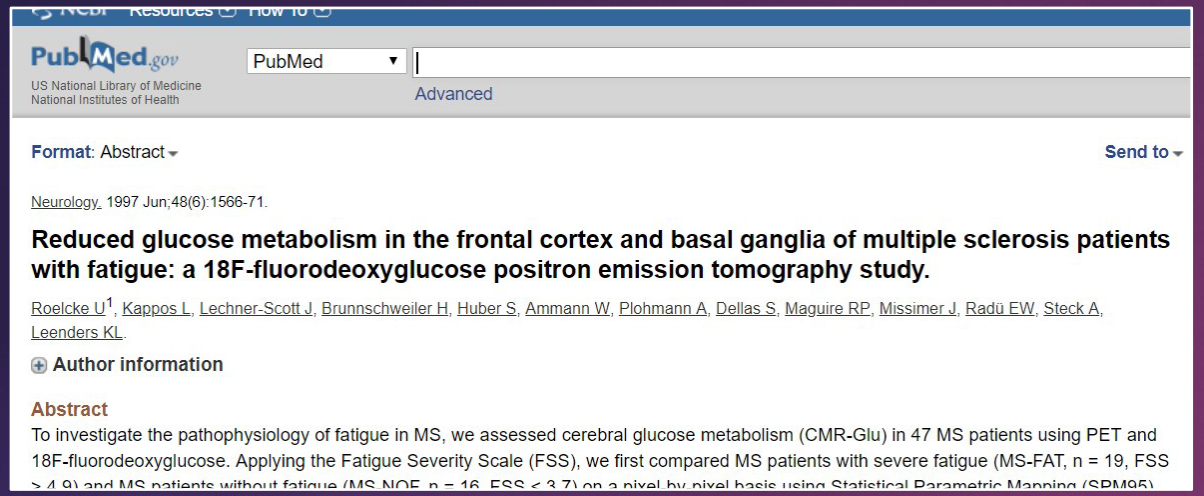
Copyright © 2016 Elsevier Ltd. All rights reserved.

KEYWORDS: Disease modification; Insulin resistance; Neurodegeneration; Parkinson's disease

"…there is growing evidence that a process analogous to peripheral insulin resistance occurs in the brains of Parkinson's disease patients, even in those without diabetes. This raises the possibility that defective insulin signalling pathways may contribute to the development of the pathological features of Parkinson's disease, and thereby suggests that the insulin signalling pathway may potentially be a novel target for disease modification. **Given these growing links between PD and Type 2 diabetes it is perhaps not unsurprising that drugs used in the treatment of T2DM are amongst the most promising treatments currently being prioritised for repositioning as possible novel treatments for PD."**

Multiple Sclerosis

Reduced Brain Glucose Uptake in MS



PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Neurology. 1997 Jun;48(6):1566-71.

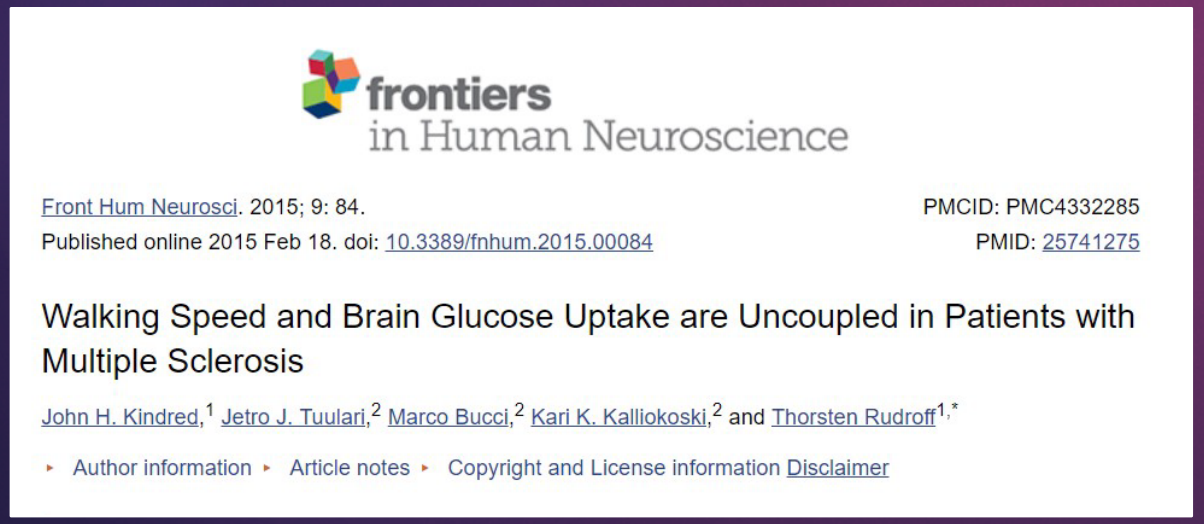
Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue: a 18F-fluorodeoxyglucose positron emission tomography study.

Roelcke U[1], Kappos L, Lechner-Scott J, Brunnschweiler H, Huber S, Ammann W, Plohmann A, Dellas S, Maguire RP, Missimer J, Radü EW, Steck A, Leenders KL.

Author information

Abstract

To investigate the pathophysiology of fatigue in MS, we assessed cerebral glucose metabolism (CMR-Glu) in 47 MS patients using PET and 18F-fluorodeoxyglucose. Applying the Fatigue Severity Scale (FSS), we first compared MS patients with severe fatigue (MS-FAT, n = 19, FSS > 4.9) and MS patients without fatigue (MS-NOF, n = 16, FSS < 3.7) on a pixel-by-pixel basis using Statistical Parametric Mapping (SPM95)



frontiers in Human Neuroscience

Front Hum Neurosci. 2015; 9: 84.
Published online 2015 Feb 18. doi: 10.3389/fnhum.2015.00084

PMCID: PMC4332285
PMID: 25741275

Walking Speed and Brain Glucose Uptake are Uncoupled in Patients with Multiple Sclerosis

John H. Kindred,[1] Jetro J. Tuulari,[2] Marco Bucci,[2] Kari K. Kalliokoski,[2] and Thorsten Rudroff[1,*]

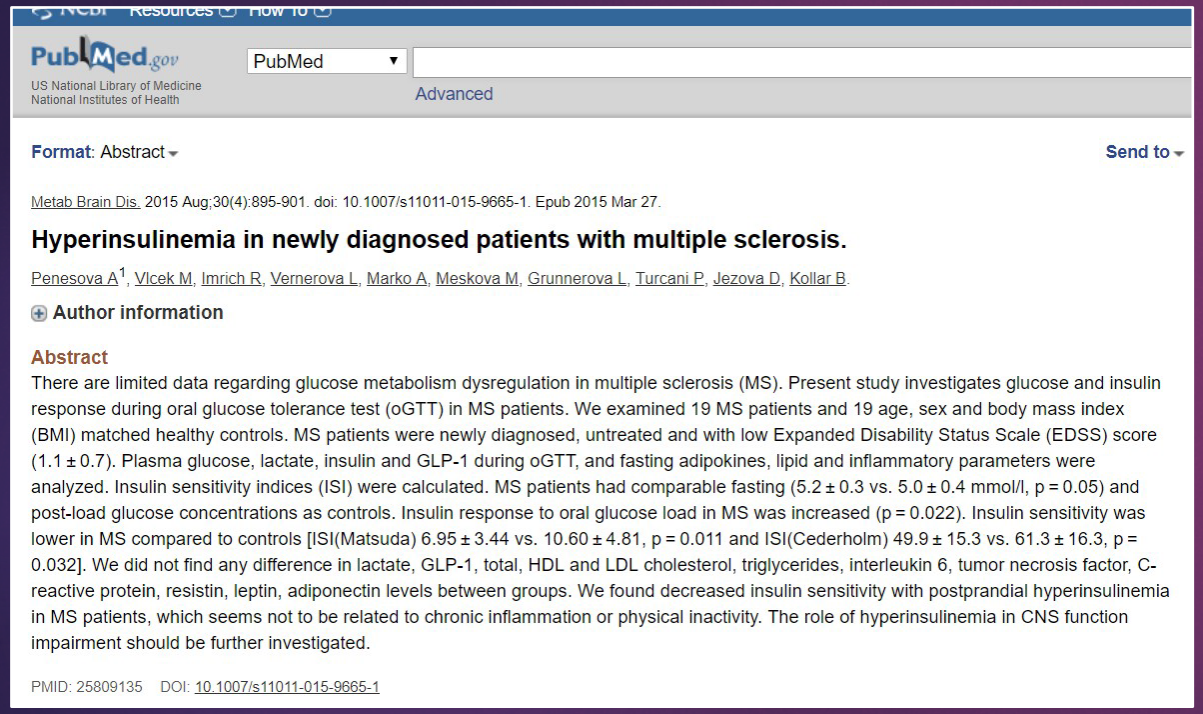
Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Patients with MS had lower FDG uptake in 40% of the brain compared to healthy controls

Decreased regional brain glucose correlates with level of fatigue

"Walking impairments in patients with MS may be due to network wide alterations in glucose metabolism."

Hyperinsulinemia in newly diagnosed patients with multiple sclerosis



PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Metab Brain Dis. 2015 Aug;30(4):895-901. doi: 10.1007/s11011-015-9665-1. Epub 2015 Mar 27.

Hyperinsulinemia in newly diagnosed patients with multiple sclerosis.

Penesova A[1], Vlcek M, Imrich R, Vernerova L, Marko A, Meskova M, Grunnerova L, Turcani P, Jezova D, Kollar B.

Author information

Abstract

There are limited data regarding glucose metabolism dysregulation in multiple sclerosis (MS). Present study investigates glucose and insulin response during oral glucose tolerance test (oGTT) in MS patients. We examined 19 MS patients and 19 age, sex and body mass index (BMI) matched healthy controls. MS patients were newly diagnosed, untreated and with low Expanded Disability Status Scale (EDSS) score (1.1 ± 0.7). Plasma glucose, lactate, insulin and GLP-1 during oGTT, and fasting adipokines, lipid and inflammatory parameters were analyzed. Insulin sensitivity indices (ISI) were calculated. MS patients had comparable fasting (5.2 ± 0.3 vs. 5.0 ± 0.4 mmol/l, p = 0.05) and post-load glucose concentrations as controls. Insulin response to oral glucose load in MS was increased (p = 0.022). Insulin sensitivity was lower in MS compared to controls [ISI(Matsuda) 6.95 ± 3.44 vs. 10.60 ± 4.81, p = 0.011 and ISI(Cederholm) 49.9 ± 15.3 vs. 61.3 ± 16.3, p = 0.032]. We did not find any difference in lactate, GLP-1, total, HDL and LDL cholesterol, triglycerides, interleukin 6, tumor necrosis factor, C-reactive protein, resistin, leptin, adiponectin levels between groups. We found decreased insulin sensitivity with postprandial hyperinsulinemia in MS patients, which seems not to be related to chronic inflammation or physical inactivity. The role of hyperinsulinemia in CNS function impairment should be further investigated.

PMID: 25809135 DOI: 10.1007/s11011-015-9665-1

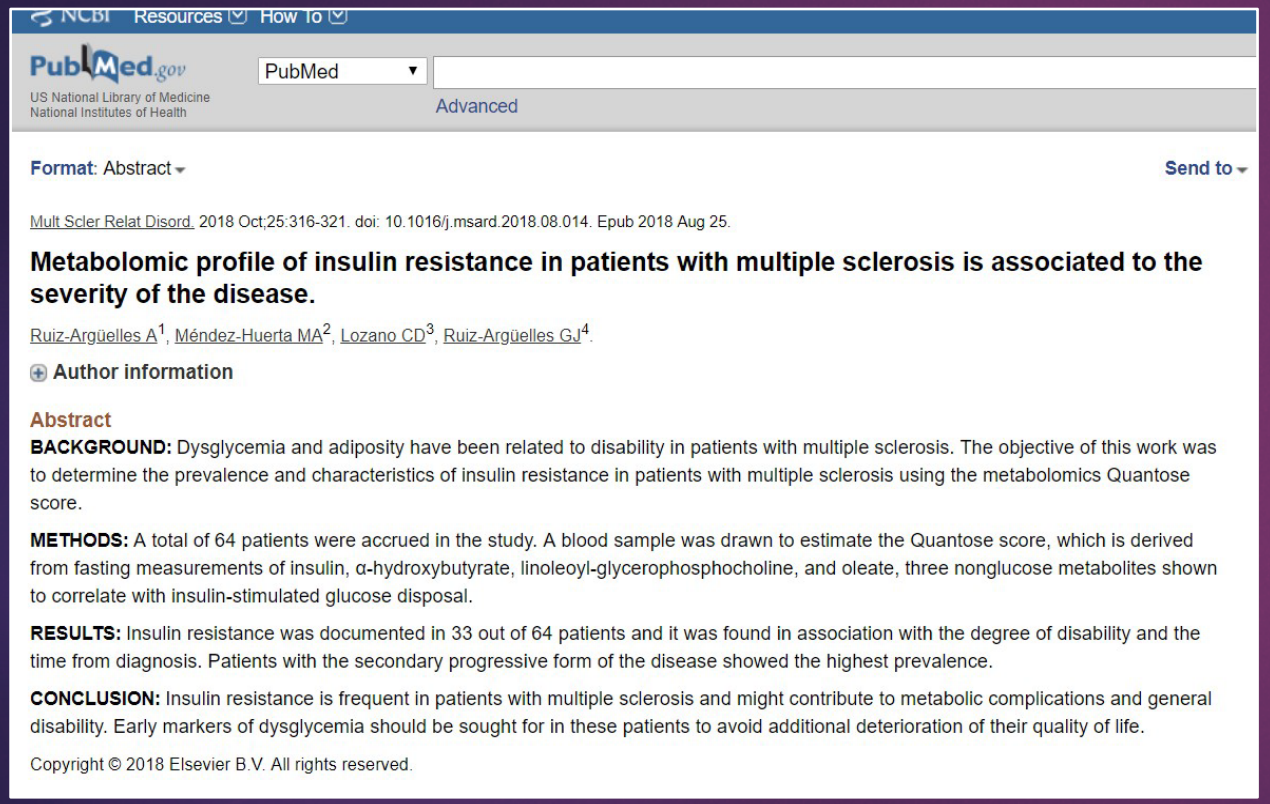
Newly diagnosed MS patients and healthy age-matched controls

OGTT:
Comparable fasting & post-load *glucose*

MS pts: increased *insulin* response:

- Postprandial hyperinsulinemia
- Decreased insulin sensitivity

IR in MS Patients Tied to Disease Severity



NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Mult Scler Relat Disord. 2018 Oct;25:316-321. doi: 10.1016/j.msard.2018.08.014. Epub 2018 Aug 25.

Metabolomic profile of insulin resistance in patients with multiple sclerosis is associated to the severity of the disease.

Ruiz-Argüelles A[1], Méndez-Huerta MA[2], Lozano CD[3], Ruiz-Argüelles GJ[4].

Author information

Abstract

BACKGROUND: Dysglycemia and adiposity have been related to disability in patients with multiple sclerosis. The objective of this work was to determine the prevalence and characteristics of insulin resistance in patients with multiple sclerosis using the metabolomics Quantose score.

METHODS: A total of 64 patients were accrued in the study. A blood sample was drawn to estimate the Quantose score, which is derived from fasting measurements of insulin, α-hydroxybutyrate, linoleoyl-glycerophosphocholine, and oleate, three nonglucose metabolites shown to correlate with insulin-stimulated glucose disposal.

RESULTS: Insulin resistance was documented in 33 out of 64 patients and it was found in association with the degree of disability and the time from diagnosis. Patients with the secondary progressive form of the disease showed the highest prevalence.

CONCLUSION: Insulin resistance is frequent in patients with multiple sclerosis and might contribute to metabolic complications and general disability. Early markers of dysglycemia should be sought for in these patients to avoid additional deterioration of their quality of life.

Copyright © 2018 Elsevier B.V. All rights reserved.

N = 64

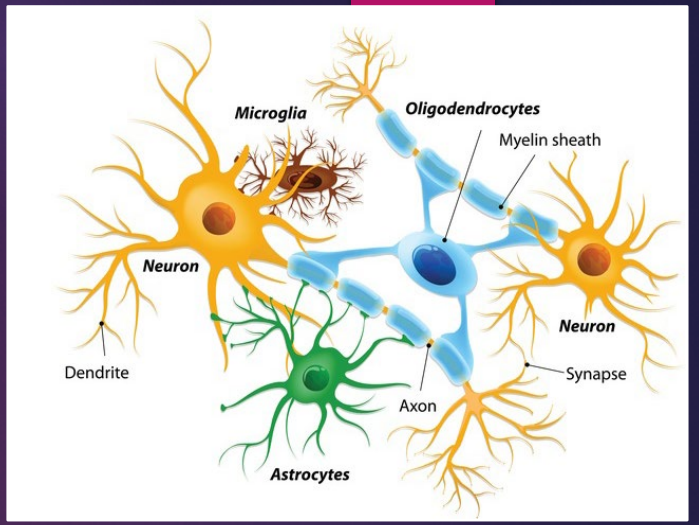
Fasting insulin only (Quantose score)

14 subjects > 10 µg/mL

33 had IR based on Quantose

…but how many more post-prandially?

Multiple Sclerosis

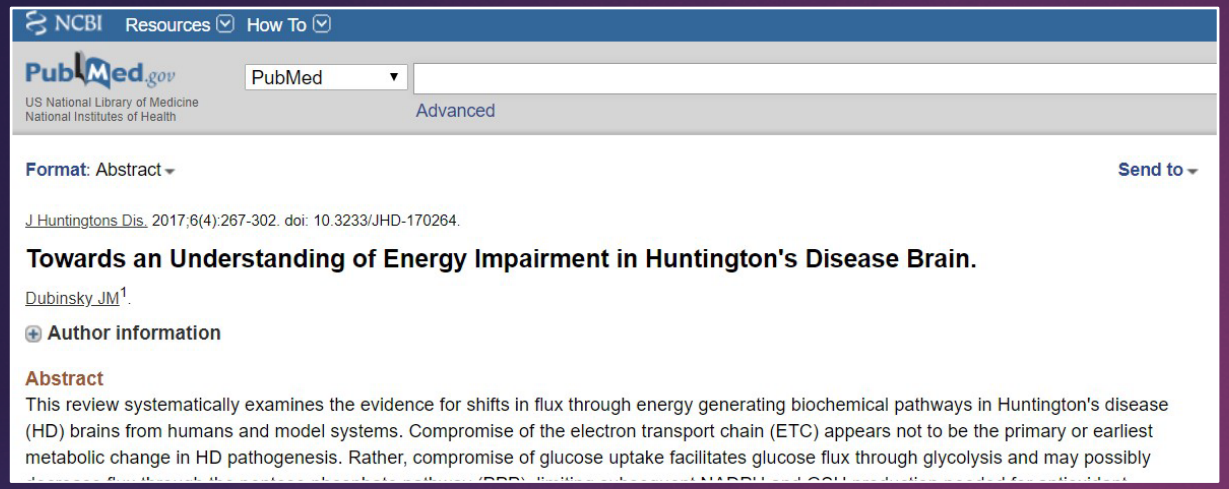


- Mice with EAE: 15-30% of spinal cord axons can be lost before permanent motor impairment occurs
- Level of disability correlates more strongly with axon destruction and degree of neuronal loss than with demyelination
- Oligodendrocytes – reduced metabolism

"**Disturbed metabolism in myelin-producing cells is associated with axonal degeneration.**"

Storoni M, Plant GT. The Therapeutic Potential of the Ketogenic Diet in Treating Progressive Multiple Sclerosis. Mult Scler Int. 2015;2015:681289.
Herz J, Zipp F, Siffrin V. Neurodegeneration in autoimmune CNS inflammation. Exp Neurol. 2010 Sep;225(1):9-17.
Campbell GR, Mahad DJ. Mitochondrial changes associated with demyelination: consequences for axonal integrity. Mitochondrion. 2012 Mar;12(2):173-9.

ALS, Huntington's


NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

J Huntingtons Dis. 2017;6(4):267-302. doi: 10.3233/JHD-170264.

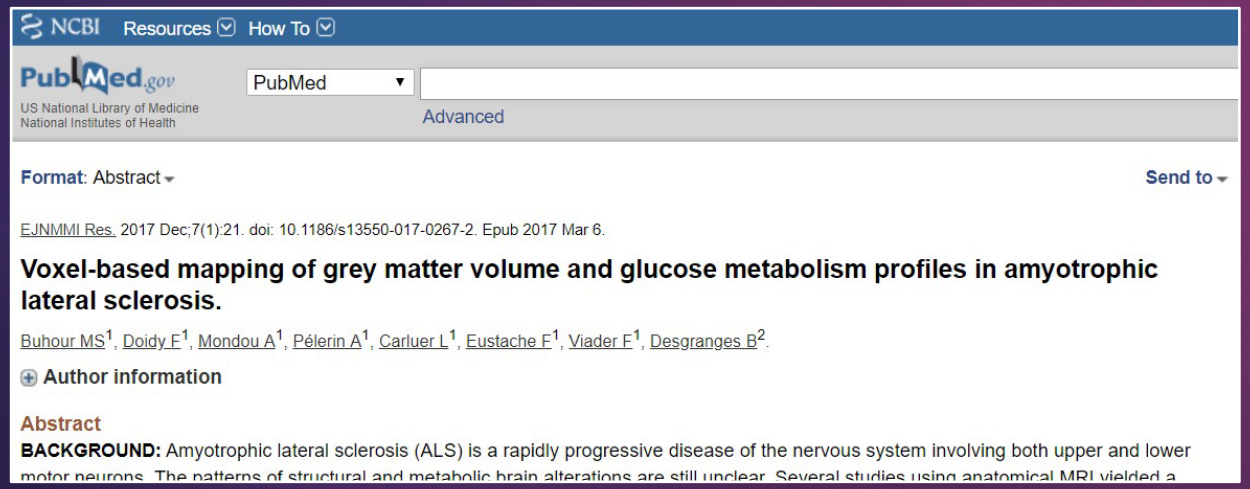
Towards an Understanding of Energy Impairment in Huntington's Disease Brain.

Dubinsky JM[1].

Author information

Abstract

This review systematically examines the evidence for shifts in flux through energy generating biochemical pathways in Huntington's disease (HD) brains from humans and model systems. Compromise of the electron transport chain (ETC) appears not to be the primary or earliest metabolic change in HD pathogenesis. Rather, compromise of glucose uptake facilitates glucose flux through glycolysis and may possibly


NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

EJNMMI Res. 2017 Dec;7(1):21. doi: 10.1186/s13550-017-0267-2. Epub 2017 Mar 6.

Voxel-based mapping of grey matter volume and glucose metabolism profiles in amyotrophic lateral sclerosis.

Buhour MS[1], Doidy F[1], Mondou A[1], Pélerin A[1], Carluer L[1], Eustache F[1], Viader F[1], Desgranges B[2].

Author information

Abstract

BACKGROUND: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive disease of the nervous system involving both upper and lower motor neurons. The patterns of structural and metabolic brain alterations are still unclear. Several studies using anatomical MRI yielded a

"Dysregulation of energetic metabolism promotes cell death and disease progression in ALS and HD."

"Neurodegenerative cells are the sites of numerous metabolic and energetic abnormalities with abnormalities in energy production. Energy is the primary determinant of neuronal viability."

"Compromise of the electron transport chain appears not to be the primary or earliest metabolic change in HD pathogenesis. Rather, compromise of glucose uptake…"

Aerobic glycolysis in amyotrophic lateral sclerosis and Huntington's disease. Rev Neurosci. 2018 Jul 26;29(5):547-555.

Disrupted Energy Supply

frontiers in Pharmacology

Front Pharmacol. 2012; 3: 59.
Published online 2012 Apr 9. Prepublished online 2012 Jan 25.
doi: 10.3389/fphar.2012.00059
PMCID: PMC3321471
PMID: 22509165

The Ketogenic Diet as a Treatment Paradigm for Diverse Neurological Disorders

Carl E. Stafstrom[1,2] and Jong M. Rho[3,4,*]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

This article has been cited by other articles in PMC.

Abstract Go to:

Dietary and metabolic therapies have been attempted in a wide variety of neurological diseases, including epilepsy, headache, neurotrauma, Alzheimer disease, Parkinson disease, sleep disorders, brain cancer, autism, pain, and multiple sclerosis. The impetus for using various diets to treat – or at least ameliorate symptoms of – these disorders stems from both a lack of effectiveness of pharmacological therapies, and also the intrinsic appeal of implementing a more "natural" treatment. The enormous spectrum of pathophysiological mechanisms underlying the aforementioned diseases would suggest a degree of complexity that cannot be impacted universally by any single dietary treatment. Yet, it is conceivable that alterations in certain dietary constituents could affect the course and impact the outcome of these brain disorders. Further, it is possible that a final common neurometabolic pathway might be influenced by a variety of dietary interventions. The most notable example of a dietary treatment with proven efficacy against a neurological condition is the high-fat, low-carbohydrate ketogenic diet (KD) used in patients with medically intractable epilepsy. While the mechanisms through which the KD works remain unclear, there is now compelling evidence that its efficacy is likely related to the normalization of aberrant energy metabolism. The concept that many neurological conditions are linked pathophysiologically to energy dysregulation could well provide a common research and experimental therapeutics platform, from which the course of several neurological diseases could be favorably influenced by dietary means. Here we provide an overview of studies using the KD in a wide panoply of neurologic disorders in which neuroprotection is an essential component.

Keywords: ketogenic diet, neuroplasticity, epilepsy, neurological disorders

"While the mechanisms through which the KD works remain unclear, **there is now compelling evidence that its efficacy is likely related to the normalization of aberrant energy metabolism.** The concept that many neurological conditions are linked pathophysiologically to energy dysregulation could well provide a common research and experimental therapeutics platform, from which the course of several neurological diseases could be favorably influenced by dietary means."

KD Mechanisms of Action

1. Alternative fuel to glucose
2. Increased ATP from fats & ketones compared to glucose
3. Reduced hyperglycemia and hyperinsulinemia
4. Decreased production of reactive oxygen species (ROS)
5. Enhanced mitochondrial biogenesis
6. Enhanced resistance to apoptosis in neurons
7. Signaling effects and actions of ketone bodies themselves (βOHB is HDAC inhibitor)
8. Decreased glutamate synthesis and increased GABA synthesis
9. Bypassing of defects in complex I of the mitochondrial electron transport chain
10. Facilitated mitophagy
11. Altered neuronal membrane potential and/or proper membrane polarization
12. Enhanced glutathione activity
13. Reduced glycolysis
14. Signaling properties of individual fatty acids
15. As-yet unidentified changes from a wholesale shift away from glucose dependence toward a fat-based metabolism
16. Effects on gut microbiome; increased butyrate via bacterial fermentation of indigestible and hard-to-digest carbohydrates

Ketogenic Diet in a Pill?

NCBI Resources How To

PubMed.gov
US National Library of Medicine
National Institutes of Health

PubMed

Advanced

Format: Abstract

Send to

Epilepsia. 2008 Nov;49 Suppl 8:127-33. doi: 10.1111/j.1528-1167.2008.01857.x.

The ketogenic diet in a pill: is this possible?

Rho JM[1], Sankar R.

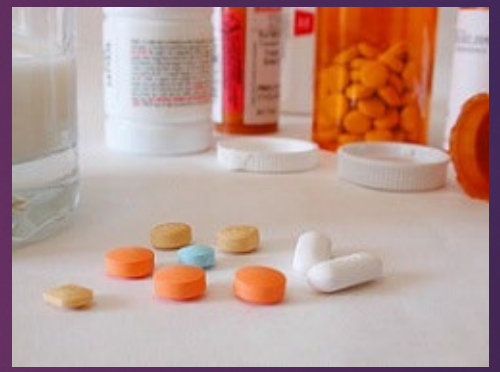
Author information

Abstract

Over the past decade, much progress has been made in understanding the mechanisms of ketogenic diet (KD) action. From the complex systemic and metabolic changes induced by the KD have emerged innovative hypotheses attempting to link biochemical adaptations to its clinical effects. Despite such developments, the fundamental question of how the KD works remains as elusive as ever. At present, it is unclear which of the many potential mechanisms proposed thus far are directly relevant to the clinical effects of the KD. It is unlikely that these numerous hypotheses can be unified into a single mechanism (or a final common pathway). Nevertheless, it may be instructive to consider each of these putative mechanisms in turn and ask the following question: if the mechanism or target in question is a critical determinant of the anticonvulsant efficacy of the KD, then would a similar intervention known to be based on that mechanism yield a comparable effect? Perhaps answering this question for each mechanistic speculation might help substantiate (or invalidate) that particular hypothesis. Can the KD be packaged into a pill? At present, the answer is likely "no." We have yet to discover a "magic bullet" that completely mirrors the anticonvulsant (and potential neuroprotective) effects of the KD. However, without a clearer understanding of the mechanistic elements comprising the complex metabolic puzzle posed by the KD, we would be left only with empiric observations, and to wonder curiously how a high-fat diet can exert such profound clinical effects.

PMID: 19049610 PMCID: PMC2692867 DOI: 10.1111/j.1528-1167.2008.01857.x

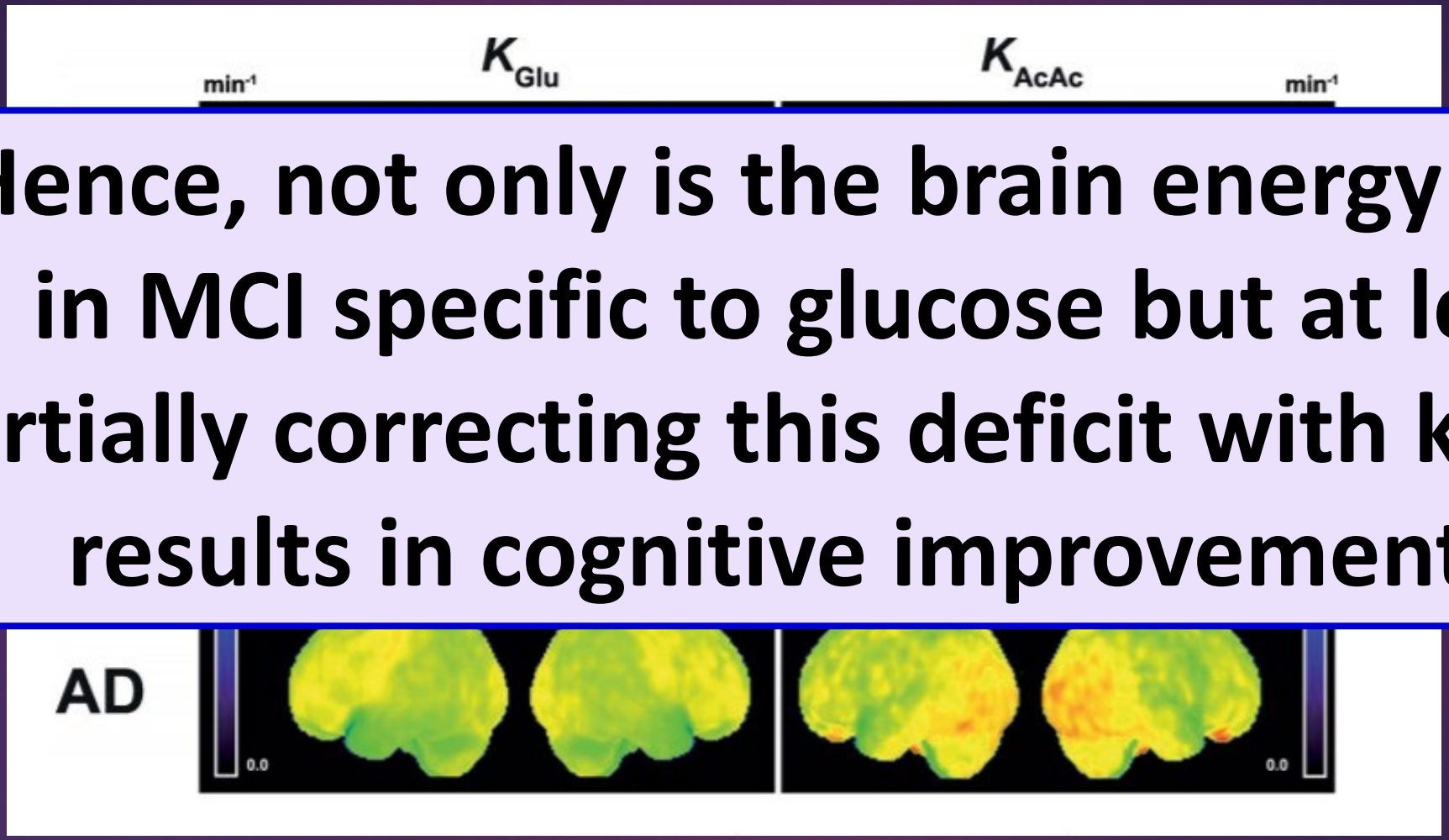
"As a generalization, it is becoming widely accepted that the mechanistic underpinnings of the KD are likely multiple, parallel, and possibly synergistic."



**"So the question remains, can the KD be packaged into a pill?
At this stage, given our state of knowledge, the likely answer is NO."**

But Does it Work?

Brain Glucose & Ketone Uptake

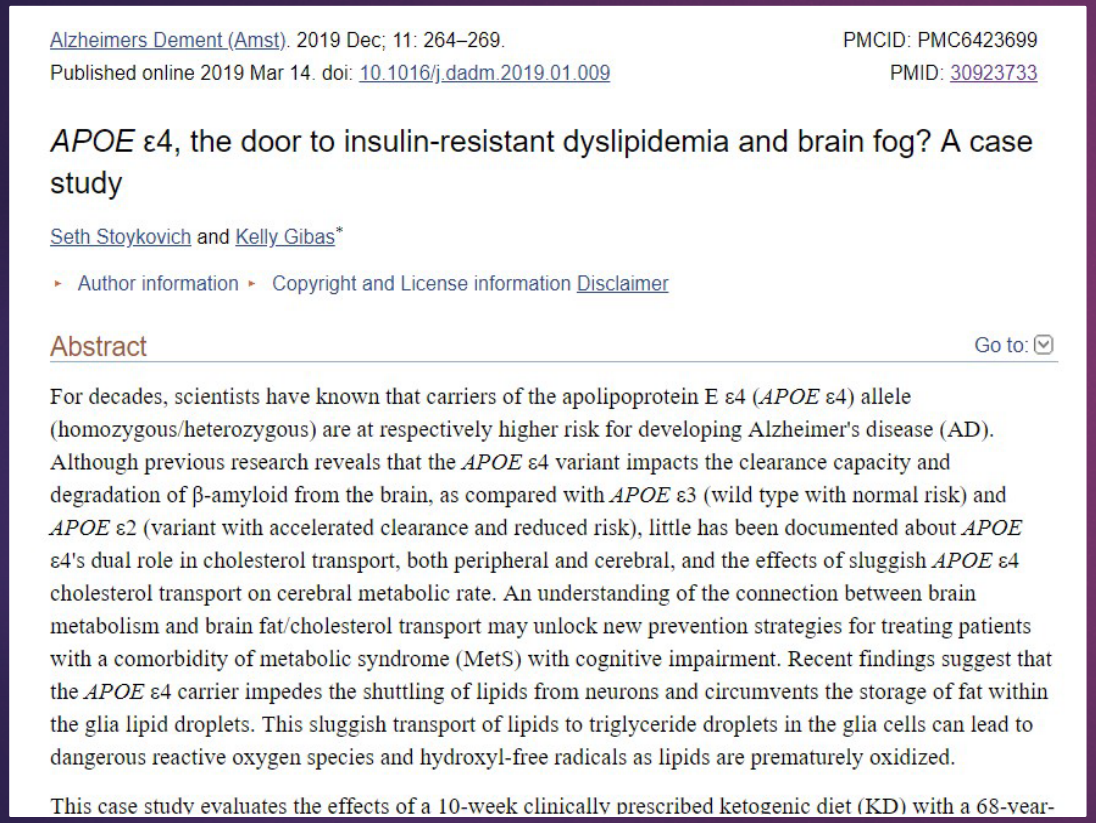


"Hence, not only is the brain energy deficit in MCI specific to glucose but at least partially correcting this deficit with ketones results in cognitive improvements."

GLUCOSE ACETOACETATE

Croteau, E., et al., A cross-sectional comparison of brain glucose and ketone metabolism in cognitively healthy older adults, mild cognitive impairment and early Alzheimer's disease. Exp Gerontol. 2018 Jul 1;107:18-26.
Fortier M, Castellano CA, Croteau E et al. Alzheimers Dement. 2019 May;15(5):625-634. t al. A ketogenic drink improves brain energy and some measures of cognition in mild cognitive impairment.

KD "reverses" mild Alzheimer's and T2DM



Alzheimers Dement (Amst). 2019 Dec; 11: 264–269.
Published online 2019 Mar 14. doi: 10.1016/j.dadm.2019.01.009
PMCID: PMC6423699
PMID: 30923733

APOE ε4, the door to insulin-resistant dyslipidemia and brain fog? A case study

Seth Stoykovich and Kelly Gibas*

Author information ▸ Copyright and License information Disclaimer

Abstract Go to:

For decades, scientists have known that carriers of the apolipoprotein E ε4 (*APOE* ε4) allele (homozygous/heterozygous) are at respectively higher risk for developing Alzheimer's disease (AD). Although previous research reveals that the *APOE* ε4 variant impacts the clearance capacity and degradation of β-amyloid from the brain, as compared with *APOE* ε3 (wild type with normal risk) and *APOE* ε2 (variant with accelerated clearance and reduced risk), little has been documented about *APOE* ε4's dual role in cholesterol transport, both peripheral and cerebral, and the effects of sluggish *APOE* ε4 cholesterol transport on cerebral metabolic rate. An understanding of the connection between brain metabolism and brain fat/cholesterol transport may unlock new prevention strategies for treating patients with a comorbidity of metabolic syndrome (MetS) with cognitive impairment. Recent findings suggest that the *APOE* ε4 carrier impedes the shuttling of lipids from neurons and circumvents the storage of fat within the glia lipid droplets. This sluggish transport of lipids to triglyceride droplets in the glia cells can lead to dangerous reactive oxygen species and hydroxyl-free radicals as lipids are prematurely oxidized.

This case study evaluates the effects of a 10-week clinically prescribed ketogenic diet (KD) with a 68-year-

- 68-yr old male, heterozygous ApoE4
- Mild Alzheimer's (MoCA 23/30)
- T2 diabetes, insulin for 15+ years

10 weeks ketogenic diet, 8-hr TRE, moderate intensity exercise 3x/wk:

- MoCA: 23/30 → 29/30
  - (Mild Alz → normal)
- HbA1c: 7.8 → 5.5 (T2DM "reversed")
- HOMA-IR: 31 → 3.5 (-88%)
- Trig/HDL ratio: 4.9 → 2.2 (-55%)
- Fasting glucose: (mg/dL) 129 → 98 (-24%)
- Fasting insulin: (mU/L) 97 → 14 (-85%)
- HDL (mg/dL): 28 → 38 (+35%)
- Weight: 257 lbs → 243 (-5.5%)
- Body fat %: 40 → 37 (-3%)

KD + exercise improves cognitive scoring & metabolic syndrome in MCI

- 38-yr old male, ApoE4 +
- Metabolic syndrome; early memory problems

Table 1
Biomarkers for MetS pre/mid/post intervention.

RESULTS	Pre-Intervention	Mid-Intervention	Post Intervention	Percent Change
HOMA-IR (<1.0)	4.3	1.8	1.63	58% reduction
Tri/HDL ratio (<2.0)	14.7	5.5	3.4	77% reduction
WHtR (<.5)	0.58	0.53	0.53	8% reduction
Fasting Insulin mU/L (3–5)	15.6	7.1	7.1	55% reduction
Triglycerides mg/dL (<150)	573	216	167	71% reduction
VLDL mg/dL (9–13)	114.6	43.2	33.4	71% reduction
Weight	221	197.5	190.1	14% reduction
BMI (<25)	31.2	27.7	26.5	15% reduction

Table 2
MoCA scores pre/mid/post intervention.

Memory Assessment	Pre-Intervention	Mid-Intervention	Post Intervention
MoCA (>26)	22	25	30

Under the supervision of healthcare professionals, the ketogenic diet was prescribed and monitored. The patient's blood glucose and ketones were monitored daily using the Abbott Precision Xtra blood glucose/ketone meter to ensure sustained fasting glucose below 100 mg/dL and blood ketones in the physiological range of 0.5–2.0 mg/dL. The MoCA cognitive assessment was administered

Ketogenic diet better than low-fat diet for improving non-motor symptoms in Parkinson's Disease

RESEARCH ARTICLE

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

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

[1]*Department of Neurology, Waikato Hospital, Hamilton, New Zealand*
[2]*Healthy Kitchen Christchurch Ltd, Hamilton, New Zealand*
[3]*Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden*

BSTRACT: Background: Preliminary evidence sug-ests that diet manipulation may influence motor and onmotor symptoms in PD, but conflict exists regarding ıe ideal fat to carbohydrate ratio.
bjectives: We designed a pilot randomized, controlled ial to compare the plausibility, safety, and efficacy of a w-fat, high-carbohydrate diet versus a ketogenic diet in hospital clinic of PD patients.
lethods: We developed a protocol to support PD group (−0.99 ± 3.63 points, representing an 11% improvement) ($P < 0.001$), with the largest between-grou decreases observed for urinary problems, pain and othe sensations, fatigue, daytime sleepiness, and cognitiv impairment. There were no between-group differences i the magnitude of decrease for Parts 2 to 4. The mos common adverse effects were excessive hunger in th low-fat group and intermittent exacerbation of the P tremor and/or rigidity in the ketogenic group.

- 8 weeks ketogenic diet or low-fat diet
- Majority male; majority Caucasian
- Ketosis confirmed daily via blood meter
- Both groups improved comparably in all aspects of UPDRS except*:
  - Ketogenic cohort improved substantially more in non-motor symptoms:
  - 41% improvement compared to 11% for low-fat diet
  - Largest between-group decreases observed for urinary problems, pain and other sensations, fatigue, daytime sleepiness, and cognitive impairment

Ketogenic Diet for MS

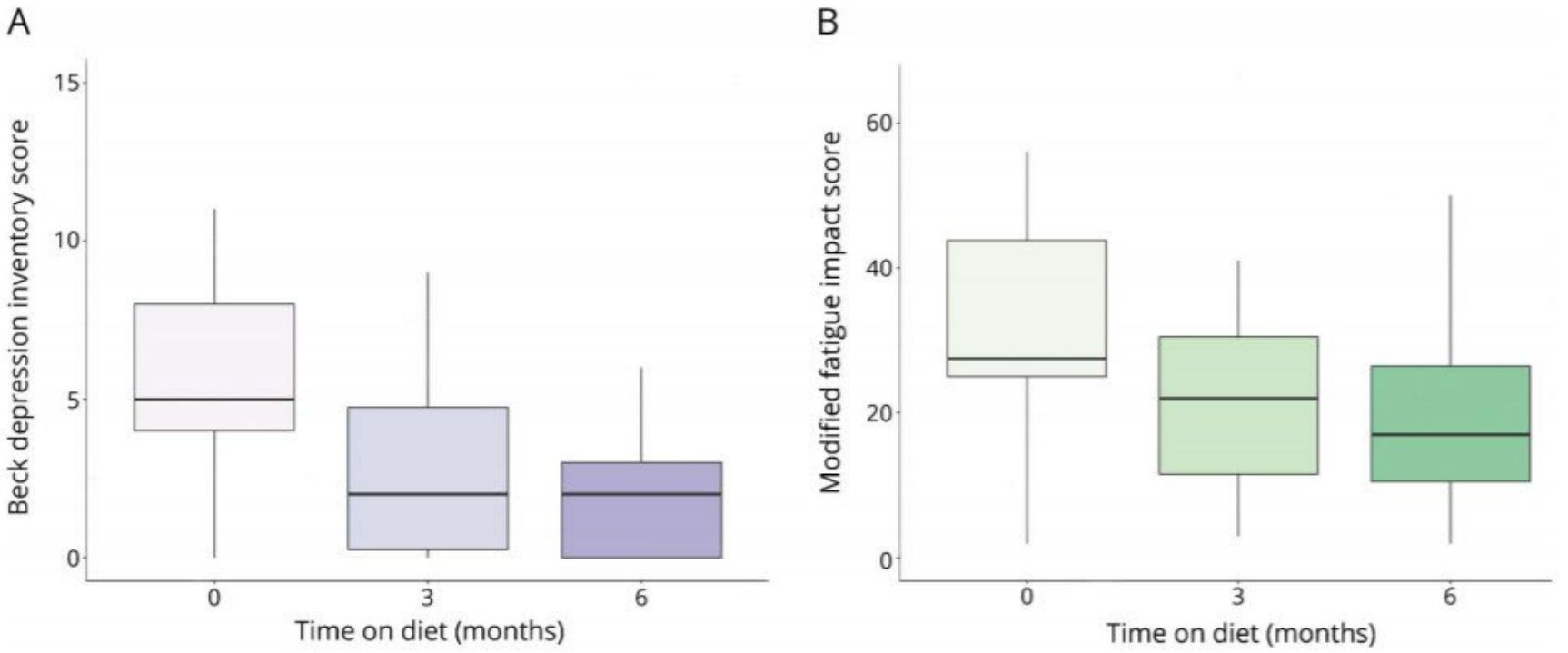
Table 3 Intention-to-treat analysis of laboratory measures pre- and post-KD^{MAD} intervention

	Baseline	Δ change at 3 months (n = 19)	*p* Value	Δ change at 6 months (n = 17)	*p* Value
Insulin resistance					
Insulin, uIU/mL	15.3 ± 10.6	−6.8 ± 9.1	**0.005**	−5.7 ± 9.1	**0.02**
Hemoglobin A_1c, %	5.4 ± 0.6	−0.2 ± 0.3	**0.005**	−0.13 ± 0.26	**0.049**
Lipid profiles					
Triglycerides, mg/dL	125 ± 47	−19 ± 46	0.09	−21.3 ± 38.5	**0.03**
Low-density lipoprotein, mg/dL	135 ± 43	+22 ± 28	**0.003**	+11.9 ± 31.4	0.13
High-density lipoprotein, mg/dL	54 ± 12	−1 ± 10	0.58	+2.7 ± 11.0	0.31
Cholesterol, mg/dL	210 ± 46	+17 ± 31	**0.03**	+11.1 ± 35.1	0.20
25-Hydroxyvitamin D, ng/mL	44 ± 20	+7 ± 16	0.06	+6.1 ± 12.6	0.06
Free carnitine, nmol/mL	36 ± 9	−5 ± 7	**0.004**	−8.9 ± 8.3	**0.0003**
Adipokines					
Leptin, ng/mL	22.9 ± 11.8	−8.9 ± 6.8	**<0.0001**	−4.9 ± 9.6	0.06
Adiponectin, mcg/mL	10.1 ± 4.3	+0.7 ± 2.7	0.25	+1.4 ± 3.6	0.12

All results within this table represent mean ± SDs. Δ change = mean 3- or 6-month value − mean baseline value. Bolded *p* values are statistically significant.

Ketogenic Diet Improves Depression & Fatigue in MS

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



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

Raising Ketone Levels

- Low carbohydrate / ketogenic diet
- Fasting
- Exercise
- Coconut oil and/or MCT oil
- Exogenous ketones

Is There a Window of Opportunity?

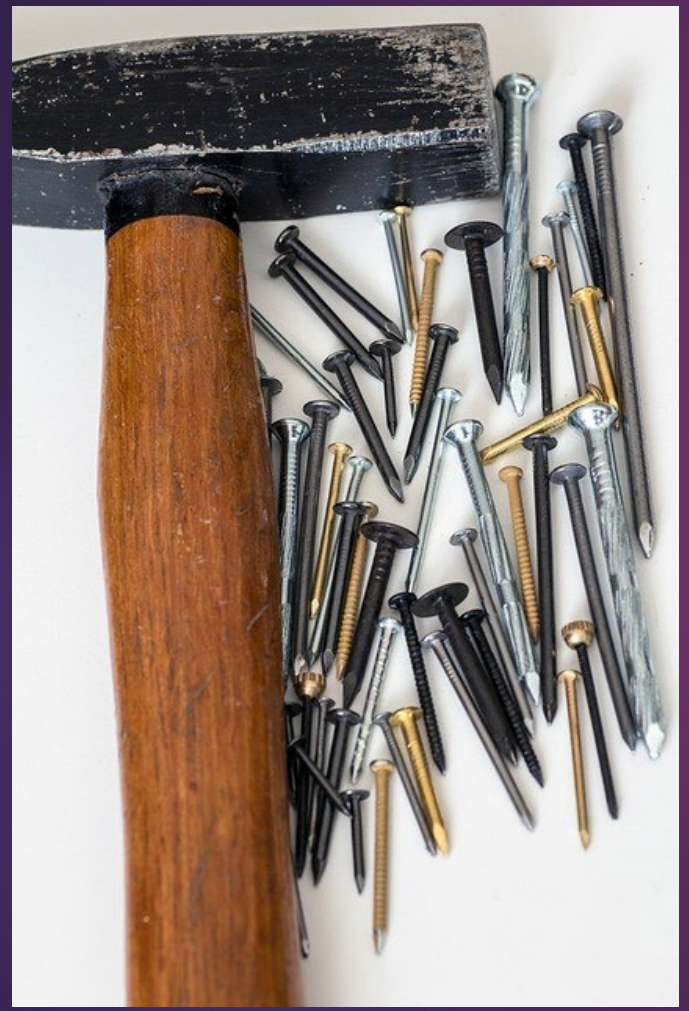
"One potentially important consideration […] – applicable to all neurodegenerative diseases – is determining whether timing of intervention is crucial for a protective effect by KD treatment. Neurological disorders in late stages of progression may have such extreme neuronal dysfunction and death to allow a "re-fueling" with metabolic substrates to help recover integrity and function."

Stafstrom CE, Rho JM. The ketogenic diet as a treatment paradigm for diverse neurological disorders. Front Pharmacol. 2012;3:59.

Why *Not* Try Ketogenic Therapies?

Existing Tools Aren't Getting the Job Done…

Maybe it's Time for the Big Hammer…



Thank you!

Thank you, Keto Chow & Keto Salt Lake organizers & volunteers.

Amy Berger, MS, CNS
adaptyourlifeacademy.com