THE KETOGENIC DIET AND NEUROLOGICAL DISORDERS

What the Science Says

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Who I am

Acute care nurse practitioner with Norton Neurology Services 2017-present

Clinical director Norton Neuroscience Institute Ketogenic Diet Therapy Clinic, currently limited to adults with refractory epilepsy, DNP from UK

RN with combined ICU, Open Heart and ER experience 9 years, BSN from U of L

7 years experience Suicide Hotline, Columbus, Ohio including one year as Assistant Director with Bachelor of Science in psychology from OSU

How I became interested in Keto for Neuro

- NNI Comprehensive Epilepsy Center
  - Level IV Epilepsy Center
  - What does “comprehensive” mean to you?

What we will be covering today:

What the ketogenic diet is

History of the ketogenic diet

How it can impact:

- Epilepsy
- TBI
- Alzheimer's Disease
- Migraine
- Parkinson's, MS, ALS, Brain Tumors

What we will be covering today:

Known and proposed mechanisms of action

Strength and limitations of the studies to date

Caution in initiation and administration of diet

How to apply what we have learned; what we can take away

What, Exactly, Is the Ketogenic Diet?

Traditional Ketogenic Diet

1. 4:1 or 3:1 ratio of fats to the sum of net carbohydrates plus protein

Net carbohydrates are the difference between total carbohydrates and fiber

It IS a low carbohydrate, high fat diet

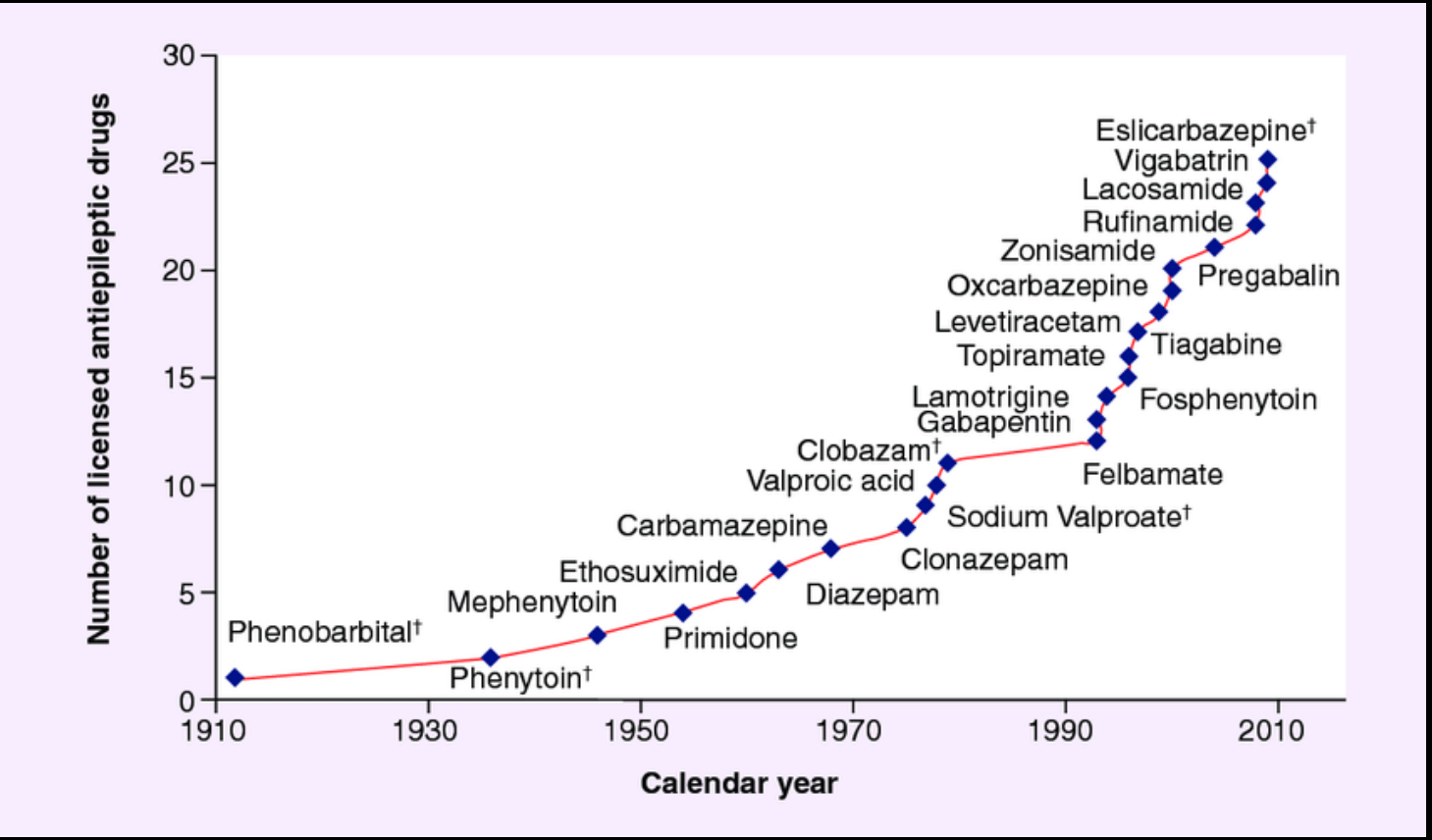
It is NOT a high protein diet (protein is low to adequate, depending on ratio)

Often limited to 20-25g net carbohydrate daily

What is the history of the ketogenic diet?

- Long understood that fasting would stop or reduce seizures
  - Hippocrates 5th Century BCE
  - Galen 3rd Century BCE
  - Jesus (Matthew 17:14-21)
  - Eastern traditions
  - Middle Ages
  - 1800's Europe
  - 1911 France
  - 1923 Russell Wilder, MD of Mayo Clinic first ketogenic diet

What happened next?



The power of one angry dad

- 1994 Charlie Abrahams
  - (Father Jim Abrahams movie credits include Airplane, Naked Gun, Hot Shots, Scary Movie 4 and First Do No Harm)
  - John Freeman, MD of Johns Hopkins University
  - Now 28 yo and seizure free for 23 years

Wheless, 2008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Today…

Epilepsy

What it is: sudden, uncontrolled electrical disturbance in the brain (MayoClinic)

Prevalence: 6.5 million globally; 1.2% of all Americans (NIH)

Usual treatment: anticonvulsants, resection, neuromodulation

Course/prognosis: 50% controlled by first AED; 65% controlled by 3 or more AEDs; 35% refractory to medical treatment, for adults it is typically lifelong, 1 in 1,000 die SUDEP (EpilepsyFoundation)

Ketogenic Diet studies on Epilepsy

First RCT 2008 children after 3 mos greater than 50% had greater than 50% in seizure frequency (Neal et al, 2008)

A meta-analysis of 19 observational studies

12 adult subjects enrolled in KD.

Brain Injury

What it is: disruption in the normal function of the brain that can be caused by a bump, blow, or jolt to the head, or penetrating head injury (traumatic) or caused by strokes, seizures, tumors, drugs, alcohol, hypoxia (CDC)

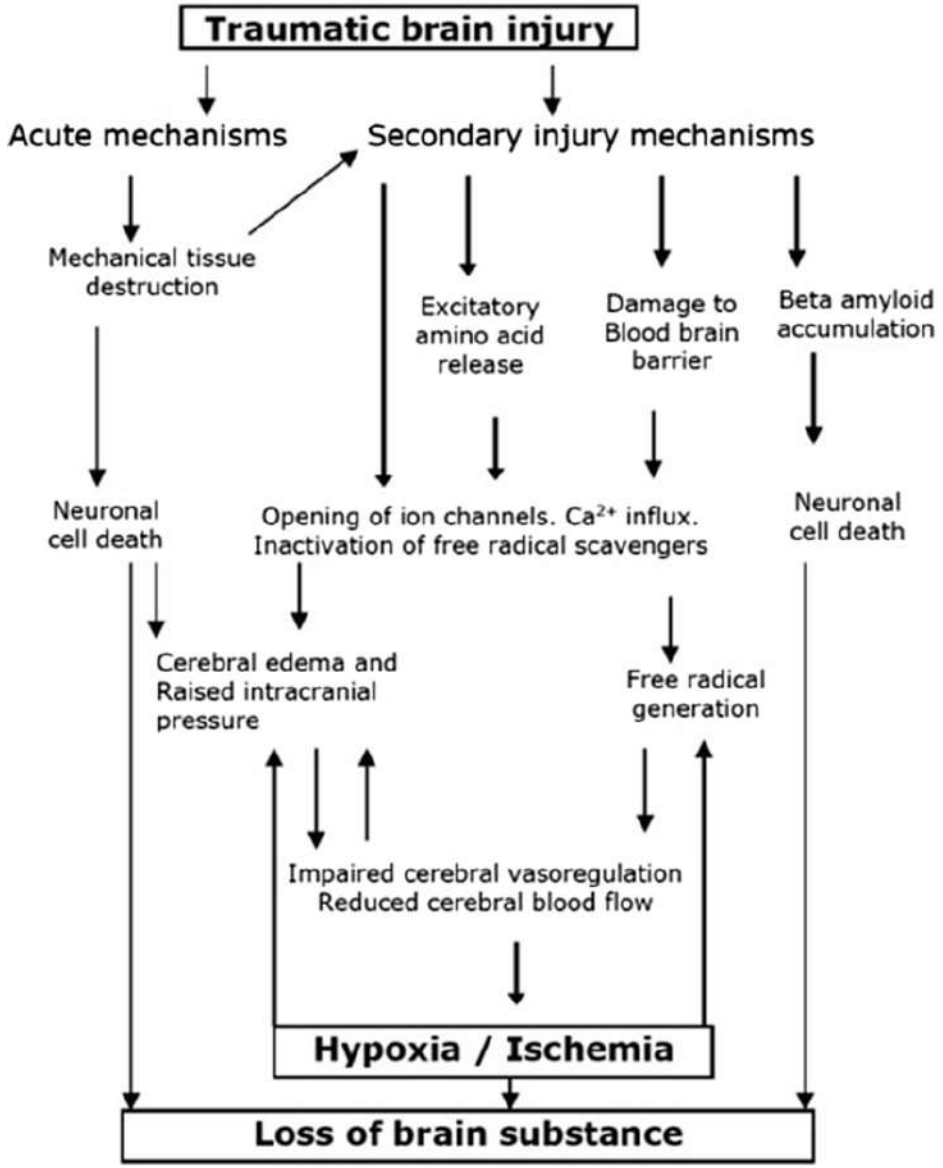
Prevalence: **Worldwide**, in 2016, there were approximately 27 million new **cases** of **TBI** with an age-adjusted **incidence rate** of 369 per 100,000—representing a 3.6% increase from 1990. In the same year, **prevalence** was 55.5 million individuals, representing an 8.4% increase from 1990 (**Global** Burden of Disease [GBD], 2019).

Usual treatment: surgery, PT/OT/SLP, voc and psych counseling (NIH)

Brain injury continued

Course/prognosis: varies considerably

TBI is the leading cause of death and **disability** in children and adults ages 1 to 44. Populations that are most affected are youth and elderly who have falls. Each year about 2.5 million individuals have TBIs of which approximately 50,000 result in death, and over 80,000 suffer permanent **disability**.


Traumatic brain injury
Acute mechanisms
Secondary injury mechanisms
Mechanical tissue destruction
Excitatory amino acid release
Damage to Blood brain barrier
Beta amyloid accumulation
Neuronal cell death
Opening of ion channels. Ca^{2+} influx. Inactivation of free radical scavengers
Neuronal cell death
Cerebral edema and Raised intracranial pressure
Free radical generation
Impaired cerebral vasoregulation
Reduced cerebral blood flow
Hypoxia / Ischemia
Loss of brain substance

Jain, 2019

Novel metabolic substrates for feeding the injured brain

1. Ketones are more energy efficient than glucose
2. Ketones protect against glutamate-mediated apoptosis
3. Ketones enhance GABA-mediated inhibition
4. Cerebral ketone metabolism alters cerebral blood flow

One can view TBI as a metabolic disease, characterized by reduced cerebral glucose metabolism

(Paoli et al, 2014 and Stafstrom and Rho, 2012)

Literature review on effects of the ketogenic diet on TBI

KD was demonstrated to reduce cerebral edema, apoptosis, improve cerebral metabolism and behavioral outcomes in rodent TBIs

Unfortunately, human trials did not establish much evidence with respect to the KD as a treatment for TBI

This was primarily due to a lack of relevant outcome measures

Safety and tolerability established

KD is an effective treatment for TBI recovery in rats and shows potential in humans

(McDougall et al, 2018)

Alzheimer's Disease

What it is: is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks. In most people with the **disease**—those with the late-onset type—symptoms first appear in their mid-6os. (NIA/NIH)

Prevalence: In 2014, as many as 5 million; projected 14 million by 2060 (CDC)

Usual treatment: SLP, Namenda, Aricept no cure (CDC)

Course/prognosis: progressively worsens over course of years through 4 stages, terminal ($200 billion annually) (CDC)

Ketogenic Diet studies on Alzheimer's Disease

Several small human studies have shown benefit on cognition in dementia with a ketogenic diet intervention (Davis et al, 2020)

Cerebrospinal fluid showed reduced Tau proteins following administration of modified Mediterranean Ketogenic Diet (Neth et al, 2020)

Migraine / headaches

What it is: severe throbbing pain or a pulsatile sensation, typically unilateral, often accompanied by nausea, vomiting, and extreme photo +/or phonophobia. **Migraine** attacks can last for hours to days; debilitating (MayoClinic)

Prevalence: 14.7% world pop; more prevalent than diabetes, epilepsy and asthma combined (WHO) women>men ~1 in 7

Usual treatment: CAI, triptans, VPA, botox, monoclonal Ab, lifestyle

Course/prognosis: intermittent v chronic, genetic v environment, another leading cause of disability $36 billion annually USA (AJMC 2018)

Ketogenic Diet studies on Migraine/headaches

From the abstract only (behind paywall): "Clinical data on KD in migraine—obtained from 150 patients investigated in case reports and prospective studies—suggest that KD may be a rapid onset effective prophylaxis for episodic and chronic migraine. KD would contribute to restore brain excitability and metabolism and to counteract neuroinflammation in migraine, although its precise mechanism is still unclear. " (Barbanti et al, 2017)

Next slide shows intervention of ketogenic diet on 18 migraineurs before and after one month on KD (Di Lorenzo et al, 2016)

Parkinson's Disease

What it is: progressive neurodegenerative disease characterized by tremor, bradykinesia, masked facies, shuffling gait, cognitive changes (MayoClinic)

Prevalence: 1 million; 10 million worldwide ~1-3% of world pop; men> women (NIH)

Usual treatment: dopamine agonists, DBS, PT/OT/SLP

Course/prognosis: progressive over many years, typically >6o,orthostasis, instability/falls, dementia, terminal, no cure

Ketogenic Diet studies on Parkinson's Disease

- probable mechanism of the neuroprotective action of octanoic acid (one of the MCT) is related to an increase in metabolic activity in striatal mitochondria
- Inherent lower protein of KD likely facilitates levodopa
- Low fat vs KD both showed motor improvement; KD showed improvements in PD nonmotor symptoms (human N=5)
- KD increases glutathione which helps ward against toxic effect of 6-hydroxydopamine
- (Włodarek et al, 2019)

Multiple Sclerosis

What it is: potentially disabling autoimmune disorder myelin sheath attacked in brain/spine symptoms depend on location of lesions, but paresthesias, Lhermitte symptoms, vision problems, balance issues common (MayoClinic)

Prevalence: 2-2.4 million globally; women>men; northern latitudes>southern latitudes (Lancet Neurology 2019)

Usual treatment: steroids, pheresis, immune suppressant/biologics, muscle relaxers, PT/OT

Course/prognosis: varies, relapsing remitting, progressive, typically years "time to chair"; no cure (MayoClinic)

Ketogenic Diet studies on Multiple Sclerosis

Due to heightened neuro-inflammation learning and memory can be impaired in MS. Studied mice with autoimmune encephalomyelitis and effects of KD. Explored lesions and tested visual spatial learning on mazes. Brain inflammation in these mice is associated with impaired spatial learning and memory function, and KD can exert protective effects, likely by taming immune response and the increased oxidative stress seen in the mice. (Kim et al, 2012)

Twenty subjects with relapsing MS enrolled into a 6-month, single-arm, open-label study of MAD/KD. 19/20 stuck with it and improvements in BMI, fatigue and depression scores noted (Brenton et al, 2019)

Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's Disease)

What it is: rapidly progressive upper and lower motor neuron degeneration, neuromuscular; 5-10% heritability onset age 40-60 (MayoClinic)

Prevalence: 1.9 per 100,000 worldwide (NIH)

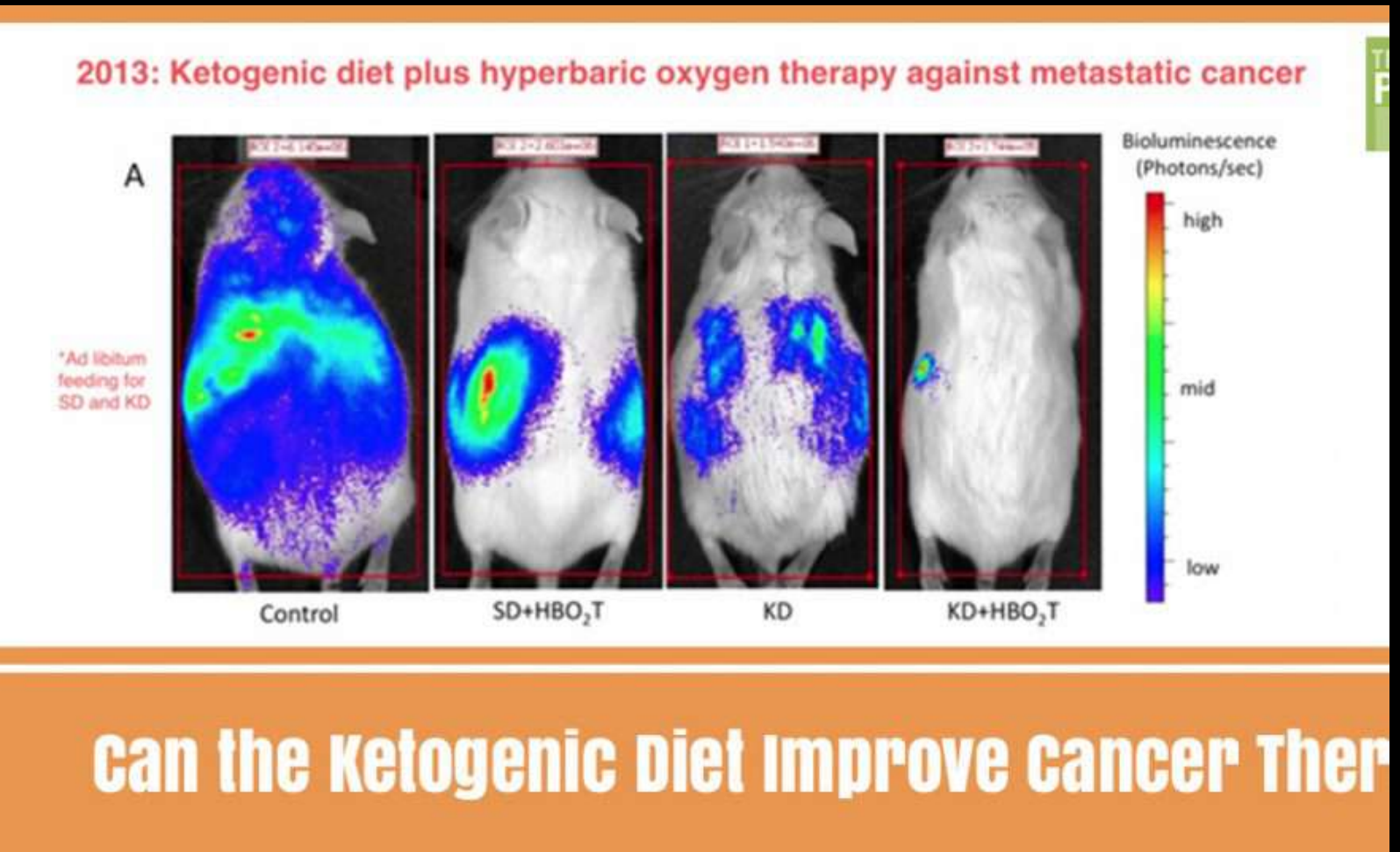
Usual treatment: Riluzole (Rilutek), Edaravone (Radicava)

Course/prognosis: median survival 2-4yrs (NIH)

Ketogenic Diet studies on Amyotrophic Lateral Sclerosis (ALS, Lou Gehrig's Disease)

- "Spanish Ketogenic Mediterranean Diet," in which <30 g of carbohydrates per day is provided, offering the antioxidant benefits of the Mediterranean diet, believed to benefit ALS combined with increase in ketone bodies by reducing carbohydrates resulting in increase in biogenesis and efficacy of mitochondria and decreased oxidative stress which will hopefully prolong life and QOL. This comprehensive review is in vitro only and studies in animals and humans need to take place for recommendations to be made. (Caplliure-Llopis et al, 2020)

A word about brain tumors…



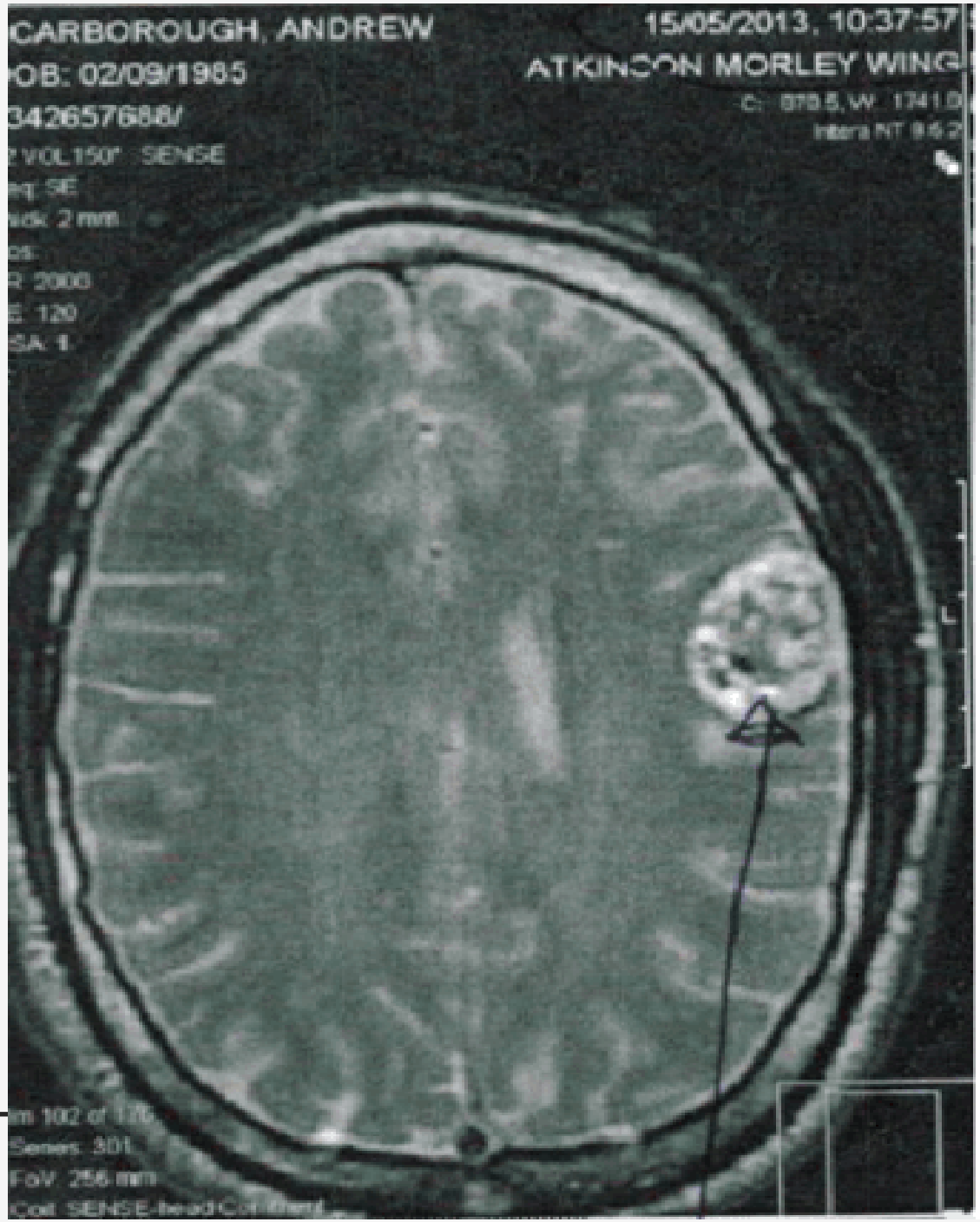
- Tumors including CNS tumors such as malignant gliomas often express a strong glycolytic (using glucose for metabolism) or Warburg phenotype, both prior to and in response to chemoradiation intervention
- Poff et al, 2013

Brain Tumors

Limited reports suggest that energy restricted ketogenic diets may have antitumor activity in aggressive primary brain cancers in humans (glioblastoma) when combined with chemotherapy or radiation in six patients in retrospective study (Schwartz et al 2015)

Next slide is MRI brain w/wo contrast on patient Andrew Scarborough, sample size N=1 who used ketogenic diet to control his epilepsy and treat his brain tumor, grade 3 anaplastic astrocytoma after failed rounds of chemotherapy from the Quantified Body Podcast available online and on iTunes

Word of caution: not all tumors will respond to ketogenic diet and some may worsen. Consult your neurologist or oncologist before trying this on your own.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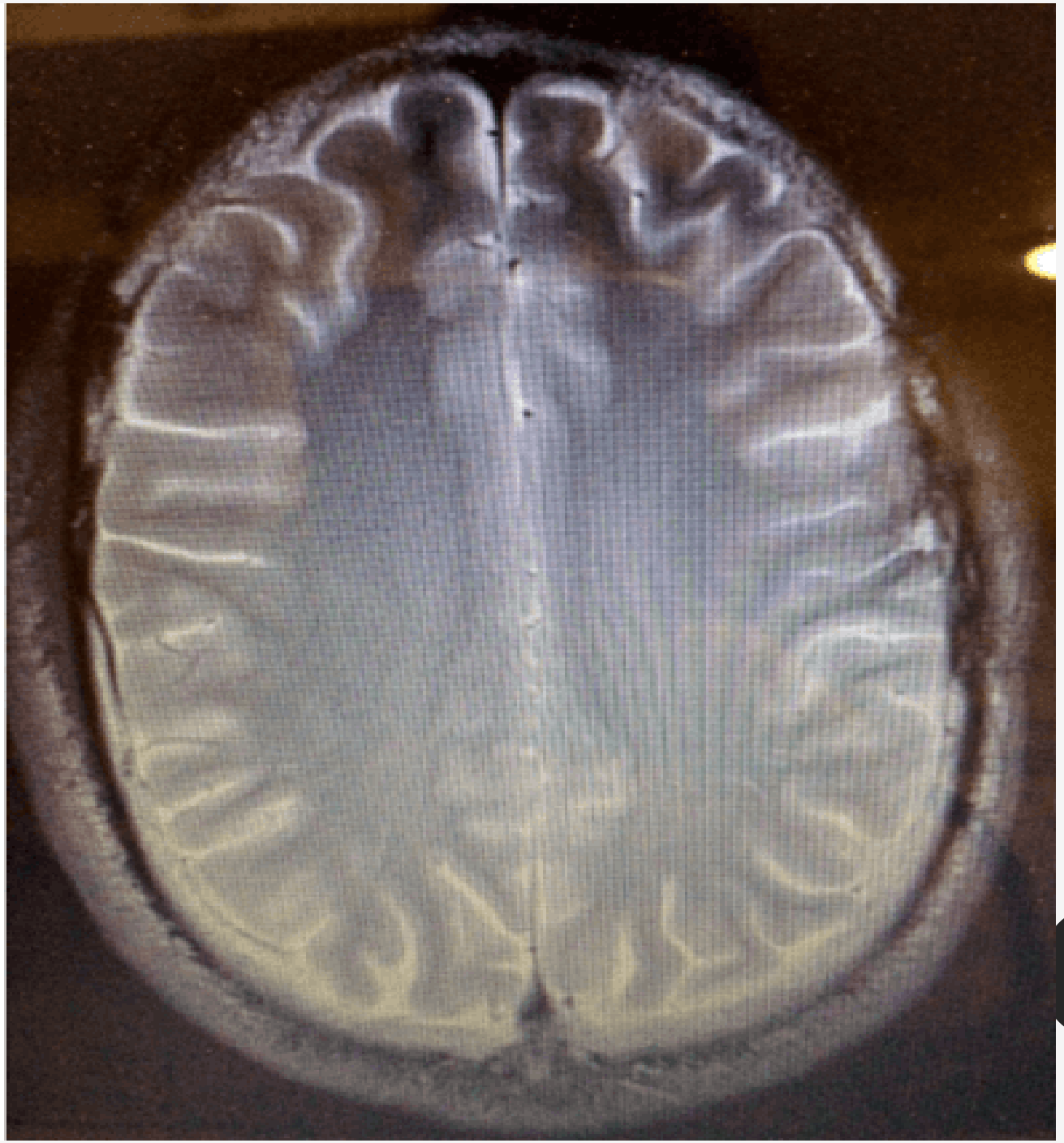


Mechanisms of Action Continued

pH hypothesis	• Lowering of pH locally reduces neuronal excitability
metabolic hypotheses	• Increase ATP, creatine and phosphocreatine, increase brain adenine nucleotides, up-regulation of transcripts encoding metabolism enzymes and mitochondrial proteins, and an increased biogenesis of mitochondria in addition to resistance to stress of hypoglycemia (?maybe) and hypoxia
amino acid hypothesis	• GABA>glutamate
ketone hypothesis	• Ketone bodies are a more efficient source of energy than glucose, because they produce more ATP per unit→more energy=less neuronal hyperexcitability

Mechanisms of Action Continued

Ketone bodies and PUFAs (increased on KD) demonstrated to exert neuroprotective activity in neurodegenerative conditions associated with impaired mitochondrial function (ALS, Parkinson's, Alzheimer's, and Huntington's diseases) (Kim et al, 2007)

Ketone bodies raise ATP levels in hippocampus (important in epilepsy and Alzheimer's) (Kim et al, 2010)

Diminish reactive oxygen species (ROS) production (Maalouf, 2007)

Gut microbiome: ketogenic diet changes natural bacteria in gut favoring Akkermensia *muciniphilia* which changes the ratio of gamma aminobutyric acid (GABA) to glutamate (Olsen et al, 2018)

Strengths and Limitations of Studies

Even in the epilepsy studies, there are too many small studies, not enough relevant outcomes measures, too few RCT, too few studies on adults, mainly a proliferation of observational and some prospective studies, but every year the evidence grows and the data support the findings that over 50% derive at least 50% reduction in seizures

The remainder of the neurological disorders, when human trials have been done, have small sample sizes, lack RCT; many are rodent studies or in vitro

That being said, the mechanisms of action are getting better understood, preliminary research is showing promise

Caution in Initiation and Administration of a Ketogenic Diet

Not for everyone; can be fatal in diseases of inborn errors of metabolism; fatty acid metabolism disorders

Screening should include urine organic acids, quantitative acyl carnitines, serum amino acids, urine creatinine/calcium, CBC, CMP, qual Hcg, AED levels, fasting lipids, Zn++, Se, Mg++, PO_4^{3-}

Other contraindications

Liver/kidney failure, pancreatic issues, Type I DM, BMI<19/malnutrition, eating disorders, pregnancy, history of noncompliance

Many people find it unpalatable, even the Modified Atkins type ketogenic diets which allow for slightly more carbs and protein

Takeaways:

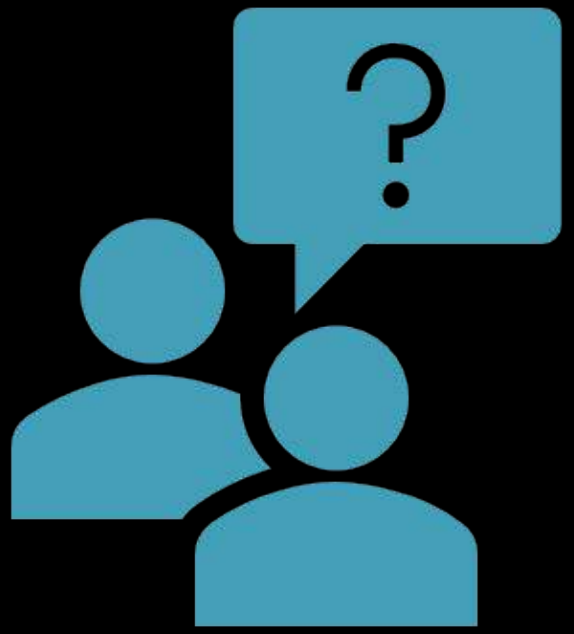
Ketogenic diet has definitively been shown to be effective in refractory epilepsy

Neuroprotective mechanisms fairly well understood and every day more are being discovered

Human studies showing promise in TBI, Tumors, Alzheimer's, and to a lesser degree PD, MS, ALS

Rodent models and preliminary human studies are suggestive that further human investigations are warranted

Moderately strong recommendation in epilepsy; cautious optimism for future use in the other neurological conditions



QUESTIONS?

- Augustin, Katrin & Khabbush, Aziza & Williams, Sophie & Eaton, Simon & Orford, Michael & Cross, Judith & Heales, Simon & Walker, Matthew & Williams, Robin. (2018). Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. The Lancet. Neurology. 17. 84-93. 10.1016/S1474-4422(17)30408-8.
- White, Hayden & Venkatesh, Balasubramanian. (2011). Clinical review: Ketones and brain injury. Critical care (London, England). 15. 219. 10.1186/cc10020.

- Paoli A, Bianco A, Damiani E, Bosco G: Ketogenic diet in neuromuscular and neurodegenerative diseases. BioMed Research International 2014, 2014:474296.
- Stafstrom CE, Rho JM: The ketogenic diet as a treatment paradigm for diverse neurological disorders. Frontiers in Pharmacology 2012, 3:59.
- Jain K.K. (2019) Neuroprotection in Traumatic Brain Injury. In: The Handbook of Neuroprotection. Springer Protocols Handbooks. Humana, New York, NY (figure)

- History of the ketogenic diet.*Wheless JW*
- *Epilepsia. 2008 Nov; 49 Suppl 8():3-5.*
- The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Maalouf M, Rho JM, Mattson MP. Brain Res Rev. 2009 Mar; 59(2):293-315.
- Kim DY, Davis LM, Sullivan PG, Maalouf M, Simeone TA, van_Brederode J, Rho JM. Ketone bodies are protective against oxidative stress in neocortical neurons. J Neurochem. 2007;101:1316–1326.

- Kim DY, Vallejo J, Rho JM. Ketones prevent synaptic dysfunction induced by mitochondrial respiratory complex inhibitors. J Neurochem. 2010;114:130–141.
- Maalouf M, Sullivan PG, Davis L, Kim DY, Rho JM. Ketones inhibit mitochondrial production of reactive oxygen species production following glutamate excitotoxicity by increasing NADH
oxidation. Neuroscience. 2007;145:256–264.

- The Gut Microbiota Mediates the Anti-Seizure Effects of the Ketogenic Diet.*Olson CA, Vuong HE, Yano JM, Liang QY, Nusbaum DJ, Hsiao EY. Cell. 2018 Jun 14; 173(7):1728-1741.e13.*
- Poff AM, Ari C, Seyfried TN, D'Agostino DP. The ketogenic diet and hyperbaric oxygen therapy prolong survival in mice with systemic metastatic cancer. *PLoS One* 8.6(June 5, 2013).
- Schwartz K, Chang HT, Nikolai M, et al. Treatment of glioma patients with ketogenic diets: report of two cases treated with an IRB-approved energy-restricted ketogenic diet protocol and review of the literature. *Cancer Metab*. 2015;3:3. 2015 Mar 25.

- https://thequantifiedbody.net/ketosis-brain-tumor-andrew-scarborough/ retrieved online 21 February 2020
- Caplliure-Llopis, J., Peralta-Chamba, T., Carrera-Juliá, S., Cuerda-Ballester, M., Drehmer-Rieger, E., López-Rodriguez, M. M., & de la Rubia Ortí, J. E. (2020). Therapeutic alternative of the ketogenic Mediterranean diet to improve mitochondrial activity in Amyotrophic Lateral Sclerosis (ALS): A Comprehensive Review. *Food Science & Nutrition*, *8*(1), 23-35.

- 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
- Brenton, J. N., Banwell, B., Bergqvist, A. C., Lehner-Gulotta, D., Gampper, L., Leytham, E., … & Goldman, M. D. (2019). Pilot study of a ketogenic diet in relapsing-remitting MS. *Neurology-Neuroimmunology Neuroinflammation*, *6*(4), e565.

- McDougall, A., Bayley, M., & Munce, S. E. (2018). The ketogenic diet as a treatment for traumatic brain injury: a scoping review. *Brain injury*, *32*(4), 416-422.
- Davis, J. J., Fournakis, N., & Ellison, J. (2020). Ketogenic Diet for the Treatment and Prevention of Dementia: A Review. *Journal of Geriatric Psychiatry and Neurology*, 0891988720901785.
- Neth, B. J., Mintz, A., Whitlow, C., Jung, Y., Sai, K. S., Register, T. C., ... & Heslegrave, A. J. (2020). Modified ketogenic diet is associated with improved cerebrospinal fluid biomarker profile, cerebral perfusion, and cerebral ketone body uptake in older adults at risk for Alzheimer's disease: a pilot study. *Neurobiology of aging*, *86*, 54-63.

- Włodarek, D. (2019). Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). *Nutrients*, *11*(1), 169.
- Barbanti, P., Fofi, L., Aurilia, C., Egeo, G., & Caprio, M. (2017). Ketogenic diet in migraine: rationale, findings and perspectives. *Neurological Sciences*, *38*(1), 111-115.
- Klein, P., Janousek, J., Barber, A., & Weissberger, R. (2010). Ketogenic diet treatment in adults with refractory epilepsy. *Epilepsy & Behavior*, *19*(4), 575-579.
- Neal, E. G., Chaffe, H., Schwartz, R. H., Lawson, M. S., Edwards, N., Fitzsimmons, G., ... & Cross, J. H. (2008). The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. *The Lancet Neurology*, *7*(6), 500-506.

- Henderson, C. B., Filloux, F. M., Alder, S. C., Lyon, J. L., & Caplin, D. A. (2006). Efficacy of the ketogenic diet as a treatment option for epilepsy: meta-analysis. *Journal of child neurology*, *21*(3), 193-198.