THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY

CLIFF HARVEY PHD(c)

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www.cliffharvey.com

ABOUT CLIFF

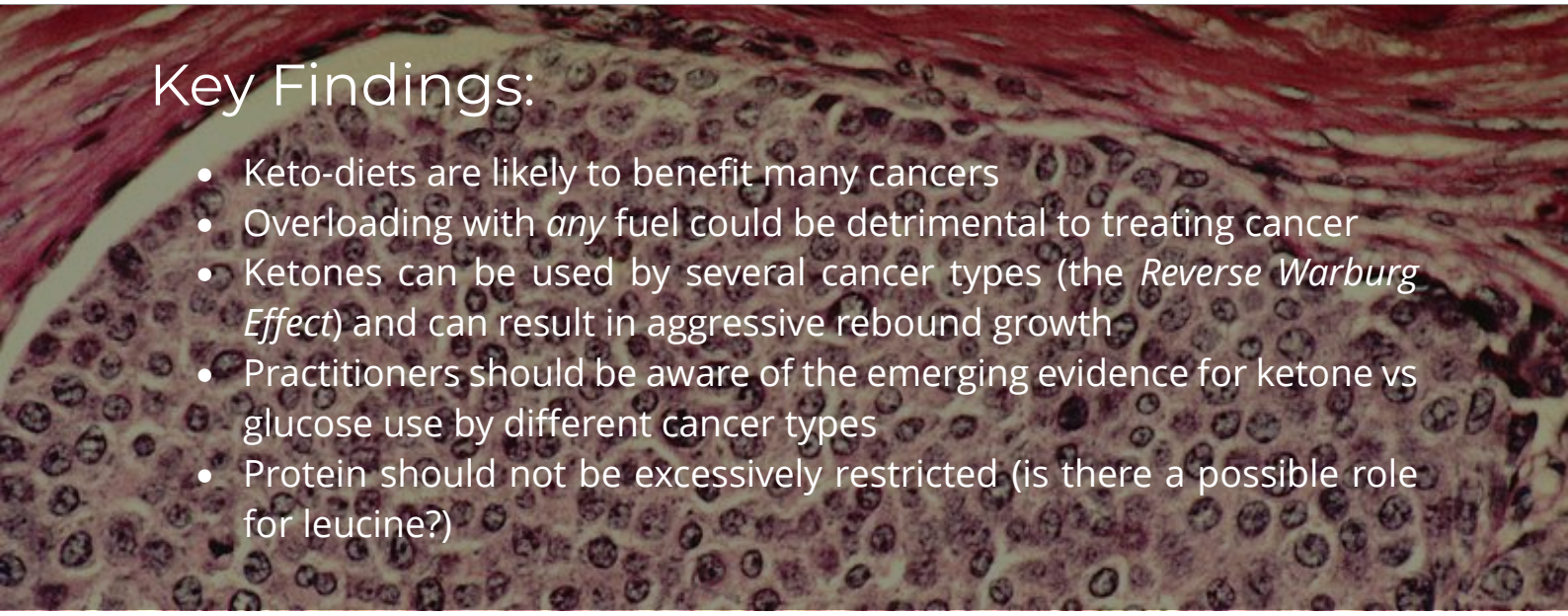
Cliff Harvey PhD (c) is an author, clinician, and researcher. He was one of the first clinical nutritionists to begin working with ketogenic and low-carb diets, way back in the 1990s and is also considered a pioneer in the area of mind-body integrative healthcare.

Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on medium chain triglycerides, 'keto-flu' and ketogenesis, and his doctoral thesis investigated individualisation of dietary prescription and 'carbohydrate tolerance'.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books.

THIS MONTH

IS THE KETOGENIC DIET *REALLY* A 'CURE' FOR CANCER?



Key Findings:

- Keto-diets are likely to benefit many cancers
- Overloading with *any* fuel could be detrimental to treating cancer
- Ketones can be used by several cancer types (the *Reverse Warburg Effect*) and can result in aggressive rebound growth
- Practitioners should be aware of the emerging evidence for ketone vs glucose use by different cancer types
- Protein should not be excessively restricted (is there a possible role for leucine?)

Ketogenic diets are now one of the, most popular diets in the mainstream consciousness. Despite this popularity, practitioners and laypeople alike often misunderstand the ketogenic diet, and there are many myths and fallacies surrounding its application and use.

It is more and more frequently claimed that keto-diets can be used as a treatment option for cancer. This is due to the observation that most cancer cells are predominantly glycolytic. In other words, cancer cells have a preference for using sugar for fuel and are quite resistant to burning fat (and ketones). This effect is known as the ***'Warburg Effect'*** as it was originally described by the scientist Otto Warburg.[1]

Mutations and further growth in tumours are related to this disturbed energy metabolism and might be, in part due to the reliance on higher carbohydrate diets and overall, calorie restricted or ketogenic diets can be effective to reduce these metabolic maladies.[2]

What does the evidence say?

Reviews of the scientific literature for both animal and human studies suggest that the ketogenic diet may be practically 'toxic' to cancer cells and effectively

starves them of fuel for continued growth and progression.[3, 4] However, these results are highly preliminary and there are heated discussions about the accuracy of these findings, their application to wider human use, and whether ketogenic diets may promote a 'rebound' effect, causing greater aggressiveness of certain types of tumours, especially with longer-term use.

> ketogenic diets may promote a 'rebound' effect, causing greater aggressiveness of certain types of tumours

What is ketosis?

Ketosis refers to the metabolic state that typically occurs during fasting or carbohydrate restriction. In this state 'ketone bodies' are created from fats and some amino acids. Restricting carbohydrate results in reduced insulin levels, which in turn reduces lipogenesis (the creation of fats) and the accumulation and retention of fat stores.

In the initial stages of carbohydrate restriction, the body continues to use considerable amounts of carbohydrates, which are provided by hepatic glucose output (release of glucose from the liver). When these glycogen reserves become depleted, an alternative fuel source is needed, primarily to fuel the brain and central nervous system which typically rely on glucose.[1]

The *ketone bodies* provide an alternative fuel, derived from fatty acids and some amino acids, and are able to be used by most cells in the body, including neurons (cells of the nervous system).

These ketone bodies are Acetoacetate, ß-hydroxybutyric acid (BOHB) and Acetone. Ketogenesis (the creation of ketones) occurs mostly in the liver, producing acetoacetate, in turn, converted to BOHB, which functions as the main fuel ketone.[2]

It is important to note that during ketosis blood glucose levels stay within normal limits (although usually at the lower end of normal) due to the creation of glucose (known as *gluconeogenesis*) from amino acids and from glycerol (the 'backbone' of fats) during fatty oxidation.[3]

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[1] For an in-depth explanation of why fat is inefficiently used by neurons see *The Carbohydrate Appropriate Diet*

[2] Technically BOHB is not a ketone body as the ketone moiety has been reduced to a hydroxyl group

[3] In silico models further suggest a plausible conversion of fatty acids to glucose more likely to occur in periods of carbohydrate restriction.

Fuelling normal vs cancerous cells

Cancer cells are considered to be less flexible than other cells of the body, especially those of the brain and CNS.[5] Indeed, it is now well accepted that the majority of tumours rely on glucose for their major source of energy and this metabolic reliance is the primary basis for ketone or ketogenic diet therapy in cancer.[6]

> the majority of tumours rely on glucose for their major source of energy

In fact, a glucose-ketone index (the ratio of glucose to ketones present in the blood) has been proposed as a clinical measure for the management of a ketogenic diet in cancer treatment.[7]

The 'Reverse Warburg Effect'

Cancer cells can, under certain circumstances (i.e. certain cell types in response to carbohydrate deprivation) begin to exploit non-glucose fuel sources such as acetate, glutamine, and aspartate, along with the ketone bodies. This means some cancer cells might actually thrive on non-glucose fuels, especially ketone bodies, and this effect is known as the *Reverse Warburg Effect.*[8] This effect has been demonstrated in brain tumour models in rats,[9] and liver cancer.[10] Although, Huang et al., have noticed this effect only when liver cells are starved of serum.[11] Conversely, De Feyter et al., have noted that there is no difference in ketone oxidation between normal and tumorous tissue in glioma models.[12]

The two-compartment model

An interesting aspect of the Warburg-Reverse Warburg effect is the *two-compartment metabolism model* in tumours. This suggests that cancer cells can induce adjacent cells (fibroblasts) to produce ketones.[8, 13, 14]

Ketogenesis within tumour cells (to provide fuel to the cell) has also been proposed.

However, in contrast to this theory of cancer-cells 'co-opting' nearby cells to produce ketone fuels for their use, other studies suggest that ketone production in cancer cells and nearby cells reduces the growth of tumours.[15]

> Cancer cells can, under certain circumstances, begin to exploit non-glucose fuels

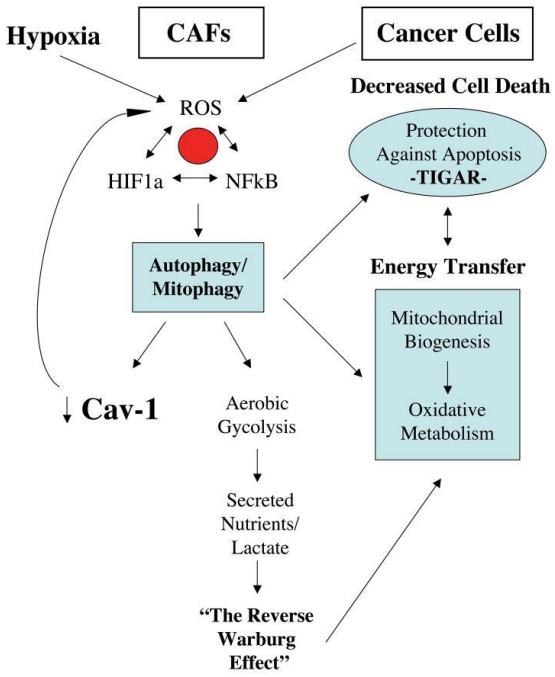


Figure 1. The Autophagic Tumour Stroma Model of Cancer[14]

Effects of the ketogenic diet and ketones *in vitro* and *in vivo* in animal models

The effects of ketogenic diets in animal models are mixed. Systematic reviews and meta-analyses show a positive role for the ketogenic diet for arresting cancer growth and improving survival times in animal models (especially for brain tumours).[16]

- Mice fed a ketogenic diet had significantly reduced tumour growth, and prolonged survival relative to mice fed a 'western-style' diet.[17]
- Mice supplemented with exogenous ketone supplements showed decreased proliferation and viability of cancer cells grown even in the presence of high glucose.
- This dietary ketone supplementation also prolonged survival in mice with systemic metastatic cancer by over 50% ($p < 0.05$)
- …and *Ketone administration showed anticancer effects in vitro and in vivo independent of glucose levels or calorie restriction*.[18]
- A review of 12 studies indicated significant improvements in survival as a result of a keto-diet. (MR = 0.85 and HR = 0.55)[19]

The ketogenic diet in humans

Total carbohydrate intake and blood glucose levels are associated with tumour growth and development, and keto-diets are tolerated well and, at least in the short-term, do not provide for significant adverse effects.[20]

In a review of the literature by Chung and colleagues, focussed on human studies, the main outcomes identified from the available literature (consisting of 10 studies) were improvement of body weight, improved body-composition (fat to lean mass), improved serum blood profiles, and reduction in markers for tumour progression (i.e. TKTL1), with no significant changes in quality of life. They concluded that "*The ketogenic diet may be efficacious in certain cancer subtypes whose outcomes appear to correlate with metabolic status, but the results are not yet*

supportive and inconsistent. Therefore, it warrants further studies".[21]

The ketogenic diet may be efficacious in certain cancer subtypes whose outcomes appear to correlate with metabolic status

The positive effects of a keto-diet for cancer in humans are likely to result from not only the reduction in glucose as a primary fuel for cancer but also due to protection against oxidative stress and inflammation, signalling cell death of cancer cells, inhibition of growth factors that encourage cancer growth (i.e. IGF-1), and the potentiation of both radiation and chemotherapy.[6]

Table 1. Clinical experience with calorie restriction or a ketogenic diet in cancer patients

Author	#pts	Primary	Regimen (duration)	Comments
Nibeling 1995	2	CNS	KD > 85 kcal/kg/d (12 mos) > 88 kcal/kg/d (8 wks)	PET, 1 pt alive at 4 years and 1 at 10 years
Bozzetti 1996	1	Abdominal desmoid	PN 28 kcal/kg/d CHO 45 g, (5 mos)	Stable disease, treatment well tolerated
Safdie 2009	10	Mixed	CR (20–140 h pre-therapy (8–56 h post-therapy)	Low chemotherapy side-effects
Zuccoli 2010	1	CNS	9.3 kcal/kg/d (8 wks)	Complete response with radiochemotherapy
Schmidt 2011	16	Mixed	>528 kcal/d (7 wks)	1/3 completed CR, 3/4 tolerated well few side-effects from CR
Fine 2012	10	Mixed	KD 17 kcal/kg/d (4 wks)	Level of ketosis (not weight loss) correlated with tumour response
Champ 2014	6	CNS	KD 21 kcal/kg/d, CHO 36 g, (7 mos)	Treatment safe and well tolerated

CNS: central nervous system; CR calorie restriction; KD: ketogenic diet; mos: months; wks: weeks; PN: parenteral nutrition; CHO: carbohydrates; pt: patient Bozzetti F, Zupec-Kania B. Toward a cancer-specific diet. Clinical Nutrition. 2016 Oct 1;35(5):1188-95. (adapted from reference 6)

Ketogenic diets with hyperbaric oxygen therapy

Mice treated with ketogenic diet plus hyperbaric oxygen therapy exhibited decreased tumour growth, reduced metastatic spread to the lungs, kidneys, spleen, adipose, and liver, decreased liver tumour vascularisation, and lived twice as long as controls.[22]

Factors to consider in the use of the ketogenic diet in cancer treatment

Ketolytic vs glycolytic enzymes in cancer cell types

It is becoming clear that at least *some* cancer cells, can 'rewire' their metabolic machinery to use ketone bodies and other alternate fuel substrates.

Ketolytic or glycolytic enzymes aid the breakdown and usage of either ketones of glucose respectively and the presence of these in cells can tell us a lot about which fuels they prefer. For example, liver cells are usually unable to use ketone bodies. However, in hepatocellular carcinomas, the ketolytic enzyme *3-oxoacid CoA-transferase 1* (OXCT1) can be activated in a carbohydrate restricted state. This can protect the cancer cells from autophagy (self-destruction of abnormal tissue like cancer cells) and enhance tumour growth.[11] Conversely, fibroblasts (nearby cells) expressing the glycolytic enzymes *pyruvate kinases* (PKM1 or PKM2) increased the growth of human breast cancer cells.[23]

Ketone or glucose dominant cell types

The evidence is certainly not clear on whether any particular cancer type of cell type is mostly ketone or glucose using and we need to always remember that cancer is not one disease, it is many types, and that even the same cancer type in a person may contain many different sub-types of cells.

Possibly more ketolytic

HeLa (Ovarian cancer cells from the infamous Henrietta Lacks cell line) have a high expression of ketolytic enzymes 3-hydroxybutyrate dehydrogenase 1 (BDH1) and succinyl-CoA: 3-oxoacid CoA transferase 1 (OXCT1). [24]

In mice with HeLa xenografts, keto-diet increased tumour growth and mouse survival decreased, whereas the keto-diet inhibited the growth of PANC-1 xenograft tumours. BOHB added to each cell culture resulted in a significantly increased proliferation of HeLa cells, while downregulation of ketolytic enzymes rendered HeLa cells sensitive to the keto-diet *in vitro* and *vivo*.[24]

Possibly more glycolytic

Human pancreatic adenocarcinoma cells (PANC-1) have a low expression of the ketolytic enzymes 3-hydroxybutyrate dehydrogenase 1 (BDH1) and succinyl-CoA: 3-oxoacid CoA transferase 1 (OXCT1) respectively.

In mice, a ketogenic diet inhibited the growth of PANC-1 xenograft tumours. BOHB added to each cell culture did not result in a significant increase in PANCI-1 cells.[24]

In Glioblastoma multiforme (GBM), an aggressive brain cancer, enzymes required for ketone metabolism (BDH1 and OXCT1) were significantly downregulated in GBM while glycolytic enzymes were significantly upregulated (HK2, HK1, SLC2A3, NAMPT, G6PD).

in 34 human cholangiocellular carcinomas (CCCs) and adjacent normal tissue by using tissue microarrays, mitochondrial mass, as indicated by VDAC1 expression, was significantly increased in CCCs compared to corresponding normal tissue ($p < 0.0001$). VDAC1 levels were inversely correlated with UICC (Union Internationale Contre le Cancer) cancer stage classification ($p = 0.0065$). Furthermore, significantly lower VDAC1 was present in patients with lymph node involvement ($p = 0.02$). Consistent with this, patients whose carcinomas expressed VDAC1 at low to moderate levels had significantly reduced survival compared to high expressors ($p < 0.05$). Therefore, low mitochondrial mass is associated with more aggressive CCC. These metabolic features are indicative of a Warburg phenotype in CCCs. This metabolic signature has potential therapeutic implications because tumours with low mitochondrial function may be targeted by metabolic therapies such as a high-fat, low-carbohydrate ketogenic diet.[25]

Mixed results in brain cancers

Conversely, while Chang and colleagues in an earlier paper had found low expression of ketolytic enzymes (OXCT1 and BDH1) in 14 of 17 GBM samples, this was not found in 4 of 5 anaplastic gliomas (i.e. anaplastic astrocytoma). At least one of the glycolytic enzymes was positive in 13 of 17 GBMs and all 5 anaplastic gliomas.[26] This suggests that ketogenic diets are more appropriate for GBM than anaplastic glioma and that attention should be paid to overall fuel availability rather than just to glucose vs ketone availability.

Glutamine usage by cancer cells

Glutamine, the most abundant amino acid in muscle tissue, can also used as fuel by many cancer cells. It has been suggested that protein and glutamine be limited in the diet to reduce glutamine availability, but due to cachexia, this could, in fact, increase glutamine availability to glutamine-using cancer cells.

In a recent study, the glutamine antagonist, 6-diazo-5-oxo-L-norleucine (DON), was administered together with an energy-restricted ketogenic diet to treat late-stage orthotopic growth in two syngeneic GBM mouse models: VM-M3 and CT-2A. This strategy helped to kill tumour cells while reversing disease symptoms, and improved mouse survival.[27]

Genetic proclivity?

When BRCA1 (a tumour suppressor gene) is knocked out in human fibroblasts, they exhibit an over 5-fold increase in ketone body production.[28] Similarly, a loss of Cav-1 (another tumour suppression gene candidate) is associated with an early increase in tumour recurrence. People lacking this gene expression also suffer

mitochondrial dysfunction associated with the reverse Warburg effect.[29]

Is cancer stable or not?

Fine and colleagues have demonstrated that those stable vs progressive exhibit 3-fold higher BOHB levels and experience better overall results from KDs.[20]

What does this all mean?

Keto-diets increase the production and use of ketone bodies (especially BOHB) and reduce the body's reliance on glucose.

The overall weight of evidence from *in vitro* and *in vivo* studies, in both animals and humans suggests that keto-diets reduce tumour growth and proliferation and increase survival times.

However, the human evidence especially for which cancer types and cells might respond 'best' to a keto-diet lacking, and the potential for an aggressive 'rebound' growth that can occur in some cancer cells (mostly shown *in vitro*), when exposed to higher amounts of ketone bodies, is a concern.

Overall, it does appear that clinical outcomes are improved by lower carbohydrate (not necessarily keto) whole food based diets, sufficient in fatty acids and protein,[6] in contrast to previous best-care models that prioritised carbohydrate and were of poorer quality overall.

Ketogenic supplements such as medium chain triglycerides, which encourage ketonaemia and ketogenesis and exogenous ketones, which provide ketonaemia without ketogenesis, also provide novel and interesting treatment approaches that warrant further investigation.[18]

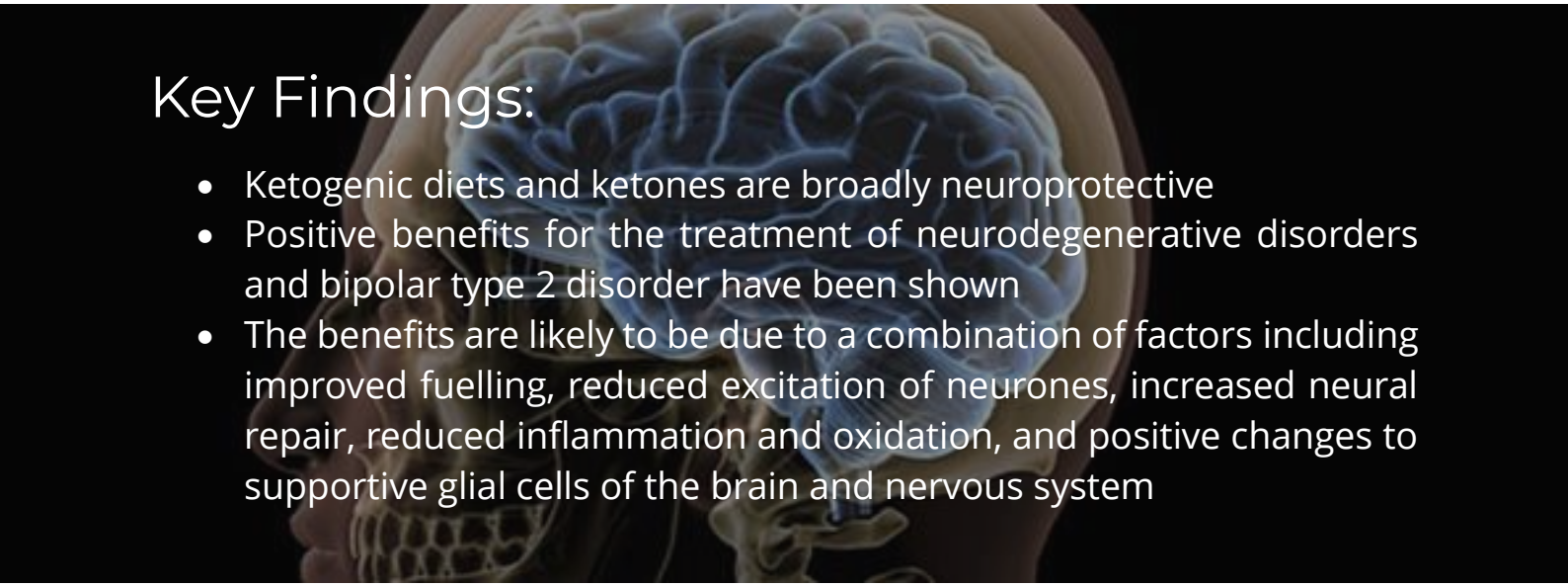
Final 'take-home' points

- Overloading with *any* fuel could be detrimental to treating cancer
- Don't 'chase ketones'
- Practitioners should be aware of the emerging evidence for ketone vs glucose use by different cancer types
- I do not believe protein should be restricted as a greater potential for damage exists from muscle-wasting, and this also frees up large amounts of glutamine (is there a possible role for leucine?)

Overall, it's important to remember that the research on ketogenic diets, ketones, and keto-supplements (and any diet!) for cancer is in its infancy.

It is crucial for anyone seeking treatment for cancer, and interested in using keto, to consult with a qualified, registered practitioner, well-versed in cancer and ketogenic diets.

CAN A KETOGENIC DIET AND KETONES IMPROVE BRAIN HEALTH?



Key Findings:

- Ketogenic diets and ketones are broadly neuroprotective
- Positive benefits for the treatment of neurodegenerative disorders and bipolar type 2 disorder have been shown
- The benefits are likely to be due to a combination of factors including improved fuelling, reduced excitation of neurones, increased neural repair, reduced inflammation and oxidation, and positive changes to supportive glial cells of the brain and nervous system

Ketosis refers to the metabolic state that typically occurs during fasting or carbohydrate restriction. In this state 'ketone bodies' are created from fats and some amino acids. In the early stages of carbohydrate restriction, the body continues to use considerable amounts of glucose provided by liver glycogen, a process known as 'HGO' or hepatic glucose output. When these glycogen reserves become depleted, an alternative fuel source is needed, especially for the central nervous system (CNS), including the cells of the brain and spinal cord, which cannot effectively use fat for fuel and so, they rely on glucose.[4] Some dietary fats, such as short and medium chain triglycerides (found in lesser amounts in full-fat dairy and coconut oil) *can* easily cross the blood-brain barrier and can be used extensively by neurons, but they are not plentiful in the diets of most people.

[4] For an in-depth explanation of why fat is inefficiently used by neurons see *The Carbohydrate Appropriate Diet*

Neuroprotection and Neurodegeneration

Neurodegenerative disorders (NDs) are increasingly common. They result in progressive debility and short survival times. For example, the average survival time after diagnosis with Alzheimer's Disease is only 3-9 years. Neurodegenerative disorders result from the loss of structure and function of neurons (brain and nervous system cells). The NDs include Alzheimer's disease, amyotrophic lateral sclerosis, Parkinson's disease, and Huntington's disease. These disorders are considered to be primarily genetic, i.e. ~ 70% in AD, but also result from environmental and lifestyle factors, especially head injuries and hypertension, and in the case of Parkinson's, past pesticide exposure.

In addition to the NDs, there is an increasing awareness of 'brain health' in general. Most people suffer some degree of age-related cognitive decline as they age, and in the internal polling of our network of patients and colleagues, improved cognition, clarity, and 'energy' are the most common desired results from seeking treatment and this is in contrast to the most desired outcome ~10 years ago, which was overwhelmingly weight loss. This is both positive (that there is a greater focus on function and health of the body rather than simply weight) and also somewhat worrying that cognitive decline and poor mental health are becoming so prevalent, for so many…

Ketone Bodies

The ketone bodies are 'brain- and body-friendly' fuels derived from fatty acids and some amino acids, especially leucine and lysine (which can only be converted to ketones, not to glucose). The ketone bodies are acetoacetate, ß-hydroxybutyric acid (BOHB) and acetone. These ketone bodies are produced through a process called 'ketogenesis' in the liver. Acetoacetate is the primary ketone body, and this is converted to BOHB, which functions as the main fuel ketone.[5] It is important to note that during ketosis blood glucose levels stay within normal physiological limits due to the creation of glucose from glucogenic amino acids and via the liberation of glycerol during fatty oxidation.[6] All these factors of ketone, fatty-acid and glucose regulation are crucially important, as certain cell types—in particular, red blood cells (RBCs), which lack mitochondria, are only able to use glucose as a fuel source and thus, the preservation of stable glucose levels is critical for survival.

Ketogenic Diets

Ketogenic diets (KDs) are low enough in carbohydrate and high enough in fat to encourage the creation of ketone bodies in higher than normal amounts (the body always produces a small amount of the

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[6] *In silico* models further suggest a plausible conversion of fatty acids to glucose more likely to occur in periods of carbohydrate restriction.

ketone bodies). This ketonaemia (the presence of ketones in the blood) is called *nutritional ketosis*, which is typically just called *ketosis.* Very low carbohydrate ketogenic diets typically result in BOHB levels of ≥ 0.5 mmol/L, [30] and this level is used as a 'cut off' point for achieving ketosis by nutrition researchers, [31-33] and the ten-fold range of BOHB from 0.5 to 5.0 mmol/L had previously been indicated low-carbohydrate researchers Stephen Phinney and Jeff Volek as the functional definition for nutritional ketosis. [34, 35] I had the opportunity of asking Dr Phinney how they originally determined this range, and the lower cut-off and he said that they arrived at these figures based on the point at which participants symptoms of keto-induction were mitigated in their studies.[7] However, time to ketosis and the reduction in keto-flu related to ketone levels had not actually been quantified until my team and I performed research specifically on this, later published in *The Journal of Nutrition and Metabolism.* [33]

a ketogenic diet is simply a diet very low in carbohydrate, low-to-high in protein, and high in fat

Exogenous Ketones

Exogenous ketone supplements provide BOHB directly to the body without requiring ketogenesis and without concurrent elevations in free fatty acids.[36] They are considered to be a safe and effective way to increase ketone body concentrations,[37] and are being studied for their use as potential treatments for brain injury,[38] cancer,[18, 39] Angelman syndrome,[40] and Alzheimer's disease,[41] amongst other conditions.

Ketone supplements have positive effects on anxiety,[41] mental performance and memory,[41] and reduce inflammation by suppressing activation of the NLRP3 inflammasome.[42]

Exogenous ketone supplements are available as either salts or esters of BOHB. Supplements containing ketone salts are some combination of sodium-, magnesium-, calcium or potassium-BOHB, and are available commercially from several companies under patent.[43] Ketone esters have only recently become available for use by the public but are not common at the time of writing and are prohibitively expensive. Both ketone esters and salts elevate BOHB to levels consistent with NK.[44] Ketone esters increase ketone levels more than equivalent amounts of ketone salts with fewer gastrointestinal symptoms per increment of increase.[45]

The distinction needs to be made between ketonaemia and ketogenesis. While exogenous ketones increase blood ketones levels, they do not encourage the production of ketones within the body. So, it is more accurate to say that exogenous

[7] Oral communication, August 28th, 2014

ketones mimic the positive effects of NK, rather than inducing it.[32]

> While exogenous ketones increase blood ketones levels, they do not encourage the production of ketones within the body

One human study has shown that exogenous administration of intravenous AcAc by inhibits endogenous ketone production.[46] However, this effect was very moderate (approx. 10-30% inhibition of endogenous ketone production) and increased linearly with the baseline levels of ketones after long-term fasting (between 3 and 10 days). So, any effect of exogenous ketones on endogenous production is likely to be extremely modest and of no clinical significance.

Ketogenic Supplements

Many supplements are purported to be ketogenic (increasing the internal creation of ketones) including leucine, lysine, short-chain fatty acids, and medium chain triglycerides (MCTs). Of these, leucine and lysine have limited effects on ketone levels. There is also limited evidence in humans for the effect of short-chain fats (such as acetic acid from vinegar, or butyric acid), however they are likely to be ketogenic and might be more so than MCT.[32] The most compelling evidence currently exists for the use of MCTs for ketogenesis, as they reliably and consistently increase ketone concentrations in the blood in a dose-dependent fashion.[32]

Ketogenic Diets, Ketosis and the Brain

The potential role of ketogenic diets for brain health has been hinted for over a century and keto-diets have been used to successfully treat childhood epilepsy since the 1920s.[47-50]

Evidence is now emerging that keto-diets could be a first-line treatment option for neurodegeneration. The exact mechanisms are not completely known at this time, but they are likely to be related to the known effects of ketones which include reduction of neuronal hyperexcitability, neuroprotection and neurogenesis, and improved fuel efficiency in the brain.

It is known that high carbohydrate diets play a role in the causation of Alzheimer's Disease and cognitive decline, and ketogenic diets offer a potential treatment option.[51] Both calorie-restricted diets and ketogenic diets are broadly neuroprotective,[52] probably due to reduced carbohydrate intake (i.e. reduced glucose-related damage to neurons) and due to the elevation of ketones and resultant reductions in oxidation and inflammation.[53]

In pilot studies, elevated ketones improve memory in adults with Alzheimer's and reviews of the evidence show a positive role for the keto-diet in its treatment. Early research also suggests that keto can reduce Parkinson's disease activity.[54, 55]

Animal studies show benefits for reducing the plaque deposits that are part of the damage inflicted by Alzheimer's,[56] along with improvements in motor function and improved neuronal fuelling.[57, 58] In human studies the keto-diet has been easily tolerated by Alzheimer's patients while improving cognition and memory performance vs a higher-carbohydrate control group.[59, 60]

elevated ketones improve memory in adults with Alzheimer's

Ketogenic diets also reduce inflammatory damage in Parkinson's disease.[61] In rat models, a ketogenic diet protects dopamine-producing neurons of the substantia nigra. These neurons are cells damaged by endotoxicity in Parkinson's, resulting in the loss of motor and other functions and so their protection is a key target of therapy,[62] and keto-diets improve motor function in rats with Parkinson's.[63]

In mouse studies, ketogenic diets reduce the loss of motor neurons on amyotrophic lateral sclerosis (ALS or 'Lou Gehrig's disease) and reduce muscle wasting.[64] Similarly, a ketogenic diet reduces wasting in Huntington's disease.[65]

Case study evidence is also beginning to show mood stabilising effects from the ketogenic diet used to treat type 2 bipolar disorder. [66]

Exogenous Ketones and Brain Health

Brain injury

Because of their anti-inflammatory actions and due to their availability as a priority fuel source for the brain, ketones are considered a potential adjunct treatment for brain injury.[38]

Alzheimer's disease

There are almost certainly positive effects for Alzheimer's disease from ketone supplementation due to improved fuel efficiency, cognition, and the neuro-relaxing effect of ketones, likely due to reduced glutamate and increased adenosine levels in the brain.[67] Ketone therapy decreased amyloid plaque (the cause of neural degeneration in Alzheimer's) deposition in the brains of mice and improved behavioural defects.[41]

Anxiety

Results of behavioural tests suggest that ketone supplemented mice exhibit significantly less anxiety.[41]

Mental performance and memory

Ketone supplemented mice exhibited significant improvements in performance on learning and memory tests.[41]

Why do Ketones Have these Effects on the Brain?

Reduced inflammation

β-hydroxybutyrate directly reduces inflammation by suppressing activation of the NLRP3 inflammasome.[42] Interestingly, inflammatory messengers like tumour-necrosis factor alpha (TNF-α) might reduce the body's ability to produce ketones,[68] and so, taking exogenous ketone supplements, or MCTs, might help the body to reduce inflammation, while also allowing there to be a better internal environment for ketogenesis. While ketones can inhibit ketogenesis, they have a relatively trivial effect on ketone production, and MCTs encourage ketogenesis, along with ketonaemia.

Reduced accumulation of malformed proteins and plaques

Proteins (like tau-protein) in the brain become distorted (mainly due to hyperphosphorylation) and accumulate in the brains of Alzheimer's patients. These cause neuronal dysfunction and additional damage to neurons. These malformed and aggregated proteins are present in most people and can cause damage even if that person does not have Alzheimer's. These proteins and plaques (β-amyloid) present in AD and other neurodegenerations are reduced by ketogenic diets/ketones.

Improved fuelling

Almost all cells, except those lacking mitochondria, such as red blood cells, can also utilise lipid-derived fatty acids (via β-oxidation) and most cell types (such as neurons and cardiac tissue) have a high affinity for ketone fuels. The entry of long-chain fats (the common dietary fats) into the brain and central nervous system tissue, is limited because the use of these fuels by neurons can cause hypoxia (lack of oxygen) and cell death. When the blood-brain barrier and cell membranes in the brain are damaged by trauma and injury, or by endotoxicity and protein damage, long-chain fats can enter the brain and neurons, causing further injury. Interestingly astrocytes in the brain and CNS might 'scavenge' some of these fatty acids, to convert them to ketones for use as fuel, thus, preventing some of that damage.[69]

> astrocytes in the brain and CNS might 'scavenge' fatty acids to convert them to ketones for use as fuel, thus, preventing damage

Glucose in excessive amounts is also undesirable, despite it being the main fuel for the brain. When glucose levels are consistently elevated, there is greater potential for *glycation* or damage to proteins caused when sugars 'stick' to proteins, which causes them to become dysfunctional. Ketones, on the other hand, are able to be used by neurons, without the

raft of negative effects caused by long-chain fats and excessive carbohydrate intake.

Ketones are also protective against the effects of ischemia (loss of blood supply to tissue),[70, 71] and cell damage caused by hypoglycaemia.[72]

> Ketones are also protective against the effects of ischemia (loss of blood supply to tissue) and cell damage caused by hypoglycaemia

Reduced excitotoxicity and neurotoxicity

Ketones improve the *GABA to glutamate ratio*. Gamma-aminobutyric acid (GABA) is a relaxing neurotransmitter, conversely, glutamate is an excitatory neurotransmitter. When there is an imbalance of these (too much glutamate, and too little GABA), *excitotoxicity* occurs. Excitotoxicity refers to the overstimulation of neurons, especially by glutamate. This causes an increase in calcium uptake into neurons which in turn, signals the activation of various enzymes which in excess, damage DNA, cell membrane, and other structures directly, and by damaging cell membranes, allow additional damage to those cells. This toxicity is implicated in Alzheimer's, ALS, Parkinson's, Huntington disease, brain injury and concussion, multiple sclerosis, alcoholism, and drug withdrawal. Excitotoxicity is reduced by ketones and a ketogenic diet, and worsened by excessive carbohydrate intake and rebound hypoglycaemia (low blood sugar, often caused by insulin resistance/pre-diabetes).[73]

Neurogenesis

Ketones initially increase oxidative stress but a rapid adaptation, along with increased antioxidant activity and reduced excitotoxicity also results in increased brain-derived neurotrophic factor (BDNF).[74] This makes it highly likely that ketones can help the neurons of the brain to both survive, and to 'regrow' and repair.

> ketones can help the neurons of the brain to both survive, and to 'regrow' and repair.

What does this all mean?

Ketones provided by diet or supplements can help to support the healthy functioning of the brain and reduce damage to neurons. They provide fuel, reduce damage to neurons, and reduce the accumulation of plaques and proteins implicated in neurodegeneration. Furthermore, they help to reduce over-stimulation of the neurons and improve anxiety.

In conclusion, a ketogenic diet is a valuable tool for the preservation of brain health or

the treatment of neuronal conditions. In addition, MCTs and exogenous ketones allow for therapeutic levels of ketones to be achieved without the need for traditional, more aggressive ketogenic diet regimes.

> a ketogenic diet is a valuable tool for the preservation of brain health or the treatment of neuronal conditions

IN THE LITERATURE

Does increased fat in the diet cause 'keto crotch'?

Dietary Intake of Selected Nutrients Affects Bacterial Vaginosis in Women

Yasmin H. Neggers Tonja R. Nansel William W. Andrews Jane R. Schwebke Kai-fun Yu Robert L. Goldenberg Mark A. Klebanoff

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Abstract

Bacterial vaginosis (BV), a condition of altered vaginal flora, is associated with various adverse reproductive health outcomes. We evaluated the association between diet and the presence of BV in a subset of 1521 women (86% African American) from a larger study of vaginal flora. Participants completed the Block Food Questionnaire and clinical assessments and self-report measures of sexual and hygiene behaviour. A total of 42% of the women were classified as having BV (Nugent score ≥7). Severe BV (Nugent score ≥9 and vaginal pH ≥5) was present in 14.9% of the women. BV was associated [adjusted OR (AOR)] with increased dietary fat (1.5, 1.1–2.4) after adjusting for other energy nutrients and behavioural and demographic covariates. Severe BV was associated with total fat (2.3, 1.3–4.3), saturated fat (2.1, 1.2–3.9), and monounsaturated fat (2.2, 1.2–4.1). Energy intake was only marginally associated (P = 0.05) with BV (1.4, 1.0–1.8). There were significant inverse associations between severe BV and intakes of folate (0.4, 0.2–0.8), vitamin E (0.4, 0.2–0.8), and calcium (0.4, 0.3–0.7). We conclude that increased dietary fat intake is associated with increased risk of BV and severe BV, whereas increased intake of folate, vitamin A, and calcium may decrease the risk of severe BV.[75]

Comment

This is a slightly older study (from 2007) that has been doing the rounds recently to support the idea that the 'keto-crotch' occurs in low-carb and keto diets. This keto-crotch refers to an increase in (unpleasant) smell from the vagina resulting either from increased bacterial vaginosis or from excretion of ketones.

Many people have suggested anecdotally that microbiome is negatively affected by a keto diet. But the research on this is equivocal at best (something I will be going into in a future research review).

Specific to bacterial vaginosis (an increase in unwanted bacteria [and fungus and yeasts] and distortion in the microbiome of the vagina) this study has been cited as a

potential reason for keto-crotch in women and lays the blame at increased fat and saturated fat in the diet.

Did this study show that keto-diets cause bacterial vaginosis?

In short, no, it didn't. The study looked at the association between many factors and vaginosis. Relatively strong associations were shown between fat (1.5, 1.1–2.4) and severe vaginosis with total fat (2.3, 1.3–4.3), saturated fat (2.1, 1.2–3.9), and monounsaturated fat (2.2, 1.2–4.1).

The diets themselves were not low-carb and there were many confounding influences on the results.

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The diets were pretty shit overall

The mean energy intake of the women studied was ~2500 calories per day (or 500-700 calories over maintenance). So, they were in an overfed state and unsurprisingly, 42% of participants were overweight or obese. This suggests poor diet quality overall which is likely to have affected the outcomes significantly. We also know that there might be detrimental effects of increased fat and saturated fat consumption in a moderate to high carbohydrate, overfeeding diet.[REF]

Interestingly, there was an association between greater intake of calories and increase in vaginosis and severe vaginosis.

Protein intakes of ~78 g per day were barely sufficient, while carbohydrate intakes averaged 308 g per day which is wildly excessive for a relatively sedentary group.

The poor quality of the diets consumed is indicated by the numbers of participants consuming less than 2/3 of the recommended daily intakes for vitamins and minerals including:

- Less than 2/3 recommended intake of Calcium: 41% of participants
- Potassium: 68%
- Zinc: 9%
- Iron: 38%
- Vitamin E: 53%
- Vitamin A: 14%
- Vitamin D: 13%
- Vitamin C: 8%
- Folate: 24%

ALL participants also failed to consume enough fibre. Given the importance of the gut microbiome to the vaginal microbiome, and protection against vaginosis, the poor-quality of the diet, excessive carbohydrate intake, and lack of essential vitamins, minerals and fibre that help to promote a healthy microbiome is incredibly informative.

Not surprisingly either, positive effects on vaginosis were associated with increased intakes of potassium and folate, which are both very good proxy measures for vegetable intake; and also associated with low intakes of vitamin E, iron, and calcium.

Other influences

Associations were also shown between the frequency of douching, greater alcohol use, and income, all suggestive of the effect of the socio-economic and food environments of individuals, that are conducive to poorer health overall.

Weird 'stuff' about monounsaturated fats...

On reading this paper, it seemed strange that a relatively strong association was shown between monounsaturated fat and vaginosis...

This effect has not been reported in the mainstream citing of this study to support the idea that fat and saturated fat cause 'keto-crotch' but this was a stronger effect that saturated fat. Monounsaturated fats are typically given a 'health halo' and olive oil, high in the omega 9 monounsaturated fatty acid *oleic acid*, is almost universally recommended by higher- and lower-carb proponents alike.

> it seemed strange that a relatively strong association was shown between monounsaturated fat and vaginosis...

While the actual food data is not available as a supplement to this paper, it would be interesting to see where these fats were coming from. I.e. *were poorer people eating high oleic vegetable oils, or eating lots of peanut butter?*

Then again, it's most likely that irrespective of the type of fats consumed, the fats themselves were simply contributing to excessive energy intake in the context of a high-calorie, relatively high-fat, high-carb diet.

> irrespective of the type of fats consumed, the fats themselves were simply contributing to excessive energy intake in the context of a high-calorie, relatively high-fat, high-carb diet.

What does this all mean?

There *could* be some detrimental effects of total and saturated fat on some markers of health in the overfed state, especially in the context of a 'metabolic shit-storm' of high carbs + high fat + low-nutrient-density.

However, this study cannot be sued to support the idea that 'keto-crotch' results from a low-carb, higher-fat diet because of bacterial vaginosis, because the diets consumed were not low-carb and they certainly weren't healthy.

Again, the take-home message is to eat a natural, unprocessed diet and then adjust your carb, protein, and fat intake based on your desired outcome, along with what you can tolerate well, and what you behaviourally can stick to.

Are low-carb diets deficient in micronutrients?

Assessing the nutrient intake of a low-carbohydrate, high-fat (LCHF) diet: a hypothetical case study design

Caryn Zinn, Amy Rush, Rebecca Johnson

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Abstract

Objective

The low-carbohydrate, high-fat (LCHF) diet is becoming increasingly employed in clinical dietetic practice as a means to manage many health-related conditions. Yet, it continues to remain contentious in nutrition circles due to a belief that the diet is devoid of nutrients and concern around its saturated fat content. This work aimed to assess the micronutrient intake of the LCHF diet under two conditions of saturated fat thresholds.

Design

In this descriptive study, two LCHF meal plans were designed for two hypothetical cases representing the average Australian male and female weight-stable adult. National documented heights, a body mass index of 22.5 to establish weight and a 1.6 activity factor were used to estimate total energy intake using the Schofield equation. Carbohydrate was limited to <130 g, protein was set at 15%–25% of total energy and fat supplied the remaining calories. One version of the diet aligned with the national saturated fat guideline threshold of <10% of total energy and the other included saturated fat ad libitum.

Primary outcomes

The primary outcomes included all micronutrients, which were assessed using FoodWorks dietary analysis software against national Australian/New Zealand nutrient reference value (NRV) thresholds.

Results

All of the meal plans exceeded the minimum NRV thresholds, apart from iron in the female meal plans, which achieved 86%–98% of the threshold. Saturated fat intake was logistically unable to be reduced below the 10% threshold for the male plan but exceeded the threshold by 2 g (0.6%).

Conclusion

Despite macronutrient proportions not aligning with current national dietary guidelines, a well-planned LCHF meal plan can be considered micronutrient replete. This is an important finding for health professionals, consumers and critics of

LCHF nutrition, as it dispels the myth that these diets are suboptimal in their micronutrient supply. As with any diet, for optimal nutrient achievement, meals need to be well formulated.[76]

Comment

A common criticism of ketogenic and low-carbohydrate diets is that they lack essential nutrients. This criticism lacks evidence.

In this study, Caryn Zinn and colleagues at AUT evaluated a hypothetical meal low-carbohydrate (<130 g carbohydrate per day) plan designed for an average man and woman.

View the meal plans here

Omega 3 intake

The omega 3 fatty acid intake in the low-carb diet plans exceeded recommended minimum intakes by 400-1200% from alpha-linolenic acid alone, with an almost 'perfect' omega 6:3 ratio of between 2:1 and 3.5:1.

Fibre

It is also commonly suggested that low-carbohydrate diets are restrictive for fibre intake. As this study demonstrated, a low-carbohydrate diet that is focussed on nutrient-dense foods like vegetables, berries, and other whole foods (in other words, a 'good' diet!) exceeds the recommended intakes for fibre by approximately 50%.

Essential vitamins and minerals

All vitamins and minerals were supplied in amounts exceeding the nutrient reference values recommended intakes with the exception of iron for the women's diet plan. In this plan, 16 mg of iron was provided per day, in contrast to the daily recommended intake of 18 mg.

All vitamins and minerals were supplied in amounts exceeding recommended intakes with the exception of iron

Protein intake in this study was sufficient, and protein sources used were mixed (for example, the protein for major meals being primarily derived from either fish or beef) but *perhaps a greater focus on beef and lamb for women is desirable to improve iron status of the diet overall?*

How does this compare to 'usual' diets?

In New Zealand, government data shows[77]:

- Around 20% of people fail to get enough vitamin A, B1 and B6
- 8% of people fail to get enough B12
- Nearly 10% of women don't get enough iron
- Around 25% of people don't consume enough zinc, and 40% of males may not get adequate zinc from their diet

- 45% of people don't get enough Selenium, a mineral lacking in New Zealand soils

People are not on balance getting sufficient amounts of the health and performance-supporting micronutrients from the 'average' diet.

What does this all mean?

There is no good reason why a low-carbohydrate diet should not be replete in all the essential nutrients. Typically, when they are, it is because the diet is either unnecessarily restrictive, insufficient in total food volume and energy, or simply founded on poor-quality, processed and refined foods. The same though could be said about any diet. The standard 'western-style' diet consumed in Australia and New Zealand, similarly to the US, is deficient in one or more of the essential vitamins and minerals and lacks sufficient protein, omega 3 fats, and fibre and resistant starch to enable people to truly thrive.

Take home points

- Any diet can be deficient in nutrients if highly energy restricted
- Any diet can lack sufficient nutrients if based on processed and refined foods
- A low-carbohydrate diet can be replete in all essential nutrients
- Any diet, whether low-carb or higher- should be based on a foundation of nutrient-dense, whole foods

Can Keto-Diets improve the structure of key brain cells?

The Impact of the Ketogenic Diet on Glial Cells Morphology. A Quantitative Morphological Analysis

Kinga Gzielo, Zbigniew Soltys, Zeon Rajfur, Zuzanna Setkowicz

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Abstract

The ketogenic diet is reported to protect against cognitive decline, drug-resistant epilepsy, Alzheimer's Disease, damaging effect of ischemic stroke and many neurological diseases. Despite mounting evidence that this dietary treatment works, the exact mechanism of its protective activity is largely unknown. Ketogenic diet acts systemically, not only changing GABA signalling in neurons, but also influencing the reliance on mitochondrial respiration, known to be disrupted in many neurological diseases. Normally, the human body is driven by glucose while ketogenic diet mimics starvation and energy required for proper functioning comes from fatty acids oxidation. In the brain, astrocytes are believed to be the sole neural cells capable of fatty oxidation. Here we try to explain that not exclusively neurons, but also morphological changes of astroglia and/or

microglia due to different metabolic state are important for the mechanism underlying the protective role of ketogenic diet. By quantifying different parameters describing cellular morphology like ramification index or fractal dimension and using Principal Component Analysis to discover the regularities between them, we demonstrate that in normal adult rat brain, ketogenic diet itself is able to change glial morphology, indicating an important role of these underappreciated cells in the brain metabolism.[78]

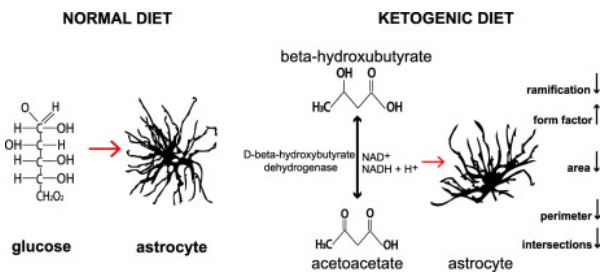

Figure 2. Normal vs. ketosis fuelling of an astrocyte

Comment

Keto-diets are known to help protect against cognitive decline, epilepsy, and neurodegenerative disorders like Alzheimer's disease and Parkinson's disease, and could help to improve aspects of mental function.

Many mechanisms are suggested for this, including improved fuelling for the brain (especially if damaged) by the ketone beta-hydroxybutyrate (BOHB), increased adenosine in the brain (a 'relaxing' neurotransmitter), improved GABA-glutamate ratios (which help to reduce over-excitation of neurons and reduces neurone damage) and increased regeneration and repair of neurons, along with reducing inflammation.

It's likely that these effects work together and that there is no one 'answer' as to the question of *why* ketogenic diets and ketones are proving so beneficial for brain health in emerging research.

In this study, the Polish research team looked specifically at the effect of effects of a ketogenic diet on *astrocytes*, a type of glial cell in the brain. Astrocytes are named due to their star-shaped structure (*astro* = star, *cyte* refers to cell) and make up around 20-40% of glial cells. Glial cells themselves are non-neuronal cells (i.e. they are not neurones and do not transmit messages in the brain and nervous system) that help to support neurons in a number of ways including:

- Regulating fluid balance in the brain (supporting extra-cellular fluid)
- Regulating repair of neurones (some increase repair, some decrease it)
- Creating the myelin sheath around cells which acts as an insulator and allows proper nerve transmission (think of it like the plastic around copper wiring)
- Clearance of glutamate and other toxic neurotransmitters, after they have played their roles, from the synapse (the junction between neurones)

What was shown in this study?

The study ran for 4 months and included 8 mice. The major finding was that astrocytes in the keto-diet brains were more diverse and complex than those in the control diet group.

> The major finding was that astrocytes in the keto-diet brains were more diverse and complex than those in the control diet group.

What are some challenges to the findings?

Mice are notoriously poor ketogenic subjects. They achieve ketosis far less easily than humans and respond differently to ketogenic diets. In particular, they are more likely to gain weight and fat on a ketogenic diet than humans, who almost universally lose fat and weight on a keto-diet (and more so than if following a eucaloric higher-carb diet). However, the structures of the brain are very similar between different mammals.

What does this all mean?

Glial cells are key supporting cells for neurones of the brain (as mentioned previously) and are involved in maintaining glucose homeostasis in the brain, sensing insulin and leptin levels, and can produce ketones for use by neighbouring neurones.

A change in 'morphology' (structure) does not always imply benefit. While in this study there were clear differences in the complexity and diversity of glia astrocytes, that does not necessarily confer benefit. However, in this study, it does seem that these changes in structure are positive and are one of the many reasons why a ketogenic diet encourages health benefits to the brain and nervous system.

Along with the other plausible mechanisms by which ketogenic diets are thought to improve brain health and function, and the functional results (improved outcomes) being demonstrated for this in human research, the change in structure of glial cells elicited by a keto-diet is likely to be one of the mechanisms by which health can be improved by a keto-diet.

> the change in structure of glial cells elicited by a keto-diet is likely to be one of the mechanisms by which health can be improved by a keto-diet

IN THE MEDIA

World Health Organisation's recommendations on saturated fat are out of date, expert team says

ABC News

https://www.abc.net.au/news/health/2019-07-04/who-saturated-fat-recommendations-out-of-date-expert-team-says/11274136

Article Summary

In a new study published in the *British Medical* Journal,[79] 18 well-known researchers have disputed the World Health Organisations dietary guideline to reduce saturated fat to less than 10% of daily calories, and have stated that this dietary guideline is not backed by evidence.

The authors summarised the key points of the paper as:

- The 2018 WHO draft guidelines on dietary saturated fatty acids and trans fatty acids recommend reducing the total intake of saturated fat and replacing it with polyunsaturated and monounsaturated fatty acids
- The recommendations fail to take into account considerable evidence that the health effects of saturated fat vary depending on the specific fatty acid and on the specific food source
- Maintaining general advice to reduce total saturated fatty acids will work against the intentions of the guidelines and weaken their effect on chronic disease incidence and mortality
- A food-based translation of the recommendations for saturated fat intake would avoid unnecessary reduction or exclusion of foods that are key sources of important nutrients

Comment

The evidence 'against' saturated fat has been lacking for the entirety of the advisement against it. Of the systematic reviews and meta-analyses published, only the Hooper analysis showed detrimental effects from increasing saturated fats at the expense of other fats and even this finding has been disputed as the statistics used gave greater weight to smaller, more biased studies (as covered in a previous CARR). It is completely baffling that a dietary guideline based on such weak evidence (at best) continues to be one of the strongest positions held by the WHO and by various health organisations around the world, including that of the Australian and New Zealand Ministries of Health.

It is time for dietary guidelines to be based on properly and thoroughly evaluated evidence.

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