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Systematic Review of the Use of Ketones in the Management of Acute and Chronic Neurological Disorders

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Abstract

Background: Ketosis is currently being utilized as treatment option in paediatric patients with resistant epilepsy. However, the evidence for efficacy in adult epilepsy and other neurological conditions is lacking. The purpose of this systematic review is to examine the evidence for inducing ketogenesis in adult humans with neurological and neurosurgical disorders, both acute and chronic.

Method: We conducted a literature review through electronic databases, including Medline, the Cochrane Library and PubMed. Our search was focussed using the following MeSH terms: ketones, ketonaemia, B-hydroxybutyrate, ketogenic diet, adults, brain trauma, traumatic brain injury, status epilepticus, carbohydrate-free diet, neurodegenerative disease, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, intracranial bleed and subarachnoid haemorrhage.

Results: From the literature search, we identified 14 publications that met the selection criteria for inclusion into this study. Of the 14 publications, 3 were randomised controlled trials, 10 were case series (6 prospective and 4 retrospective) and one was a non-randomised placebo control trial. Study subjects included Alzheimer's disease, severe refractory status epilepticus, intracranial neoplasms, traumatic brain injury and idiopathic Parkinson's disease. Although studies suggested ketosis may be beneficial, interpretation is limited by poor quality of evidence.

Conclusion: This is the first systematic review of the role of ketones in the management of neurological and neurosurgical disorders. Ketone administration may prove beneficial in the management of a number of these conditions. Better quality studies are required before firm conclusions can be drawn.

Keywords: Ketones; Beta-hydroxybutyrate; Status epilepticus; Cerebrovascular disease; Traumatic brain injury; Neurodegenerative disease; Ketogenesis

Introduction

Neurological disorders are common and sometimes catastrophic, leading to significant morbidity and mortality. At a pathophysiological level, many of these disorders are characterized by a disruption of normal metabolic pathways [1]. Following injury, cellular energetics plays a vital role in maintaining cerebral homeostasis. The adult brain consumes approximately 20% of basal metabolism, most of which is provided by the oxidation of 100-120g of glucose over 24 hours [2]. However, during times of starvation or injury, the primary cerebral metabolic substrates may alter. Ketones may represent an alternative fuel in these instances.

Ketogenesis is the process by which ketone bodies are produced via fatty acid metabolism in the liver. They provide an alternative pathway for the metabolism of acetyl CoA through the β-oxidation of free fatty acids. Ketones are generally produced as an alternative fuel source during states of starvation, or in conditions that biochemically mimic starvation such as in diabetic ketoacidosis (DKA) [1]. Plasma concentrations of circulating ketone bodies range from <0.1 mM in the post prandial state to as much as 6mM during prolonged fasting. Levels may reach 25 mM in DKA [2-4]. During times of starvation, the brain has the capacity to adapt to the use of ketones as its major energy source. In long-standing starvation, ketones can provide up to 60% to 70% of cerebral energy requirements [5].

There are unique properties of ketone metabolism that may make it a more suitable cerebral fuel under various neuro-pathologic conditions [6,7]:

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 improves cerebral blood flow.

Induction of ketosis has therefore been attempted in various neurological states. Ketosis may be induced via the intravenous or enteral route. However, largely owing to the high cost of producing intravenous IV solutions, most researchers have employed enteral feeding formulations. Ketogenic diets were initially employed in the management of refractory epilepsy in children [8,9]. This came about from the observation that starvation states were associated with improved seizure control [10]. Until recently, the benefits of the ketogenic diet were contentious and restricted to specialist units such as John's Hopkins and Harvard medical school. However, the benefits of the ketogenic diet for seizure control in children have now been demonstrated in two randomized controlled trials [11,12]. The evidence in adults however is far less clear with case reports and case series dominating the literature [13-15].

Ketogenic diets have been examined in a wide range of animal and human models of neurological disorders including autism, Alzheimer's disease, migraine, strokes, hypoxic-ischemic encephalopathy, Parkinson disease, amyotrophic lateral sclerosis, and traumatic brain injury [16-19]. More recent studies have examined the use of these diets in the management of brain tumours based on the fact that altered glucose metabolism may have anti-tumour effects [20].

Most published research has investigated the role of ketogenesis in children for the management of refractory epilepsy [8,21]. Recent reviews have examined the use of ketogenic diets in the management of seizure disorders in adults [22-24]. The purpose of this systematic review is to examine the evidence for inducing ketogenesis in adult humans with neurological and neurosurgical disorders, both acute and chronic. We have excluded seizure disorders (other than status epilepticus) as this was recently reviewed by others [21].

Methods

Data sources

We conducted a literature review through electronic databases, including Medline, the Cochrane Library and PubMed. Additionally, we performed a search through www.clinicaltrials.gov to check for new or ongoing studies. Our search was focussed using the following MeSH terms: ketones, ketonaemia, B-hydroxybutyrate, ketogenic diet, adults, brain trauma, traumatic brain injury, status epilepticus, carbohydrate-free diet, neurodegenerative disease, Parkinson's disease, dementia, Alzheimer's disease, mild cognitive impairment, intracranial bleed and subarachnoid haemorrhage.

We limited our search to papers published between January 1st 1980 and June 30 2016. We further limited our search to include only studies involving adult humans (over the age of 18).

Study selection

Two authors (HW and KV) performed the literature search as per the parameters listed above and compiled the relevant studies. Discrepancies were resolved by mutual discussions. Studies were selected if they were trials assessing ketosis in adult humans with current neurosurgical or neurological disorders. Both HW and KV were in consensus that for the purpose of this study, studies would be included if they assessed ketogenic diet, ketone supplementation, carbohydrate-free diet, induction of ketosis, or markers of ketone biochemistry in the study population.

Studies were only included if they were original trials or case reports; they were excluded if they were reviews, meta-analyses or letters to the editor. Furthermore, studies were excluded if they were not written in English.

Definitions

Neurosurgical disorders were defined as traumatic brain injury, space-occupying lesions and any type of intracranial haemorrhage. Neurological disorders included cerebrovascular accidents, status epilepticus, and any neurodegenerative conditions where the primary pathology was occurring within the brain.

Results

Study selection

From the literature search, we identified 14 publications that met the selection criteria for inclusion into this study **(Figure 1)**. These are listed and summarized in **Table 1** below.

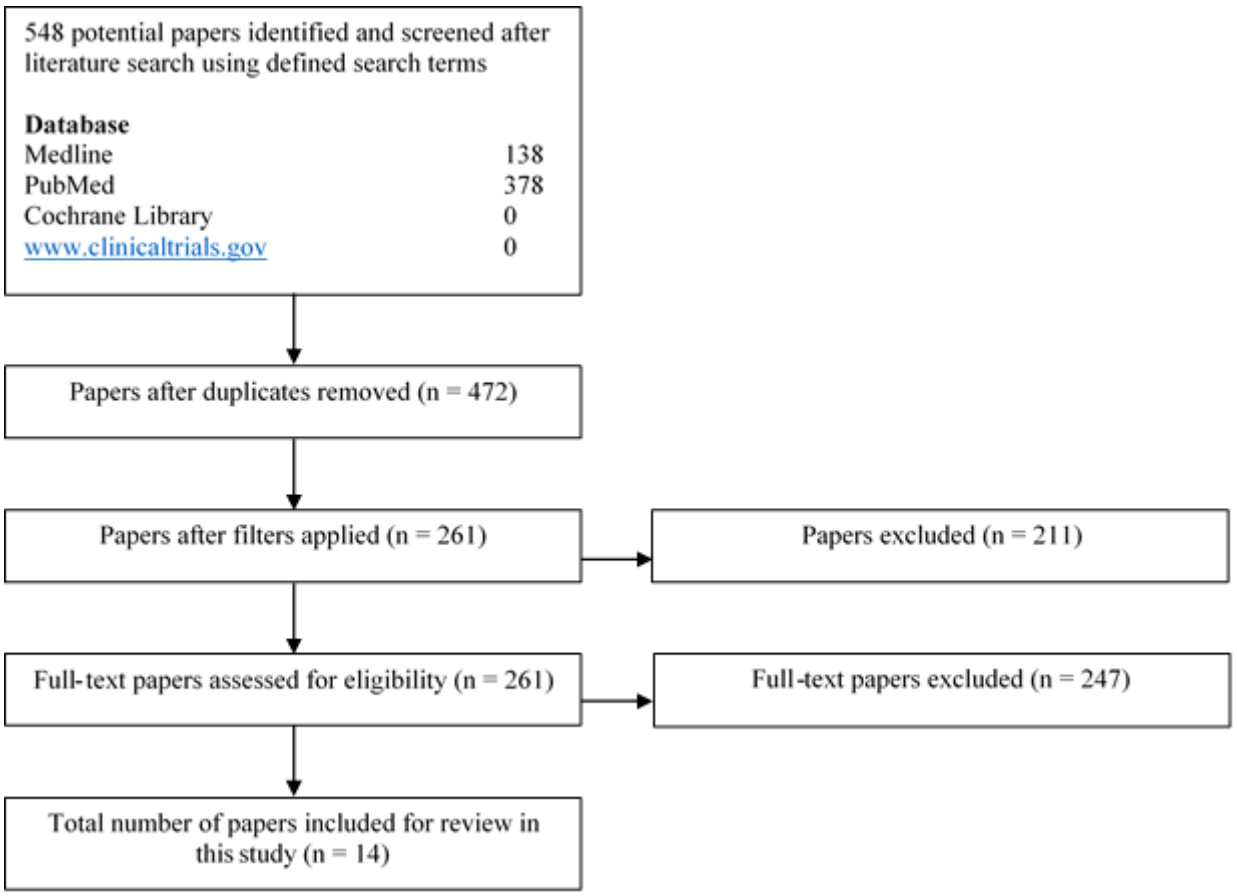

Figure 1 Search strategy for selection of papers for inclusion into this review.

Table 1 Summary of studies selected for inclusion into this review.

Study	Author, year	Type of study	Population	Number	Intervention	Primary endpoint	Main findings
1	Cervenka et al., [25]	Case report	Adult patient with SRSE	1	Administration of enteral KD after 58 days of SRSE	To assess whether administration of enteral KD may be effective in SRSE	Administration of enteral KD to adult male patient after 58 days of SRSE was associated with improvement in clinical and electroencephalographic seizure activity. Patient able to weaned off parenteral anticonvulsants. No significant adverse effects reported related to KD.
2	Champ et al., [26]	Retrospective case series	Adult patients with GBM	53	Ketogenic diet vs. normal diet in patients with GBM	To assess biochemical profile and toxicity of KD in patients with GBM	6 out of the 53 patients reviewed trialled the KD. There were no episodes of hypoglycaemia associated with the KD and there did not appear to be any issues related to toxicity.
3	Henderson et al., [27]	Randomised, double blind, placebo-controlled multicentre trial	Adult patients with mild-moderate AD	152	OKC vs. placebo over 90 days	To assess whether oral ketogenic compound could improve cognitive performance compared to placebo	Administration of oral ketogenic compound caused increased serum levels of B-hydroybutyrate and significantly improved cognitive scores compared to placebo. Reduced response to oral ketogenic compound in APOE4+ patients.

4	Krikorian et al., [28]	Randomised-controlled trial	Adults with MCI	23	High CHO diet vs. low CHO diet over 6 weeks	To assess differences in cognitive function between patients on high CHO diet and low CHO diet	Improved neurocognitive function was observed in the low CHO diet arm. Low CHO diet was reasonably well-tolerated however long-term feasibility was questionable
5	Nam et al., [29]	Retrospective case series	Patients with SRSE	5 (1 adult and 4 children)	Administration of KD in patients with RSE over course of admission	To assess the efficacy and safety profile of the KD in patients with RSE	In the adult patient, there was complete resolution of SRSE within one month and return to normal function, with nil adverse effects reported in this patient
6	Newport et al., [30]	Singe-patient case study	Patient with younger-onset AD	1	Administration of OKC over 20 months	Compare cognitive function pre and post implementation of OKC as per	Administration of OKC was deemed safe, convenient and tolerable. Improved cognitive function and activities of daily living were observed in the patient. However, nil discussion of pre and post formal cognitive function testing scores.
7	Reger et al., [31]	Double-blind placebo-control trial	Adult patients with AD or MCI	20	Administration of either OKC or placebo	To compare the effects of increased ß-OHB on memory and cognitive function, compared to placebo. Also to assess effect of ß-OHB on patients with APOE genotype vs. those without.	Administration of OKC was associated with improved memory and cognitive function, compared to placebo. However it was noted that patients positive for APOE genotype were less responsive to OKC than those who were negative for the gene.
8	Reiger et al., [32]	Prospective case-control pilot study	Adult patients with recurrent GBM	20	Administration of low carbohydrate diet over 16 weeks	To assess feasibility of the KD as judged by percentage of patients who discontinued diet	Over the study time period, 17 out of 20 (85%) of patients were able to adhere to the KD. No significant adverse outcomes were reported in patients.
9	Ritter et al., [33]	Randomised open-label control trial	Adult patients with traumatic brain injury	20	Administration of either OKC or normal diet	Evaluate the biochemical parameters associated with administration of the OKC compared to those in patients on a normal diet, particularly assessing the glycaemic profile.	Patients fed on the normal diet had higher arterial glucose concentrations compared to the group on the OKC diet. Arterial ketone concentrations were significantly higher in the OKC group than the normal diet group. There was insufficient power to draw conclusions on neurological outcomes with either group.
10	Schwartz et al., [34]	Case studies with literature review	Adult patients with GBM	2	Administration of an energy-restricted KD over 12 weeks	Assess the efficacy of KD in treating malignant gliomas, and to assess the safety and feasibility of a ketogenic diet.	The two patients studied in the trial showed progression of their tumours while on the ketogenic diet. The ketogenic diet was deemed to be safe without major side effects and ketosis was easily inducible with ketogenic diet.
11	Strzelczyk et al., [35]	Retrospective case study	Adult patient with SRSE	1	Intravenous administration of KD	To assess the efficacy and safety profile of intravenous KD in treating SRSE	Administration of intravenous KD was associated with resolution of SRSE and was a safe and feasible option for management of SRSE.
12	Thakur et al., [15]	Retrospective case series	Adult patients with SRSE	10	Administration of a KD	Assess the effects of a KD on timing of resolution of SRSE	9 out of 10 patients achieved ketosis, with all 9/10 achieving resolution of SRSE within median of 3 days of starting KD.
13	Vanitallie et al., [36]	Prospective case series	Adult patients with idiopathic PD	7	Home-prepared KD over 28 days	Assess the feasibility of patients preparing a KD themselves and adhering to it	5 out of the 7 patients were able to prepare the KD themselves and adhere to it over the study course. There

							appeared to be some degree of improvement in symptoms of PD but insufficient sample size to draw conclusions on this.
14	Wusthoff et al., [37]	Prospective observational case series	Adult patients with SRSE	2	Patient 1: administration of enteral KD, Patient 2: Initial induction of ketosis via starvation and then enteral administration of KD	Assess the efficacy of the KD in treating patients with SRSE (both in hospital and after discharge)	In patient 1, administration of KD resulted in reduced seizure frequency with complete cessation of seizures by Day 11 post KD initiation. In patient 2, initiation of ketosis resulted in a reduction of seizure frequency and cessation of seizures after 8 days of KD.

Abbreviations: AD: Alzheimer's Disease, APOE: Apolipoprotein E, β-OHB – β-Hydroxybutyrate, CHO: Carbohydrate, GBM: Glioblastoma Multiforme, KD: Ketogenic Diet, MCI: Mild Cognitive Impairment, OKC: Oral Ketogenic Compound, PD: Parkinson's Disease, SRSE: Severe Refractory Status Epilepticus.

Study characteristics

Of the 14 publications, 3 were randomized controlled trials, 10 were case series (6 prospective and 4 retrospective) and one was a non-randomized placebo control trial. The study populations of the 14 studies were as follows: 4 assessed patients with either mild cognitive impairment or Alzheimer's disease, 5 investigated patients with severe refractory status epilepticus, 3 evaluated patients with intracranial neoplasms and there was one study each in patients with traumatic brain injury and idiopathic Parkinson's disease.

In each study, the investigators aimed to induce hyperketonaemia either via carbohydrate restriction, or implementation of a ketogenic diet, or via the administration of oral ketogenic compounds (OKC). The OKCs were all high in lipids with low proportion of carbohydrates.

Mild cognitive impairment and Alzheimer's disease

Four studies investigated the role of ketone supplementation in patients with either mild cognitive impairment (MCI) or Alzheimer's disease (AD). Henderson et al. and Reger et al. both compared the effects of an OKC on memory and cognition compared to placebo, in double-blind trials [27,31]. In both trials, higher plasma ketone levels were associated with improvements in memory and cognitive function. Sub-analysis in the cohorts was performed to assess for the Apolipoprotein-E4 (APO-E4) status of the patients (APO-E4 positivity is a mutation associated with increased risk of developing Alzheimer's disease). In both studies, APO-E4-positive status was associated with a reduced response to ketone supplementation. Krikorian et al. compared a low carbohydrate diet with a carbohydrate-rich diet in adult patients with MCI, and assessed each diet's effects on cognitive function [28]. The group in the low-carbohydrate diet arm had improvements in their memory compared to the other group; however there was no significant difference in executive cognitive function between the groups. Newport et al. report a case study of an adult patient with AD who was commenced on an oral ketone ester to stimulate ketosis and to assess the effects of this on cognitive function [30]. Improvements were noted in the patient's cognitive performance (however not assessed objectively, with additional amelioration in social and self-care functions).

Traumatic brain injury

Only one study investigated the role of ketosis in adult patients with traumatic brain injury (TBI). It investigated whether sufficient caloric intake could be met with a low carbohydrate diet in patients with TBI (compared to standard nutrition), and whether there were significant adverse effects between the two groups [33]. Patients in the low carbohydrate arm received adequate dietary calories without hypoglycaemia. There were no differences in CSF and cerebral lactate concentrations between the two groups. The study had insufficient sample size to draw any conclusions regarding the nutritional effects on neurological outcome following TBI.

Parkinson's disease

VanItallie et al. prospectively investigated the feasibility of a ketogenic diet (KD) in adult patients with idiopathic Parkinson's disease (PD) [36]. Seven patients were assessed over one month and were required to prepare KDs at home by themselves. Five of the seven patients adhered to the diet over the course of the study. The diet was associated with improved symptoms of PD (as per the Unified Parkinson's Disease Rating Scale) however there was insufficient power to draw significant conclusions from this finding.

Status epilepticus

Nam et al. retrospectively reviewed the effects of an oral KD in patients with severe refractory status epilepticus (SRSE) [29]. Five patients were reviewed, of which one was an adult patient. In this patient there was complete resolution of seizures within one month with no significant adverse effects reported, and the patient was discharged home with normal neurological function. Strzelczyk et al. investigated the effects of an intravenous and enteral ketogenic diet in an adult patient with SRSE [35]. Commencement of the KD was associated with a resolution of status epilepticus, however there was ongoing myoclonus and the patient still had generalised tonic-clonic seizures every 3-4 days. There were no episodes of status epilepticus in the 4 months of follow up. Wusthoff et al.

reported a case series of two adults with SRSE treated with a ketogenic diet [37]. The first patient was an adult female with SRSE despite 3 months of maximal medical therapy. An enteral ketogenic diet was commenced on hospital day 101 and within four days a reduction in seizure frequency was noted; there was complete resolution of seizures after 11 days of KD. At the time of discharge, the patient's neurological function improved however did not return to her pre-hospital baseline. The second patient was an adult male with SRSE with no clinical response to maximal antiepileptic therapy after 18 days. Ketosis was induced on day 18 initially with fasting and then an enteral KD. Midazolam was weaned on day 26 and the patient was subsequently discharged on antiepileptics and a modified KD. At one year of follow up, only one self-limiting seizure was reported and he had returned to work.

Intracranial neoplasms

Schwartz et al. investigated whether the oral KD could alter glioma progression in two adult male patients with Glioblastoma Multiforme (GBM) [34]. Both patients had advanced posterior GBM and had already received surgery, radiotherapy and chemotherapy. The first was commenced on an oral KD 20 months after his initial diagnosis. He continued the diet for 4 weeks but subsequently withdrew from the study after serial imaging revealed further progression of the tumour. The second patient was enrolled into the study 14 months after his initial diagnosis. He was commenced on the oral diet and maintained it for 12 weeks, however clinical and radiological assessment at this time point revealed tumour progression and he subsequently withdrew from the study. Rieger et al. prospectively investigated 20 adult patients with recurrent glioblastoma to assess the feasibility of a very-low carbohydrate diet as a potential treatment modality in this group, over a 16-week period [32]. After 2-3 weeks, three patients (15%) discontinued the diet due to the impact on their quality of life. The remaining 17 patients adhered to the diet over the entire course of the study. Champ et al. [26] retrospectively reviewed a case series of 53 patients with GBM, 6 of whom trialled a KD during their treatment course. The purpose of the study was to assess the biochemical and toxicity profile of the ketogenic diet in this population. The authors reported no significant adverse effects related to the diet with no documented episodes of hypoglycaemia or toxicity related to the diet.

Adverse effects and issues related to ketosis

Poor compliance was associated with the KD due to poor palatability [34,36]. Henderson et al. reported a higher rate of diarrhoea in the ketogenic diet group compared to the placebo group however this was not discussed in the other studies [27].

Krikorian et al. questioned the long-term feasibility and safety of the diet, particularly with respect to adequate nutrient intake. The other concern was regarding the potential for weight loss, particularly the effects this may have on elderly patients susceptible to sarcopenia [28].

There were no reports of hypoglycaemia in patients' trialling the KD in any of the studies. Thakur et al. reported acidosis as a complication in one of their patients and in the study by Wusthoff et al., bicarbonate was supplemented on a daily basis to maintain acid-base balance [15,37]. There were no other reports of metabolic acidosis secondary to ketogenesis. Thakur et al. reported two patients developing complications of hypertriglyceridaemia [15].

Discussion

The purpose of this systematic review was to review the evidence pertaining to the use of ketogenic therapy in the management of neurological and neurosurgical disorders in adults. At the time of writing this is the first review of the topic in the literature. While ketogenic therapies have been extensively studied in epileptic children, evidence in adults is lacking. Of the papers included, there is significant heterogeneity between the studies, including differences in study populations, trial designs, methods of ketosis induction and chosen primary end points. The studies included in our review have focussed on the role of ketosis in status epilepticus, or in patients with mild cognitive impairment and Alzheimer's disease, brain tumours or traumatic brain injury.

A number of cellular mechanisms are thought to underlie the neuroprotective activity of ketones. Ketones enhance cerebral mitochondrial energy usage by providing enhanced energy stores and providing a more efficient source of energy per unit oxygen consumption as compared to glucose. Ketones may interfere with glutamate mediated toxicity, possibly via attenuation of glutamate-induced reactive oxygen species (ROS) formation. GABA levels are enhanced with subsequent increase in GABA mediated inhibition [38], a possible explanation for the anti-epileptic effects. ROS species may decrease via a number of mechanisms including a reduction in coenzyme Q semiquinone and increased activity of glutathione peroxidase activity [39,40]. Apoptosis or programmed cell death plays an important role in cellular damage following injury. The ketogenic diet may mitigate apoptosis by inhibition of kainic acid-induced accumulation of the protein clusterin, thought to influence apoptotic signaling [41]. And lastly, carbohydrate restriction itself is neuroprotective via various mechanisms including suppression of ROS production, stabilization of intracellular calcium and improvements in mitochondrial function.

Status epilepticus is a serious and an often fatal condition. The use of the KD to control status epilepticus in adults has been reported in several case reports and one case series, with a total of 13 patients (12 treated with an enteral diet, one treated with a parenteral KD) [15,35,37]. Patients were generally in status for a number of days prior to the initiation of the ketogenic diet as a rescue therapy. Although evidence is currently limited to case series, ketosis appears to be effective in controlling seizures in adults with status epilepticus. Furthermore, no significant issues were present with regards to safety of ketosis. However, larger more rigorous studies are necessary before firm recommendation can be made.

The ketogenic diet may have a role in modifying disease progression in a number of neurodegenerative disorders. Much of the pathophysiology of Parkinson's and Alzheimers disease relates to mitochondrial dysfunction and ketones may play a neuroprotective role. In Parkinson's disease for example, it is hypothesized that the death of the dopaminergic neurons may partly reflect impairment of mitochondrial complex I activity. Ketones may play a role by either bypassing complex I and providing an alternative fuel source or enhancing mitochondrial function with subsequent improvements in ATP production and neuroprotection [42,43]. The VanItallie study confirmed that patients able to tolerate a ketogenic diet improved their Unified Parkinson Disease Rating Scale scores with no harmful effects [36]. Although the study had insufficient power to allow any conclusions on the clinical effects of the KD, the data appears promising and certainly invites further study into the potential therapeutic effects of ketones in this group of patients.

In Alzheimers disease, the neuroprotective effects of ketogenic diets have been demonstrated in a number of small studies. Castellano et al. have shown through nuclear imaging that patients with Alzheimer's disease can have regional brain hypometabolism secondary to impaired glucose uptake [44]. Subsequently, ketosis may offer an alternative metabolic substrate for the brain in this population. Secondly, by improving mitochondrial efficiency, ketones may provide protection against the deposition of Amyloid-B 1-42 (AB), which is thought to be crucial to the development of this disease [45]. This has been observed in transgenic mice models of AD where animals fed the ketogenic diet had 25% less soluble AB in their brains after only 40 days [46]. In humans, there is evidence that this process may be determined by the presence or absence of the APO-ε4 allele; the presence of which is a risk factor for developing AD. Henderson et al. found a beneficial effect of the ketone inducing diet only in individuals where the allele was absent [27]. More research is necessary to clarify the importance of various supplements in mitigating the ongoing neuro-degeneration in patients with AD disease.

Despite a number of animal studies [47,48] investigating the benefits of ketone administration in a variety of models of acute brain injury, only a single study has been published in humans. In Ritter et al.'s study, the intervention group, blood glucose concentration remained well controlled, arterial lactate concentrations were lower and plasma ketones higher compared to the control standard feeding group [33]. Otherwise, there was no difference between the groups and they did not report any major side effects. Animal studies have suggested that acute brain injury induces rapid changes in cellular transporters that favour ketone uptake and metabolism. In a rodent model, Prins et al. found that administration of intravenous β-hydroxybutyrate after TBI mitigated the reduction in ATP availability after injury and an associated reduction in cortical contusion volume [48]. Similar findings have been observed in a stroke model, where Suzuki et al. found a decrease in stroke size in a hypoxic animal model treated with β-hydroxybutyrate [49].

Adverse effect profile of ketogenic diets

In our review, induction of ketosis did not appear to have significant safety or adverse effects in the studied populations. Data on the adverse effects of ketone administration are limited in the adult population. In the acute setting, effects of parenteral formulations on pH, Na, lipids and glucose are likely to predominate. This was confirmed by Hiraide et al. who noted a significant increase in pH and Na concentrations following the IV administration of a 20% solution of NaBHB to severe trauma patients [50]. Also of potential concern is the reduction in cerebral glucose metabolism and increased cerebral blood flow demonstrated by Hasselbalch et al. during administration of intravenous BHB [6]. The long term consequences of this are not known, but may have implications in the short term to patients with traumatic brain injury, cerebral oedema or raised intracranial pressure. Some side effects are predictable following enteral administration such as dehydration and hypoglycaemia. Others are less common and present following prolonged use, including growth retardation, obesity, nutrient deficiency, decreased bone density, hepatic failure, and immune dysfunction. Freeman has reported a significant rise in mean blood cholesterol to over 250 mg/dl following prolonged intake a of ketogenic diet [11]. This in turn may be atherogenic, leading to lipid deposition in blood vessels. Finally an increased incidence in nephrolithiasis in patients on the ketogenic diet as well as increases in serum uric acid secondary have been reported [51,52].

Limitations of this systematic review

This systematic review was limited by the small number of studies and a preponderance of case reports and case series. While results from the studies suggest a clinical benefit from ketosis, the paucity of well-designed clinical trials creates problems when interpreting the data. In many instances it is difficult to definitively prove a causal relationship between initiation of ketosis and neurological improvement including cessation of seizure activity. There is often a prolonged lag time between initiation of the ketogenic diet and seizure cessation (>1 week in 6 out of the 13 patients). Moreover, the studies did not have a sufficient sample size and power to show a treatment effect. Furthermore, there is a bias to publish positive results and it is not known how many patients failed to respond to treatment. Additionally, there are minimal prospective data available on this topic. Of the case reports on status epilepticus, 3 deaths were reported during hospitalization, however; the long term outcomes of the other patients were not reported.

Conclusion

This is the first systematic review of the role of ketones in the management of neurological and neurosurgical disorders. The evidence for the use of ketogenic diets or induction of ketosis for the management of neurological conditions in adults is limited. Although there might be a suggestion of benefit in limiting the frequency of seizure episodes in patients

with refractory status epilepticus, a number of case reports and case series are available, but high quality research is yet to be produced. Theoretically, the induction of ketosis is a promising therapeutic tool in the management of both acute and chronic neurological and neurosurgical disorders. It is time for a well-designed study to be undertaken in adults to determine if the potential benefits translate into clinical success.

Author Contributions

Hayden White: Study concept and design, acquisition of data, preparation of manuscript.

Karthik Venkatesh: Acquisition of data, preparation of manuscript.

Bala Venkatesh: Study concept and design, critical revision of manuscript for intellectual content.

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