UC DAVIS
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for Food and Health

KETONES: THE FOURTH MACRONUTRIENT

WHITE PAPER
JUNE 2022

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INTRODUCTION

We have long understood that our body relies on three main classes of macronutrients to function at its optimal state – carbohydrates, fats, and proteins – as well as micronutrients. Recently, it has become clear that there is a fourth macronutrient – ketone bodies – that play a role in both energy metabolism and also appear to have drug-like properties which address conditions from inflammation and oxidative stress attenuation to their effects on aging, cognition, immunity, gene expression, stem cells and vascular functions [1].

What are ketones? What has been their history in health? And what is their potential?

OVERVIEW OF KETONES

Ketone bodies were first discovered in the late 19th century as a byproduct found in abundance in the urine of patients in diabetic coma, associated with potentially fatal diabetic ketoacidosis [2]. This was only in the early 20th century that ketones were recognized as an alternative energy source produced in the liver to fuel peripheral tissues in response to disrupted carbohydrate metabolism [3]–[6]. Our cells require adenosine triphosphate (ATP) as their principal energy source, and the body's preferred way to produce ATP is through the utilization of glucose as primary fuel by mitochondrial oxidation – a process called glycolysis. However, our bodies also developed a secondary pathway to produce the energy needed by mitochondria through the conversion of body fat to ketones. This process called ketogenesis takes place when carbohydrates are limited in a manner similar to the fasting periods experienced by our ancestors. However, in the developed and developing world, we are no longer experiencing prolonged period of food scarcity and starvation.

Ketones bodies include three main metabolites:

- **Acetoacetate (AcAc)**: produced in the liver from the breakdown of fatty-acids in fasted state, it can be converted into Beta-hydroxybutyric acid or Acetone.

- **Beta-hydroxybutyric acid (BHB)**: technically not a "true" ketone due to its slight difference in structure but considered as the most efficient derived ketone synthetized from AcAc during prolonged ketosis.

- **Acetone**: a byproduct of AcAc that cannot be used for energy production. Excreted in our breath, urine and sweat, Acetone is responsible of the unpleasant so-called "keto breath".

How does this work? Both AcAc and BHB undergo a series of oxidative reactions leading to ATP production. As our organs demand for energy increase in a carbohydrate limited diet, more AcAc is produced and converted into BHB freely navigating through the body and driving the KREBS cycle to preferentially fuel the brain, muscles, and other peripheral tissues.

Until recently, the only way to produce ketones and be in ketosis, has been to embrace a very low carbohydrate diet (VLCD) - less than 50 grams a day. This means that eating just one apple would account for almost a third of your daily carbohydrate intake allowed on a ketogenic diet. For proteins – the building blocks of our body – many ketogenic diets restrict intake to about 100 grams a day. Then what’s left? Fat, a lot of it.

Examples of keto-friendly foods include eggs, oil, butter, cheese, avocado, fatty fish, and marbled steak. Flipping the conventional “healthy food pyramid” – comprised of about 65% of carbs and fibers, 30% of proteins and 5% of fat – will result in a typical ketogenic diet.

THE BEGINNING, DECLINE, AND RESURGENCE OF KETONES IN MEDICINE

The therapeutic potential of ketones as a part of our diet has a long history. The use of fasting – which would have resulted in ketone body generation – in the treatment of epilepsy has been documented as early as 400BC with Hippocrates describing how certain diet practices could exacerbate seizure [7]. However, a constant fasting state is not sustainable for the body and seizure will eventually resume as the person gets back to a regular diet.

In the 1920s, Dr. Russell Wilder at the Mayo Clinic coined the term "Ketogenic diet", a High Fat Low Carbs diet (HFLC) used to mitigate the symptoms of epilepsy as physicians realize its potential in mimicking a fasting state. Tested and adopted by other institutes it quickly became recognized as a viable method to dramatically reduce episodes of seizure in epileptic patients. After two decades, this therapy slowly declined with the emergence of antiepileptic drug treatment [8]. Yet, drugs have their limits. With a third of epileptic patients remaining resistant to medication [9], keto diet still constitutes a valuable alternative. "Rediscovered" in the 1970s at Johns Hopkins with the creation of the Pediatric Ketogenic Diet Center to treat epileptic children, we are seeing a resurgence of ketogenic diet therapies for neurological treatment [10]. Nowadays, particular attention is given to individual tolerability through the creation of more flexible and palatable forms of ketogenic programs including Modified Atkins Diet (MAD), the low glycemic index treatment (LGIT), or the ketogenic diet combined with medium chain triglyceride oil (MCT) [11].

Given the potential benefits conferred by ketosis for glycemic control, ketogenic diet is seen as a promising tool for the management of diabetes in therapeutic settings and became recognized as a valuable alternative by the healthcare system [12], [13]. When dietary carbohydrate is restricted signs and symptoms of insulin resistance may improve. Recent studies reported both short and long-term effects of nutritional ketosis with a significant improvement in glucose metabolism, lipid marker and restoration of insulin sensitivity in T2DM patients fed a keto diet [14]–[16]. It is worth noting that to precisely decipher the role played by ketones in metabolic disorder and establish a causal link regarding their action in glycemic control, more studies performed in individuals with elevated circulating ketones and normal carbohydrate profile are required.

Based on observation from fasting treatments, ketogenic diet is making a comeback in cancer therapy as well. The rationale in providing a fat-rich, low-carbohydrate diet in cancer therapy is to reduce circulating glucose levels and induce ketosis such that cancer cells are starved of energy while normal cells adapt their metabolism to use ketone bodies and survive [17]. Indeed, a hallmark of cancer cells is their deviant energetic metabolism characterized by an increased rate of glucose uptake with high glucose level being an important factor for tumor proliferation [18]. While chemotherapy is one of the first-line treatment strategies for many forms of cancer it also appears to drive glucose usage in the surrounding environment of cancer cells [19]. However, combined with KD, it may potentiate the anti-cancer effect of chemotherapy treatment by reducing the glucose availability to cancer cells and making tumors more sensitive to oxidative stress. Recent findings suggest that, in mouse model of pancreatic cancer, the association of KD with chemotherapy treatment tripled survival time compared with chemotherapy alone [20]. While ongoing clinical trial will reveal whether these results can be replicated in human, this constitutes a promising avenue to improve cancer therapy efficacy.

THE POPULARIZATION OF THE KETOGENETIC DIET

Beyond the recognized therapeutic effects of keto diet in epilepsy and related neurological conditions, the ketogenic diet has been popularized as a diet that is identified with weight loss. Eighty-four percent of keto-adopters [17] ranked weight loss as the primary motivation in using the ketogenic diet. Widely advertised as an effective and quick way to lose pounds, “keto” was the most Googled food-related topic in the world with 25.4 million searches in 2020 [18].

While it technically has the ability to be efficacious in this regard – for the same reasons the ketogenic diet is effective as a treatment in diabetes (eg; in most part linked to carb restriction) – achieving ketosis through nutrition requires drastic changes in lifestyle and this makes adherence difficult. No single diet is suitable for everyone. Adverse effects associated with keto diet known as “keto flu” include, digestive discomfort, gut microbiome alteration, nausea, sleep issue and increased hunger. Without proper medical supervision it can have deleterious health consequences especially for people with pre-existing condition such as pancreatitis, liver failure or dyslipidemia [19].

However, regardless of the inherent efficacy of any dietary practices, patient adherence remains a critical challenge to overcome – especially considering the restrictive nature of keto-diet. Whether these barriers may be cultural, religious, or socio-economic they constitute crucial factors hindering dietary compliance to ketogenic regimen [20] making the development of alternative solutions to achieve ketosis [21] a priority.

THE DEVELOPMENT OF EXOGENOUS KETONES

What if, instead of the imposing dietary restrictions to force the body to generate ketones, you could – like other macronutrients – make ketones and consume them? This has been the interest in developing exogenous ketones. So far, exogenous ketones have limitations and side effects. There are several options on the market to exogenously increase your circulating ketones level, including Ketone Salt, Ketone Mono or Di-Esters (mostly utilizing BHB over AcAc for its better stability and efficacy), various formulation of Butanediol (BHB precursors) and free-BHB acids.

Ketone Salts: Formulated as powder that can be dissolved in liquid to be consumed as a drink, Ketone salts contain KBs (BHB) bound to amino acids or minerals, commonly sodium, magnesium, or calcium. While they usually are less expensive and don't taste as bad as Ketone esters, there are not as efficient in raising your blood ketone [22]. Studies conducted in animals and humans show low to moderate (0.6 to 1 mM) elevation of blood BHB level after ketone salt consumption [23], [24]. In addition most ketone salts are synthetic and produced in racemic form – L-BHB and D-BHB – meaning that only half of it (the D-BHB) is bioavailable. Therefore to significantly increase blood circulating ketones, high intake of ketone salt is needed. The presence of salt significantly increases electrolyte levels which can in turn be damaging for the kidney, can dangerously increase blood pressure (people with hypertension, stay away) and cause GastroIntestinal (GI) distress and dehydration.

Ketone Ester: Research on Ketone ester began in the early 90's through a collaboration between Oxford University and National Institutes of Health (NIH) research group working on endogenous ketone projects. It constituted the groundwork for the initiation of a program involving the Defense Advanced Research Projects Agency's (DARPA), aiming to develop novel, energetically efficient food that would allow soldiers to maintain their physical and mental performance [25]. From this effort resulted the creation of D-β-hydroxybutyrate-(R)-1,3 butanediol monoester. Essentially, BHB linked to a monoester, which when broken down, releases in the bloodstream a molecule of D-BHB readily available to supply peripheral tissues along with butanediol (BDO). Once metabolized in the liver BDO generates a second molecule D-BHB for slower release leading to a longer elevation of circulating ketone in the blood. As compared to salt ketone monoester not only allows individuals to reach maximum plasma level of ketone (3.30 mM within 1 to 2 hours) faster and more continuously – without exceeding a safe range – but also present the advantage to alleviate GI symptoms observed with ketone salts. From a practical standpoint ketone monoesters are very expensive and have an unpleasant taste.

Medium-Chain Triglycerides (MCTs): Technically not considered as ketone, these types of fat made-up of glycerol bound to 6-12 carbon chains of fatty acids are frequently found on the keto supplement shelf in form of oil or powder for their ability to serve as precursors for ketogenesis. Once ingested MCTs directly enter the liver to be broken down and metabolized into ketones and are less-likely to be stored as fat than their long-chain counterpart. MCTs include caproic acid (C6), caprylic acid (C8), capric acid (C10), and lauric acid (C12) – abundant in Coconut oil – with caprylic acid (C8) offering the most ketogenic benefits. While they are not as efficient as Ketone salts and esters to rise circulating ketones level and can still create GI issues, they constitute more palatable, versatile and cost-effective options for new keto-adopters.

Consumer needs addressed by the commercialization of exogenous Ketones fall into three 3 major segments: Physical performance, Mental performance, and On-demand Ketosis for keto-lifestyle adopters (mostly motivated by weight loss). Although consumers associated with each segment may exhibit different sensitivity and adherence to exogenous ketone, so far, the market is still heavily constrained by taste issues, excessive price point and lack of clinical studies that would facilitate stronger claims. The science behind ketone biology is still maturing, and not all the benefits advertised are necessarily supported by solid scientific evidence. Depending on the type of product and dosage used, results on physical and cognitive performance remain inconsistent (Table. 1). As the number and type of exogenous ketone consumer products continue to grow, further research is required to overcome current challenges associated with the market and the products themselves. In parallel, the emergence of non-consumer approaches such as medical food products are expected to unlock new market segments.

	Compound	Model	Test	Dose	[BHB] (mM)	Result	Reference	Efficacy
ENDURANCE	BHB KE	Cyclists	60' pre fatigue +30' TT	573mg/kg liquid KE +CHO (Fasted)	2 – 3 mM	+ 2% distance	Cox et al '16	✓
	BHB KE	Rowers	30' TT	(powdered KE) +CHO (Fasted)	2.5 mM	+0.7% distance	Patent & Cox Thesis unpublished	✓
	BHB KE	Soccer	LIST Continuous Running	750mg/kg liquid KE +CHO (Fed)	1.5 - 2.5 mM	NS	Evans et al '18	=
	BHB KE	Runners	60' pre fatigue +10km TT	573mg/kg liquid KE +CHO (Fed)	0.9 – 1.3 mM	NS	Evans et al '19	=
	BHB KE	Cyclists	3h mixed intensity then 15' TT and TTE sprint	65g of KE (Fed)	3 mM	NS	Poffé et al '20a	=
	BHB KE + Bicarbonate	Cyclists	3h mixed intensity then 15' TT and TTE sprint	65g of KE (Fed) + bicarbonate	3 mM	+5% power: KE+BIC	Poffé et al '20b	✓
	BHB KE + Bicarbonate	Cyclists	3h mixed intensity then 15' TT and TTE sprint	65g of KE (Fed) + bicarbonate	3 – 3.7 mM	NS	Poffé et al '21a	=
	BHB KE + Bicarbonate	Cyclists	30' TT	50g KE (Fed) + bicarbonate	3-4 mM	-1.5% power: KE & KE+BIC	Poffé et al '21b	X
	BHB KE	Firefighter	Live burn	500mg/kg	~3 mM	NS time to complete	Waldman et al '22	=
	AcAc KE	Cyclists	~31km TT	500mg/kg liquid KE +CHO (Fed)	~1 mM	-2% time	Leckey et al '18	X
	KS	Runners	5k TT	0.3g/kg KS +MCT	0.7 mM	NS	Prins et al '20	=
	KS	Cyclists	4' TT	30ml KS	0.6 mM	NS	Rodger et al '17	=
	KS	Cyclists	~12' TT	0.3g/kg KS	0.8 mM	-7% power	O'Malley et al '17	X
SPRINT EXERCISE	BHB KE	Cyclists	Ramp test	330mg/kg KE	2.5-3.5 mM	NS	Dearlove et al	=
	BHB KE	Soccer	LIST Sprint Speed	750mg/kg KE +CHO	1.5 - 2.5 mM	NS	Evans et al '18	=
	KS	Cyclists	Wingate	11g BHB	0.5 mM	NS	Waldman et al	=
COGNITIVE PERFORMANCE	BHB KE	Soccer	Multi Tasking Test	750mg/kg liquid KE +CHO	1.5 - 2.5 mM	Small sig. improvement	Evans et al '18	✓
	BHB KE	10km running	Multi Tasking Test	573mg/kg liquid KE +CHO	0.9 – 1.3 mM	NS	Evans et al '19	=
	KS	Cyclists	Cognitive challenge + exercise	0.3g/kg	0.8 mM	NS	O'Malley et al	=

Table. 1: Studies reporting the efficacy of exogenous ketone (KE: Ketone Esters and KS: Ketone Salts) on physical and cognitive performance. (TT: time trial; TTE: time-to-exhaustion; ✓: positive; =: null; **X**: negative effect). From Brianna Stubbs.

THE POTENTIAL HEALTH BENEFITS OF EXOGENOUS KETONES

Despite the early challenges, the recent availability of ketone esters has made it possible to study the effects of ketones beyond their application in the body's energy system. Initial findings seem to indicate that the potential of ketone supplement for improved physical performance, metabolic health, and mental health is significant. From neuroproctection, blood sugar control improvement, enhanced physical performance all the way to extended longevity in animal models [16], [26], evidence is accumulating – so let us look at the science behind it.

Brain Health

While the brain is a demanding organ in terms of energy – consuming nearly 20% of the body's total energy expenditure – glucose is not necessarily its preferred energy source [27]. Ketone appears to be a more efficient fuel. Studies suggests that under ketosis, 75% of the brain energetic needs are fulfilled by ketone bodies and only 25% by glucose [28]. Moreover, BHB – the most abundant and potent form of ketone – yields to more energy as compared to glucose. Indeed, studies show that cultured neurons utilize ketone bodies for oxidative metabolism at rates far greater than they utilize glucose and can prevent neuronal death [27], [29]. In addition to their well-established role in epilepsy, a neuroprotective role attributed to ketone bodies is supported by their effects in the treatment of brain dysfunction and neurodegenerative diseases in which brain glucose metabolism is altered, such as Alzheimer, Parkinson, or dementia. In the context of mild cognitive impairment or moderate Alzheimer disease, exogenous supplementation with ketogenic drink over a 6 months period has been shown to improve recall, verbal fluency, confrontation naming, visual attention and task switching [30]. Studies suggests that the aging brain favors ketone metabolism, perhaps as compensatory response to glucose hypometabolism [31]. Glucose transporter 1 deficiencies associated with oxidative stress can reduces our antioxidant defenses and favors aggregation of misfolded protein, promoting inflammation [32]. Recent evidence suggests that ketone bodies, in contrary, can mitigate oxidative stress, reduce inflammation and regulate neuronal excitability through direct and indirect pathways [27], [33].

Implication in Metabolic Syndrome

The health benefit provided by ketone bodies may not be limited to the brain and could extend to other body systems, as well. Since ketone bodies affect the way our body burns energy, it appears as an effective tool to improve a range of health markers associated with Metabolic syndrome – a cluster of conditions leading to increased risk of type II diabetes, heart disease and stroke. A study investigating the role exogenous ketones suggests that ingestion of BHB not only acutely increased BHB blood concentration but lowered the glucose plasma concentration in adults with pre-diabetes [34]. Although results on endogenous insulin secretion are unclear and required further investigation to determine the effects of exogenous ketone on glucoregulatory mechanisms, it illustrates their effectiveness in achieving ketosis without undergoing drastic dietary change. Research on cardiovascular health is promising too, as other studies suggest positive effects of keto supplement on Cardio Vascular Diseases (CVD) through an improved management of blood pressure, inflammation, oxidative stress, endothelial functions, and lipid metabolism [35]. In addition, a recent study performed on animal models suggests that chronic oral supplementation with ketone ester is effective in both prevention and treatment of heart failure [36]. The potential of Ketones in metabolic and endocrine functions is also supported by the beneficial role that endogenous production of butyrate plays on intestinal homeostasis and energy metabolism [37]. Butyrate and BHB share similar signaling pathway and their coupling may translate into synergistic effect for ketosis induction

[38]. A better understanding of the mechanism of action of butyrate in intestinal physiology and lipid metabolism will facilitate the application of exogenous ketone in gut health improvement as well as the control and the prevention of metabolic diseases.

Muscle Health and Performance

During exercise our muscle demand for ATP skyrockets. Ketosis may provide thermodynamic advantages over other carbon substrates by increasing the free energy conserved in ATP by the oxidation of ketones during mitochondrial oxidative phosphorylation. By providing an alternate fuel source to the muscle for oxidative respiration, KBs may improve energetic efficiency and translate into higher power output during exercise [39]. In addition, it may also offer the potential to limit oxidative stress and inflammation during exercise and spare the proteins required to build muscle. In aging mice ketogenic diet results in an increase in muscle mass and strength through a maintenance of fast oxidative muscle fibers usually impacted with age. Interestingly recent findings suggest a role of ketogenic diet and exercise in connecting muscle and brain health through the regulation of kynurenic acid – a neurotoxic molecule [40]. However, results vary greatly depending on how ketosis is achieved. Exercising under ketogenic diet may hinder performance due to its inherent lack of carbs and altered macronutrient composition [41]–[43]. Ingestion of exogenous ketone to achieve ketosis, on the other hand, present the advantage to increase fat oxidation while preserving intramuscular glycogen storage which in turn may result in improved endurance performance. However, in the context of high-intensity exercise relying on rapid glycolytic flux, performance may be negatively affected during exogenous ketosis [44].

Immunity

As evidence is accumulating regarding the drug-like signaling properties of KBs in immune activity, the use of induced ketosis as metabolic strategy to target viral disease progression is receiving increasing attention. BHB have been associated with a series of molecular effects including reduced inflammation and oxidative stress, stimulation of antioxidant genes and anti-inflammatory pathways, apoptosis resistance and metabolic maintenance [45]. The immunomodulatory properties of KBs constitute a promising avenue to mitigate respiratory viral infection and help with recovery. Recent study in mice infected with influenza A virus suggest that KD feeding resulted in an expansion of γδ T cells in the lung that improved barrier functions, thereby enhancing anti-viral resistance [46]. In human, the use of ketogenic diet is currently under clinical investigation to determine whether it can halt cytokine storm in patients with SARS-COV2 [47], which will provide insights on the potential of Ketones in human immunity. It is important to highlight that most of the effects of KBs on immune response have been characterized under KD and that it is still unclear whether similar results can be obtained using Ketone supplements.

Potential barriers to mainstream adoption

While the potential of exogenous ketone on human health is considerable, large public adoption will require to overcome some challenges. Currently the poor palatability of ketone esters constitutes an important barrier for consumer and extensive work is needed to improve their organoleptic properties. The role of ketones has been heavily tied to the weight-loss components of the ketogenic diet contributing to the confusion between the effect driven by ketosis through the adoption of low carb regimen and the benefit provided purely by ketones consumed exogenously under normal diet. In addition, ketone is produced by the body and cannot be measured directly in food which constitute a major point of resistance in people mindset and consider ketone as a 4th macronutrient. The development of more advanced monitoring techniques and wearables to track ketone blood level is expected to facilitate the shift in public perception to therefore demonstrate to consumer the effect of exogenous ketone on their entire energy metabolism. As consumers will gain visibility on the continuous trends of their energy biomarkers – Glucose, BHB, Lactate – they will be able to measure how their own metabolism responds to them, to clearly evaluate the impact of exogenous ketones on their overall health.

Conclusion

Improving the characteristics of exogenous ketones could create opportunities for individual to realize the many health benefits of ketones without the challenges of adherence that come with the conventional ketogenic diet. Additional science-based evidence is still needed; we can expect more to come as our understanding of ketone biology progresses.

So far only few studies referring to the role of dietary intake of ketone supplement in interaction with substrate metabolism and muscle fuel selection have been published and further investigation is needed. Several mechanisms have been proposed on how ketone supplement can alleviate fatigue and help with recovery, including reduction in ammonia production, decrease in protein breakdown and improved post-exercise glycogen replenishment [48], [49].

Nonetheless, it is important to keep in mind that elevated circulating ketone in the presence of normal muscle glycogen, co-ingested carbohydrate and elevated insulin is not something naturally occurring in our body. While the promise offered by exogenous KBs supplementation is seducing, further research is required to precisely understand how this unique association can affect our entire metabolism. Finally, ongoing studies focusing on doses responses and formulation will shed the light on the optimal intake of ketone supplements required to mediate more targeted health benefit such as enhanced physical performance or brain health, depending on consumer needs and therapeutic objectives.

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