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ORIGINAL ARTICLE

Rethinking fat as a fuel for endurance exercise

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Abstract
A key element contributing to deteriorating exercise capacity during physically demanding sport appears to be reduced carbohydrate availability coupled with an inability to effectively utilize alternative lipid fuel sources. Paradoxically, cognitive and physical decline associated with glycogen depletion occurs in the presence of an over-abundance of fuel stored as body fat that the athlete is apparently unable to access effectively. Current fuelling tactics that emphasize high-carbohydrate intakes before and during exercise inhibit fat utilization. The most efficient approach to accelerate the body's ability to oxidize fat is to lower dietary carbohydrate intake to a level that results in nutritional ketosis (i.e., circulating ketone levels >0.5 mmol/L) while increasing fat intake for a period of several weeks. The coordinated set of metabolic adaptations that ensures proper interorgan fuel supply in the face of low-carbohydrate availability is referred to as keto-adaptation. Beyond simply providing a stable source of fuel for the brain, the major circulating ketone body, beta-hydroxybutyrate, has recently been shown to act as a signalling molecule capable of altering gene expression, eliciting complementary effects of keto-adaptation that could extend human physical and mental performance beyond current expectation. In this paper, we review these new findings and propose that the shift to fatty acids and ketones as primary fuels when dietary carbohydrate is restricted could be of benefit for some athletes.

Keywords: *Metabolism, nutrition, performance*

Historical perspective

Over evolutionary time, fat has played a major if not dominant role in supplying the human body with fuel. In times of plenty, the majority of the dietary energy of hunter/gatherers, primary hunters and nomadic herders came from fat. During lean times, the body energy reserves we rely upon to tide us over consist almost exclusively of fat. It would thus seem reasonable to expect that in the 2 million plus years of evolution since our ancestors parted company from the great apes, our greater exposure to dietary fat would have equipped us to effectively use it as our primary functional fuel. As shown in Table I, a slender human – even as low as 7–14% body fat – still has in excess of 30,000 kcal of adipose tissue reserves, an order of magnitude greater than maximum carbohydrate stores in the body.

With the advent of agriculture, humans acquired the ability to produce and store large reserves of carbohydrate, facilitating continuous consumption throughout the year. This has increasingly shifted our daily caloric intake towards a majority of energy coming from starches and sugars. For the earliest agrarian societies in Asia and the Fertile Crescent, this process began perhaps 10,000 years ago. This process of exposure and acclimation to dietary carbohydrates has been even shorter for peoples living in temperate and colder regions. Thus, the proportion of our evolutionary history available for adaptation to a high-carbohydrate diet has been at most one-half of 1% of the last 2 million years, and for many humans with recent aboriginal hunting ancestors, far less (Orr & Gilks, 1931).

Beginning a century ago, the modern science of metabolism has paid a great deal of attention to human fuel use during starvation, rest and exercise. In particular, a major goal has been to determine the

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Table I. Body energy reserves by habitus (1000 kcal)

	Thin	Normal	Obese
Carbohydrate	2	2	2
Protein	25	30	35
Fat	30–60	100	200

ideal human diet before and during exercise to optimize performance during both physical labour and sport. In 1939, Christensen and Hansen (1939) reported that athletes prescribed a high-carbohydrate diet for seven days performed better during submaximal exercise than when they ate a high-fat diet for a week. Subsequently, Bergström et al. (Bergström, Hermansen, Hultman, & Saltin, 1967; Bergström & Hultman, 1966; Bergström & Hultman 1967) demonstrated a positive association between pre-exercise muscle glycogen concentrations and subsequent submaximal exercise capacity. Furthermore, they and others observed that a brief period of carbohydrate restriction (and/or exercise-induced glycogen depletion) followed by a few days of a high-carbohydrate diet (aka, carbohydrate loading) maximized pre-exercise muscle glycogen concentrations and endurance capacity.

As a result of this work, the idea has gained credence that only a high-carbohydrate diet can optimize human exercise capacity (Noakes, 2002). Despite the important observation that none of these studies was placebo-controlled, the only placebo-controlled study of carbohydrate loading failed to show any beneficial effect (Burke et al., 2000). A recent meta-analysis has concluded that although high-carbohydrate diets appear to improve performance over high-fat diets, this may not be true in more well-trained individuals; therefore, "a conclusive endorsement of a high-carbohydrate diet based on the literature is difficult to make" (Erlenbusch, Haub, Munoz, MacConnie, & Stillwell, 2005).

In addition to this published research experience, those promoting the necessity of a high-carbohydrate diet for optimum sports performance seem to have missed the numerous empiric observations of Arctic explorers who performed prodigious feats of prolonged exercise (e.g., overland travel on foot, canoe voyages) in the virtual absence of ingested dietary carbohydrate. For example, from 1878 to 1880, Lt Frederick Schwatka travelled 3000 nautical miles on foot in the company of two Inuit families. This overland expedition from the west coast of Hudson's Bay to the Arctic coast was undertaken to determine the fate of the Royal Navy's lost "Franklin Expedition" last seen in 1845. Schwatka and his aboriginal guides started this 13-month trek with one month's provisions and then "lived off the land" for the duration. Schwatka observed in his diary (Stackpole, 1965):

> When first thrown wholly on the diet of reindeer meat, it seems inadequate to properly nourish the system, and there is an apparent weakness and inability to perform severe, exertive, fatiguing journeys. But this soon passes away in the course of two to three weeks.

This and the published observations of other explorers (Rae's Arctic Correspondence, 1953; Stefansson, 1921) indicate that well-being and perfect human function can be maintained for a year or more without ingesting appreciable dietary carbohydrate. In fact, Stefansson spent most of the calendar year of 1928 eating an Inuit diet (85% fat, 15% protein) under close observation in Bellevue Hospital in NYC without any impairment or signs of nutrition deficiency (McClellan & Dubois, 1930).

It is accepted that high-carbohydrate intake can offer advantages for athletes, but the effects are not uniform. Equally clear is the reality that many athletes are experimenting with low-carbohydrate diets and experiencing a spectrum of self-perceived benefits. This fact is verified by a growing number of competitive ultra-endurance athletes who often win races and in some cases set records after adapting to a low-carbohydrate diet. This fact is not meant to serve as proof that a low-carbohydrate diet is equal or superior to a high-carbohydrate diet, but it does provide provocative empirical evidence to pursue critical research into their metabolic, physiological and performance effects. The purpose of this brief review is to provide an alternative perspective on the role of fat for fuel and the role of dietary carbohydrate restriction as a strategy to enhance performance and recovery in athletes. Admittedly, there is a scarcity of research specifically addressing long-term ketogenic diets in athletes, so we present a historical perspective of low-carbohydrate diets, basic scientific knowledge of ketones as metabolic fuel and regulator of gene transcription, and human low-carbohydrate diet work that is relevant to athletes.

Keto-adaptation

This body of historic empiric data suggesting recovery of exercise capacity after two or more weeks on a ketogenic diet remained hidden until re-discovered in the early 1980s. At that time, stimulated by reports of unimpaired performance from patients on ketogenic weight-loss diets, Phinney et al. (Phinney, Bistrian, Evans, Gervino, & Blackburn, 1983; Phinney, Bistrian, Wolfe, & Blackburn, 1983; Phinney, Horton, Sims, Hanson, & Danforth, 1980) conducted two studies demonstrating the process of keto-adaptation. The first

of these studies used overweight, untrained subjects on a weight-loss diet, whereas the second study employed lean, highly trained athletes fed a eucaloric diet patterned after that in the original Stefansson Bellevue study (McClellan & Dubois, 1930).

The endurance capacity and metabolic responses of the cyclists in this latter study (Phinney, Bistrian, Evans, et al., 1983) are shown in Table II. In both studies (Phinney et al., 1980, Phinney, Bistrian, Evans, et al., 1983), the dietary carbohydrate totalled less than 10 grams per day, and protein intakes were about 15% of daily energy expenditure. Blood beta-hydroxybutyrate (BOHB) rose to the 1–3 mmol/L range in the first week, but endurance capacity lagged (both tested and self-reported) until 4–6 weeks of dietary carbohydrate restriction. By that time, however, the extent to which both groups had switched to fat oxidation was shown by changes in the respiratory exchange ratio (RER) values during exercise. The untrained subjects posted RER values below 0.7, indicative of both a high proportion of fat use and net ketogenesis (i.e., ketone production exceeding ketone oxidation). The cyclists mean submaximal exercise RER of 0.72 following four weeks of keto-adaptation (determined after an overnight fast) establishes that >90% of their fuel was derived from the oxidation of fat while cycling at an intensity expending 930 kcal/hr.

These astounding whole-body fat oxidation rates determined by indirect calorimetry are particularly remarkable in the context of a subsequent study by Venables, Achten, and Jeukendrup (2005), which to the best of our knowledge represents the most rigorous work to document peak rates of fat oxidation. They developed a protocol to determine peak fat oxidation rates during a graded exercise test in 300 adults ranging in fitness from the untrained and obese to highly trained athletes. Their highest reported value in any single individual was 60 grams of fat oxidized per hour (1 g/min). In contrast, among the five keto-adapted bicycle racers reported by Phinney, Bistrian, Evans, et al. (1983), the lowest value of fat oxidation was 84 g/hr (1.4 g/min) with a mean of 90 g/hr (1.5 g/min; Figure 1). Another important finding of the studies by Phinney, Bistrian, Evans, et al. (1983) was that muscle glycogen content was lowered but not totally depleted by these very low-carbohydrate diets and that the rate of glycogen use at the same power output was sharply decreased following keto-adaptation (Table II).

Table II. Endurance capacity and fuel use before and after keto-adaptation in athletes

	Baseline	Four-week ketosis
VO_2max (L/min)	5.1	5.0
Endurance @65% VO_2max (min)	147	151
Exercise RQ (VCO_2/VO_2)	0.83	0.72
Pre-exercise muscle glycogen (mmol/kg w.w.)	143	76
Post-exercise muscle glycogen (mmol/kg w.w.)	56	53
Change muscle glycogen (mmol/kg)	87	23

Source: Adapted from Phinney, Bistrian, Evans, et al. (1983).

The practical implications of the process of keto-adaptation are that the human body can adapt to use fat as its primary fuel during submaximal exercise, while at the same time freeing itself from obligate high rates of liver and muscle glycogen use. This can be appreciated by translating 90 g/hr of fat oxidation to 810 kcal/hr (56 kj/min) of fat use in the keto-adapted bicycle racers when their total exercise energy expenditure was 930 kcal/hr (65 kj/min), thus leaving only 120 kcal/hr (8.4 kj/min) required from all other substrates (e.g., glucose, glycerol, amino acids). This demonstrates the degree to which these athletes were able to release themselves from carbohydrate dependence during endurance exercise, relying upon their much more copious reserves of body fat (see Table I).

A similar finding is predicted from a simulation of the metabolic requirements of running a 2 hr 40 min marathon at the end of the Ironman Triathlon (Noakes, 2002; pp. 141–143). Since high-carbohydrate-adapted Ironman triathletes must have extremely low muscle glycogen concentrations at the start of the final 26.2 mile marathon leg, they would require a minimal fat oxidation rate of 1.15 g/min to complete the marathon in 2 hr 40 min when the carbohydrate contribution to

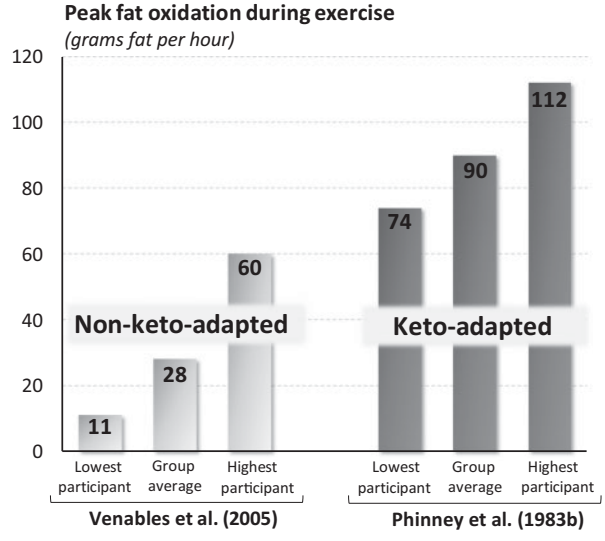

Figure 1. The rate of fat use during exercise at 64% VO_2max in trained cyclist (Phinney et al., 1983) compared to peak fat oxidation rates recorded in 300 people that included highly trained individuals (Venables et al., 2005).

energy production (from the oxidation of blood glucose and lactate) would be less than about 43%. An athlete able to oxidize fat at a rate of 1.5 g/min would be able to produce 56 kj/min from fat oxidation alone or 73% of the 76 kj/min needed to run at that pace. Provided the athlete was able to produce 1.2 g/min from liver gluconeogenesis, he or she would be able to run at that pace without requiring any external source of feeding. It remains to be determined the importance of other substrates (e.g., ketones, lactate, glycerol, amino acids, very low-density lipoprotein-triglyceride) to the fuel demands in the keto-adapted athlete, but some of these alternative fuel sources generally thought to contribute minimally to energy expenditure, may take on a proportionately greater role.

It is important to note that many studies have examined so-called "high-fat" diets and reported moderately higher levels of fat oxidation (Burke et al., 2000, 2002; Helge, Watt, Richter, Rennie, & Kiens, 2001; Lambert, Speechly, Dennis, & Noakes, 1994), but the level of carbohydrate restriction was not at a level permitting nutritional ketosis. Alternatively, the duration of adaptation was insufficient to allow keto-adaptation, thus resulting in less pronounced shifts in fuel use compared to those observed by Phinney, Bistrian, Evans, et al. (1983).

With regard to the effects of diets higher in fat, but not ketogenic diets, on exercise capacity, some studies in the past 35 years of short-term (7–14 days) adaptation to low-carbohydrate diets have shown a beneficial effect on exercise capacity (Lambert et al., 1994, 2001); others suggest a beneficial effect (Burke et al., 2000; Carey et al., 2001; Havemann, 2008; Rowlands & Hopkins, 2002) but are limited by small subject numbers; yet others found no effect (Burke et al., 2002; Helge, Wulff, & Kiens, 1998; Phinney, Bistrian, Evans, et al., 1983; Vogt et al., 2003), whereas bouts of higher intensity exercise interspersed during a 100-km laboratory time trial were negatively affected (Havemann et al., 2006). Perhaps expectedly the longest laboratory time trial yet studied (200 km lasting up to eight hours; Havemann, 2008) produced suggestive evidence for a benefit during the most difficult part of the test – a simulated mountain climb that occurred after about ~four hours cycling – but the conclusions are limited by small subject numbers. Exercise capacity during the mountain climb was improved in eight of nine subjects when eating the low-carbohydrate diet. For the overall trial, five of nine subjects improved their exercise capacity on the low-carbohydrate diet. Interestingly, subjects with low-habitual RER improved on the mountain climb by an average of 375 seconds compared to their performance when eating the high-carbohydrate diet. The author concluded that athletes with low-habitual RER may be the more likely to benefit from the low-carbohydrate dietary intervention.

Although it is difficult to make definitive conclusions from these studies due to methodological differences, especially as it relates to the composition and adherence to the diets and duration of intervention, these studies clearly provide encouragement that adaptation to a low-carbohydrate diet can produce a positive effect, especially when the diet has been maintained for an extended period, and the duration of exercise is long. There is clearly an ongoing need for appropriately designed and conducted studies of long-term low-carbohydrate diets on human physiology and performance, especially during prolonged exercise when the probability of a beneficial effect is more likely (Havemann, 2008).

Brain fuel

The other apparent benefit to exercise in the keto-adapted state is the steady supply of energy to the brain in the form of ketones. Although it is commonly stated that the brain is a glucose-dependent organ (Dietary Guidelines for Americans, 2010), elegant studies have clearly shown that ketones supply the majority of fuel for the brain when carbohydrate availability is reduced and circulating BOHB concentrations are in the 1–5 millimolar range. A brain capable of deriving the majority of its energy needs from ketones would have been an essential survival mechanism during prolonged periods of carbohydrate deprivation, and perhaps no more spectacular example of this evolutionary advantage is the experimental data showing complete protection from any signs or symptoms of profound hypoglycemia in the keto-adapted state (Cahill & Aoki, 1980; Owen et al., 1967).

Whereas prolonged intense exercise when one is dependent upon glucose/glycogen progressively depletes fuel reserves available to sustain the brain, the keto-adapted athlete may benefit from the opposite effect. As endurance exercise progresses, unlike the blood glucose concentration, the blood ketone concentration does not decline but tends to rise somewhat, ensuring a stable supply of fuels to the brain. Consistent with this improved cerebral fuel delivery, ultra-endurance athletes frequently report that mental clarity is maintained better during prolonged exercise in the keto-adapted state. This is in stark contrast to the problems of central fatigue and "hitting the wall" that commonly occur in athletes who follow a high-carbohydrate fuelling strategy and to which a progressive hypoglycemia that develops during prolonged exercise may contribute to fatigue. While ingesting carbohydrate during exercise may delay these fuel flow problems in athletes consuming high-carbohydrate diets, it does not always prevent them.

Recovery

Another reported benefit of performing high-volume training in the keto-adapted state may be reduced delayed onset muscle soreness and accelerated post-exercise recovery. Whereas it is common to take many weeks off from training after a 100-mile running event, keto-adapted athletes report that they can resume training and even competition within a week or two.

These empiric observations are interesting in contrast to the considerable literature linking "high-fat diets" with increased inflammation and oxidative stress (Djuric et al., 2001; Erhardt, Lim, Bode, & Bode, 1997). When examined carefully, however, the bulk of these studies (often performed in rodents) utilized "high-fat diets" consisting of 40–60% of energy as fat and 20–40% of energy as carbohydrate. Given these macronutrient distributions, none of these diets resulted in nutritional ketosis (i.e., serum BOHB concentrations >0.5 mmol/L) because they are too high in carbohydrates. Thus, these diets would more accurately be described as "moderate high-fat, moderate carbohydrate non-ketogenic" diets. Moreover, the link between dietary fat and inflammation is often made on the grounds that high-fat meals promote a pro-inflammatory state (Herieka & Erridge, 2014), but these studies involve ingestion of a single fat-rich meal by individuals not habitually accustomed to eating the majority of calories from fat and who are definitely not keto-adapted. Volek et al. (2009; Sharman, Gómez, Kraemer, & Volek, 2004) have repeatedly shown that keto-adaptation is associated with significantly enhanced postprandial processing of dietary fat and improved metabolic-risk markers including those relating to vascular function and flow-mediated dilation of the brachial artery.

In contrast to these moderate-fat diets and single-meal feeding studies, the bicycle racers ingesting >80% of their dietary energy as fat (Phinney, Bistrian, Evans, et al., 1983) showed no evidence of increased inflammation. In fact, after four weeks of nutritional ketosis, their total white blood cell counts declined significantly from 5.1 to 4.5 × 10^9/L. Furthermore, in studies using mild caloric restriction, Volek's group has reported significant reductions in biomarkers of inflammation in those ingesting a low-carbohydrate ketogenic diet compared to those eating a hypocaloric, high-carbohydrate, low-fat diet (Ballard et al., 2013; Forsythe et al., 2008). In addition, other studies of low-carbohydrate diets have reported reduced levels of the inflammatory marker, C-reactive protein (Ruth et al., 2013; Seshadri et al., 2004).

In all of these ketogenic diet studies, dietary fat (including the contribution of endogenous fat during hypocaloric studies) provided more than 60% of daily energy expenditure. Thus, there appears to be a discontinuity in the inflammatory response as one progresses from low-fat to moderate-fat (i.e., 40–60% of energy) to high-fat (>60% from fat). This paradox might be explained by the increasing evidence that BOHB is a potent signalling molecule acting at the gene expression level and in the regulation of mitochondrial proteins (Shimazu et al., 2013).

Non-metabolic effects of ketones

Shimazu et al. (2013) have demonstrated that BOHB levels characteristic of nutritional ketosis, whether induced by fasting or by BOHB infusion in the fed state, potently down-regulated expression of Class-I histone deacetylase (HDAC) enzymes in mice. When active, these gene-silencing enzymes turn off the body's endogenous defences against oxidative stress and inflammation. By reducing the activity of these HDAC enzymes, BOHB reduces oxidative stress, as confirmed in the experiments by Shimazu et al. which showed reduced levels of hydroxynonenal and oxylipids after exposure to carbon tetrachloride.

The other place where HDAC enzymes are known to have an important role is in the regulation of mitochondrial protein activity, roughly a third of which are regulated by acetylation/deacetylation processes (Anderson & Hirschey, 2012). It has been observed that nutritional ketosis is associated with a reduction in the generation of reactive oxygen species (ROS) by mitochondria (Sato et al., 1995). While this may be a direct result of BOHB oxidation, it could also result from an indirect effect of BOHB on mitochondrial protein functions via reduced HDAC activity.

Nutritional ketosis: a new paradigm

Nutritional ketosis may offer a range of benefits for both recreational and performance athletes working through both energetic and epigenetic mechanisms (Figure 2). The classic role of BOHB is to fuel the brain, as incontrovertibly demonstrated by Cahill and Aoki (1980), whereas muscles prefer to rely on fatty acids in the keto-adapted state, providing more consistent fuel flow during extended training or competition. The greater reliance on fatty acids and ketones and dramatically reduced dependence on glycogen and flux through glycolysis are associated with less generation of free radicals and hydrogen ions. Reduced generation of ROS during exercise will potentially translate into less tissue damage, better protection of critical membrane essential fatty acids (Forsythe et al., 2008), which correlate highly with insulin sensitivity (Borkman et al., 1993), and thus more rapid recovery. These effects are

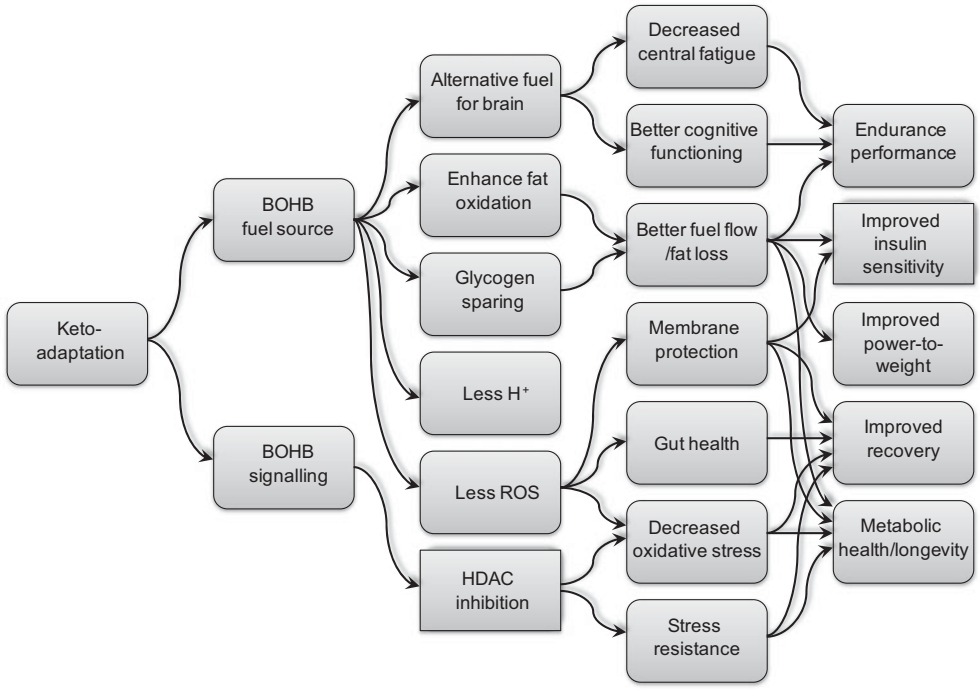

Figure 2. Theoretical paradigm by which ketogenic diets may benefit athletes. Very low-carbohydrate ketogenic diets result in elevated BOHB, which has both energetic effects affecting metabolism and epigenetic effects altering gene expression. The physiologic manifestations of nutritional ketosis may positively impact performance, recovery and health.

commonly reported by athletes who have pioneered the use of ketogenic diets in a variety of sports.

The other benefit for athletes on a well-formulated ketogenic diet is the relative ease with which excess body fat can be lost, while maintaining or even building muscle mass, thus benefitting one's power-to-weight ratio. In addition to endurance athletes, this can benefit strength and power athletes who must "make weight" or for appearance competition in which body shape is important. A ketogenic diet is highly effective at improving body composition, especially when combined with resistance training (Paoli et al., 2012; Volek, Quann, & Forsythe, 2010), while preserving strength and power performance in the keto-adapted state. Low-carbohydrate diets have also been employed by ageing athletes for whom progressive insulin resistance with increasing weight and oxidative stress threaten to become career-ending consequences.

While there are many recent individual examples of athletes who have made effective use of low-carbohydrate or ketogenic diets, the sport where this dietary paradigm shift is becoming dominant is in ultra-marathon running. In addition to the near certainty of bonking/hitting the wall unless copious amounts of carbohydrates are ingested, ultra-runners commonly experience a range of additional problems such as mental confusion and gastrointestinal distress. Gastric erosions have been documented by endoscopy in humans after a marathon (Oktedalen, Lunde, Opstad, Aabakken, & Kvernebo, 1992), and frank gastrointestinal bleeding is common in sled dogs running events like the Iditarod.

Ultra-runners who have previously experienced gastrointestinal distress with a high-carbohydrate diet commonly report dramatic improvement when competing after keto-adaptation (Volek & Phinney, 2012). Perhaps this is simply due to less need to consume calories during the event. Common lore dictates consuming about 6000 kcal of carbohydrates during a competitive 100-mile race, but low-carbohydrate runners commonly finish (and often now win) these events on 1500 or less "in-race" calories. However, the improved recovery following such events implies less tissue damage, and this may be why the gastrointestinal tract is less affected in low-carbohydrate runners (i.e., less ROS means less membrane damage which leads to better mucosal cytoprotection during and after the event).

In conclusion, after a period of 3–4 weeks with total daily carbohydrates at a level that induces nutritional ketosis, the human body adapts to be able to use almost all fat for its fuel. In athletes, we posit that this may facilitate extended performance without the need for the frequent ingestion of carbohydrate-based fuels during exercise. In addition to these direct fuelling benefits in the keto-adapted athlete, BOHB is associated with reduced oxidative stress and inflammation, and its signalling

mirrors many of the pathways associated with stress resistance and longevity (Newman & Verdin, 2014).

In stark contrast to long-standing dogma (Erlenbusch et al., 2005) in sports nutrition emphasizing the essential need for dietary carbohydrate in all forms of exercise regardless of duration or intensity, these observations have brought us to a threshold beyond which exercise capacity may be improved by those who reduce their dependence on dietary sugars and starches before and during especially prolonged exercise. There is a need to better understand the level of carbohydrate restriction (and the overall composition of the diet) necessary to elicit these effects, as well as the factors contributing to inter-individual variability in responses to these diets.

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