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KETOGENIC DIETS AND EXERCISE PERFORMANCE: A PERFECT MATCH?

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Abstract

Every athlete health depends both on good food and on the ability to improve endurance performance optimizing training, nutrition and recovery.

Nutritional strategies are crucial to support athletes to perform at the highest level, and several strategies have been considered to maximize fat metabolism, due to limited muscle and hepatic glycogen stores. Among these, the ketogenic diet has been proposed as a possible method for providing energy during prolonged periods of exercise.

Recent scientific evidence highlights the Ketogenic diet (KD), a low-. Carbohydrate, high-fat diet creates the state of ketosis- the raised level of ketone bodies, from which the diet gets its name, and it represents a promising strategy to treat obesity, diabetes and cardiac dysfunction. In addition, studies support ketone body supplements as a potential method to induce ketosis and supply sustainable fuel sources to promote exercise performance.

An overview of the metabolism of ketone bodies is provided in this narrative review, emphasizing the importance of effective and safe ketogenic protocols as a weight loss therapy or as an ergogenic aid. Additionally, we looked at recent evidence indicating that the body's ketone metabolism is a potential target for cardiac dysfunction.

Keywords: *ketosis; endurance performance; ketone supplements; obesity; ketone bodies; metabolism.*

Introduction

Within the athletic community both amateur and professional athletes are looking for innovative strategies and/or techniques to improve their performance.

Nutritional intervention and supplementation remain popular strategies for the reduction of body weight and/or for the enhancement of exercise performance. Recently, the ketogenic diet (KD), used for certain health conditions, has emerged as a celebrated and successful dietary plan for the treatment of obesity, diabetes [1] and for the cardiovascular disease (CVD). It has been used for weight and body composition management in addition to the "keto" supplements. [2,3]

The use of the KD as a performance-enhancing substance is still a subject of debate.

High volume of training requires an adequate caloric intake that may be difficult to obtain with high carbohydrate diet and it may detrimental for increasing fat oxidation considering the hyperinsulinism induced by high intake of carbohydrates.

KD may represent a good option to support high energetic demand and, at the same time, to maximize fat oxidation. The ability of KD to support low-medium intensity efforts in ultra-endurance events without stressful carbohydrate-loading prior the event and exogenous carbohydrates supplementation during the event also may be helpful to avoid gastrointestinal upset and logistic problems.

In some specific cases and sports, KD may be used to facilitate weight loss in a short period of time without affecting performance.

KDs are low-carbohydrate, high fat, moderate protein diets that typically supply approximately 80% of calories from fat, 15% calories from protein, and 5% calories from carbohydrates [4,5].

For almost 100 years, the diet has been used for the treatment of epilepsy, but has been reintroduced to the public over last few years.

In theory, the high fat content combined with the low carbohydrate intake is purported to stimulate fat oxidation and promote fat loss.

The consumption of KD induces a physiological metabolic state that causes an increase in serum ketone bodies inducing a state known as "ketosis" in which the cellular oxidation of ketone bodies is enhanced [8]. Recent evidence suggests that following the metabolism of ketone bodies there is a metabolic advantage in the weak heart and an ergogenic aid for physical performance [2,3,9-11].

These and other studies have stimulated interest in the potential health and performance enhancing benefits of KDs.

The simple way of finding KD in the mainstream and on social media, combined with the presence of "keto" supplements available for purchase, makes dieting and supplements the most fascinating for weight loss and athletic performance enhancement. However, the medical community does not approve, due to the potentially negative side effects inherent in consuming an extremely high-fat, low-carbohydrate diet. Furthermore, the few prominent inconsistencies in the research literature offer little support from the scientific community. Here we will describe the metabolism of the ketone body, define KD, and summarize the available literature on the potential benefits of KDs and keto supplements for physical performance.

Overview of Ketone Body Metabolism

Ketosis, that is not to be confused with ketoacidosis, is a metabolic state associated with ketogenic diet and it is considered as a physiological condition in which a remarkable serum and urine concentration of ketone bodies, called acetone, acetoacetate and beta-hydroxybutyrate are combined. Ketoacidosis instead is a pathological condition with elevated serum ketone levels (3.8–25 mM) and decreased arterial pH values (7.30 to 7.20) that may be seen in diabetics. [31–33]. Ketone bodies are normally present in the circulation, although serum concentrations are generally low under baseline conditions, typically 0.1 to 0.4 mM in humans and rodents. The concentration of the ketone body is elevated during periods of nutrient deficiency or low carbohydrate availability, such as fasting / starvation [14], exercise [15] or diabetes [16,17], which include both physiological and pathological. In humans, serum body ketone levels are 1–4 mM after a short fast (2–

3 days) and rise to 7–9 mM with prolonged fasting (17–24 days) [5,18]. Following exercise, humans can reach serum body ketone concentrations of 1–2 mM [19,20]. With a low-carb or KD diet, serum ketone levels in the body can rise above 5 mM [19]. The data in mice show values of serum ketone bodies comparable to those of humans: 0.2–0.4 mM (baseline); 0.6–0.8 mM (6 hours of fasting); > 3.0 mM (prolonged fasting); 0.8-1.2 mM (post-exercise); ~ 1.0 mM (KD) [14,15,21–23].

Ketone bodies are short-chained, four-carbon molecules synthesized in liver mitochondria through a process called "ketogenesis." The ketogenic process (Figure 1A) requires acetyl-CoA, generated via the beta-oxidation of fatty acids, and continues with the aid of several enzymes, including mitochondrial acetyl-CoA acetyltransferase 1 (also known as thiolase), 3-hydroxy-3-methylglutaryl-CoA synthase (HMGCS2), HMGC-CoA lyase, and mitochondrial beta-hydroxybutyrate dehydrogenase (BDH1).

This process ultimately results in the production of the primary ketone bodies released into the bloodstream: acetoacetate (AcAc) or β-hydroxybutyrate (βOHB). The ketone body with the highest concentration within the blood is βOHB; therefore, the breakdown or "ketolysis" pathway generally begins with βOHB (Figure 1B). Once in the circulation, β-OHB may enter the heart or skeletal muscle cell via monocarboxylate transporters, MCT1 and MCT2 [24]; however, β-OHB is a short-chain fatty acid, and simple diffusion can occur. βOHB is rapidly oxidized to AcAc via BDH1 and converted to acetyl CoA via succinyl-CoA: 3-oxoacid-CoA transferase (SCOT) and thiolase, for entry into the tricarboxylic acid (TCA) cycle.

Ketone bodies are suggested to be a more energy efficient substrate than glucose or fatty acids [5,25].

But there are different ways of interpreting energy efficiency. When considering the efficiency of ATP production, fatty acids produce ~ 6.7 ATP per carbon atom, compared to ~ 5.2 for glucose and ~ 5.4 for ketone bodies [26,27]. while if we consider the energy efficiency based on the yield of ATP per oxygen atom (i.e., P / O ratio). The P / O ratio for fatty acids is ~ 2.33, while glucose is 2.58 and ketone bodies is 2.50[26,27].

For some researchers, cardiac (or muscle) efficiency is a critical measure, which determines the ratio of mechanical work to oxygen consumed. Determination of these values requires complex experimental designs and data collection techniques, which are commonly performed in isolated, perfused heart preparations. In addition, the intricate interactions of certain biochemical pathways may lead to increased energetic costs and/or losses, particularly for fatty acids [5]. Compared to glucose alone, ketone bodies combined with glucose have been shown to cause greater cardiac efficiency [28,29].

Although ketone bodies have been shown to increase energy production, particularly in hypertrophic hearts, a significant improvement in cardiac efficiency has not been achieved [30]. It is unclear whether a significant alteration in the efficiency of the heart or skeletal muscle, diseased or healthy, the dispositions of ketone bodies, glucose and / or fatty acids is conducted.

Ketogenic Diets and Exercise Performance. Overview of Metabolism During Exercise

Ketogenic Diets can be surely considered as a non-pharmacological treatment strategy especially when it's required a rapid weight loss.

Actively-contracting muscles receive the contributions of three major energy pathways, which are influenced by the time and intensity of the exercise [34]. The phosphocreatine (PCr) to ATP reaction, regulated by creatine kinase (e.g., the phosphagen system), is essential in resynthesizing ATP during immediate, high intensity work and is a dominant system during the initial seconds of exercise.

In moderate to high-intensity exercise sessions, lasting up to ~90 s, the short-term lactic acid system is a major contributor. During this interval, ATP resynthesis is primarily met by glycogen-dependent glycolysis [35].

In moderately intense, long-duration exercise, the long-term aerobic system supplies metabolic substrates to support oxidative metabolism. Oxygen demands and oxygen uptake determine response to exercise.

During the initial moments of exercise, a large increase in oxygen uptake is required to match the energetic demands of the contracting muscle cells. However, a mismatch between the metabolic demands and oxygen uptake exists for several seconds to several minutes, called the "oxygen deficit" [36].

During the oxygen deficit, the phosphagen system and lactic acid system are the major supporters of ATP resynthesis. Once oxygen uptake and oxygen demand are in balance, oxidative phosphorylation via the aerobic system becomes the dominant pathway to maintain ATP regeneration.

Once steady-state aerobic metabolism is reached, a steady supply of exogenous substrates are needed to maintain exercise. As shown in Figure 2, these exogenous substrates are supplied by the liver and adipose tissue. During aerobic exercise, the liver has the primary role of maintaining blood glucose levels via glycogenolysis, and to a smaller degree, gluconeogenesis. In addition, the liver can produce ketone bodies from elevated serum concentrations of fatty acids. A sustained rise in serum fatty acids occurs due to the lipolysis of adipose tissue, activated by beta-adrenergic stimulation [37].

Through the union of the efforts of the liver and adipose tissue, with a sufficient supply of substrates (glucose, ketone bodies and fatty acids) it conditions the contraction of cardiac and skeletal muscle. Cardiac muscle demonstrates greater ability to utilize lactate produced by skeletal muscle during higher workloads [38].

The Effects on Aerobic Endurance Exercise

The contribution of fatty acids to oxidative metabolism varies with exercise intensity and duration [39]. During low-to-moderate intensity exercise, the oxidation of exogenous fatty acids is a significant source of energy. During exercise of a moderate intensity, the contribution of fatty acids to oxidative metabolism increases, as the duration of the exercise bout is prolonged. In that regard, strategies that promote the availability of fatty acids may be critical to optimizing endurance exercise performance.

The use of fats rather than carbohydrates as an energy base can be especially advantageous for aerobic endurance exercise, thus making KD more beneficial. The elevated ketone bodies, resulting from KD, can provide an alternative or supplemental fuel source to support endurance exercise, in fact fat from adipose tissue is considered a constant supply of energy, while glycogen stores in skeletal muscle and liver are limited.

Numerous studies have examined the effect of low carbohydrate (LC) or KD (LC / KD) diets on endurance exercise performance in humans [20,40–49]. Most of them are focused on Hellenistic and male resistance individuals. The percentage of average calorie intake from fat in the diets used in the studies ranged from 63-80%, carbohydrates 3.5–15% and protein 15–29%. Treatment times varied from as little as 3 weeks [40,46] up to 20 months [20].

There is reportedly no correlation between fat composition or treatment time of diets with increasing serum concentrations of body ketones (mainly βOHB) from 0.5 mM to 1.2 mM. Most of these studies reported significant reductions in body weight or fat mass [40,44-47,49] demonstrating that LC / KD diets appear to be an effective dietary strategy for inducing weight loss and improving body composition. in trained athletes.

However, despite the improvement in body mass, LC/KD diets are not effective in producing significant improvements in physical performance, despite the significant decrease in the respiratory exchange ratio (RER), which represents an increase in fatty acid oxidation (FAO). LC/KD did not significantly alter total time to exhaustion (TTE) [42,47], maximal oxygen uptake (VO2max) [41–44,47,49], or endurance cycling performance [45]. In contrast, the consumption of a LC/KD for 3 weeks, combined with exercise training, impaired the training adaptations of elite race walkers by elevating oxygen consumption rates during activity [40]. In 30-year-old endurance trained males fed a LC/KD for 1 month, TTE was reduced at 70% intensity, despite no change at 60% intensity [47]. Two studies that included a population of women presented interesting results [43,49]. In a small study of 90% female endurance athletes, the TTE was significantly decreased after 10 weeks of LC / KD [49].

Likewise, females from a cross-fit cohort who did recreational training, fed LC / KD, experienced a non-significant 5% decrease in VO2max, while males were unexpected from the diet. [43]. These studies clearly show that LC/KD in trained individuals offers no enhancement in exercise performance, and may lead to decreased performance, particularly in females.

Studies on the effects of LC / KD on physical performance in overweight / obese individuals are few and have revealed variable results [50-53]. An initial study suggested that individuals, mostly women, moderately obese following a reduced-carbohydrate (CHO) diet (45% calories) lost significant body weight and fat mass and improved endurance times during a moderate exercise intensity [52]. Although obese females consuming a diet of 33% CHO combined with exercise training experienced 20% greater weight loss, the improvement in TTE was similar to high CHO diet [52].

A LC/KD for middle-aged, obese adults for 52 weeks led to a greater decrease in body weight and fat mass, compared to a low calorie or mixed diet, but did not result in improved exercise performance [54].

In overweight/obese adults, a LC/KD diet led to significant weight loss only in males, with no significant change in TTE or VO2max in males or females compared to a low fat diet [50]. However, a 2-week LC/KD diet in overweight adults did not lead to weight loss, but increased fatigue and perceived effort [53]. It should be noted that the keto-adaptation period is suggested to be 2–4 weeks [55], so results of very short dietary interventions should be interpreted with caution. Although LC/KDs appear effective in the management of body weight and fat mass in overweight and obese individuals, the effects on exercise performance remain unclear and may depend on the degree of carbohydrate restriction and length of the dietary intervention.

Studies in rodents fed a LC/KD diet may provide some additional mechanistic insight into the effects of the LC/KD on exercise performance, particularly since the diet can be well controlled and the capability of performing bio-molecular measures is not limited. The composition of the LC/KD fed to rodents typically ranges from 70–78% fat with 1–5% CHO and 9–20% protein [56–60]. In C57BL6/J male mice, 8 weeks of KD improved exercise treadmill times and molecular markers of recovery [57,58]. However, 4 weeks of KD administered to female C57BL6 mice reduced aerobic capacity [60]. While in Sprague Dawley rats, voluntary running distance was no different during the 6 weeks of KD [56]; however, run-to-exhaustion time on a treadmill improved after 1 to 5 weeks of KD [59], compared to controls fed a food-only diet. Some negative side effects have been shown, in addition to variable ratios in physical performance, increase in adipose tissue mass [58,60], and decrease in muscle glycogen content [59], increased serum triglycerides [60], and decreased cardiac function [60], were noted. However, KDs may decrease mortality [61,62], improve memory [61], and increase muscle citrate synthase [62] in aged mice. Perhaps additional studies in animal models are necessary to help derive definitive conclusions.

Its Effects on Anaerobic Exercise

Anaerobic exercise is a high intensity, low duration exercise that lasts less than 2 min.

Energy demands are met by the phosphagen system and lactic acid system, which are highly dependent upon skeletal muscle glycogen. During anaerobic exercise, high contractile forces occur within the muscle, and muscle fibers become damaged. In addition to the replenishment of carbohydrates during the recovery period, adequate consumption of essential amino acids is important to support the protein synthesis necessary to repair and rebuild the muscle. In this regard, LC/KDs typically provide sufficient protein intake (~15% of daily calories) to avoid amino acid deficiency. However, aerobic performance can be adversely affected due to a greater dependence of amino acids on gluconeogenesis and impaired glycogen storage due to low carbohydrate intake.

Some studies in the literature showed the effects of LC/KDs (from 6 weeks up to 12 weeks) on anaerobic performance, in endurances athletes [45], Cross-Fit participants [63,64], gymnasts [65], and powerlifters [66]. In general, consumption of the

LC/KD did not result in strength [44,44–66] or power [63,64] measures that were.
One study reported a significant increase in relative power, but not absolute power, which was due to the decreased body weight experienced by the subjects [45]. In some studies, significant decreases in skeletal muscle thickness [44] or lean body mass [63] were noted. Moreover, muscle hypertrophy from resistance training may be blunted with the LC/KD [67]. These studies showed that the LC / KD diet has the potential to nullify the expected gains in lean mass during anaerobic workouts and is not an effective strategy for increasing anaerobic performance in trained individuals or athletes.

Ketone Body Supplementation

As LC/KDs require high fat consumption and present difficulty with long-term adherence, alternative methods for targeting ketosis as a potential intervention for weight loss or as an ergogenic aid are required. In support of these, several studies examined the benefits of ketone body supplements on exercise performance [2,68–72]. Ketone body supplements are commercially available and commonly present in the form of ketone salts (KS) or ketone esters (KE). Additionally, medium chain triglycerides (MCT) are sometimes used to induce ketosis [69] or are combined with KS to maximize the ketogenic response [73].

There are some potential problems with the consumption of KS, and the KS formulation may include βOHB or 1,3-butanedenol (BD), bound to sodium, potassium or calcium. First, βOHB in the salt form could include both D and L enantiomers of βOHB. Since D-βOHB is the biologically active form, approximately 50% of elevated serum βOHB levels are due to the presence of the non-metabolizable L-βOHB that must be excreted via the urinary system [74]. As such, KS appears less effective at elevating serum βOHB comparatively [73,74]. Second, BD is a compound that must be converted to βOHB in the liver via dehydrogenase enzymes [75], which may result in delays in increased serum βOHB concentration [73]. Finally, the increased consumption of mineral salts, particularly sodium, may adversely affect blood pressure.

In the last few years, most research studies utilized KE, which appears to be the most effective method to cause immediate and sustained increases in serum ketone bodies. There are several formulations of KE supplements, but the most identifiable is the (R)-3-hydroxybutyl (R)-3-hydroxybutyrate ketone monoester, which converts to in D-βOHB and BD upon ingestion [76]. This particular KE, when taken in combination with CHO, results in a 2% increase in exercise performance in trained cyclists [2].
However, not all KE supplements increase exercise performance [70–72], calling into question whether the precise formulation of the KE is essential or whether an additional substrate like CHO is required.
Of note, the available studies focused on exercise performance in trained endurance athletes, so whether supplementation in recreational athletes or fitness enthusiasts is appropriate is not known.

Conclusions

The literature supports LC / KD for endurance athletes as an effective strategy for reducing body weight and fat mass, particularly over the 3-12 week period. Few studies show significant improvement in exercise performance at submaximal intensities (~ 60%), but physical performance at higher intensities may be impaired. Short-term consumption of LC / KD for athletes interested in power and anaerobic strength does not adversely affect, but it can lead to reductions in lean body mass or hypertrophy of blunt skeletal muscles.

Therefore, the literature does not support the use of LC/KD as an effective dietary strategy to increase athletic performance.

Ketone body supplements, including KS and KE, are readily available commercially. But all supplements are not rated or approved by the Food and Drug Administration (FDA), consumers need to pay close attention to the components.

KS supplements are found to be less effective than KE supplements in inducing ketosis; Some studies show that there are improvements in the physical performance of trained athletes.

Furthermore, the benefits of KE supplementation in non-athletes are unknown.

Recent research findings provide support for targeting the body's ketone metabolism for physical performance, but more research is needed before implementing dietary interventions or supplements.

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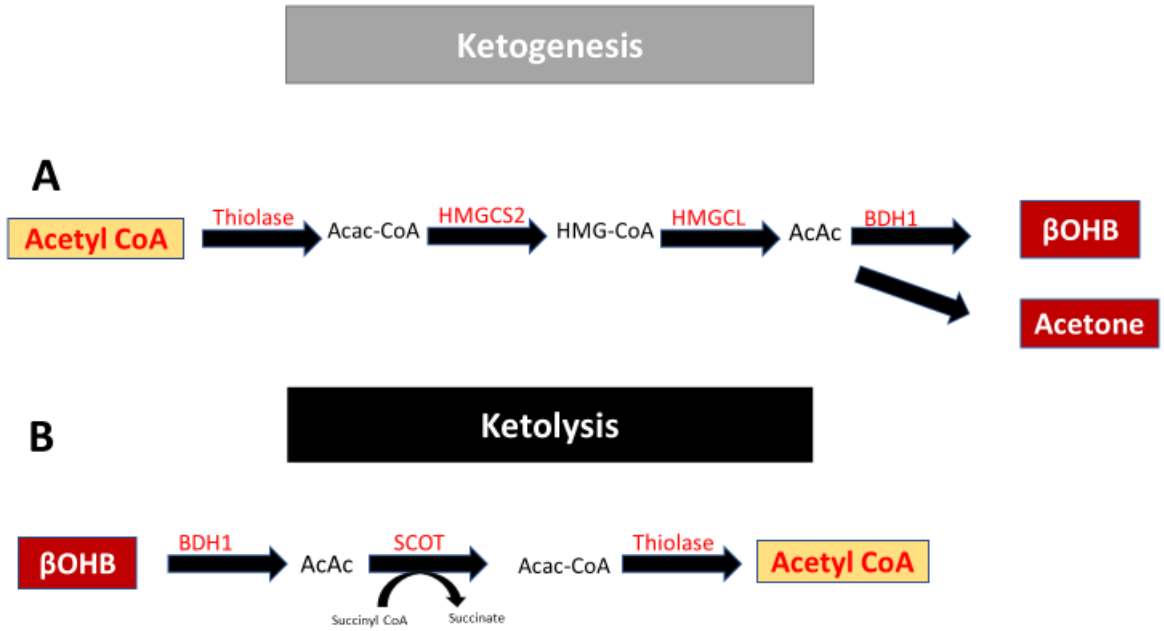

Figure 1. The formation (**A**) and breakdown (**B**) of ketone bodies

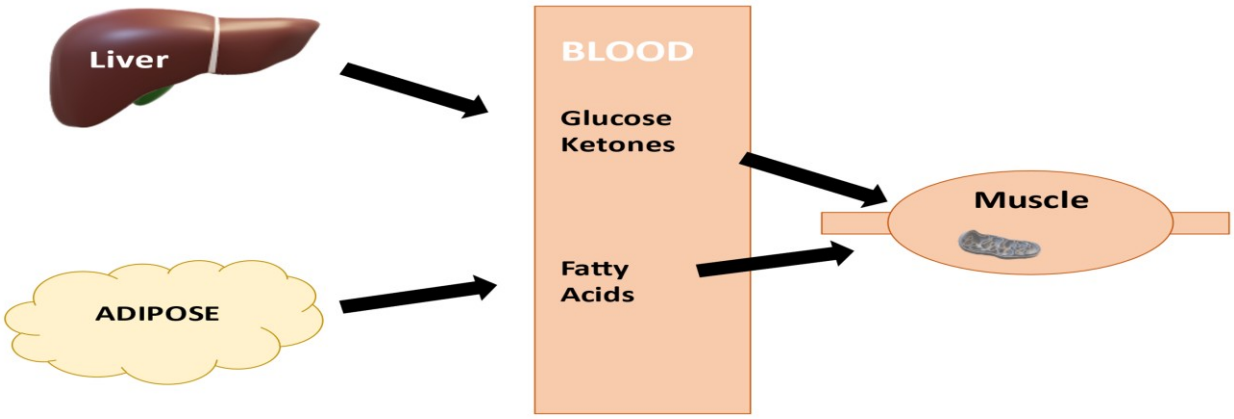

Figure 2. The exogenous supply of substrates during exercise: the liver provides glucose and ketone bodies via gluconeogenesis and ketogenesis, respectively the adipose tissue lipolysis maintains serum fatty acid concentrations.