The role of the ketogenic diet in exercise performance

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Abstract. Muscle glycogen storage and degradation are nearly universally accepted as crucial metabolic processes for ensuring adequate intramuscular energy levels during prolonged, high-intensity activity. However, a growing body of data illustrates that alternative substrates, such as ketone bodies, may be equally as effective in transducing energy during exercise. Ketosis, wherein ketones serve as the primary oxidative fuel, can be achieved nutritionally through a low-carbohydrate, high-fat ketogenic diet (KD). Though the KD is unequivocally successful in facilitating weight-loss with minimal sacrifice to lean mass, current research indicates a complex role for the KD in both anaerobic and aerobic exercise performance. This review discusses: 1) the mechanisms behind KD adaptation, and the effect of KD adaptation on 2) glycogen metabolism, 3) aerobic exercise performance and 4) anaerobic exercise performance.

Key words: low-carbohydrate, high-fat, metabolism, athlete.

Introduction
Use of a low-carbohydrate, high-fat ketogenic diet (KD) is widely recognized as an efficacious therapy for a range of metabolic and neurodegenerative diseases and cancers (1-7). Clinical use of the KD has gained popularity as its effects often mirror those reached pharmacologically yet are attained with little off-target risk. However, interest in the KD extends beyond the clinical landscape as mounting evidence suggests that the KD may also influence exercise performance and adaptation. Though its precise role within exercise training and performance remains elusive, the notion that the KD might enhance exercise performance remains contentious, as it challenges traditional, carbohydrate (CHO)-centric guidelines for exercise and sport nutrition. Though past reviews have cohesively and comprehensively summarized ketone biochemistry and its clinical role, this paper aims at unifying current findings most directly implicated in exercise performance including: 1) the cellular mechanisms of KD adaptation as well as (2) the effects of KD on glycogen metabolism, 3) aerobic exercise and 4) anaerobic exercise (8-12).

Due to its storage abundance, intracellular location and rapid energy provision, muscle glycogen has long been held as the most important energy substrate during prolonged, high intensity exercise. This belief has resulted in the decades-long practice of CHO loading prior to competition among endurance athletes looking to achieve supra-maximal glycogen levels (13). The high fat and low CHO nutrient apportionment of the KD conflicts with conventional, CHO-centered sports nutrition guidelines, which recommend up to 12 grams/kilogram body weight for those engaged in high intensity endurance programs (14). Depending on the goal of the individual, the KD may be hypocaloric, eucaloric or hypercaloric and is typically comprised of a 3:1 to 4:1 energy ratio of fat to protein and CHO; though CHO restrictive diets with lower ratios of fat to protein can also be ketogenic (2, 15).

The biochemical underpinning of the KD is hepatic synthesis of ketone bodies, Acetoacetate (AcAc) and H-β-hydroxybutyrate (βHB). Hepatic ketogenesis, upregulated as a consequence of limited carbohydrate supply and abundant fatty acid availability, converts acetyl CoA’s, generated at rates prohibiting tri-carboxylic acid cycle entry, to AcAc and βHB (16). Both AcAc and βHB are transported via systemic circulation to extrahepatic tissues, where they are oxidized as needed (16, 17). In healthy fed adult humans, ketone oxidation represents only a minor fraction of total body energy expenditure, however, its contribution to energy metabolism in the heart, brain and muscle significantly increases in many physiological and pathological states including the neonatal period, fasting, starvation, repressed insulin production, insulin resistance prolonged exercise and low-carbohydrate diets (2, 11, 12, 17-19).
In fact, ketones -mainly βHB- supply up to 70% of the energy used by the brain during starvation with the remainder provided by endogenously derived glucose (17). Traditionally, in the before mentioned conditions, ketosis is seen as a metabolic means of holding serve until an adequate supply of blood glucose is available.

Mechanisms of KD Adaptation
Understanding the mechanisms by which the body responds to the considerable shifts in macronutrient consumption and subsequent fuel utilization is crucial, as adaptation to a KD must be attained in order to normalize or improve performance. Dietary fat, ingested in substantial quantities to induce a state of ketosis, becomes the primary oxidative fuel by mass action. Subsequently, active tissues undergo a two-fold response to accommodate elevated fatty acid flux: increased mitochondrial β-oxidation and reduced glucose oxidation. Ample support for this tissue-level response has been provided, however, it is imperative to understand the cellular mechanisms responsible for this metabolic shift. Heightened β-oxidation is accomplished through an adaptive cellular response observed in studies of both animals and trained cyclists wherein prolonged KD (>1 week) amplified the activity of skeletal muscle carnitine acyltransferase (CAT) and hydroxyacyl-coenzyme A dehydrogenase (3-HAD) relative to the activity of citrate synthase (CS) (20-24). Analogous gene expression data has revealed a pointed prioritization of fat oxidation over its storage as upregulation of CD36, butyrate dehydrogenase (HBDH) and mitochondrial uncoupling protein-2 (UCP-2) was concomitant to reduced expression of fatty acid synthase (FAS) in the livers of KD-adapted mice (25). Similar studies of high-fat diet adaptation provide evidence of depressed glucose oxidation associated with reductions in pyruvate dehydrogenase activity and both insulin and exercise stimulated muscle glucose transport (26, 27). Provided that endurance training boosts capacity for fat oxidation, these tissue and cell-level adaptations suggest that the KD might catalyze physiological responsiveness to an endurance exercise program (28).

KD Adaptation and Glycogen Utilization
Significant evidence links adaptation to the KD to altered muscle glycogen metabolism. Short term (3-14 days) KD has been reported to decrease baseline liver and muscle glycogen levels in rats and trained cyclists (20, 29, 30). However, in a study of moderately obese subjects following six weeks of a KD, resting muscle glycogen content was 57% of baseline after week 1 but increased to 69% of baseline values after week 6 (31) Newer findings demonstrate that ultra-endurance runners fully habituated to the KD (>20 months) experience similar baseline and post-exercise muscle glycogen levels compared to controls on a mixed-diet (32). These studies indicate that initial depletion of muscle glycogen induced by the KD may be at least partially reversed through habituation to the diet. Moreover, normal post-exercise glycogen repletion in KD-adapted individuals may be attained by increased lactate-mediated hepatic glucose production i.e. gluconeogenesis, and muscle glycogen synthase activity, especially in type II fibers (26, 33-35). Additionally, KD-adaptation has been shown to preserve liver and muscle glycogen during exercise; KD-adapted rats and trained humans have been shown to exhibit reduced exercising muscle and liver glycogen degradation rates without sacrifice to endurance performance (20-22, 29, 35, 36). These evidence, though somewhat indirect, suggest that chronic reliance on fat as a primary fuel increases its inherent rate of oxidation, an especially useful adaptation that reduces muscle glycogen degradation while maintaining cell energy levels during exercise (36).

Ketogenic Diet in Practice
Ketogenic Diet and Weight Management
Perhaps the most understood and implemented application of the KD is within bariatric medicine, as obese individuals undertaking a hypocaloric KD experience a significant reduction in weight that is vastly attributed to fat loss with minimal loss in muscle mass (18, 37-39). Less studied, yet perhaps equally intriguing, is apparently even a eucaloric KD may promote fat loss and lean mass preservation in both obese and healthy weight individuals (15, 40, 41). Most recently, investigators reported that obese and overweight individuals following either an eight-week resistance training (RT) with a eucaloric, carbohydrate restrictive diet (<30grams/day) or RT with a conventional, hypocaloric diet saw equal improvements in fat composition and strength (42). Driving these KD-induced anthropometric adaptations is increased sensitivity to both insulin and thyroid hormone, which helps to limit rates of skeletal muscle catabolism during periods of weight-loss (15, 43).
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These findings lend intriguing sports nutrition research opportunities for weight-category athletes who must reduce body mass while retaining muscle mass during competition preparation (43). The KD could represent a healthier nutritional strategy for these athletes compared to commonplace rapid weight loss practices such as severe caloric and hydration restriction and induction of hyperthermia.

**Ketogenic Diet and Aerobic Exercise**

The manner in which KD affects aerobic performance appears to be determined by three factors: exercise intensity, training status and length of diet habitation. Bergstrom et. al., 1967, (12) illustrated that three days of a KD was enough to compromise submaximal endurance (75% $\text{VO}_2\text{max}$) in healthy, untrained individuals. Similarly, a six-week high fat diet (HFD) significantly reduced work output in untrained subjects during a 45-minute bicycle test. The authors attributed this finding to an increased proportion of fat oxidation observed through decreased exercising respiratory exchange ratio (RER) (40). However, the purported sacrifice to high intensity exercise performance may represent a tradeoff for increased fatigue resistance. Indeed, moderately obese subjects adhering to a six-week KD exhibited reduced exercise intensity but greater stamina during a treadmill exercise test to subjective exhaustion (31). These studies suggest that enhanced fat oxidation may not be energetically compatible with high intensity exercise but it may augment long duration exercise. Interestingly, aerobic performance in KD-adapted endurance athletes appears to be less susceptible to shifts in energy substrate utilization. Initial studies in trained cyclists revealed that 4-weeks of a KD did not affect moderate intensity (~65%$\text{VO}_2\text{max}$) endurance exercise performance; apparently, enhanced exercising fat oxidation rates, observed through lower RER, were able to compensate for reductions in steady state glucose oxidation rates (36). More recently, elite ultra-endurance runners habituated (>20 months) to a low-carbohydrate diet (LC) displayed significantly greater rates of fat oxidation and lower rates of carbohydrate oxidation during a 180-minute run at 64% of $\text{VO}_2\text{max}$. Peak fat oxidation rates were also significantly greater in the LC group and were reached at a higher percentage of $\text{VO}_2\text{max}$ compared to controls (32). Furthermore, following just two-weeks of a high fat diet (~70% fat), trained cyclists experienced lower RER values and enhanced endurance during moderate intensity (60% $\text{VO}_2\text{max}$) exercise (29). More notably, HFD did not impair performance during a high-intensity (85% $\text{VO}_2\text{max}$) time to exhaustion test. Likewise, 6-15 days of HFD enhanced fat oxidation and decreased CHO oxidation rates in trained cyclists while either not affecting or even improving performance during 20-100 kilometer cycling time trials (22, 35, 44). However, Zajac and colleagues (20) provide new insights revealing that competitive off-road cyclists undergoing 4 weeks of a KD experienced reduced exercising RER concomitant to diminished maximal workload and workload at lactate threshold (45). Collectively, current findings surrounding the KD and aerobic exercise performance, though inconclusive, highlight the need for further examination of how training status impacts adaptation to the KD and resultant performance. Moreover, if the KD does not impair higher intensity aerobic intensity exercise performance (<80% $\text{VO}_2\text{max}$), future evidence needs to support both morphological and functional changes in mitochondria that would allow the cell to meet the increased rate of ATP demand requisite during high intensity aerobic exercise.

**Ketogenic Diet and Anaerobic Exercise**

The existing pool of knowledge vis-à-vis the KD and anaerobic performance is scarce. In fact, equivocal results from a mere six studies and one abstract currently encompass the subject. Four studies report that the KD negatively impacts anaerobic performance. Of these, one study utilized recreationally trained subjects and found that KD significantly reduced isotonic strength as measured by a three-set squat repetition total at 80% 1RM (46). Two other studies utilized cycle ergometer to measure anaerobic power output in healthy non-highly trained subjects but their results differed slightly. While one found that KD limited both mean and peak power, the other noted only a decrement in mean power (30, 40). In the former study, the authors noted that the reduction in mean power was mitigated when corrected for a loss in body mass in the KD group. These findings corroborate additional findings in which well-trained cyclists subjected to 6-days of HFD followed by 1-day of CHO loading exhibited reduced exercising fat oxidation rates and impaired high intensity cycle sprint performance (44). Still, three other studies provide evidence supporting the use of the KD in conjunction with strength and power training; the most compelling of which showed that elite female gymnasts following a KD during normal training did not exhibit impairments in muscular strength, endurance or power (41). Significantly,
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this was the only investigation of athletes. Likewise, a pilot study found that KD did not deter gains in either strength or anaerobic power in response to an 8-week periodized resistance-training regimen (47). One other study highlighted the clinical utility of the KD in showing that overweight women lost body fat while maintaining lean body mass when combining a KD with resistance training (48-50). Worth noting, two of the aforementioned studies that approximated glycolytic flux while evaluating the effect of KD on anaerobic power and muscular strength generated similar results. Both studies reported depressed blood lactate levels in subjects adhering to a KD immediately following 30-second supra-maximal intensity cycling attempt and 3 sets of squats (30, 51). The authors of each study speculated that this might account for the observed reductions in power and strength since lactate production is positively correlated with glycolytic capacity during high intensity efforts. The overarching limitation of the above studies is that none allowed for adequate adaptation to the KD, allotting a dubious task of synthesizing interpretations. Future studies must allow for at least 8-weeks for diet adaptation before testing commences. Furthermore, significant attention must be given to how adaptation to the KD alters intramyocellular energetics during anaerobic exercise. Studies must specify creatine phosphate (CP) turnover rates during sets and rest periods of anaerobic exercise as well as whether KD affects intramyocellular CP storage levels. Finally, modalities of anaerobic activities must be diversified, i.e. resistance based training, and should aim to better mimic “real world” anaerobic exercise.

Practical Application of the KD

Though the precise impact of ketosis on exercise performance remains unclear, practitioners looking to integrate this nutrition strategy into their training may consider several methods. Dietary induction of ketosis is most successful when >60% caloric energy is derived from fat and <5% is from CHO (52). Protein should constitute a significant proportion of dietary energy (>20%) as it retards muscle wasting and amino acids such as leucine and lysine are ketogenic (53). Upon absorption, medium chain triglycerides (MCT’s) avoid systemic circulation and instead enter portal circulation for immediate oxidation by the liver, making MCT oil a possible adjuvant to a KD (54). However, tolerability of MCT oil, especially at higher doses, may be individualized, thus care should be taken when considering this method (55). Beyond the scope of nutritional and supplemental methods, is an exciting new patent for a synthetic ketone body and ketone ester, providing an intriguing new possibility for inducing ketosis, preventing muscle glycogen breakdown, aiding muscle recovery and preventing muscle wasting. Before undertaking a KD, the practitioner must consider performance goals, health and nutritional access in an effort to maximize effectiveness, adherence and safety.

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