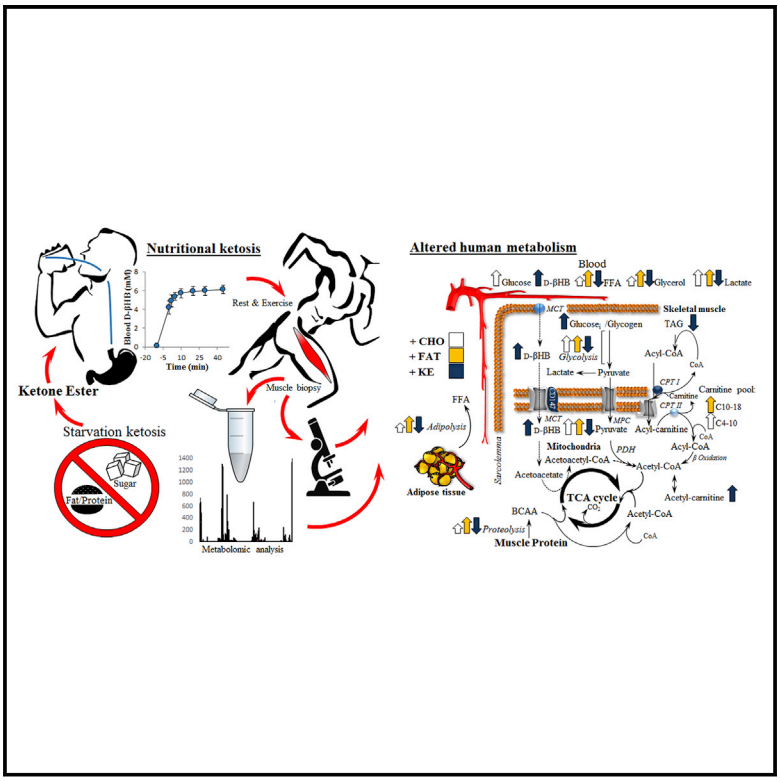
Clinical and Translational Report

Cell Metabolism

Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes

Graphical Abstract



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In Brief

Cox et al. show the metabolic benefit of ketone metabolism through the administration of a ketone ester-based drink to athletes during exercise. The physiological alterations achieved by acute nutritional ketosis may improve human physical performance in some athletes as indicated by initial endurance test results.

Highlights

- Nutritional ketone bodies can promote the advantageous aspects to starvation ketosis
- Nutritional ketosis alters the hierarchy of substrate competition for respiration in exercise
- Ketosis increases metabolic flexibility during exercise, reducing glycolysis and increasing muscle fat oxidation
- Improved performance during cycling time trial suggests ketosis during exercise may be beneficial for some athletes

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Nutritional Ketosis Alters Fuel Preference and Thereby Endurance Performance in Athletes

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SUMMARY

Ketosis, the metabolic response to energy crisis, is a mechanism to sustain life by altering oxidative fuel selection. Often overlooked for its metabolic potential, ketosis is poorly understood outside of starvation or diabetic crisis. Thus, we studied the biochemical advantages of ketosis in humans using a ketone ester-based form of nutrition without the unwanted milieu of endogenous ketone body production by caloric or carbohydrate restriction. In five separate studies of 39 high-performance athletes, we show how this unique metabolic state improves physical endurance by altering fuel competition for oxidative respiration. Ketosis decreased muscle glycolysis and plasma lactate concentrations, while providing an alternative substrate for oxidative phosphorylation. Ketosis increased intramuscular triacylglycerol oxidation during exercise, even in the presence of normal muscle glycogen, co-ingested carbohydrate and elevated insulin. These findings may hold clues to greater human potential and a better understanding of fuel metabolism in health and disease.

INTRODUCTION

Ketone body metabolism is a survival trait conserved in higher organisms to prolong life during an energy deficit or metabolic crisis. The advantages of ketone body metabolism during starvation are clear; providing an oxidizable carbon source to conserve precious glucose/gluconeogenic reserves while simultaneously satisfying the specific fuel demands of the brain. Ketone bodies, when present, act not only as respiratory fuels to power oxidative phosphorylation but as signals regulating the preferential oxidation and mobilization of fuel substrates (Robinson and Williamson, 1980). The conservation of CHO reserves in the form of glycogen and gluconeogenic skeletal muscle protein is a hallmark of starvation induced ketosis (Cahill, 1970), dramatically increasing survival duration (Cahill and Owen, 1968; Felig et al., 1969). Ketosis may also provide thermodynamic advantages over other carbon substrates by increasing the free energy conserved in ATP (ΔG_{ATP}) by the oxidation of ketones during mitochondrial oxidative phosphorylation (Sato et al., 1995). The combination of improved energetic efficiency and fuel sparing is vitally important not only during famine, but could also provide clues to new methods of sustaining human performance, or restoring dysregulated substrate metabolism.

Produced continuously under normal physiological conditions, a significant increase in the ketone bodies, D-β-hydroxybutyrate (D-βHB) and acetoacetate (AcAc), rarely manifests in concentrations above 1 mM (Robinson and Williamson 1980). However, the production of ketone bodies increases rapidly in response to calorie deprivation or energy deficit such as starvation, prolonged exercise, and as part of the clinical manifestations of diseases, such as uncontrolled diabetes (Robinson and Williamson, 1980).

As a fuel source, ketone bodies are readily oxidized by most body tissues (Robinson and Williamson, 1980), the major exception being the liver due to its lack of the enzyme succinyl-CoA:3-ketoacid CoA transferase, which permits oxidative disposal of ketones in the TCA cycle. The favorable thermodynamic characteristics of ketone body oxidation and their regulatory role controlling the preferential use and release of other substrates, such as fat (FAT) and glucose, may also have therapeutic utility for the treatment of disease (Veech, 2004; Keene, 2006).

Achieving ketosis by feeding D-βHB in an acid or salt form is not advisable due to the accompanying acid/salt load. To circumvent this, and the unwanted dietary restriction of adhering to a ketogenic diet, we generated an edible form of a ketone body by transesterifying ethyl *(R)*-3-hydroxybutyrate with *(R)*-1,3-butanediol using lipase (Figure 1; Table S1). Previously we have shown the nutritional ingestion of this *(R)*-3-hydroxybutyl *(R)*-3-hydroxybutyrate ketone ester (KE) is a safe and effective way of elevating blood ketone levels (Clarke et al., 2012; Shivva et al., 2016) and provides a means of investigating human ketone metabolism independent of caloric or CHO deficit.

In some ways, the metabolic demands of prolonged exercise parallel (albeit on a more rapid scale) the metabolic conditions important to survival in starvation; it being well known that