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JOURNAL CLUB

Novel fueling strategies for exercise performance: Can exogenous ketone esters be the answer to prevent overtraining?

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Background

The endogenous ketone bodies acetoacetate (AcAc) and β-hydroxybutyrate (ß-OHB) are produced by the liver and act as oxidative fuels and lipid precursors. Endogenous ketone production is stimulated to a greater extent during carbohydrate restriction (e.g. very low carbohydrate diets) or during caloric restriction (e.g. prolonged fasting) (Evans *et al.* 2017). These dietary strategies generally induce some positive physiological adaptations such as weight loss, reduced oxidative stress and inflammation. However, ketogenic diets and fasting are not ideal for endurance exercise performance (Cox *et al.* 2016). Thus, there could be utility in using exogenous ketones in the absence of carbohydrate or caloric restriction to elucidate the specific role of β-OHB on performance physiology and health. Until recently, many studies infused exogenous ketones intravenously to achieve this; however, β-OHB infusions have limited translational value as a therapeutic strategy or ergogenic aid. Therefore, the recent development of oral exogenous ketone supplements has created great enthusiasm.

Periods of intense endurance training (i.e. functional overload training) are required for sustained increases in athletic performance. However, excess overload can paradoxically contribute to tissue catabolism and long-lasting performance decrements, requiring several weeks (i.e. non-functional overreaching) to several months (i.e. overtraining) to achieve full recovery (Poffé *et al.* 2019). Given the utility of ketone bodies to attenuate net muscle protein breakdown and tissue catabolism (Evans *et al.* 2017), there is reason to determine the effects of exogenous oral ketones on preventing symptoms of overreaching during functional overload training.

In a recent report by Poffé *et al.* (2019) published in *The Journal of Physiology*, the investigators sought to determine, for the first time, the effect of (*R*)-3-hydroxybutyl (*R*)-3-hydroxybutyrate ketone monoester (KE) on indices of endurance training-induced overreaching. In this randomized controlled trial, nine fit male participants consumed a KE supplement (25 g of ketone ester) immediately following each training session and 30 min before sleep. Nine additional participants in a paired control (CON) group received an isocaloric drink containing 16.4 g pure medium-chain triglycerides. Importantly, the authors designed the drinks to be similar in taste and appearance. KE consumption effectively increased whole blood [β-OHB] and induced ketosis within 30 min following ingestion.

The authors hypothesized that KE would attenuate symptoms of overreaching and enhance exercise performance. To test this hypothesis, they compared specific endurance exercise outcomes in KE and CON groups before, during and after a 3-week training intervention, designed to induce a state of non-functional overreaching. These outcomes included training load (total work), a 30-min time trial (TT_{30min}), and a 90-s isokinetic sprint to assess power output. In addition, all participants completed one 120-min endurance performance test (EPT_{120min}) on day 18 of the intervention. The TT_{30min} and 90-s sprint were repeated 3 and 7 days into the recovery phase (post-training). Since no specific physiological outcomes have been consistently identified and accepted as markers/predictors of overreaching, the study also aimed to elucidate potential 'biomarkers' of non-functional overreaching by analysing blood and urine samples taken at distinct time points throughout training in both groups. Identifying said biomarker(s) has potential practical application for athletes.

Ketone ester improves performance during overload training

Three key results highlight the performance benefits of KE supplementation during overload training. First, the KE group managed to produce a 15% greater workload than the placebo-supplemented group during the third week, providing evidence of improved work output during the overload training protocol with KE supplementation. Second, the KE group increased power output on the TT_{30min} by ~5% during the third week, while the CON group failed to increase their power output after training. Third, the KE group had a 15% greater power output during the EPT_{120min} performed on day 18 of overload training, suggesting a greater ability to maintain exercise capacity during extended endurance training sessions. While both groups experienced a reduction in submaximal and maximal exercise heart rate, these changes were blunted in the KE group. This attenuation of 'parasympathetic overreaching' could contribute to improved performance in the KE group, as higher exercising heart rates would allow for a greater cardiac output.

Hormonal responses differ between KE and CON groups

Several 'energy homeostasis and appetite hormones' were markedly different between the two groups. Specifically, serum growth-differentiation factor 15 (GDF15) increased in both groups throughout training, but to a greater extent in the CON compared to the KE group. Serum leptin was threefold lower in the control group after training, with no change in the KE group. Similarly, serum adrenaline and noradrenaline increased twofold in CON, but did not change in the KE group throughout training, suggesting that KE intake favourably modulated the

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nervous system to prevent 'sympathetic overreaching'.

Post-exercise ketosis as a potential recovery tool

An important aspect of these findings to consider is that the effects observed between the groups are not likely to be due to direct effects of ketosis or oxidation of KE as a fuel source during exercise *per se*, since ketone levels were similar between groups prior to and during exercise sessions. The implications of this should be underscored, since the presence and metabolism of KE during exercise could have effects such as glycogen sparing, preventing the deamination of amino acids, and/or reduced glycolytic metabolism throughout exercise, which would consequently influence the catabolic effects of exercise and the post-exercise recovery process (Cox *et al.* 2016). Thus, the current study effectively isolated the effects of post-exercise (exogenous) ketosis on symptoms of overreaching. The KE group was able to tolerate a greater training load by week 3 of the study, when more severe overreaching symptoms were observed in both groups. Given that the ability to utilize ketones is greater in exercise-trained skeletal muscle (Evans *et al.* 2017), it is possible that group differences emerged only once the KE group had become more trained, but there is no direct evidence to support this speculation.

Importantly, a greater training capacity may have been the result of a greater energy intake between the KE and control groups, particularly in the form of carbohydrates. Overreaching is commonly known to result in appetite suppression, which intake of KE seemed to prevent in the present study. The KE group increased their energy intake in proportion to the increase in training load throughout the study period, maintaining energy balance. In contrast, the CON group failed to increase their energy intake, resulting in a relative energy deficiency of ∼1470 kJ at week 2 and ∼2800 kJ by week 3. While the authors note that 'predictors' of overreaching including elevated noradrenaline, decreased heart rate and increased serum GDF15 manifested before any differences in energy intake, it is still likely that sub-optimal nutrition contributed to the performance disparities observed between the groups in the post-test measures. A future study implementing paired feeding could more effectively isolate the influence of KE.

Implications and future directions

These data are the first to support a beneficial influence of KE on integrated physiological responses during overload training. The protocol was successful at inducing a state of non-functional overreaching, indicated by alterations in several autonomic, hormonal and performance markers. Thus, this study design clearly examined the effects of the KE intervention on performance outcomes.

Previous interventions have studied short-term effects of exogenous ketone ingestion, with findings generally showing an impairment in high-intensity exercise performance (Leckey *et al.* 2017; O'Malley *et al.* 2017). It should be noted that these studies used acute ingestion of β-OHB salts or the AcAc diester, rather than chronic β-OHB monoester supplementation. In contrast, the β-OHB monoester used in the current study has previously produced a ∼2% improvement in acute endurance performance in trained athletes (Cox *et al.* 2016). However, these studies have focused on the acute effects of exogenous ketones on exercise performance rather than their long-term effects when ingested during training as part of the 'recovery milieu'.

Exogenous ketones are a potential recovery strategy not available through conventional means. That is, post-exercise intake of carbohydrates inherently limits post-exercise ketosis. However, exogenous KE enables post-exercise ketosis with concomitant intake of carbohydrate and protein, which may synergistically stimulate recovery and adaptation while preventing excess catabolic activity. This is supported by the known role of ketones in sparing protein and carbohydrate stores when carbohydrate availability is low (Evans *et al.* 2017).

Poffé *et al.* (2019) have a vested interest in applying their findings to real-world scenarios as they themselves work alongside professional cycling teams. The ability to maintain a greater training load while mitigating systemic dysfunction or overreaching is the holy grail of exercise training. As such, athletes and teams may begin to apply exogenous ketone supplements to their nutritional regimens. Future studies using KE in athletes in other disciplines (e.g. resistance training, MMA, team sports) may provide novel information on how exogenous ketones influence the response to other modes and intensities of training. Finally, these findings could have implications for individuals who have reduced work capacities due to illness or injury as KE may be a potentially helpful therapeutic tool during rehabilitation.

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Additional information

Competing interests

The authors declare no competing interests.

Author contributions

All authors have read and approved the final version of the manuscript and agree to be accountable for all aspects of the work. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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