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Exogenous ketone supplementations in sports:
Metabolic, physical, and cognitive effects

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Abstract (ENG): Supplements are a part of many athletes' nutrition regimes and exogenous ketones are gaining more interest, especially in elite cycling, with claims such as improving cognition, better recovery, weight loss and improved performance. This review of exogenous ketone supplementations focuses on the applications of these supplements in sports. There are two types of ketones available on the market: salts and esters. Esters have higher potential than salts to elevate plasma ketones within optimal range and dosing should be calculated from individual body mass and effect on ketone levels in blood. For elite endurance-trained cyclists, supplementation can increase endurance but at the potential risk for gastrointestinal discomfort that might affect performance negatively instead. For high-intensity work, ketone supplements may blunt performance. Positive effects have been seen on glycogen and protein synthesis in skeletal muscles when ingested post-workout. For cognition, lactate, and exercise metabolism, research is still inconclusive. To the current understanding of these supplements, the risks are considered low but the impact on athletes' performance is unclear and it is of minimal value to recommend. As a recovery supplement however, some potential benefits have been seen. For non-athletes, effects of the supplements are even more vague and should not be recommended.

Keywords: β -hydroxybutyrate, diet supplementation, exercise metabolism, nutritional ketosis, sport performance

Abstrakt (SVE): Många atleter använder sig av kosttillskott för att optimera sin nutrition och ett tillskott som på senare tid fått mycket uppmärksamhet, speciellt inom cykling, är exogena ketoner. Ketontillskott sägs ge kognitiva-och prestationsfördelar, hjälpa vid viktnedgång och ge bättre återhämtning. I denna artikel ges en överblick av det nuvarande forskningsläget kring dessa typer av tillskott. Det finns två huvudsakliga varianter: saltbaserad och ester. Vid användning av ester är det lättare att nå de spekulerade önskvärda nivåerna av plasma ketoner. Dosering bör ske utifrån individuell kroppsmassa och den resulterande nivån av ketoner i blodet. För uthållighetstränade elitcyklister kan tillskott ge ökad uthållighet men med potentiell risk för magbesvär som kan verka distraherande istället. Vid högintensiv arbetsbelastning kan tillskotten möjligen försämra prestationen. Positiva resultat har setts på glykogen- och proteinsyntesen i skelettmuskulaturen när intag sker efter träning. För kognition, träningsmetabolism och laktatackumulering är forskningen ännu inte enig. Användningen av exogena ketoner anses säkert, men utifrån rådande forskningsläge går det inte dra slutsatser kring hur atletes prestation påverkas. Därför är det av litet värde att rekommendera tillskottet som prestationshöjande. Som återhämtningstillskott är det mer sannolikt att det finns potentiella fördelar. På motionärnivå finns inga bevis för att tillskotten har någon påverkan och bör inte rekommenderas.

Nyckelord: β -hydroxybutyrate, kosttillskott, metabol ketos, sportslig prestation, träningsmetabolism

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1 Introduction

Athletes are always trying to optimise their training, lifestyle, and nutrition to be able to perform at their best. Supplements are a part of many athlete's nutrition regime and exogenous ketones are gaining more and more interest, with claims from retailers such as improved cognition, better recovery, weight loss and improved performance. Ketones are lipid-derived molecules that can serve as an energy source for the body while fasting (Newman & Verdin, 2014) or starving (Cahill, 1976). The body can produce ketones endogenously during these conditions and an increase of circulating ketone bodies in the blood is known as ketosis (Prabhakar et al. 2015). Ketosis can also be achieved after a prolonged exercise when the body's glycogen storages are depleted (Koeslag, Noakes & Sloan, 1980), or by maintaining a ketogenic diet, containing low carbohydrate and high fat (Miller, Villamena, & Volek, 2018). All examples of endogenous production of ketone bodies requires low levels of available carbohydrates in the form of glycogen or glucose in the body (Balasse & Fery, 1989; Stubbs et al. 2017).

In recent years, ketogenic diets in different forms have been trending mostly for its potential weight loss outcomes (Astrup, Meinert Larsen & Harper, 2004) and the point is to reach that ketonic state in which the body burns fat as main energy, instead of carbohydrates. This state can also be reached by fasting, and after a >12 h fast metabolic changes known as the metabolic switch takes place and fatty acids starts to mobilise (Anton et al. 2018). This mobilisation means an increase in lipid oxidation and when in a state of high lipid oxidation, there is an elevation of circulation ketone bodies in the blood stream. (Prabhakar et al. 2015).

The body is mainly fuelled by carbohydrates and fat, but the glycogen storages are limited and can run out during training (Bergström et al. 1967). Ketone bodies can serve as an additional fuel source reserving the glycogen storage, theoretically making it possible to remain active for longer time as in endurance training (Evans, Cogan & Egan, 2017) and the claims about improved cognition are originally based on brain metabolism research, showing how ketones can serve as fuel for the brain while fasting (Owen et al. 1967).

Although elevation of blood ketone levels may positively influence physical performance, achieving it by keto-diets or fasting may have negative impact (Cox & Clarke, 2014). When limiting the carbohydrates in the diets the available glycogen lowers and the performance decrease (Burke et al. 2016). While exercising in a fasted state results in higher fat oxidation (Vieira et al. 2016), physical performance is still better in a fed state (Aird et al. 2018). Being in the fasted state means less available energy and performance will decrease after only 24 h fasting (Gleeson, Greenhaff & Maughan, 1988). Mainly the body's carbohydrate storage in form of glycogen stored in liver and skeletal muscle is reduced which is key in high intensity training (Burke et al. 2011). The ultimate goal for athletes would be to unlock the long-lasting energy from fat while not having to compromise on available carbohydrates as mandatory in fasting or ketogenic diets (Burke, 2020) and this is where the ketone supplements may be an alternative. The natural ketone levels for a healthy human are $<0.5\text{mmol/L}$ of βHB (β -hydroxybutyrate) but can reach as high as $5\text{--}7\text{mmol/L}$ after one weeks fasting (Cahill, 1976). By taking exogenous ketones, it is possible to create hyperketonemia ($\beta\text{HB}>0.5\text{mmol/L}$) without ketogenesis induced by diet manipulation (Stubbs et al. 2017).

Ketone supplements can be categorised into two types: ketone salts (KS) and ketone esters (KE). The most commonly available ketone supplements on the market are KS where βHB is bound to a salt such as potassium or sodium. Depending on brand, commercial salts contains around $8\text{--}12\text{ g}$ of βHB and $\sim 1\text{g}$ of sodium per serving (Pinckaers et al. 2017). For KE, the βHB is bound to alcohol molecules into either mono- or diester but there are currently few products of KE available for commercial use. Some studies use a component part of KE called 1,3-butanediol (1,3-BD), which can through oxidation be conformed into βHB in the liver (National Center for Biotechnology Information), this component will be classified as an ester in this review.

When deciding dosage of exogenous ketone supplements, the key factor is looking at the resulting elevation in blood ketone levels. The speculated optimal range (See Figure 1) for improved performance with exogenous ketones, is to induce an acute nutritional ketosis of $1\text{--}5\text{mmol/L}$ (Evans, Cogan & Egan, 2017). Both KE and KS

can increase concentration of blood ketone but are not equal in effect. KE contains almost solely (>99%) the D-isomer of β HB (D- β HB) with faster uptake and oxidation, while KS contains ~50% of the L-isomer of β HB (L- β HB) that is slower to metabolise. KE therefore often results in a higher peak of β HB in the blood than salts do (Stubbs et al. 2017).

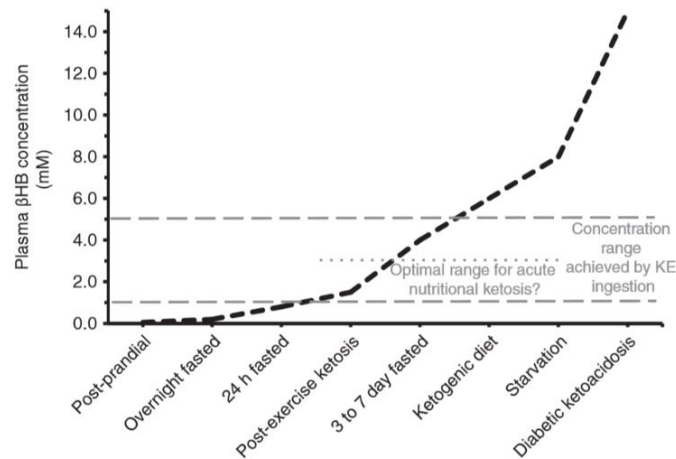


Figure 1: Levels of β HB is affected by conditions such as diet, fasting and starving. With ketone supplementation it is possible to increase β HB concentration. Figure from Evans, Cogan & Egan, 2017

Achieving better performance is not only a product of exercise itself, it also includes recovery and maximising gains from the training. For elite athletes following an intense training regime, the need to balance training and recovery is crucial to maintain high-level performance. While training is the starting stimulus for skeletal muscle adaptations, recovery is where the actual adaptations occurs (Cheng, Jude & Lanner, 2020). On the other side of the spectrum, insufficient recovery can then lead to maladaptation such as catabolic events where muscles start to break down, which eventually leads to performance impairment. During starvation, the endogenous release of ketones serves as a survival mechanism, preventing from catabolic events such as breakdown of cells in muscles, heart, and nervous tissue (Cahill, 1976). This is how the theory emerged that exogenous ketones might have a positive role in recovery (Poffe et al. 2019).

This review summarises the current understanding of exogenous ketone supplementations and their potential application in sport nutrition and effect on performance. The study will investigate three topics: Firstly, looking at how it should be dosed, then examining the claims of these supplements compared to their actual effects in sport settings, and lastly investigate the potential side effects.

2 Method

2.1 Literature search

Article search was conducted via PubMed, 19/ 3 -2020 by using keywords listed below in one search string and limited to clinical trials and randomized control trials, and all non-human trials were excluded. For first selection, titles were reviewed followed by reading abstract of potential suitable articles, then full scripts were read to ensure that all inclusion criteria were met. All reference lists of the selected articles were then screened for additional articles that might be suitable for this review.

Keywords used in literature search:

“Ketone supplement”, “Exogenous ketones”, “Ketone ester/ monoester/ diester”, “Ketone salt”, “Ketone body/ bodies”

2.2 Inclusion criteria

Peer-reviewed clinical trials or randomized controlled trials testing exogenous ketone supplementation was the main criteria for this review. For the topics of dosing and side effects: studies of tolerance and dosing were included even if no physical intervention was conducted. For the topic of sport application: Studies had to include a physical test related to sport, training or exercising for either elite or non-elite. For cognitive ability studies: A physical performance had to be included before/during test to be of value for sport specific settings. The original study had to be conducted on humans, but no limitation for age, sex or performance level was set. No limitation was set for publishing date, but the study had to be published in English.

2.3 Exclusion criteria

Only original studies were chosen, ruling out all forms of reviews and meta-analyses. No form of animal study was included. If no physical test or testing of tolerance to different doses was executed, the study was ruled out. Ketosis by diet, if not compared to supplement, was disqualified. More qualitative studies, concentrating only on sentiment aspects such as perceived focus, enjoyment or

motivation were excluded due to possible bias. Articles not in English, or with only abstract in English, were excluded.

3 Results

3.1 *Compilations of literature*

Out of an initial 622 hits in PUBMED, a total of 14 articles qualified for this review (search strategy, see figure 2). After excluding non-human trails, the remaining 507 hits were screened. 12 scripts met the criteria and by hand-searching the reference list of these publications, an additional 2 articles were found.

Two articles focus on tolerance and dosing of KE were found (see Table 2) but no article focusing solely on KS tolerance was found. A total of 12 articles were found on the subject of sport performance, cognition or metabolic effects of ketone supplements (see Table 3). In 9 of the interventions connected to sport performance, cognition or metabolic effects, the participants blood β HB reached within the speculated optimal range as proposed by Evans, Cogan & Egan (2017). Three studies tested ketone salts and 11 ketone esters.

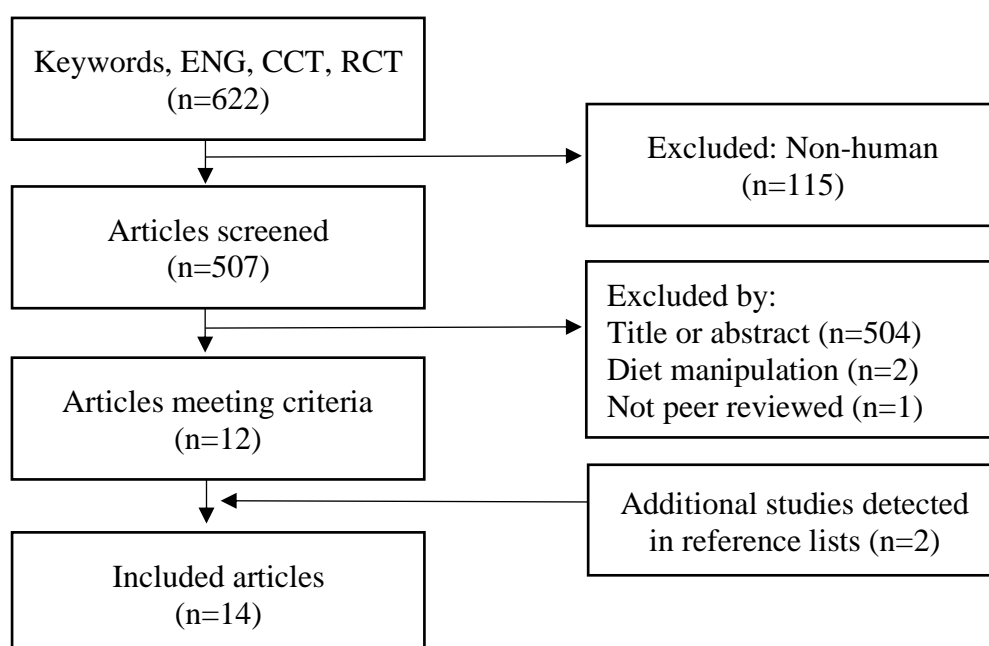


Figure 2: Search strategy in PUBMED. ENG= English full text, CT= Clinical trial, RCT= Randomized controlled trials

3.2 Dosage

Ketone salts (KS)

To use an absolute dosing of KS can lead to high variation in blood β HB. A single dose of 11.7g was speculated to result in β HB levels of >0.5 mmol/L but resulted in an individual range of 0.3–1.1 mmol/L (James & Greer, 2019). O'Malley et al. (2017) saw that a dose of 0.3 g/kg BW seems to elicit levels within optimal range, but their reporting is unclear (See Table 1).

Table 1. Doses of ketone salts tested, and the reported maximum elicit of plasma ketone levels.
BW= Body weight

Ketone salt supplement examples		
Dose	β HB mmol/L	Reference
11.38 g	0.53 ± 0.19	Waldman et al. 2018
11.7 g	0.69 ± 0.3	James & Greer. 2019
0.3 g/kg BW (19.5 g for 65 kg BW)	$\sim 1-1.2$	O'Malley et al. 2017

Ketone ester (KE)

Dosage should be calculated according to body weight (BW) for better prediction but even then, there is still individual differences in uptake that could be influenced by variables such as sex and lean body mass (Shivva et al. 2016). KE a generally well tolerated in moderate doses and after ingestion it takes around 1.5-2 h to reach peak levels in blood (Clarke et al. 2012). To achieve the suggested optimal range, a single dose of 192-573 mg/kg BW is sufficient (See Table 2).

Table 2. Doses of KE tested, and the reported maximum elicit of plasma β HB levels. BW= Body weight

Ketone monoester supplement examples		
Dose	β HB mmol/L	Reference
192 mg/kg BW	1.5	Shivva et al. 2016
291 mg/kg BW	3.5	Shivva et al. 2016
573 mg/kg BW	5	Shivva et al. 2016
2142 mg/kg BW (3x714 mg/kg BW/day x 5 days)	5.5	Clarke et al. 2012 (Not recommended: Vomiting & severe GI problems)

3.3 Performance outcomes

Table 3. Listing all articles on sport performance. KE= Ketone Esters. KE* =1,3-BD. KS= Ketone Salts. Highest blood or plasma BHB reported

Study	KE/KS	β HB mmol/L	Outcome
Cox et al. 2016	KE	~2	- Higher endurance performance
Evans & Egan, 2018	KE	~1.5 - 2.6	- No impairment of high intensity - Cognition benefits - Decreased lactate accumulation
Evans et al. 2019	KE	1.0 - 1.3	- No improvements for endurance - No cognition benefits - No effect on RER or lactate
Holdsworth et al. 2017	KE	5.3 \pm 0.5	- Increased muscle glycogen synthesis
James & Greer, 2019	KS	0.69 \pm 0.3	- No effect on walking economy - No change in RER
Leckey et al. 2017	KE	~1.2 (Uncertain measuring)	- Impairment of endurance performance
O'Malley et al. 2017	KS	~1–1.2 (Unclear reporting)	- Impairment of high intensity performance - Decreased RER
Poffe et al. 2019	KE	2.6 \pm 0.2	- Higher endurance performance when using KE repeatedly - Possible improved recovery
Scott et al. 2019	KE*	~1	- No improvements for endurance
Shaw et al. 2019	KE*	0.44–0.79	- No improvements for endurance - No effect on lactate accumulation
Waldman et al. 2018	KS	0.53	- No effect on high-intensity work - No cognition benefits
Vandoorne et al. 2017	KE	4.3 \pm 0.5	- No effect on muscle glycogen synthesis - Increased protein synthesis in muscle cells

ENDURANCE (≥ 30 min performance): Five studies have tested ketone supplements effects on endurance work. Testing eight highly trained endurance athletes, cycling distance was improved with 2 %, ($p < 0.05$) in a 30 min time trial following a 1 h steady state cycling when consuming a drink with a combination of KE (573 mg/kg BW) and carbohydrates pre-exercise compared with ingesting carbohydrates alone (Cox et al. 2016). In contrast to this study, Leckey et al. (2017) reported a $2 \pm 1\%$ ($p < 0.001$) decrease in cycling performance at a ~ 50 min time trial after a KE drink (500mg/kg BW of 1,3-BD acetoacetate). After an 85 min steady state cycling, designed to deplete glycogen stores, an incremental time trial of ~ 25 -35 min was conducted to test male cyclists to voluntary exhaustion (Shaw et al. 2019). The cyclists did not perform any different after supplementation (700 mg/kg BW of 1,3-BD) compared to placebo.

Two similar trials have tested KE effects on running. After a submaximal running for 1 h, a time trial of 5 km (Scott et al. 2019) or 10 km (Evans et al. 2019) was conducted. Supplementation gave no effect on running performance in the time trials for neither study.

The most promising results of KE use are shown in Cox et al. (2016) with a 2 % increase to endurance performance but that study is also unique. They did not report any GI discomfort which may be one reason for the positive outcome. If this was due to having test subjects with good tolerance for the supplement, the way of combining it with carbohydrates or just a fortuitous outcome is hard to tell since no other studies can back this up.

HIGH INTENSITY: Three studies have observed high-intensity work in different forms. At a simulated 10 km cycling time trial, participants took longer to complete the time-trial after ingesting KS (711 ± 137 s) when compared to placebo (665 ± 120 s, $p = 0.03$) and their power output decreased with an average $\sim 7\%$ (O'Malley et al. 2017). This is a reasonable result since increasing of circulation ketones causes an inhibition of skeletal muscle glycolysis that is one of the key factors in high intensity performance. KS has no negative effect on power output for shorter burst of high intensity work of cycling (Waldman et al. 2018). On four repeated 15s Wingate test, power output was similar between placebo and KS. When ingesting

KE with carbohydrates, no impairment was seen on repeated sprinting performance, but it had no positive effect either (Evans & Egan, 2018).

COGNITION: Three studies have tested ketone supplement on cognition in sport specific settings, the idea being that extra fuel in form of supplemented ketones could serve as a boost for the brain, even in a non-fasting state. Team sports athletes managed to maintain their cognitive ability better after a session of high-intensity training when consuming KE compared to placebo (Evans & Egan, 2018). This result could not be reproduced in a later study testing a similar cognition test after an endurance session, no difference in reaction time or multi-tasking tests was found (Evans et al. 2019). Waldman et al. (2018) also tested reaction and response time, but with KS after high intensity cycling. They found no improvement to cognition after supplement consumption but they themselves recognised a problem with improved performance between trials due to participants learning of the test.

3.4 Metabolism, lactate, and recovery

METABOLISM: Theoretically, increased ketone levels in blood should lower RER but several studies still have not been able to detect a difference after neither KS nor KE ingestion. For KE, no differences have been found in RER when running (Evans et al. 2019) or cycling (Leckey et al. 2017). At recreational level, KS does not enhance fat oxidation for walking (James & Greer, 2019). The same lack of results has been seen in tests with 1,3-BD (Scott et al. 2019; Shaw et al. 2019). One study though reports significant impact ($p = 0.05$) on exercising substrate metabolism after a KS ingestion (O'Malley et al. 2017). Lowering RER during steady state cycling at 30% and 60% of ventilatory threshold and thereby increasing fat oxidation with 23% compared to placebo. However, this change was only visible at the lower levels and was not detectable at an intensity of 90% of ventilatory threshold.

LACTATE: Cycling at a constant load for 1 h, lactate accumulation dropped by ~50 % (2-3mmol/L) when KE was consumed pre-exercised compared to carbohydrates (Cox et al. 2016) and even greater decrease of lactate accumulation of up to ~4.5 mmol/L has been noted in time trials for cycling (Leckey et al. 2017). It should however be noted that some of that decrease reported in Leckey et al.

(2017) could in part be explained by the variation in power output between treatment and placebo. Others report the same trend with a decrease in plasma lactate after repeated sprinting (Evans & Egan, 2018) and after 30 min run, but not at 60 min or following a time trial of 5 km running (Scott et al 2019). The decrease of accumulated lactate is probably a consequence of the inhibition of skeletal muscle glycolysis, where lactate is a by-product. In two of the studies where the levels of β HB did not reach ≥ 1 mmol/L, there was no difference in lactate for either endurance (Shaw et al. 2019) or high intensity work (Waldman et al. 2018). In a study from Evans et al. (2019), KE did elicit β HB levels within the range (1.0 - 1.3 mmol/L) but still could not report any difference in lactate levels in running tests. Why Evans et al. (2019) could not observe this effect in their study was probably because participants did not reach their lactate threshold in the physical test, not raising their lactate in either control or experimental condition.

RECOVERY: In periods of high training load when the athletes risk a non-functional over-reaching, KE supplement may prevent symptoms of overtraining (Poffe et al. 2019). During a three-week program of intensive cycling training, they compared one group receiving KE post-exercise and before sleep with a control group. The KE group could maintain a $\sim 15\%$ higher training intensity in week three then control, the improvement being seen in endurance sessions but not for high intensity sessions.

After an overnight fast followed by a glycogen depletion exercise protocol on a cycle ergometer, glucose uptake was enhanced with 32 % during 2h post-exercise when KE was combined with glucose compared to glucose alone. Muscle glycogen synthesis improved as well and increased by 50 % in KE condition (Holdsworth et al. 2017).

In a study from Vandoorne et al. (2017), subjects underwent an intense one-leg glycogen depletion exercise followed by ingestion of a protein/carbohydrate drink with added KE or an isocaloric placebo. Vandoorne et al. (2017) could not observe an improvement in glycogen resynthesize but they could see an increase in the protein complex mTORC1 that can increase protein synthesis.

3.5 Side effects: Gastrointestinal discomfort

Several studies report that participants experience mild to severe gastrointestinal (GI) problems, especially after KE supplementation. One of the studies reporting impaired performance is Leckey et al. (2017), testing elite cyclists on a time trial. All participants (n =11) experienced different levels of GI problems such as retching and nausea, to moderate reflux after ingesting a drink containing KE. They ingested two doses of 250 mg/kg BW at ~30 min prior to cycling and all participants decreased their performance, themselves blaming it on the distraction of the GI discomfort. One participant even got so sick he could not complete the experiment (Leckey et al. 2017). When KE is added to a carbohydrate drink, 82% reports GI discomfort compared to only 36 % when the carbohydrates are ingested alone (Evans & Egan, 2018). With repeated high doses of ketone monoester (2142 mg/kg BW/day, 5 days), some individuals can experience severe GI problems such as vomiting and abdominal pains and most individuals will experience at least mild to moderate symptoms at this dosage (Clarke et al. 2012). When ceasing the treatment, these symptoms stopped. Severe symptoms are detectable even at recommended doses and there is a shortage of repeated testing to see if the individual's tolerance is constant or if each occasion present a new possible outcome. For an athlete taking supplement before a real competition it could therefore be a gamble, in the worst-case scenario making them incapable to compete. For higher doses (2142 mg/kg BW/day) everyone will probably experience GI problems (Clarke et al. 2012), but since it posed no long-term effect Clarke et al. (2012) still did not advise against this high dose. They claimed that the milk consumed together with the supplement could be the reason some participants experienced severe problems such as vomiting, chest pain and abdominal pain. Until this is further investigated, it would be negligent to propose this high dose for an athlete outside research settings.

4 Considerations for future research

Not all ketone supplements are the same and the inconsistency in dosing, type, timing, and outcome between all studies presented here, testifies to the need for more quality research in the area. For the trials not reaching nutritional ketosis of ≥ 1 mmol/L (Evans, Cogan & Egan, 2017), regardless the type of supplement used,

none showed any real impact on physical performance or cognition (James & Greer, 2019; Scott et al. 2019; Shaw et al. 2019; Waldman et al. 2018). Even though well executed studies, they only augment blood β HB marginally and are probably not fair to use as representation for making claims about the supplements effects or not, but they still might be of value when discussing dosage. None of the studies testing salts presented here, found any benefits to performance or otherwise (James & Greer, 2019; O'Malley et al. 2017; Waldman et al. 2018). The problem with KS is that it does not have the same potential to increase blood β HB as high as esters, and increasing the dosage further also increases the amount of sodium consumed which is undesirable since high salt consumption has negative effects on health (Malta et al. 2018). Ketone esters is the more potent way to induce nutritional ketosis and have more potential in the sport field. A commercially available KE has a single dose, serving size of 25 g (H.V.M.N. Ketone Ester, USA) equalling ~ 384 mg/kg BW for a person of 65 kg. This intake should be sufficient to reach well within the potentially optimal range since a 291 mg/kg BW single dose of KE should elicit a blood ketone levels of 3.5 mmol/L (Shivva et al. 2016).

Ketone supplements goes under many names in the literature and even though the keywords were chosen to capture that, it is still possible that articles relevant in this area have been missed in this review. The restriction to only use one database also limited the available material and should be considered a weakness of this study. However, the numbers of studies testing ketone supplements in sport is underwhelming and some of the published articles have methodology issues, making it even harder to draw definitive conclusions. Marketing of this products includes claims such as improving cognition, better recovery, and improved performance and though some evidence of this is presented here, the data is still scarce and inconsistent. Suggestions for further research is to administer KE according to body mass to ensure β HB levels of ≥ 1 mmol/L in blood, after which sport performance, cognition and lactate accumulation should be tested. For metabolism, studies should include tests of both high and low intensity work for different durations. Studies with female participants and participants of different ages is required. More in vivo experiments using muscle biopsies, looking at both protein and glycogen synthesis could provide further understanding for ketone supplements use in recovery.

5 Conclusion:

Research about ketone supplements are still in its early stage and no definite recommendations of dose or claims about its purposes can be made for cognitive or physical performance at either endurance or high intensity settings. Therefore, it is unwise to recommend supplementation of exogenous ketone to athletes, as a way to enhance performance in competition until further research has been done on when this sort of supplements actually can be of benefit. For training it is deemed safe to use but may cause GI discomfort and have unclear benefits. The most promising results is in the area of recovery where exogenous ketones may have several benefits that should be explored further.

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