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Gastrointestinal Effects of Exogenous Ketone Drinks are Infrequent, Mild, and Vary According to Ketone Compound and Dose

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Exogenous ketone drinks may improve athletic performance and recovery, but information on their gastrointestinal tolerability is limited. Studies to date have used a simplistic reporting methodology that inadequately represents symptom type, frequency, and severity. Herein, gastrointestinal symptoms were recorded during three studies of exogenous ketone monoester (KME) and salt (KS) drinks. Study 1 compared low- and high-dose KME and KS drinks consumed at rest. Study 2 compared KME with isocaloric carbohydrate (CHO) consumed at rest either when fasted or after a standard meal. Study 3 compared KME+CHO with isocaloric CHO consumed before and during 3.25 hr of bicycle exercise. Participants reported symptom type and rated severity between 0 and 8 using a Likert scale at regular intervals. The number of visits with no symptoms reported after ketone drinks was $n = 32/60$ in Study 1, $n = 9/32$ in Study 2, and $n = 20/42$ in Study 3. Following KME and KS drinks, symptoms were acute but mild and were fully resolved by the end of the study. High-dose KS drinks caused greater total-visit symptom load than low-dose KS drinks (13.8 ± 4.3 vs. 2.0 ± 1.0; $p < .05$) and significantly greater time-point symptom load than KME drinks 1–2 hr postdrink. At rest, KME drinks caused greater total-visit symptom load than CHO drinks (5.0 ± 1.6 vs. 0.6 ± 0.4; $p < .05$). However, during exercise, there was no significant difference in total-visit symptom load between KME+CHO (4.2 ± 1.0) and CHO (7.2 ± 1.9) drinks. In summary, exogenous ketone drinks cause mild gastrointestinal symptoms that depend on time, the type and amount of compound consumed, and exercise.

Keywords: ketone ester, ketone monoester, ketone salt

In human metabolism, the term "ketone bodies" refers to D-beta-hydroxybutyrate (D-βHB), acetoacetate, and acetone, which are synthesized in the liver from fatty acids during periods of dietary carbohydrate (CHO) restriction. Recently, interest in health and performance applications of exogenous ketone drinks has grown (Egan & D'Agostino, 2016). These drinks rapidly increase blood ketone concentrations to achieve ketosis (blood D-βHB >0.5 mM) without dietary modification (Stubbs et al., 2017).

Two classes of exogenous ketone compounds exist: ketone esters and ketone salts (KS). Ketone esters comprise either βHB or acetoacetate esterified to a ketone precursor, such as butanediol (Figure 1a). KS contain βHB with varying amounts of D-βHB and L-βHB enantiomers bound to a cation, such as sodium (Figure 1b).

Using ketone drinks to achieve "fed ketosis" may improve athletic performance and recovery. Early studies indicate that a ketone monoester (KME; *R*-3-hydroxybutyl-*R*-1,3-hydroxybutyrate) may improve physical (Cox et al., 2016; Murray et al., 2016) and improve or maintain cognitive performance (Evans & Egan, 2018; Murray et al., 2016), and favorably affect recovery when consumed with other macronutrients (Holdsworth et al., 2017; Vandoorne et al., 2017). However, studies of a ketone diester (*R*,*S*-1,3-butanediol diacetoacetate; Leckey et al., 2017) and KS drinks (O'Malley et al., 2017; Rodger et al., 2017; Waldman et al., 2018) found no ergogenic effects; thus, there remain many unresolved questions on the applications of exogenous ketone drinks.

A critical concern for athletes is gastrointestinal (GI) tolerability. For example, risk of severe GI side effects caused by sodium bicarbonate may limit its use, despite proven ergogenic effects (Kahle et al., 2013; Peart et al., 2012). Symptoms have been reported following the consumption of KME at rest (mild flatulence, nausea, and dizziness) and taken with exercise (upper abdominal discomfort; Clarke et al., 2012; Evans & Egan, 2018; Vandoorne et al., 2017), ketone diester taken preexercise (dry retching, nausea; Leckey et al., 2017), and preexercise KS drinks (nausea, diarrhea, vomiting, and light-headedness; Evans et al., 2018; Waldman et al., 2018). These studies report symptoms using a simplistic outcome description (symptom/no symptom), which does not provide adequate insight into type, time course, or severity. A more detailed understanding of GI symptoms is important if exogenous ketone drinks are to be consumed by athletes.

Herein, we describe the type, time course, and severity of GI symptoms that were reported during ingestion studies of KME and KS drinks at rest and during exercise. Such information forms a valuable reference for future studies of exogenous ketones.

Materials and Methods

Study Design

Incidence of GI symptoms after exogenous ketone drinks was investigated in three independent studies (Figure 1). First, a randomized, four-arm, cross-over study with equal amounts of

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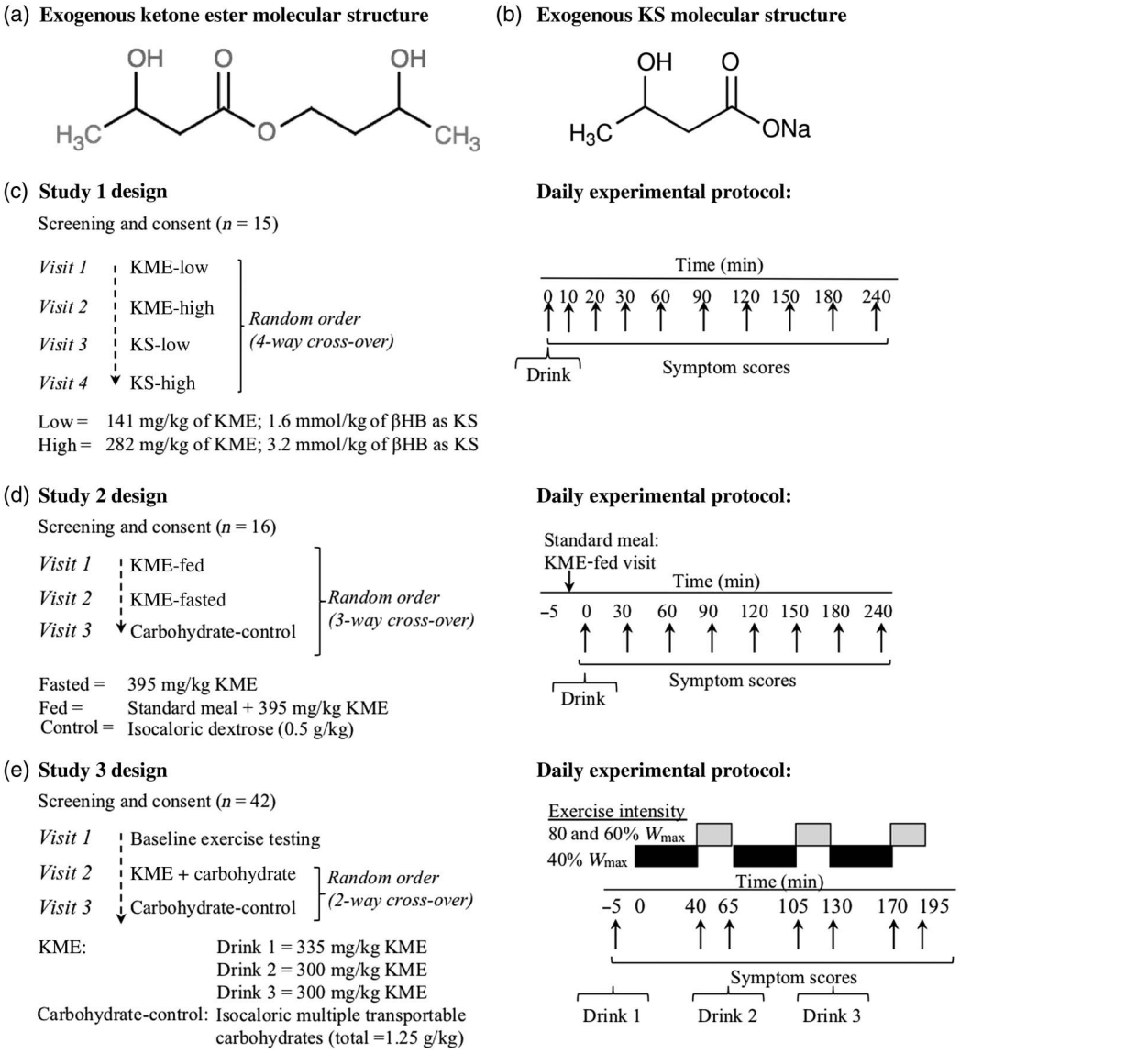

Figure 1 — (a) KME molecular structure. (b) KS molecular structure. (c–e) Schematic showing protocol for all studies. KME = ketone monoester; KS = ketone salt; βHB = beta-hydroxybutyrate.

βHB as KME or KS at two doses, ingested by healthy volunteers at rest (Study 1, $n = 15$; Stubbs et al., 2017). Second, a randomized, three-arm, cross-over, single-blinded study, following identical KME drinks taken by healthy volunteers either after a standard meal or an overnight fast and a taste-matched, isocaloric CHO drink (Study 2, $n = 16$). These data were collected as part of a study with multiple visits per condition; the first visit in each condition was used for symptom analysis (Stubbs et al., 2017). Finally, a randomized, two-arm, cross-over, single-blinded study with KME+CHO or taste-matched, isocaloric CHO drinks taken by well-trained athletes during prolonged bicycle exercise as longer low-intensity blocks with intermittent, high-intensity efforts (Study 3, $n = 42$).

Participants and Screening

Studies were approved by the external NHS Research Ethics Committees (Studies 1 and 2) and the U.K. Ministry of Defense Ethics Committee (Study 3) and conducted in accordance with the Declaration of Helsinki. Participants were healthy, aged 21–42 years, with no history of major illness and provided written informed consent with a confidential medical questionnaire prior to inclusion. Females were not pregnant or planning pregnancy. Anthropometric characteristics are shown in Table 1.

General Visit Procedures and Data Collection

Participants refrained from alcohol and caffeine for 24 hr prior to each visit. All studies were conducted at the University of Oxford, starting at 08:00 hr following an overnight (>8 hr) fast, with a minimum of 72 hr between visits. Following the consumption of study drinks, the type and severity of GI symptoms were recorded regularly using a Likert-type questionnaire previously utilized in sport science studies, where 11 symptoms were given a score between 0 (not present) and 8 (unbearable) (Figure 2; Pfeiffer et al., 2012).

Table 1 Physical Characteristics of Subjects

Characteristics	Study 1 ($n = 15$)	Study 2 ($n = 16$)	Study 3 ($n = 42$)
Age (years)	22.3 ± 2.0	27.6 ± 6.4	25.9 ± 5.0
Height (m)	1.8 ± 0.1	1.8 ± 0.1	1.8 ± 0.7
Weight (kg)	70.5 ± 11.1	72.7 ± 15.4	76.3 ± 9.9
BMI (kg/m^2)	22.7 ± 2.2	22.5 ± 2.5	23.1 ± 2.1
M/F	9/6	10/6	42/0

Note. Values are represented as mean ± SD. BMI = body mass index; M = male; F = female.

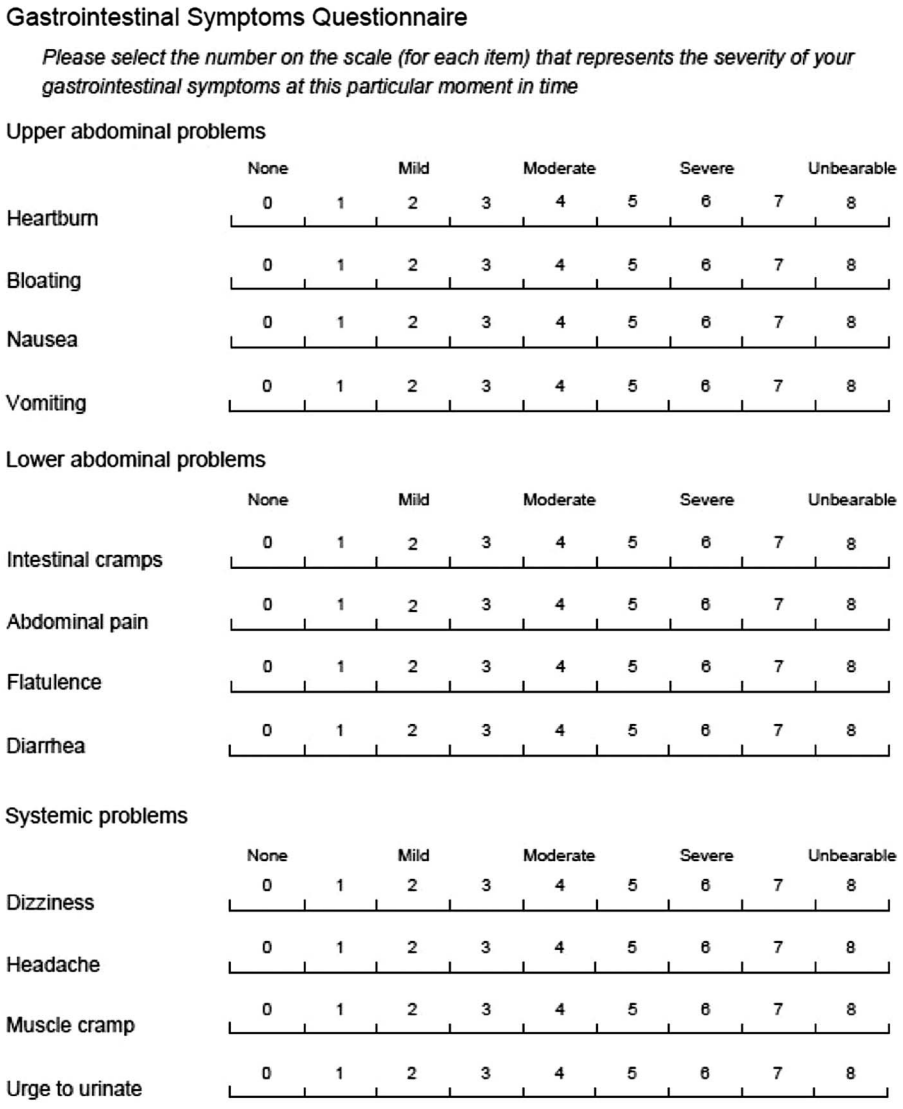

Figure 2 — Questionnaire used to collect symptom scores in all studies.

Study Interventions

Study 1. Over four visits, participants consumed 141 and 282 mg/kg of KME or matched amounts of βHB as KS (sodium and potassium βHB; KetoForce, KetoSports, Seymour, IL), plus 6 g of sweetener, diluted to 300 ml using water. Drinks were consumed within 2 min. Full blinding was not possible because of unmaskable differences in taste (Figure 1c).

Study 2. Over three visits, participants consumed 395 mg/kg of KME: once while fasting and another following a standard meal or a CHO drink (0.5 g/kg glucose) without a meal. To improve palatability, both drinks were diluted to 500 ml with a commercially available, citrus-flavored drink containing 65 kcal from CHO (Glaceau, London, UK). The CHO drink was calorie-, volume-, and taste-matched using a bitterness additive (Symrise, Holzminden, Germany). Drinks were consumed within 2 min.

The standard meal consisted of oats (54 g), semiskimmed milk (360 ml), and banana (120 g; Figure 1d).

Study 3. Over two visits, participants consumed isocaloric, volume-, and taste-matched drinks containing either a total of 995 mg/kg of KME or a 1.25 g/kg glucose/fructose (1:1 ratio). Participants completed 195 min (3.25 hr) of continuous bicycle ergometer exercise, consisting of three 65-min blocks, with both low intensity (40 min at 40% of predetermined maximal wattage—W_{max}) and high intensity (25 min alternating between 80% and 60% W_{max} every 5 min). KME ingestion was split into one 395 mg/kg serving consumed prior to exercise within 2 min and two servings of 300 mg/kg taken at 65 and 130 min into exercise (Figure 1e).

Data Analysis and Statistical Methods

Scores from all participants for all symptoms at a given time were summed to give a time-point "symptom load" for each condition. Peak time-point symptom load for each participant was recorded. Finally, each participant's scores for all symptoms over the visit were summed to give a total-visit "symptom load" for each individual.

Statistical analysis utilized Prism 6™ software (GraphPad Software, San Diego, CA). Initial tests of normality and sphericity assumptions were undertaken. Subsequent nonparametric statistical tests were performed as appropriate: Freidman's test with post hoc Dunn's correction and Wilcoxon test. Values are expressed as total (time-point symptom load) and median (interquartile range [IQR]) for peak symptom load and total-visit symptom load, with significance considered at $p < .05$.

Symptoms were categorized into three groups: upper GI, lower GI, and systemic (see Figure 2). The number of participants reporting each type of symptom was recorded according to the maximal severity: none = 0, mild = 1–2, moderate = 3–4, and severe = 5+. McNemar's test was used to compare incidence (symptom vs. no symptom) between paired test conditions.

Results

Study 1

Directly following all ketone drinks, symptom load increased and returned to baseline by the end of the 4-hr study (Figure 3a). Peak symptom load was highest after high-dose KS drinks at a score of 3 (IQR = 8) out of a possible 88 score (Figure 3b). An effect of increasing dose was apparent in the total-visit symptom load after KS drinks, which was significantly greater after high (8 [IQR = 24]) versus low (0 [IQR = 2]) doses of KS ($p < .005$; Figure 3c); however, in all conditions, the total-visit symptom load was far below the maximum possible visit symptom load of 880. There was no significant effect of increasing KME dose on either peak or total-visit symptom load. There was no significant effect of ketone compound at matched doses on peak or total-visit symptom load. Total symptom load was 0 in $n = 32/60$ study visits.

There was a low frequency of all symptom types for both KME drinks and low-dose KS drinks (no symptoms in 10/15 and symptoms reported were mild to moderate; Table 2). "Severe" symptoms were reported only following a high-dose KS drink; these were upper GI (nausea, $n = 1$) and lower GI (abdominal cramp, $n = 1$) and three participants experienced diarrhea. The highest number of upper (8/15) and lower (5/15) GI symptoms was seen following a high-dose KS drink. The highest number of systemic symptoms (5/15) was seen after both high-dose KS and KME drinks.

Study 2

Time-point symptom load was similar to that in Study 1, rising after the KME drinks and returning to baseline by the end of the 4-hr study (Figure 3d). There was no increase in symptoms with the CHO drink taken when fasted. Peak symptom load was 1.5 (IQR = 2.5) out of a possible 88 after the KME drink taken when fasted (Figure 3e). There was a significantly greater total-visit symptom load with KME taken when fasted compared with CHO drinks (fasted = 3 [IQR = 7], control = 0 [IQR = 0]; $p < .01$), but no further differences between conditions (Figure 3f). Total symptom load was 0 in 9/32 KME visits.

There were very few symptoms reported in the CHO arm, and similar symptom type and severity (mild to moderate) in the fed and fasted KME conditions, with $n = 1$ severe symptom (headache) (Table 2). Lower GI issues were rare, with no symptoms in 15/16 in both the fasted and fed conditions. There was a low frequency of upper GI symptoms, with no symptoms in fasted = 10/16 and fed = 11/16 conditions, and a similar frequency of systemic symptoms in fasted = 9/16 and fed = 8/16 conditions.

Study 3

Time-point symptom load increased throughout exercise in both KME+CHO and CHO conditions, with larger increases following each of the high-intensity blocks in both conditions, indicating an intensity and/or duration dependency of symptoms (Figure 3g). Peak symptom load was 2 (IQR = 3) in the KME+CHO (Figure 3h) out of a possible 88. There was no statistically significant difference in total-visit symptom load between conditions (KME + CHO = 2 [IQR = 5], CHO = 1.5 [IQR = 10]; Figure 3i). Total symptom load was 0 in 20/42 KME+CHO visits.

Types of symptoms were similar and equally common in the KME+CHO and CHO arms (Table 2). Following KME+CHO there were reports of severe bloating ($n = 2$), while following CHO, there were severe incidences of nausea ($n = 1$), bloating ($n = 1$), flatulence ($n = 1$), dizziness ($n = 2$), and muscle cramp ($n = 3$).

Discussion

These results are the first detailed description of the symptoms associated with the ingestion of exogenous ketone drinks at rest and during exercise, analyzed by type, time course, and severity. At rest, ketone drink consumption caused a short-lived, mild increase in symptoms that were greater than with CHO drinks. Taken during exercise, symptoms after KME drinks were not different to CHO drinks. These results provide information for future resting and exercise studies utilizing exogenous ketones.

Our finding that exogenous ketone drinks are associated with some symptoms is consistent with a previous study using KME and ketone diesters (Clarke et al., 2012; Leckey et al., 2017) and KS (Evans et al., 2018; Waldman et al., 2018), studied at rest and during exercise. Although it is beyond the scope of this work to determine the causes of these symptoms, we believe that several factors may contribute to the observed effects.

It is likely that many symptoms, especially nausea and the feeling of bloating reported directly following ketone drinks at rest, were linked to rapid ingestion of a large bolus of unpleasant-tasting drinks. It is important to note that in Study 1, the KME and KS drinks were not taste matched as the KME has a subjectively stronger, bitter taste, and this could have impacted our results. In nature, bitter taste is associated with toxins; bitter taste stimulation,

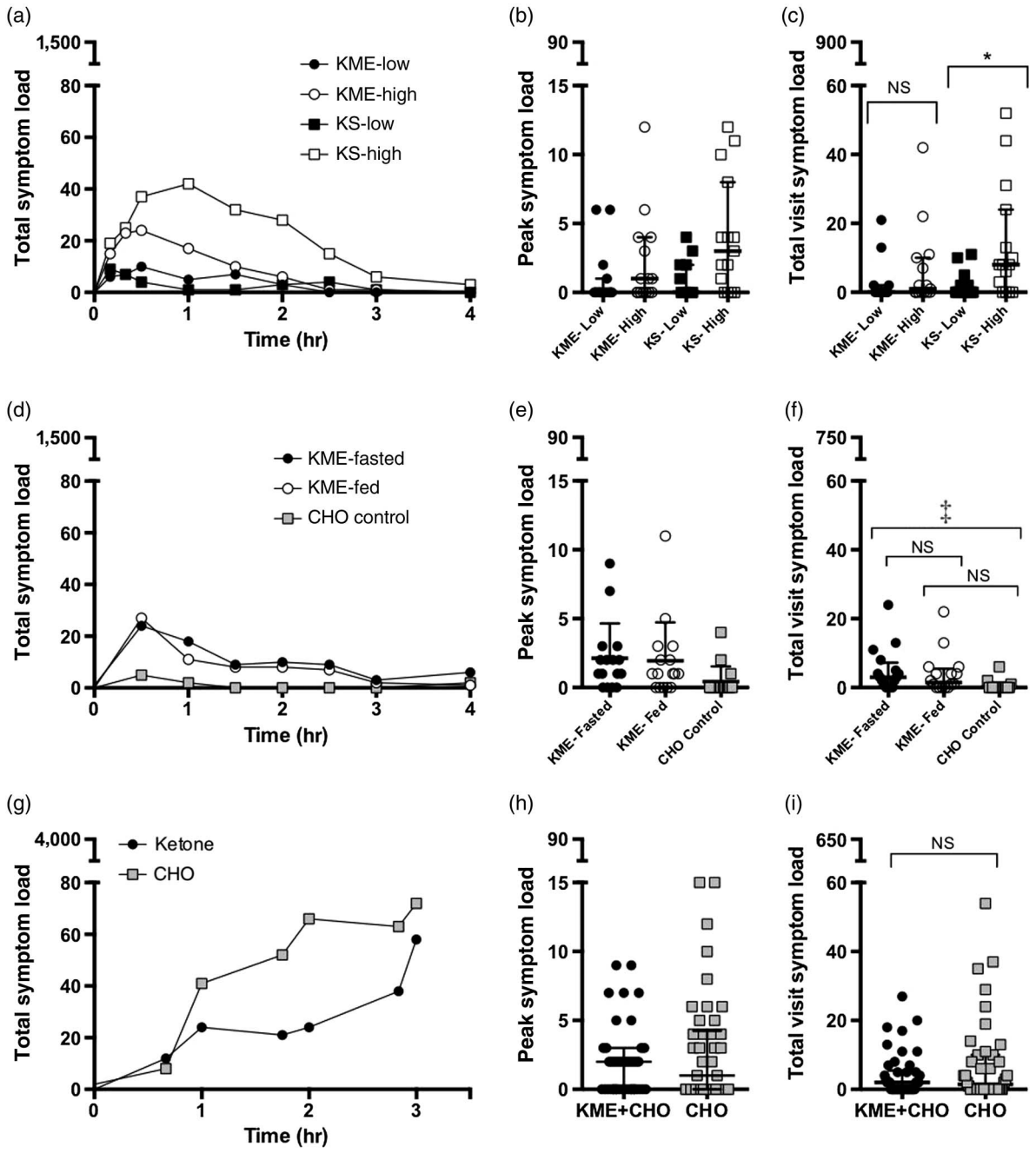

Figure 3 — Subjective reporting of gastrointestinal symptoms over the course of study visits during which the participants consumed exogenous ketone drinks under different conditions. Eleven symptoms were ranked between 0 (not present) and 8 (unbearable), and scores were combined to give symptom load at each data collection point and a total symptom load for each visit. (a) Total symptom load at $n = 10$ time points from $n = 15$ participants following the consumption of ketone monoester (KME) and ketone salt (KS) drinks at low and high doses. Maximum possible time-point symptom load for this study = 1,320. (b) Peak symptom load for each individual in Study 1. Maximum possible peak symptom load = 88. (c) Visit symptom load for each individual in Study 1. Maximum possible visit symptom load = 880. (d) Total symptom load at $n = 8$ time points from $n = 16$ participants following the consumption of KME and isocaloric carbohydrate (CHO) drinks at rest and while fed or fasted. Maximum possible time-point symptom load for this study = 1,408. (e) Peak symptom load for each individual in Study 2. Maximum possible peak symptom load = 88. (f) Visit symptom load for each individual in Study 2. Maximum total-visit symptom load for this study = 704. (g) Total symptom load at $n = 7$ time points from $n = 42$ participants following the consumption of KME+CHO drinks and isocaloric CHO drinks before and during 3 hr 15 min of mixed-intensity bicycle exercise. Maximum possible time-point symptom load for this study = 3,696. (h) Peak symptom load for each individual in Study 3. Maximum possible peak symptom load = 88. (i) Visit symptom load for each individual in this study. Maximum possible visit symptom load = 616. Values are total (a, c, g) or individual values with median and interquartile range shown. Axis breaks indicate the maximum symptom load for each condition. *$p < .05$ difference between low- versus high-dose ketone drinks, ‡$p < .05$ difference between KME and control or KME+CHO versus CHO.

Table 2 Number of People Reporting Each Class of Symptom and Maximal Severity Reported

	Study 1				Study 2			Study 3 (exercise)	
Maximal severity reported	**KME-low**	**KME-high**	**KS-low**	**KS-high**	**KME-fasted**	**KME-fed**	**CHO-control**	**KME+CHO**	**CHO**
Upper GI									
None	12	10	11	7	10	11	15	33	33
Mild	2	2	3	4	4	3	0	6	5
Moderate	1	3	1	3	2	2	1	1	2
Severe	0	0	0	1	0	0	0	2	2
Total with symptoms	3	5	4	8	6	5	1	9	9
Lower GI									
None	15	13	14	10	15	15	16	35	31
Mild	0	2	1	2	1	1	0	7	4
Moderate	0	0	0	2	0	0	0	0	6
Severe	0	0	0	1	0	0	0	0	1
Total with symptoms	0	2	1	5	1	1	0	7	11
Systemic									
None	12	10	12	10	7	8	15	32	29
Mild	2	4	1	5	7	6	1	5	3
Moderate	1	1	2	0	2	1	0	5	5
Severe	0	0	0	0	0	1	0	0	5
Total with symptoms	3	5	3	5	9	8	1	10	13
Peak blood D-βHD ±SD (mM)	1.4 ± 0.5	2.8 ± 0.8	0.8 ± 0.3	1.0 ± 0.3	3.3 ± 0.7	2.2 ± 0.5	0.2 ± 0.0	4.5 ± 0.2	0.1 ± 0

Note. KME = ketone monoester; KS = ketone salt; CHO = carbohydrate; GI = gastrointestinal; D-βHB = D-beta-hydroxybutyrate.

but not sweet, salty, or umami, can induce nausea in a prophylactic aversion response (Peyrot des Gachons et al., 2011). Until KME drinks become more palatable, it is difficult to determine if acute symptoms such as nausea and bloating are caused by physiological effects of elevated ketones, an aversive reaction to the poor taste or discomfort due to gastric distension.

It has been suggested that hyperketonemia resulting from ketone drinks could directly drive GI symptoms (Leckey et al., 2017). Despite consistent, robust (0.8–4.5 mM peak D-βHB) hyperketonemia in all visits with KME or KS consumption across all studies (Table 2), subjects reported no symptoms in many of these visits (Study 1 = 53%, Study 2 = 22%, and Study 3 = 48%). Furthermore, despite the consumption of three ~300 mg/kg KME drinks prior to and during the exercise protocol in Study 3, elevating D-βHB to 4.5 mM (unpublished), there were no differences in symptoms between KME+CHO and CHO. Therefore, at the levels attained here and under these study conditions, hyperketonemia itself is not a consistent cause of symptoms.

Fundamental differences between exogenous ketone compounds may contribute to the differences in symptoms. Herein, KS drinks were associated with a number of moderate to severe lower GI symptoms, especially at higher doses. In contrast to KS drinks, lower GI issues were rare with KME drinks, with only two subjects reporting mild issues following high-dose KME, compared with two mild, two moderate, and one severe issues with high-dose KS. Lower GI symptoms with KS drinks could be caused by the coingested inorganic cations (3.2 g of both sodium and potassium) leading to a hyperosmolar gut lumen and, hence, gut water retention (Jeukendrup et al., 2005; Rehrer, Wagenmakers, et al., 1992). Although this study was conducted in the resting state, the prevalence of lower GI symptoms here could be particularly problematic for athletes, as the risk of lower GI distress is greatly increased during exercise (Rehrer, Brouns, et al., 1992). Upper GI and systemic symptoms seen with KS drinks may be an effect of salt bolus consumption on fluid homeostasis, where fluid shifts or changes in blood pressure result in headache or nausea (Farquhar et al., 2005).

Ketone monoester consumption was more commonly associated with upper GI and systemic effects; however, the cause of these symptoms is unclear. The KME is hydrolyzed in the gut, before the βHB and butanediol components are absorbed into the blood and butanediol undergoes first-pass metabolism to D-βHB. Previous studies did not detect unhydrolyzed KME in the blood after consumption (Clarke et al., 2012) and levels of blood butanediol did not exceed 1 mM, despite a KME delivery of 714 mg/kg and peak D-βHB of 3.3 mM (Clarke et al., 2012). Any exercise-induced changes to KME metabolism, fate of its downstream metabolites, and resulting effects on athletic performance are currently unknown.

One important observation of this study was that symptom load following KME+CHO consumption prior to and during exercise was not different than following isocaloric CHO drinks. This finding is of interest if exogenous ketones are to be used as a foodstuff for athletes, as GI symptoms negatively impact athletes' performance. In both conditions, symptom load increased over the course of the study, with largest increases seen following the three higher intensity blocks, indicating that exercise intensity and duration are important contributors to symptom occurrence. This may explain the increased incidence of symptoms seen when KME was taken in conjunction with intermittent, high-intensity sprinting (Evans & Egan, 2018). High rates of CHO consumption during exercise can cause GI distress (Rehrer, van Kemenade, et al., 1992). In this study, the CHO dose (~95 g over the protocol) is far lower than the recommended dose (~60–90 g/hr). The ergogenic effects of CHO mean that athletes modulate rather than forgo CHO intake; KME drinks might require similar, individualized

attention to detail. Notably, observations from Study 3 are inconsistent with those from Study 2, where KME drinks (taken when fed or fasted) caused more symptoms than a CHO drink. The reasons for this discrepancy are unclear; exercise may have been a distraction (Janal, 1996) or tolerance of unpleasant sensations may have been greater in athletes compared with sedentary individuals (Janal, 1996). Another consideration is that different CHO sources were used in Study 2 (glucose) and Study 3 (multiple transportable CHO) although the combination of glucose with fructose has been shown to decrease GI issues during exercise (Wilson & Ingraham, 2015). Finally, it is unclear if exercise offsets or alters the physiological effects or metabolism of the KME in a way that might alter the chance of symptoms.

Our results illustrate that context is a vital determinant of symptoms following ketone drinks. We saw differences in symptoms as a result of ketone compound and dose at rest; but these observations should be extended and repeated during exercise, including different modalities, intensities, and duration. We used a flavored water form-factor throughout, but the formulation of the ketone compound into thicker, "protein," or meal replacement beverages can impact on gastric emptying, ketone absorption, and may also alter tolerability (Shivva et al., 2016; Vandoorne et al., 2017).

Conclusion

Previous reports have provided simplistic insights into symptoms associated with exogenous ketone drinks. This work gives the first detailed description of the type, severity, and time course of GI and systemic symptoms following the consumption of different exogenous ketone compounds during resting and exercising studies. These findings have immediate relevance to both researchers and athletes, providing an insight into how ketone compound and dose may alter the symptoms experienced.

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