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Considerations for ultra-endurance activities: part 1- nutrition

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ABSTRACT

Ultra-endurance activities (≥ 4h) present unique challenges that, beyond fatigue, may be exacerbated by sub-optimal nutrition during periods of increased requirements and compromised gastrointestinal function. The causes of fatigue during ultra-endurance exercise are multi-factorial. However, mechanisms can potentially include central or peripheral fatigue, thermal stress, dehydration, and/or endogenous glycogen store depletion; of which optimising nutrition and hydration can partially attenuate. If exercise duration is long enough (e.g. ≥ 10h) and exercise intensity low enough (e.g. 45–60% of maximal oxygen uptake), it is bio-energetically plausible that ketogenic adaptation may enhance ultra-endurance performance, but this requires scientific substantiation. Conversely, the scientific literature has consistently demonstrated that daily dietary carbohydrates (3-12g/kg/day) and carbohydrate intake (30-110g/h) during ultra-endurance events can enhance performance at individually tolerable intake rates. Considering gastrointestinal symptoms are common in ultra-endurance activities, effective dietary prevention and management strategies may provide functional, histological, systemic, and symptomatic benefits. Taken together, a well-practiced and individualized fuelling approach is required to optimize performance in ultra-endurance events.

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Energy; Carbohydrate; Protein; Ketogenic; Gastrointestinal Symptoms; Epithelium

Introduction

Ultra-endurance events (≥ 4h) and total participation numbers have consistently increased for several decades (Hoffman & Krouse, 2017; Hoffman, Ong, & Wang, 2010; Knoth, Knechtle, Rüst, Rosemann, & Lepers, 2012). Such events include single- and multi-stage ultramarathons or cycling, ultra-distance triathlons/duathlons, multi-sport adventure racing, expeditions, open water swimming, rowing/kayaking, and cross-country winter sports. These events are particularly challenging because participants are required to perform prolonged strenuous physical exertion in one bout or on consecutive days and manage their nutritional and hydration needs in order to maintain optimal physical and mental performance. Additionally, many events are conducted in extreme environments (e.g. ≤ 0°C to ≥ 30°C ambient temperature, and altitude > 3000m) and

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over harsh terrains (e.g. arctic, mountain, desert, forest, or jungle). The burden of self-sufficiency criteria in some events also involves consecutive days of loaded physical exertion (e.g. carrying clothing, equipment, and nourishment; 5–15kg of pack-weight) and rough sleeping conditions (e.g. outdoors with minimal shelter), further enhancing the difficulty.

Associations between sub-optimal nutritional status and decrements in exercise performance are well documented (Thomas, Erdman, & Burke, 2016). This highlights the importance of strategically supplying sufficient foods and fluids to meet requirements on single or consecutive days of ultra-endurance participation (Costa et al., 2013). Accordingly, nutrition has often been considered the "fourth event" in ultra-endurance competition (i.e. triathlon), and its importance to performance consistently merits discussions on public domains. However, sub-optimal nutritional status and competition interventions is a common feature in ultra-endurance events, due to factors such as the lack of nutrition education, cultural norms within ultra-endurance sports, development of unintentional symptoms (e.g. appetite suppression, taste fatigue, and gastrointestinal symptoms (GIS)), and/or practical logistical issues (e.g. lack of food preparation facilities, equipment, location, time, and/or motivation), which may limit the total intake of foods and fluids (Costa, Gill, Hankey, Wright, & Marczak, 2014; Costa et al., 2013).

A high incidence of mild and severe GIS reported by participants during ultra-endurance events has been linked to a reduced ability to meet energy and nutritional requirements through food and fluid intake, reduced prolonged physical performance, and withdrawal from ultra-endurance competition (Costa et al., 2017a; Costa, Snipe, Camões-Costa, Scheer, & Murray, 2016; Hoffman & Fogard, 2011; Stuempfle & Hoffman, 2015). Considering the underlying causal mechanisms and exacerbation factors for exercise-associated gastrointestinal disturbances are well researched, there is growing evidence for effective dietary-based prevention and management strategies targeting GIS, improved food and fluid intake (i.e. quantity and quality), and subsequently optimize ultra-endurance performance (Costa, Snipe, Kitic, & Gibson, 2017b).

With these background factors in mind, and acknowledging the hydration consideration for ultra-endurance activities will be covered in part 2 (Hoffman, Stellingwerff, & Costa, 2018), the primary aims of this review are to: 1) examine the ultra-endurance bio-energetic performance constraints; 2) provide general and competition specific nutrition recommendations; and 3) provide an evidence based update of prevention and management strategies for exercise-associated GIS.

Metabolic considerations

Bio-energetic considerations during ultra-endurance activities

Our mechanistic understandings of the various causes of fatigue during extreme endurance exercise are scientifically limited, but potentially include cognitive and central nervous system fatigue, thermal stress, dehydration, and/or endogenous glycogen store depletion. Indeed, a recent series of studies on central *vs*. peripheral (muscle) fatigue has started to shed some light on the complex interactions of fatigue in ultra-endurance settings; with muscle fatigue being more dominate in shorter races and central fatigue being an ever increasing source of fatigue as race duration extends

(Martin et al., 2010; Temesi et al., 2014). Interestingly, nutrition can partially address both of these causes of fatigue.

Only a few studies have assessed whole body and muscle fuel utilisation using contemporary methodologies at exercise durations ≥ 3h (Jeukendrup et al., 2006; Romijn et al., 1993; Stellingwerff et al., 2007). Therefore, most recommendations of metabolic needs for ultra-endurance activities are either laboratory extrapolations or indirect estimates. Nevertheless, total caloric expenditure rates are inversely correlated with exercise duration, with data demonstrating a 5-fold increase in energy expenditure above basal metabolic rate with sustained physical exertion for 10-days (Cooper, Nguyen, Ruby, & Schoeller, 2011), 8000–12000kCal reported for an Ironman triathlon over 8–16h (Cuddy, Slivka, Hailes, Dumke, & Ruby, 2010), and 6000–18000kCal/day for multi- and single-stage ultramarathons (Alcock, McCubbin, Camões-Costa, & Costa, 2018; Costa et al., 2014).

There is significant complexity in calculating whole body fuel utilisation during an ultra-endurance event, as the fitness level, course topography, and environment conditions ultimately influence relative exercise intensity and dictates carbohydrate (CHO) *vs.* fat utilization rates of a given athlete. During prolonged exercise, energy provision predominates from aerobic metabolism, which utilizes a combination of both fat and CHO energy substrate. Fat is the primary fuel substrate utilized during low intensity exercise, and can be trained to be up-regulated at a given relative exercise intensity (Bergman et al., 1999) or in response to dietary fat or ketogenic adaptation (Burke et al., 2017; Volek et al., 2016). It is well established that CHO oxidation is more aerobically efficient and economical than fat oxidation; with 5.0kCal/L of O_2 consumed produced when oxidizing 100% CHO, compared with 4.7kCal/L of O_2 from 100% fat (Krogh & Lindhard, 1920). For example, shifts in the respiratory quotient from 0.90 to 0.95 (66% to 83% CHO oxidation, respectively) will theoretically improve running economy and ~ 2h elite marathon performance by 60–90s. Nevertheless, total endogenous muscle (i.e. 1500–2000kCal) and liver (i.e. ~ 400kCal) glycogen stores are rather limited, and increasing exercise intensities, especially at ≥ 70% of peak oxygen uptake, increases overall muscle glycogen utilisation and subsequent depletion (Rapoport, 2010). Conversely, endogenous fatty acid stores are substantial, but do not provide muscle contractile energy (i.e. adenosine triphosphate) at rates that sustain higher intensity exercise or high force contractions. From an ultra-endurance perspective, such contractile force could be associated with braking and climbing against gravity on undulating or extreme course topographies. For ultra-endurance sports, many would argue that central fatigue, thermal stress, muscle damage, and/or the limited endogenous muscle glycogen content and blood glucose availability are the major limiting factors to endurance performance. Such fuel burdens, however, may be circumvented by either increasing exogenous CHO fuelling and/or increasing endogenous fat oxidation rates at a given intensity. Theoretically, a fat or ketogenic adapted athlete could provide 700 to 800kCal/h of energy from fat oxidation alone (Burke et al., 2017; Volek et al., 2016). Accordingly, if exercise duration is long enough (e.g. ≥ 10h) and exercise intensity low enough (e.g. 45–60% of maximal oxygen uptake ($\dot{V}O_{2max}$)) an athlete might benefit from fat or ketogenic adaptation for performance, but this requires further substantiation and validation over ultra-endurance events to confirm (McSwiney et al., 2018).

General ultra-endurance daily macronutrient recommendations

Since 2000, nutrition consensus statements have recommended daily CHO intake to be individually adapted to the energy expenditure demands relative to the athlete's body weight (3–12g/kg/day) (Thomas et al., 2016). Beyond the scope of this review, emerging scientific evidence suggests the possibility of strategically conducting some acute training sessions in a low-glycogen state to potentially induce greater endurance training adaptations (Hawley & Burke, 2010; Impey et al., 2016). Interestingly, the self-selected daily CHO intake of world-class African runners is > 70% of total energy accounting for > 10gCHO/kg/day (Fudge et al., 2006; Onywera, Kiplamai, Boit, & Pitsiladis, 2004).

Recent reviews have hypothesized that increasing numbers of ultra-endurance athletes purposely undertake chronic low-CHO ketogenic diets in the belief that such dietary behaviors maximize fat oxidation, prevent glycogen depletion, and improve endurance performance (Volek, Noakes, & Phinney, 2015). In this context, to reach nutritional ketosis, it is generally recommended that individuals consume < 50g CHO/day over > 3 weeks (Burke et al., 2017; Phinney, Bistrian, Evans, Gervino, & Blackburn, 1983). Indeed, ketogenic diets have consistently shown a doubling of peak fat oxidation rates at exercise intensity of 60–80% $\dot{V}O_{2max}$, compared to a high-CHO diet (1.5–1.8g/min *vs*. 0.5–0.6g/min, respectively) (Burke et al., 2017; McSwiney et al., 2018; Phinney et al., 1983; Volek et al., 2016). However, high fat oxidation rates also appear to be inherent in ultra-endurance athletes regardless of background macronutrient dietary modifications, as a recent study (n = 15 men) found a wide range of fat oxidation rates (0.84–1.74g/min) over 3h of running at 60% $\dot{V}O_{2max}$ while adhering to a macronutrient balanced diet (20% protein, 52% CHO, 28% fat) (Costa et al., 2017a). Although the ketogenic ultra-endurance performance hypothesis is intriguing, supporting evidence does not provide or cite empirical performance improvements. More recently, a definitive 3 weeks ketogenic dietary intervention study was conducted on a cohort of elite 50km race-walkers (Burke et al., 2017). Similar to previous studies, a significant increase in total fat oxidation was found in the ketogenic diet group; but as consistently shown, low-CHO high-fat and ketogenic diets caused a reduction in exercise economy (increased oxygen cost of exercise), which translated into a lack of enhanced endurance exercise performance compared to the high or periodized CHO groups. Similarly, no substantial difference in 100km cycling time trial performance was observe between low-CHO high-fat ketogenic and high-CHO dietary groups after 12-weeks of a training and dietary intervention (McSwiney et al., 2018).

The daily protein intake requirements for endurance athletes have been measured at 1.5–1.8g/kg/day (Kato, Suzuki, Bannai, & Moore, 2016; Tarnopolsky, 1999). However, these subjects were nowhere close to training loads typical of elite ultra-endurance athletes (e.g. > 20h/week). During endurance exercise, protein oxidation can provide 2–10% of total energy expenditure, especially during situations when muscle glycogen becomes limited (Tarnopolsky, 1999). Interestingly, Tour de France cyclists and elite Kenyan runners self-select 2.0–2.5g/kg/day of protein (Onywera et al., 2004; Saris, Van Erp-Baart, Brouns, Westerterp, & Ten Hoor, 1989); which may be required to stay in nitrogen balance as a result of augmented training induced protein oxidation. Accordingly, more well-controlled protein balance data are needed in elite endurance athletes with very high training loads to ascertain daily protein requirements in these extreme exertional situations.

Fuelling during ultra-endurance activities

The scientific literature has consistently demonstrated that ingesting CHO throughout competition should augment ultra-endurance performance (Jeukendrup, 2011; Sawka et al., 2007; Stellingwerff & Cox, 2014). Indeed, a recent systematic review (n = 679 subjects; 61 papers) showed that 82% of published endurance-based papers showed significant performance benefits by consuming CHO *vs*. water alone (Stellingwerff & Cox, 2014). From an ultra-endurance perspective, a significant correlation between total exercise time and performance improvements with CHO quantity was also observed. Furthermore, glucose-fructose CHO blends (e.g. 1:1 to 2:1 ratios) have been shown to be superior in augmenting CHO oxidation and performance over single blends (e.g. glucose alone). However, the maximal amount of CHO oxidation through intravenous infusion, thus by-passing the gut, is ~ 2g/min (Hawley, Bosch, Weltan, Dennis, & Noakes, 1994). Therefore, from a theoretical perspective, CHO consumption during ultra-endurance exercise should not go beyond ~ 120g/hr, even with the consumption of CHO blends. Conversely, gastric emptying rates of CHO rich fluids during exercise appear to be more limited, and dependant on several factors (e.g. individual body mass, volume, nutrient content, osmolality, and temperature) (Leiper, 2015). It has recently been established that consuming CHO quantities above individual gastrointestinal tolerance levels (i.e. gastric emptying, digestibility, and absorption capabilities) and muscle total CHO oxidative capabilities, irrespective of the CHO blend, during prolonged strenuous exercise may lead to malabsorption and GIS (Costa et al., 2017a; Miall et al., 2018). In cases where tolerance to CHO intake during exercise is an issue, mouth rinsing with a CHO beverage may enhance the maintaining of workload, especially at the point of muscle glycogen depletion, through the oral-cortex sensory network (i.e. oral carbohydrate receptors sending positive signals to the insula operculum, orbitofrontal cortex, and striatum) that generate negative feedback to peripheral strain (Jensen, Klimstra, Sporer, & Stellingwerff, 2018; Peart, 2017). Overall, individual exercise specific assessment for CHO gastric tolerance, digestibility, absorbability, and oxidation is recommended, with outcomes being integrated into competition nutrition plans (Table 1).

A more recent descriptive study analyzed the fuelling intakes of three elite ultra-endurance runners, (Stellingwerff, 2016). Throughout their respective 161-km races, athletes consumed 76gCHO/h, which aligns with contemporary recommendations (Jeukendrup, 2011; Stellingwerff & Cox, 2014). In further support, Yannis Kouros, considered the best ultra-endurance runner of all-time, averaged 96gCHO/h while running over a 5-day 960km ultramarathon event (Rontoyannis, Skoulis, & Pavlou, 1989). And, a recent 5-day 250km ultramarathon laboratory-controlled simulation at 55% $\dot{V}O_{2max}$ showed that consuming 75.0gCHO/h of a 2:1 glucose-fructose blend resulted in less walking time, lower rating of perceived exertion and subjective fatigue, and lower stress hormone and inflammatory cytokine responses compared with 32.5gCHO/h, despite a heavier carrying load (14.0kg *vs*. 9.2kg pack weight, respectively; Alcock et al., 2018). From a recreational ultra-endurance athlete perspective, individual assessment for gastrointestinal and total CHO oxidation capacity during exercise in ultra-endurance runners

Table 1. (A) Practical recommendations for individualised fuelling during ultra-endurance participation, and (B) prevention and management pathway for GIS originating from exercise-induced gastrointestinal syndrome.

A. Practical Recommendations

- Practice with carbohydrate habituation in training sessions, and specifically focus on race nutrition quantity (g/h) and quality (food and fluid forms). Optimal race nutrition training should be conducted at goal race pace and in projected race weather conditions.
- Continually experiment with different carbohydrate intake rates (thus altered % carbohydrate solutions) to find an optimal individual solution. Start with increasing fluid volumes, and then try increasing carbohydrate concentration.
- Continually experiment with different carbohydrate types (e.g. blends such as glucose-fructose) and forms (e.g. fluids, gels, bars, fruits, and other carbohydrate rich foods).
- Undertake a gastrointestinal assessment during exercise to establish individual tolerance to carbohydrate types and forms.
- Alter the acute rate of intake (e.g. spread a 250ml drink over several minutes), and experiment with higher intake rates early in a race when GIS are generally lower.
- Practice in less important races to try and identify "outside" contributing factors (e.g. travel effects, competition stress, changes in habitual food availability, weather conditions, and pacing).
- Experiment with different bottled water brands both chronically (throughout the day) and during exercise (to use with carbohydrate gels and powders), to minimize effects of different electrolytes and other purification ingredients. This is especially important to consider when racing in different countries.
- Use carbohydrate mouth washing to maximise performance outcomes while minimising or exacerbating GIS. This can be especially beneficial in the late stages of races when GIS is generally worse.
- In longer races (≥ 8h) experiment with various easily digestible solid food sources of energy; such as pretzels, soups, potato chips, panni's, rice cakes, etc.

B. GIS Prevention & Management

Essential:

- Gut challenge assessment during exercise for identification of primary causal mechanism and secondary gastrointestinal integrity and functional outcomes.
- Identify and manage extrinsic and intrinsic exacerbation factors.

First line action	Adjunct strategies	Unlikely to help
- Start exercise euhydrated and maintain throughout (within individual tolerance). - Identify individual carbohydrate tolerance & oxidation rates. - Carbohydrate consumption before and frequently throughout exercise. - Gut training protocol.	- Protein before and throughout exercise within tolerance. - Fluid intake of cold beverages. - Short term low FODMAP diet after assessment to establish tolerance. - Antiemetic administration.	- Antioxidants, sodium, L-citrulline, L-arginine, glutamine, and bovine colostrum supplementation. - Probiotics: commercial beverage and/or capsules, single or multi-strain, with and without additions (e.g. prebiotics, antioxidants, or amino acids). - Gluten free diet for non-coeliac individuals.

Other potential beneficial recommendations:

- Considering any content entering the stomach through food and/or fluid ingestion will stimulate the gastric-colonic reflex (i.e. acute rapid onset of defaecation urgency), attempt to evacuate and empty bowels prior to the commencement of exercise.
- Undertake a gastrointestinal assessment during exercise to establish exercise-associated malabsorption, especially of high FODMAP sources (e.g. fructose, lactose, sorbitol, mannitol, and lupin flour) that are common ingredients found in sports nutrition products, and adapt pre- and during exercise nutrition accordingly.
- Avoid NSAID medication in the day leading up to, immediately before, and during ultra-endurance events (both single and multi-stage). Choose appropriate pain management medications that do not aggravate the gastrointestinal tract (e.g. paracetamol).
- Despite limited empirical evidence, it has frequently been reported by ultra-endurance athletes that consuming high fibre food leading into and during single- and multi-stage events results in increased lower-abdominal discomfort, flatulence, urge to defecate, defaecation, and abnormal sools (e.g. loose and watery stools, and diarrhoea). In such cases, high fibrous foods and fluids should be avoided and alternatives adopted.

and triathletes showed average values of 1.0g/kg/min and 0.8 g/kg/min in men and women, respectively (Costa et al., 2017a). Conversely, despite limited empirical evidence, there have been testimonials and anecdotally reports of ketogenic ultra-endurance athletes demonstrating improved endurance performance on limited CHO intake (Noakes, Volek, & Phinney, 2014); theoretically due to their augmented fat oxidation rates. Although this type of intervention is energetically plausible, field and laboratory-controlled studies and methodologies are required to substantiate these claims.

Gastrointestinal perturbations and symptoms

Gastrointestinal symptoms during ultra-endurance activities

GIS are a common feature of ultra-endurance sports, with 60 to 96% incidence rate of severe upper- (gastro-oesophageal and gastro-duodenal originated: regurgitation, urge to regurgitate, gastric bloating, belching, stomach pain, and heartburn/gastric acidosis) and lower- (intestinal originated: flatulence including lower-abdominal bloating, urge to defecate, abdominal pain, abnormal defecation including loose water stools, diarrhoea and blood in stools) GIS, and/or other related symptoms (e.g. nausea, dizziness, and acute transient abdominal pain) during ultra-endurance events (Costa et al., 2016; Jeukendrup et al., 2000; Stuempfle & Hoffman, 2015; Stuempfle, Hoffman, & Hew-Butler, 2013). GIS have been reported as major factors associated with withdrawal from competition, and linked to severe clinical episodes of acute colitis with accompanying faecal blood loss (Costa et al., 2017b; Hoffman & Fogard, 2011).

Primary causal mechanisms and secondary outcomes

The causes of adverse GIS during and after ultra-endurance events appear to be multi-factorial in nature, but all can be linked to an "*exercise-induced gastrointestinal syndrome*" (Figure 1). Costa et al. (2017b) provides a thorough description of primary causal mechanisms and associated secondary outcomes of exercise-induced gastrointestinal syndrome.

Extrinsic factors such as exercise mode/intensity/duration, environmental conditions (especially heat), and the use of non-steroidal anti-inflammatory drug (NSAIDs, e.g. aspirin and ibuprofen) have been shown to exacerbate gastrointestinal disturbances (Costa et al., 2017b; Horner, Schubert, Desbrow, Byrne, & King, 2015; Snipe, Khoo, Kitic, Gibson, & Costa, 2018a, 2018b; Temesi et al., 2014; ter Steege & Kolkman, 2012). Moreover, intrinsic factors such as individual feeding tolerance during exercise, active or predisposition to gastro-intestinal diseases/disorders, and possibly the total bacterial abundance and diversity of the gastrointestinal microbiome may also determine the occurrence and magnitude of exercise-induced gastrointestinal syndrome (Costa et al., 2017b). The management of these exacerbating factors appears to be the first line action in reducing gastrointestinal perturbations and symptoms associated with extreme endurance exercise (Table 1). Whereas, certain dietary strategies before and/or during exercise may also be beneficial, favourable, neutral, or damaging in supporting gut health and performance in ultra-endurance athletes (Figure 2).

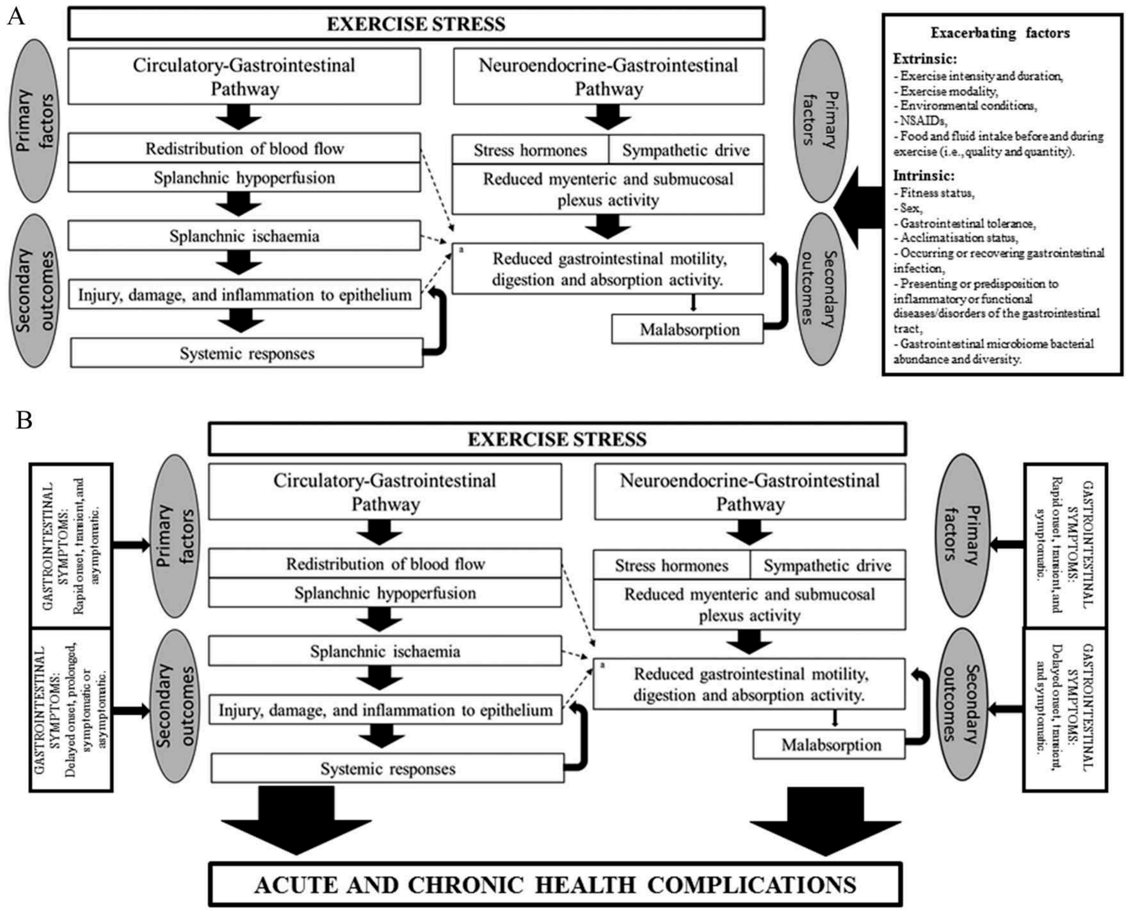

Figure 1. Schematic description of exercise-induced gastrointestinal syndrome and factors that exacerbate disturbances to the circulatory-gastrointestinal and neuroendocrine-gastrointestinal pathways (A) and potential pathway links to gastrointestinal symptoms (B). With permission, adapted and modified in accordance with Costa et al., 2017b.

[a] Splanchnic hypoperfusion and subsequent gastrointestinal ischaemia results in alterations to gut motility. NSAIDs: Non-steroidal anti-inflammatory drugs.

Hydration status

Pre-exercise dehydration before 90min of cycling at 70% $\dot{V}O_{2max}$ resulted in impaired gastric emptying, and greater GIS, compared with exercise commenced in a euhydrated state (Van Nieuwenhoven, Vriens, Brummer, & Brouns, 2000). Additionally, a 1.5% body mass (BM) loss in response to 1h of running at 70% $\dot{V}O_{2max}$ in moderately trained subjects was sufficient to increase gastroduodenal and intestinal permeability above resting levels (Lambert et al., 2008). This is supported by field and controlled laboratory studies in ultra-endurance populations, showing that progressive body water losses may exacerbate endotoxaemia, and subsequent cytokinaemia, in the post-exercise period (Gill et al., 2016, 2015a, 2015b). Conversely, it is important to bear in mind that over-hydration has also been associated with GIS (Hoffman et al., 2014). Recently, it has been shown that the temperature of ingested water during exertional-heat stress may influence the magnitude of exercise-induced gastrointestinal syndrome (Snipe & Costa, 2018). Water at 0°C or 7°C consumed pre-exercise and frequently during 2h running at 60% $\dot{V}O_{2max}$ in 35°C ambient conditions resulted in modest reduction in intestinal epithelial injury and upper-GIS, compared with water consumption at 20°C. Together these outcomes suggest that maintenance of euhydration with cooler fluids might be beneficial in ameliorating gastrointestinal disturbances associated with extreme endurance exercise, especially in hot ambient conditions.

Dietary modification

A substantial amount of testimonials and anecdotal comments exist in the public domain indicating improvements in GIS and sports performance on adherence to a gluten-free diet (Lis, Stellingwerff, Shing, Ahuja, & Fell, 2015). These anecdotes were recently examined via a double-blind randomised cross-over study, where participants adhered to a gluten-containing diet or gluten-free diet for seven-days. After the dietary

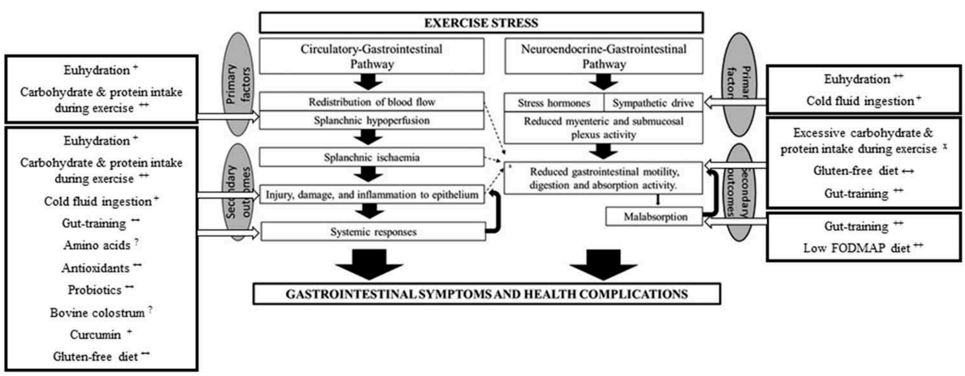

Figure 2. Schematic description of updated evidence for dietary modification and nutritional supplement interventions for the prevention and management of exercise-induced gastrointestinal syndrome. With permission, adapted and modified in accordance with Costa et al., 2017b.

++ Evidence of substantial beneficial effect; + some evidence of beneficial effect, but modest in nature; ↔ none or insufficient evidence of effect; ? inconclusive, unknown, and (or) conflicting efficacy. [b] Amino acids glutamine, L-arginine, and L-citrulline.

intervention, participants were asked to cycle at 75% of maximal power output for 45min followed by a 15min time trial. No difference in performance, gastrointestinal, intestinal injury or systemic cytokine responses were observed between groups (Lis, Stellingwerff, Kitic, Ahuja, & Fell, 2015). Considering the exercise stress of such an experimental model resulted in modest gastrointestinal perturbations (Costa et al., 2017b), the translation of these findings into ultra-endurance sports, particularly ultra-marathon running, remains to be determined. Nevertheless, the perceived improvements in GIS and performance reported by many non-coeliac athletes following a gluten-free diet appear not to be predominantly due to any physiological alteration to the GI tract in response to acute exercise.

Alternatively, perceived improvements in GIS may be associated with reductions in dietary fermentable oligo- di- mono-saccharides and polyols (FODMAP), as emerging evidence has demonstrated improved exercise-associated GIS with short-term (i.e. as little as 24 h) adherence to a low FODMAP diet (Costa, Snipe, Kitic, & Gibson, 2017c; Snipe et al., 2018a, 2018b). For example, two case studies have confirmed that a six-day low FODMAP diet (i.e.≤ 7g/day) resulted in an abolition of exercise-associated GIS during running and rest periods in ultra-endurance athletes, with and without gastrointestinal disease/disorder (Gaskell & Costa, 2018; Lis, Ahuja, Stellingwerff, Kitic, & Fell, 2016). Moreover, a recent study has shown significantly less daily resting GIS in 80% of recreationally competitive endurance runners with persistent exercise-associated GIS, from a 6-day low FODMAP (8.1g/day) compared to a high FODMAP (41.4g/day) diet (Lis, Stellingwerff, Kitic, Fell, & Ahuja, 2018). Considering this study failed to observe changes in GIS during exercise between groups, potentially due to insufficient exertional-stress required to induce any adverse symptoms (Costa et al., -2017b), it is still unknown whether a low FODMAP diet supports GIS prevention or amelioration in responses to extreme endurance exercise.

Nutritional supplementation and medications

Various nutritional supplement interventions have been proposed to optimise gastrointestinal integrity and/or function in response to exercise in humans. These include: antioxidants (i.e. ascorbic acid, tocopherol), certain amino acids (i.e. L-arginine, glutamine, and L-citrulline), bovine colostrum, curcumin, and probiotics. Considering nutritional supplement interventions primarily target the secondary outcomes of exercise-induced gastrointestinal syndrome (Figure 2), it is unlikely that these play any substantial role in preventing the primary causal mechanisms, with only amelioration of secondary outcomes potentially feasible, and no evidence of prevention or reduction in exercise-associated GIS. Therefore, to date, the use of nutritional supplements for preventing and managing exercise-induced gastrointestinal syndrome, and associated GIS in ultra-endurance activities is not justified (Costa et al., 2017b).

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used during ultra-endurance events (Didier et al., 2017) yet are known gastrointestinal irritants, affecting stomach gastric secretions and bicarbonate release in the duodenum, and causing erosion of the mucosal lining along the gastrointestinal tract. NSAID use has been linked to gastrointestinal injury and dysfunction, including nausea, regurgitation, dyspepsia, gastrointestinal ulceration, gastrointestinal bleeding, and abnormal defecation (e.g. diarrhoea;

Warden, 2010). Increases in intestinal injury, and increased gastroduodenal and intestinal permeability can be markedly increased after exercise with the use of NSAIDs (e.g. aspirin or ibuprofen administration) before exercise (Lambert, Boylan, Laventure, Bull, & Lanspa, 2007; Ryan, Chang, & Gisolfi, 1996). Moreover, I-FABP (marker of intestinal injury) was elevated by ~ 85% after endurance cycling in which 400mg of ibuprofen was administered before exercise compared with no ibuprofen administration (Van Wijck et al., 2012). How NSAID induced increases in gastrointestinal permeability and epithelial damage translates to the incidence and severity magnitude of GIS is still uncertain, especially in ultra-endurance activities. On the contrary, the antiemetic ondansetron, dispensed as 4mg orally dissolving tables, has recently been found to reduce nausea and vomiting in 66% of symptomatic participants taking the drug during a 160km ultramarathon (Pasternak, Fiore, & Islas, 2018). These outcomes suggest ondansetron may play a part of the field practitioners' tool kit in the prevention and management of exercise-associated GIS.

Macronutrient intake during exercise

The most impressive outcomes in preventing and/or attenuating exercise-associated perturbations to epithelial integrity, systemic responses and GIS have been with CHO supplementation during exercise and gut-training. For example, CHO consumption during exercise maintains splanchnic perfusion (Rehrer, Goes, DuGardeyn, Reynaert, & DeMeirleir, 2005) and reduces intestinal permeability in response to exercise stress and NSAID administration with adjunct glutamine supplementation having no additional benefit (Lambert, Broussard, Mason, Mauermann, & Gisolfi, 2001). An abolition of epithelial injury, reduced small intestinal permeability, and improved endotoxin profile have been observed with the consumption of 15g of glucose pre-exercise and every 20min during running at 60% $\dot{V}O_{2max}$ in 35.0°C ambient conditions, compared with water alone (Snipe, Khoo, Kitic, Gibson, & Costa, 2017). Such quantities of CHO (45g/h) appear to be well tolerated, showing no significant increases in GIS compared with water alone. Interestingly, 15g of whey protein hydrolysate administered pre-exercise and every 20min during running in the heat also resulted in similar beneficial GI integrity outcomes as CHO. However, symptoms were substantially higher, suggesting difficulties in tolerating protein during exercise stress (Snipe et al., 2017).

Despite general advice to practice race nutrition in training, to date, two publications have comprehensively reported outcomes of a strategic gut-training protocol to prevent or attenuate exercise-associated GI symptoms. A two weeks period of daily repetitive gut-challenge using 90g/h multi-transportable CHO (2:1 glucose-fructose ratio) or a CHO rich food during 1h of running at 60% $\dot{V}O_{2max}$ resulted in substantial reduction in gut discomfort, upper-, and lower-GIS in response to a 3h gut-challenge trial, with no substantial changes from placebo observed (Costa et al., 2017a; Miall et al., 2018). Considering improvements in GIS were observed across a wide range of runner characteristics (e.g. level, gender, and symptom history), these outcomes suggest all ultra-endurance athletes might benefit from a structured gut-training protocol for two-weeks leading into competition.

Conclusions

The various causes of fatigue during ultra-endurance activities are scientifically ambiguous, but potentially include central and peripheral fatigue, thermal stress, dehydration, and/or endogenous glycogen store depletion; all of which can be attenuated through optimising nutrition and hydration. In the context of ultra-endurance exercise stress it is bioenergetically plausible, from a theoretical perspective, that ketogenic adaptation may enhance ultra-endurance performance, but this requires substantiation. Conversely, the literature clearly demonstrates that dietary CHO prior to and CHO intake during ultra-endurance activities, within individually identified tolerable levels, can enhance performance and promote gastrointestinal tract and systemic benefits.

Exercise-induced GIS have the potential to impair endurance exercise performance and have acute and/or chronic health implications. Recent findings suggest that management of exacerbating factors, maintenance of euhydration using cool fluids, consuming tolerable amount of CHO during exercise, acute FODMAP restriction, avoidance of NSAIDs and potentially antiemetic dispensing are promising strategies to moderate alterations in gastrointestinal integrity and function, and associated symptoms, in response to ultra-endurance exercise. Other aforementioned strategies are more ambiguous in nature and their true clinical relevance is not certain.

An individualised approach is essential for an efficacious nutritional support intervention in athletes participating in ultra-endurance sports. This advancing area of research is anticipated to improve knowledge and understanding, from a research and practitioner perspective, for the optimal nutritional intervention for those participating in ultra-endurance activities.

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