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Review

Exercise-Induced Gastrointestinal Symptoms in Endurance Sports: A Review of Pathophysiology, Symptoms, and Nutritional Management

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Abstract: Strenuous exercise can be associated with "Exercise Induced Gastrointestinal Syndrome" (Ex-GIS), a clinical condition characterized by a series of gastrointestinal (GI) disturbances that may impact the physical and psychological performance of athletes. The pathophysiology comprises multi-factorial interactions between the GI tract and the circulatory, immune, enteric, and central nervous systems. There is considerable evidence for increases in the indices of intestinal damage, permeability, and endotoxemia associated with impaired gastric emptying, slowing of small intestinal transit, and malabsorption of nutrients. Heat stress and racing mode seem to exacerbate these GI disturbances. GI symptomatology that derives from strenuous exercise is similar to that of IBS and other GI functional disorders defined in the Rome IV Criteria. To manage Ex-GIS, the exercise modality, state of dehydration, environmental temperature, concomitant therapies, and self-managed diet should be evaluated, and if risk elements are present, an attempt should be made to modify them. Multiple strategies can be successively adopted to manage Ex-GIS. Nutritional and behavioral interventions appear to be the principal ones to avoid symptoms during the exercise. The aim of this review will be to explore the pathophysiology, clinical aspect, and current literature on behavioral and nutritional strategies to manage Ex-GIS, regarding a gluten-free diet and low-fermentable oligo-, di-, and mono-saccharides and polyols (FODMAP) diet.

Keywords: gastrointestinal symptoms; endurance sport; diet; IBS

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1. Introduction

Physical activity has many positive effects on health, especially on the musculoskeletal, cardiovascular, and gastrointestinal (GI) systems. Its effect depends on the intensity, duration, and modality of physical activity. Mild- to moderate-intensity exercise with a regular duration (e.g., between 3.5 and 4 h per week) plays a protective role against colon cancer, diverticular disease, gallstones, and constipation [1,2]. On the other hand, strenuous exercise and endurance sports may cause exercise-induced gastrointestinal symptoms (Ex-GISs) in up to 70% of athletes, and they can manifest as upper symptoms (e.g., regurgitation, upper abdominal bloating, belching, epigastric pain, and heartburn) and lower symptoms (e.g., flatulence, urge to defecate, lower abdominal bloating, abdominal pain, abnormal defecation including loose water stools, diarrhea, and fecal blood loss) [3]. Endurance exercise is considered a sport aimed at improving the ability to sustain intense physical activity over time, without significant loss of performance. Endurance includes different physical activities with different levels of intensity and thus workouts can differ greatly according to the disciplines practiced. Cycling, swimming, marathons, triathlons, running, mountain

biking, and climbing are some of those considered endurance sports simply because they require an expenditure of energy for a long time [4]. Ex-GIS might result from responses to exercise that compromise gastrointestinal integrity and function and may even be the reason why some stop sports participation [3]. The mechanisms leading to GI discomfort during exercise are not yet fully understood [5]. Exercise responses may involve two different pathways: a circulatory–gastrointestinal pathway [6] and a neuroendocrine–gastrointestinal pathway [7]. The combination of splanchnic hypoperfusion and altered enteric nervous system activity may result in a compromised GI system. The loss of epithelial integrity observed during strenuous physical exercise leads to increased intestinal permeability with bacterial translocation and inflammation. This alteration may negatively impact exercise performance and post-exercise recovery due to abdominal distress and impairment in the uptake of fluid, electrolytes, and nutrients. Exercise may also have a substantial impact on gut microbiota (GM) composition and structure, but the role of the microbiota in exercise adaptation remains unknown [8]. Notable differences have been described between competing athletes and inactive people. Zhao et al. [9] examined the GM and fecal metabolites of amateur runners before and after a half marathon, and they showed shifts in the relative abundance of the GM at several different taxonomic levels [9]. Therefore, there is a need to integrate the evidence more comprehensively for all elements of exercise-associated GI disturbances. In this light, the purpose of this article is firstly, to review the physiological and pathophysiological changes of the GI tract during endurance exercise, exploring the pathophysiology of Ex-GIS; secondly, to describe the clinical aspects of the syndrome and its effect on athletes' performances; and thirdly, to review the current literature on behavioral and nutritional strategies to manage the condition, with particular regard to dietetic regimens adopted by athletes to reduce symptoms.

2. Methods

Three databases (PubMed, MEDLINE, Cochrane, Canada) were searched for relevant publications. The search was performed up to March 2023. The search strings utilized for the chapter's introduction and pathophysiology of Ex-GIS, proposed mechanisms for GI distress, and gastrointestinal symptoms during exercise were "endurance", "endurance sports", "endurance activity", "gastrointestinal symptoms", and "exercise-induced gastrointestinal symptoms". We identified studies published from 1965 to 2023. The search performed in PubMed returned 290 results, in MEDLINE 216 results, and in the Cochrane library 97 trials. The search strings utilized for the chapters nutritional and behavior strategies to reduce Ex-GIS and efficacy of specific diets applied by endurance athletes to avoid Ex-GIS were "endurance", "endurance sports", "endurance activity", "diet", and "nutrition". We identified studies published from 1972 to 2023. The search performed in PubMed returned 2663 results, in MEDLINE 2197 results, and in the Cochrane library 1038 trials. The selection process began with the evaluation of the title and the abstract of the works. All the works in which the keywords and the purposes of the review were not present were excluded. In terms of inclusion criteria, only studies in the English language were selected. Studies that did not address the impact of diet on endurance performance or health-related parameters were excluded. Finally, the authors discussed the research findings and selected the studies that were clinically and practically relevant for the purposes of this review. Based on our inclusion and exclusion criteria, we identified 142 research articles.

3. Pathophysiology of Ex-GIS: Proposed Mechanisms for GI Distress

The pathophysiology of Ex-GIS includes two primary pathways: (I) the neuroendocrine–gastrointestinal pathway, involving an increase in sympathetic activation, reducing overall GI functional capacity [3] and (II) the circulatory–gastrointestinal pathway, involving the redistribution of blood flow to working muscles and peripheral circulation, subsequently reducing total splanchnic perfusion and nutrient absorption [10,11]. It is still under debate whether the neuroendocrine pathway may affect the circulatory–gastrointestinal one and, in cascade, reduce the total splanchnic perfusion, or

whether the splanchnic hypoperfusion in response to the intensity/duration of muscle activity may influence the neuroendocrine activation. It is plausible that the combination of the altered enteric nervous system activity and the splanchnic hypoperfusion may result in GI symptoms and/or in acute or chronic health complications [5]. The proposed mechanisms for gastrointestinal discomfort are summarized in Figure 1.

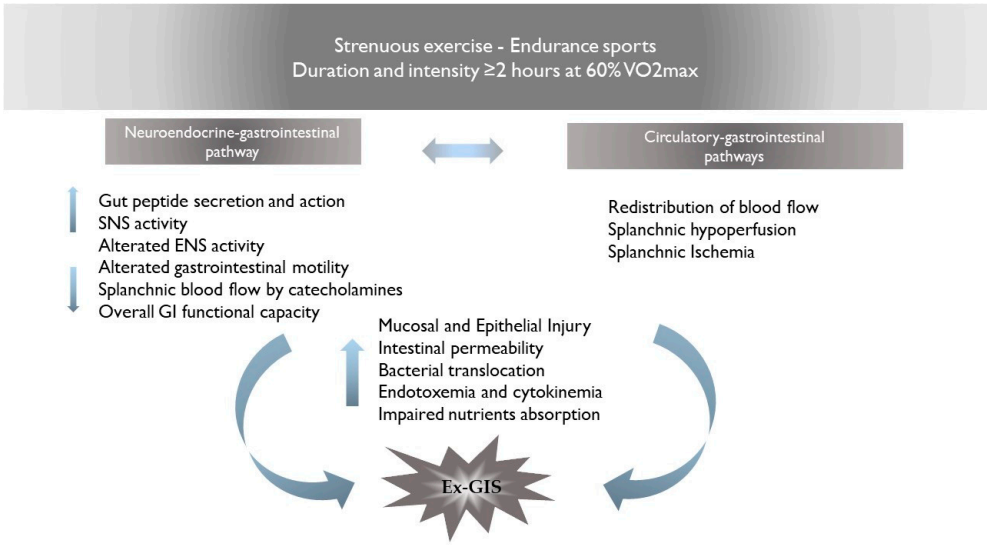

Figure 1. Proposed mechanisms for Ex-GIS pathophysiology. Abbreviations: Ex-GIS: exercise-induced gastrointestinal symptoms; VO2max: maximal oxygen consumption; SNS: sympathetic nervous system; ENS: enteric nervous system.

3.1. Neuroendocrine–Gastrointestinal Pathway

The alteration of the enteric nervous system (ENS) activity, through a cascade of events, results in clinical complications and GI symptoms known as Ex-GIS. Physical activity induces sympathetic activation, which is considered the main cause of altered ENS activity [12,13]. The digestive system is controlled by the bidirectional activity of the central nervous system (CNS) and the ENS, both of which participate in the regulation of the various functions of the intestines. ENS can independently regulate GI functions without central input. Indeed, the ENS is considered a quasi-autonomous part of the nervous system including several neural circuits that control motor functions, local blood flow, and mucosal transport and secretions and modulate immune and endocrine functions [14]. Enteroendocrine cells (EECs), which are basal-granulated cells dispersed in the gut epithelium, represent the endocrine elements of the intestine and release gut peptides, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY), all having an anorectic effect. Ghrelin, on the other hand, is an orexigenic peptide produced by the enteroendocrine cells in the oxyntic glands of the stomach and upper intestine; thus, its plasma levels are high before meals and are suppressed in response to food intake [15]. These neuropeptides act either in a paracrine fashion on both intestinal and neural cells in proximity or enter the bloodstream and can have peripheral effects, such as change in gastric emptying and gut motility [16]. Briefly, CCK is synthesized and released from I cells of the upper intestine in response to food intake. It slows down gastric emptying and stimulates pancreatic and gallbladder secretions. CCK exerts its satiety action primarily through the activation of vagal afferent fibers innervating both the stomach and the upper intestine [17,18]. CCK levels rapidly increase after food ingestion, present a peak a few minutes after meal initiation, and decline to baseline levels with meal termination [19]. In contrast, the other gut peptides have patterns of release and actions that are consistent with effects beyond the meal. Indeed, plasma levels of both PYY and GLP-1, which are synthesized and released from L cells located primarily in the distal intestine, occur more slowly, not peaking until after meal termination and remaining high for several hours after

a meal [20,21]. Both PYY and GLP-1 inhibit food intake. Few data are currently available regarding the modification of gut peptide levels in response to physical activity. Various animal and cell models have demonstrated that the activation of adenosine receptors induces the release of GLP-1 and PYY from EECs [22,23], and concentrations of both are increased during moderate- and high-intensity exercise. Moreover, exercise induces the vago-vagal reflex from the brain back to the gut [24], which plays a role in the ability of CCK to regulate gastric emptying and intestinal motility [25]. Some studies have evaluated the modifications of gut peptide levels in response to different kinds of exercise. Halliday TM and colleagues demonstrated that circulating concentrations of the anorexic gut peptides, namely PYY and GLP-1, are increased following aerobic exercise as compared to resistance exercise and that circulating concentrations of the orexigenic gut peptide, namely ghrelin, are also higher following aerobic exercise and sedentary control vs. resistance exercise [26]. Other similar results were reported by Broom et al. [27] and Balaguera-Cortes et al. [28]; they both found blunted ghrelin responses to resistance exercise as compared to aerobic exercise. Furthermore, enteric neurons contain receptors for GABA, serotonin, and dopamine, neuropeptides that have been found to be influenced by exercise [29]. In detail, high-intensity exercise causes an increase in GABA concentrations in the sensorimotor cortex, while acute exercise increases plasma dopamine levels [30]. Although exercise induces changes in neuropeptides and may affect enteric neuron activation and function, it is not fully known whether exercise directly affects local levels of enteric neuropeptides. It is plausible that alterations in gastric emptying and gut motility during exercise are due, at least in part, to increased gut peptide secretion and action. Among the neurotransmitters, catecholamines and serotonin have recently been a topic of interest because of their roles in gut physiology and their potential roles in GI and CNS pathophysiology. There are three main catecholamines: norepinephrine (noradrenaline) and epinephrine (adrenaline), which are peripheral catecholamines, and dopamine, which is a central-acting catecholamine. As mentioned above, endurance exercise increases sympathetic nervous system (SNS) activity, increasing the circulating concentrations of norepinephrine and epinephrine [31]. The main function of norepinephrine is in vascular smooth muscle; indeed, it mainly acts on the alpha receptors at all concentration ranges, and causes vasoconstriction, increased vascular resistance, and decreased overall blood flow to the intestine. Epinephrine instead acts in a dual way; at low doses, it stimulates the beta receptors, leading to vasodilation, meanwhile at high doses, it acts similarly to norepinephrine and causes vasoconstriction. Finally, dopamine receptor affinity is also concentration-dependent and, indeed, low dopamine levels cause vasodilation and increased splanchnic blood flow through interaction with D1 receptors, meanwhile at high doses, it acts like the other catecholamines and can be classified as a vasoconstrictor, decreasing splanchnic blood flow [29]. Serotonin exerts a wide range of actions on the GI tract by binding to seven classes of specific receptors (5-HT1 to 5-HT7), each of which produces its own response. For instance, 5-HT4 agonists relieve visceral pain and increase intestinal motility [32], while the activation of 5-HT3 receptors following the ingestion of irritants causes a rise in serotonin release by EECs, which in turn increases peristalsis and causes diarrhea. Regarding exercise-induced motility changes, data available to date are not unique, and many variables need to be considered. The duration and intensity of exercise, for example, may have different effects on the ENS, and while a short duration (i.e., <60 min) appears to promote GI motility, more prolonged (i.e., up to 90 min) exercise may cause inhibition [5]. Likewise, low-intensity exercise has little effect on GI motility, meanwhile in more vigorous exercise, ESN and relative GI functions become progressively inhibited [5]. Therefore, it can be assumed that most changes occurring in the intestinal tract are intensity- and duration-dependent and that exercise stress of $\geq$2 h at 60% VO2max may represent the threshold at which significant GI perturbations manifest [5]. Specifically, motility alterations have been observed in different levels of the GI tract, including the esophagus, the stomach, and the intestines, and generally are summarized as a slow gastric emptying and a delay of orocecal transit time (OCTT). In more detail, esophageal modifications are represented by a decrease in

esophageal peristaltic activity, a decrease in lower esophageal sphincter tone, and increased transient lower sphincter relaxation, which together could be linked to gastro-esophageal reflux symptoms (GERD) experienced during exercise [33]. Effects on gastric emptying are less clear, and especially in this case, the intensity of physical activity appears to be the key regulator of the gastric emptying rate. Indeed, a very early work [34] reported no effect of moderate exercise on gastric emptying, while later studies demonstrated a reduction following very-high-intensity exercise or during intermittent activity [35]. Endurance sports, through stress and the potent sympathetic activation, cause the inhibition of gastric motility [36]. These data were also confirmed in an animal model, in which by decreasing the sympathetic activity through the electrical stimulation of the spinal cord, there was an increase in gastric emptying and intestinal transit [37]. Information about small intestine and colonic motility is scarce, and the impact of exercise on OCTT is unclear. For instance, Rao KA and colleagues measured OCTT using a telemetric pH sensor and demonstrated that symptomatic and asymptomatic runners presented similar small bowel and colonic transit times during rest and exercise sessions. Interestingly, the diarrhea seen in the study did not result from an accelerated colonic transit and hence the researchers concluded that other mechanisms must be sought [38]. In contrast, the OCTT measured with lactulose breath tests decreased in both running [39] and cycling [40,41]. Considering the heterogeneity of results and the complex interaction of hormonal and neurological factors in the control of motility, other studies are needed to better elucidate the effect of different kinds of exercise (duration, intensity, and mode) on OCTT [5].

3.2. Circulatory–Gastrointestinal Pathways

The splanchnic vasculature is a system with an extraordinary capacity to adapt to physiological stressors affecting vasodilation or constriction in response to neuroendocrine, humoral, and paracrine mechanisms [42]. During strenuous exercise, the release of norepinephrine generates splanchnic vasoconstriction, thereby raising total splanchnic vascular resistance [43]. Blood is rapidly redistributed from the splanchnic vasculature to the periphery for use in tissues with increased activity during exercise, such as the heart, lungs, active muscles, and skin [10]. As a result, the splanchnic blood flow (SBF) can be depleted by up to 80%, leading to significant gastrointestinal tract hypoperfusion and damage [44].

SBF hypoperfusion can be assessed through gastric tonometry [45], a functional test that measures the accumulated mucosal carbon dioxide (CO_2). In response to inadequate tissue perfusion and tissue hypoxia, the gap between gastric and systemic PCO2 reflects the adequacy of splanchnic perfusion [46]. The application of tonometry during exercise shows the most pronounced change in splanchnic perfusion during the first 10 min of strenuous exercise [11], indicating a rapid response of the splanchnic vascular bed. In addition, tonometry shows that splanchnic hypoperfusion can be aggravated by younger age, exercise intensity and duration, dehydration, and high environmental temperature [3]. The reductions in SBF are less conspicuous in the elderly (mean age 64 years) compared with younger people [47]. SBF hypoperfusion despoils enterocytes of oxygen and adenosine triphosphate (ATP), leading to cell damage and loss of epithelial integrity [48], which may be responsible for the mucosal erosions and GI bleeding observed during endoscopy after strenuous endurance running [49]. Consequently, the loss of epithelial integrity in the intestine is reflected by significantly increased plasma levels of intestinal fatty acid binding protein (I-FABP), a small cytosolic protein present in the enterocytes of the small intestinal villi, rapidly released into circulation upon cellular injury [50]. Van Wijck et colleagues demonstrated that 1 h of moderate physical exercise results in splanchnic ischemia followed by an increase in I-FABP, suggesting that hypoperfusion occurs in the early stages of exercise and intestinal epithelial damage occurs over time [11].

Loss of epithelial integrity, including disruption of the tight junctions interconnecting the intestinal epithelial cells, is associated with increased GI permeability, intestinal inflammation, and bacterial translocation [51]. Bacterial translocation induces endotoxemia, which is characterized by the presence of circulating bacterial lipopolysaccharides (LPSs).

Loss of tight junction integrity and/or enterocyte damage cause passage of LPSs into the circulation, which in turn triggers the activation of T lymphocytes, monocytes, and tissue macrophages. The local immune response induces the release of proinflammatory cytokines such as tumor necrosis factor and interleukin-1, interferon-γ, and nitric oxide (NO) [52], which can generate a vicious cycle that promotes greater intestinal barrier dysfunction through production of these mediators [53]. Brock-Utne and colleagues [54] provided the initial evidence that the intestinal barrier was being compromised during prolonged, strenuous exercise. In that study, 81% of the 89 marathon runners (89.4 km) were found to be endotoxemic [54]. Several other investigators have subsequently reported increased intestinal permeability and/or endotoxemia during strenuous exercise, intensified by heat stress conditions [55,56] or by dehydration [57]. Endotoxemia in resting humans produces GI symptoms, increased pro-inflammatory cytokine release, and fever. Similar effects are also likely mediated by endotoxemia during exercise heat stress [53]. In extreme endurance exercise where an increased intestinal permeability or significant increase in plasma LPS and pro-inflammatory cytokine concentration was described, GI symptoms such as nausea, vomiting, cramping, and diarrhea were reported [56,58,59].

The translocation of endotoxic microorganisms into circulation may also be dependent on the presence of indigenous bacterial species within the GI tract, such as *Enterobacteriaceae*, *Proteobacteria*, *Firmicutes*, *Bacteroides*, and *Actinobacteria* [40]. The impact of exercise on GM composition and structure needs to be mentioned in this context. Remarkable differences have been described between competing athletes and sedentary people, related to a huge microbiota ⍺-diversity in athletes—mostly associated with dietary patterns and protein consumption. ⍺-diversity is an index to describe the quality of the GM and is expected to decrease in disturbed conditions such as disease and poor health [60–62]. Zhao et al. described the GM and fecal metabolites of runners before and after a half marathon, demonstrating an increase in GM at several different taxonomic levels [9]. A total of 26 operational taxonomic units (OTUs) were detected in the group after running group, while 15 special OTUs were found in the before running group. Lentisphaerae and Acidobacteria, whose functions in the human gut are unknown, were the phyla specifically detected after running [9].

Interestingly, the modulation of microbiome diversity with an abundance of microorganisms known to enhance epithelial barrier and tight junction integrity, stability, and function (e.g., *Bifidobacterium*, *Lactobacillus*, and *Clostridium leptum*) [63] may be protective against exercise-associated GI barrier perturbations and systemic responses. On the contrary, a microbiome profile abundant in bacterial species with endotoxins (e.g., *Escherichia coli* lipopolysaccharide) may promote endotoxemia and local epithelial and systemic responses [63]. Axelrod et al. assessed the efficacy of a probiotic strain, namely UCC118, on exercise-induced GI permeability in healthy humans. Seven healthy adults received 4 weeks of daily UCC118 or placebo supplementation, and GI hyperpermeability was induced by strenuous running performed before and after each supplementation period [64]. The authors showed that 4 weeks of UCC118 supplementation attenuated exercise-induced intestinal hyperpermeability, and a significant reduction in the phylum Verrucomicrobia ($q < 0.001$) was detected [64].

Considering the potential of GM, it is reasonable to speculate how dietary regimens or probiotic supplementation may modulate microbiota composition and consequently the systemic response to physical exercise [65].

There is also evidence that exercise impairs intestinal nutrient absorption transport mechanisms, leading to malabsorption [66]. The urinary excretion of non-metabolizable glucose analogs, used to evaluate the intestinal carbohydrate transporter activity, was lower in response to running compared to rest or after running in one study [65]. A study conducted with 25 healthy endurance-trained runners showed that 68% of them presented carbohydrate malabsorption during the recovery period, and breath H_2 responses also correlated with the incidence and severity of GI symptoms [67].

In conclusion, the first mechanism of Ex-GIS onset depends on the alteration of the circulatory-GI pathways caused by endurance activity. This damage is directly dependent on the unavoidable gut hypoperfusion, which causes ischemic damage of the intestinal barrier. In addition to intestinal ischemia, the resulting bacterial translocation with endotoxemia and inflammatory response then trigger intestinal symptoms. However, these are not the only changes dependent on endurance exercise; indeed, endurance also causes an alteration in the neuroendocrine-GI pathway.

4. Gastrointestinal Symptoms during Exercise

If an athlete experiences GI symptoms during exercise, it should be ascertained that they are not a sign of underlying disease. Once medical causes have been excluded, Ex-GIS can be considered. The vascular and neuroendocrine alterations that occur during endurance physical activity led to the occurrence of GI symptoms that can affect the athlete's physical performance and psychophysical well-being [5]. There is a great variability in the severity of symptoms amongst individuals, and these may range from minor discomfort to significant health disturbances that impair their ability to compete in races and even lead to hospitalization in some cases [5]. Symptoms may appear hours to days after exposure and range from GI (e.g., abdominal bloating, loose stool, abdominal pain) to extraintestinal symptoms including fatigue, headaches, and cognitive difficulties. Several of these symptoms can be confused with irritable bowel syndrome (IBS) [5], a functional disorder of gut–brain interaction (DGBI) [68]. IBS and EX-GIS share similar pathogenesis in some respects, including alterations in the GM, intestinal permeability, gut immune function, motility, visceral sensation, brain–gut interactions, and psychosocial status [69]. Furthermore, in strenuous exercise resulting in impaired gastrointestinal function and integrity as described above, the undigested food molecules entering the small bowel may contribute to osmotic translocation of water and an increased fecal volume, resulting in loose stools or diarrhea, in a similar manner to that observed in IBS. Moreover, like IBS patients, many athletes who experience EX-GIS believe that certain foods are responsible for their symptoms. This concept could explain why EX-GIS responds to the analogous nutritional strategy of IBS in some cases (see next paragraph concerning "low FODMAP diet").

We underline that IBS has the possibility of being underdiagnosed in endurance athletes, specifically marathon, ultramarathon, half-distance triathlon, and full-distance triathlon participants. One assessment of IBS in endurance sport showed that a great percentage of symptoms met the Rome Criteria, but they were not diagnosed. Killian LA and colleagues documented an IBS prevalence of 9.8% overall with 2.8% diagnosed, and an additional 10.8% had not been diagnosed [70]. Similar results were observed by Hungin et al., who reported an IBS prevalence of 14.1% overall with 10.8% undiagnosed meeting either the Manning or Rome (I or II) diagnostic criteria [71]. Underdiagnosed IBS may occur in those athletes who have not consulted a medical professional regarding their symptoms and are attempting to manage their symptoms through various strategies. In theory, if these strategies are not effective in managing their symptoms, these athletes will not be considered as IBS sufferers. Furthermore, while Ex-GIS tended to decrease between rest and exercise, athletes with IBS did not experience the same decreases as those without IBS. In our opinion, those athletes would experience Ex-GIS as a manifestation of IBS triggered by strenuous exercise and endurance sports, and they would have the same benefit from dietetic and pharmacological strategies of IBS.

Regarding Ex-GIS, an estimated 30–90% of endurance athletes engaging in marathons, triathlons, and running report experiencing GI symptoms during exercise [1]. To investigate the prevalence of Ex-GIS, Ter Steege and colleagues included 2076 athletes competing in a long-distance run to assess the prevalence, risk factors, and timing of GI disturbances [72]. They received a questionnaire where the reported GI complaints were related to variables such as age, gender, distance, fluid, and food ingestion, running experience, and environmental conditions. Three athletes dropped out because of GI complaints, 45% had at least one GI complaint during running, 11% referred to serious GI complaints, and 2.7% had

complaints during the first 24 h after the run [72]. In another study, Pfeiffer et al. reported severe GI distress ranging from 4% in marathon running and cycling up to 32% in Ironman races [73]. Currently, several observational studies have exhaustively assessed GI symptoms during endurance sport; they can be divided into upper- (e.g., regurgitation, upper abdominal bloating, belching, epigastric pain, and heartburn) and lower- (e.g., flatulence, urge to defecate, lower abdominal bloating, abdominal pain, abnormal defecation including loose water stools, diarrhea, and fecal blood loss) GI tract symptoms. Upper-GI symptoms are reported in up to 40% of runners but may rise to 70% in cyclists [3]. The prevalence of reflux/heartburn is usually the most frequent of the upper-GI symptoms and is estimated between 15% and 20% in runners [74]. As described above, exercise induces an increase in intra-gastric pressure and perturbation of LES function, leading to GI symptoms like heartburn, chest pain, belching, and dyspepsia [40]. Moreover, the intragastric pressure may rise due to ingestion of hyperosmolar carbohydrate sport drinks delaying the gastric emptying time in athletes [75,76]. On the other hand, athletes emptied their stomachs significantly faster than controls both at rest and during exercise, suggesting an effect of training [77]. Effectively, athletes not trained for fluid/food ingestion had a twofold risk of developing GI symptoms compared with athletes habituated to fluid/food ingestion during exercise [72]. Effectively, the adaptation observed in athletes may protect against the development of GI symptoms associated with delayed gastric emptying, such as nausea, vomiting, and side stitch.

Concerning other GI symptoms, side ache, stitch, and subcostal pain, commonly referred to as exercise-induced transient abdominal pain (ETAP), are common during exercise. ETAP was reported in 18% of the competitors in a recreational run, whereas 4% reported severe abdominal pain, but the incidence of ETAP is influenced by the type of sport [78]. In a study conducted on 965 sporting participants, ETAP was most prevalent in activities that involved repetitive torso movements, bouncing, or longitudinal rotation [78]. Furthermore, the incidence of ETAP was higher in young patients and after recent ingestion of fluid and food [76,79].

Finally, the lower-GI-tract symptoms, such as abdominal pain, flatulence, cramping, the urge to defecate, diarrhea, and rectal bleeding, are more severe compared to upper-GI disturbances, having the potential to impair performance [80]. The incidence of severe lower GI symptoms during a recreational run is up to 30%, but the percentage may increase up to 50% in cyclists and to 70% in competitive long-distance runners [81]. Recreational athletes are least likely to report symptoms. Usually, they are competing at lower intensities and thus have fewer symptoms, as GI symptoms are reported to increase with distance and exercise intensity [82].

In addition to performance level, other variables can influence symptom severity [83]. Jill A. Parnell et al. [83] showed a higher prevalence of GI symptoms in younger female athletes, who experienced urge to defecate, diarrhea, and the highest rates of gas, nausea, fullness, and stomach pain/cramps. Other studies support a higher prevalence of GI symptoms in female athletes [84,85], suggesting further research to determine the potential relationship to sex hormones and female gut physiology. Age is another variable that can impact GI symptoms' prevalence [84–86]. Increased age may protect against GI symptoms due to reduced splanchnic vasoconstriction through impaired catecholamine response and consequently increased oxygen supply [86].

Finally, exercise is beneficial for mental status, resulting in an improved mood and a better quality of life. In turn, a good state of mind is needed to achieve better sports performance [87]. In this context, observational studies linked chronic stress to the development of GI disorders such as IBS [88]. We specified that even in the healthy general population, stressful events can trigger GI symptoms, and it is plausible that the link between stress, anxiety, and GI symptoms observed under resting conditions also occurs during exercise. In this direction, psychological factors may influence the development of GI distress during exercise [89]. Patrick B. Wilson conducted a study to evaluate if stress and anxiety may contribute to running-related GI distress [90]. Runners (74 men, 76 women) prospectively

recorded running duration and intensity and GI symptoms for 30 days. After 30 days, participants completed a questionnaire on GI symptoms and filled in the Perceived Stress Scale (PSS) and Beck Anxiety Inventory (BAI). The analysis of the data showed PSS scores and BAI scores were positively correlated with GI distress occurrence [90]. To date, most research on EX-GIS has focused on nutritional, pharmacologic, and mechanical origins, but this study provides rationale for further research into psychological sources of GI distress with exercise.

5. Nutritional and Behavior Strategies to Reduce Ex-GIS

We believe that in the framework of Ex-GIS, risk factors screening should be recommended. Exercise modality, state of dehydration, environmental temperature, concomitant therapies, and diet should be evaluated, and if risk elements are present, an attempt should be made to modify them. Since Ex-GIS may also be linked to food-related reactions, the habitual diet should be investigated. Food intolerance appears to be on the rise among athletes, but unvalidated food intolerance tests and self-reported incidence do not allow an accurate estimate of true intolerances [91]. Given the multifaced food intolerances or malabsorption manifestation, there is a tendency for athletes to self-diagnose intolerances and subsequently restrict foods or food groups. Lactose and fructose malabsorption, which result from insufficient enzyme and functional capability of the transporter, respectively, are the most-reported food intolerances [92]. To ensure adequate energy intake, current guidelines recommend a carbohydrate intake of about 60 g for exercise lasting for up to 2 h. When the exercise lasts 2 h, slightly greater amounts of carbohydrates (90 g/h) would be recommended, and generally, these carbohydrates should consist of a mix of multiple transportable carbohydrates, e.g., glucose and fructose or maltodextrin and fructose [93]. Finally, food choice pre-exercise has a significant impact on the gut's tolerance to running, and athletes self-manage their diet to reduce Ex-GIS.

Dietary elements including high fiber, fat, and protein intake, as well as concentrated carbohydrate loads, have been reported to trigger GI symptoms in triathletes [83]. Dark chocolate needs to be mentioned in this paragraph, since it has been proposed as an ergogenic aid via increased nitric oxide [94], but caution should be advised for chocolate since it has been described as a food that provokes GI disturbance, particularly constipation [95]. GI effects may depend on the concentration of cocoa or other biologically active compounds, including caffeine and fat, which may aggravate EX-GIS [96]. This evidence may explain why morning caffeine intake has been associated with increased lower GI symptoms in triathletes [97]. On the other hand, competitive athletes and longer-distance runners were less likely to avoid coffee or tea, and this may be due to the potential ergogenic effects of caffeine in endurance exercise [98]. Concerning sport beverages, energy drinks are a mix of vitamins, sugars, sweeteners, and plant extracts, especially stimulants, but GI upset is included in the list of commonly reported symptoms after their use [99].

To assess dietary restrictions pre-racing and GI symptoms, Jill A. Parnell et al. [83] designed a questionnaire and administered it to 388 runners. Their analysis showed the foods regularly avoided were meat (32%), milk products (31%), fish/seafood (28%), poultry (24%), and high-fiber foods (23%). Caffeinated beverages were commonly avoided in events 10 km or less, while high-fiber foods were avoided in females. Rates of food avoidance were elevated in younger and more competitive runners. Interestingly, athletes did not identify the consumption of high-osmolarity carbohydrate supplements as a risk factor for the development of symptoms. In fact, symptoms may depend on the quantity and quality of carbohydrates ingested before exercise. Besides its importance in maintaining energy stores [100], a way to reduce the incidence of GI symptoms is to try to incorporate high carbohydrate intake into the weekly routine and regularly ingest carbohydrates during exercise. With these strategies, the gut may be trained to absorb and oxidize more carbohydrates, which in turn should result in less GI distress and better performance [93]. The ability to absorb carbohydrates is a result of an upregulation of SGLT1 transporters of the intestinal lumen. Considering this, Cox and colleagues [101] suggest "gut training" in

endurance cycling, which means several days and 2 weeks of a high-carbohydrate daily diet [101].

Another strategy to manage Ex-GIS was proposed by van Wijck et al. [10]. Since the perfusion of the gut is implicated in EX-GIS pathogenesis, upregulating intestinal nitric oxide (NO) production could be a way to reduce symptoms. Manipulation of intestinal NO can be obtained through nitric-oxide-synthase-dependent (glutamine–arginine–citrulline) and nitric-oxide-synthase-independent (nitrate–nitrite) supplementations or by increasing the dietary nitrate intake [10]. However, currently recognized vegetable sources of dietary nitrate, such as chard, celery, rapeseed, spinach, radish, and lettuce, are also sometimes associated with GI symptoms. Therefore, a way to supplement dietary nitrate would be to take these foods as vegetable extract juice.

We propose an overview of the principal nutritional and behavioral strategies to reduce Ex-GIS in accordance with the current evidence (Table 1).

Table 1. Possible nutritional and behavioral strategies to manage Ex-GIS in endurance sports.

GI Symptoms	Nutritional and Behavior Strategies
Upper-GI symptoms • Reflux and regurgitation • Nausea • Vomiting	Avoid high-calorie and fatty meals three hours prior to exercise [50,53] Avoid hypertonic fluids during exercise [50,53]
Lower-GI symptoms • Urgency • Diarrhea • Bloating • Abdominal cramps	Defecate prior to exercise to prevent the urge to defecate during exercise [71] Drink small amounts of hypotonic carbohydrate fluids to prevent the risk of osmotic diarrhea [72] Avoid hypertonic solutions, including fatty, high-calorie meals, or high-glycemic-index foods three hours before exercising and during exercise [73] Train the gut to ingest a high amount of carbohydrates and fluids before competition [70] Avoidance of food and fluid intake at least two hours prior to exercise [3]
Side stitch or ETAP	Wait 2–3 h before exercising after a meal or drink [74] Take small amounts of drink during exercise and abstain from hypertonic fluids [3]

Abbreviations: Ex-GIS: exercise-induced gastrointestinal symptoms, GI: gastro-intestinal, ETAP: exercise-induced transient abdominal pain.

6. Efficacy of Specific Diets Applied by Endurance Athletes to Avoid Ex-GIS

Endurance athletes need a regular nutrition program to fill their energy stores before training/racing and to provide nutritional support during training/racing and effective recovery after training/racing. Some nutritional regimens may benefit the performance of athletes but somehow have a negative impact on the development of symptoms [102–105]. An example is represented by the vegetarian diet; it has been suggested that a vegetarian diet may improve endurance performance by increasing exercise capacity and performance, modulating exercise-induced oxidative stress [106] and inflammatory processes, including anti-inflammatory, immunologic responses [107], and upper-respiratory-tract infections (URTIs) [108], finally providing better cardiovascular parameters. On the other hand, a vegetarian diet may theoretically result in developing GI symptoms due to high fiber content, but some cross-sectional studies and available case reports have not evaluated this aspect [109].

Another diet applied by endurance athletes aiming to improve performance is a high-fat diet (HFD), but results of studies are conflicting. This regimen has been widely applied as a treatment option for neurological diseases such as epilepsy or as an effective dietary strategy for weight loss [110]. The goal of an HFD is to increase the body's ability to use ketone bodies (KBs) and fatty acids as energy sources. The utilization of fatty acids and KBs may lead to many advantages, such as sparing muscle glycogen stores, increasing body fat mass loss, improving aerobic capacity, improving time to exhaustion and time-trial performance, and increasing cognitive performance [109]. Conversely, unresolved aspect includes the ability of long-term keto-adaptation to restore muscle glycogen content to levels normally achieved with a carbohydrate (CHO)-rich diet and the impairment

of muscle's ability to use glycogen for oxidative fates [107]. Moreover, potential risks regarding an HFD are GI symptoms, including nausea, reflux, dizziness, euphoria, and upper-abdominal discomfort [111,112], which in turn may potentially reduce athletes' performances. Finally, to alleviate exercise-associated GI symptoms, numerous nutritional interventions have been investigated. Gluten-free and low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diets appear to be the most effective for this purpose [113–116].

In the last decade, one of the most common dietary strategies used to manage GI symptoms has been the exclusion of gluten from the diet. In recent years, the GFD has become a trendy diet among the general population, followed in about 5–10% of cases, and it is even more widespread among non-celiac athletes (NCAs), in whom the percentage rises to over 40% [114] since many athletes believe that gluten removal might reduce GI symptoms [73]. The elimination of gluten from the diet is particularly prominent within endurance athletes, likely due to their higher frequency of EX-GIS (15–30%) compared to other types of athletes [73]. Despite the paucity of supportive evidence, NCAs choose to adhere to a GFD for various reasons including clinically or self-diagnosed NCGS and the belief that a GFD is healthier because it reduces inflammation and gastrointestinal discomfort, or it may improve exercise performance through the reduction in fatigue [114]. The main clinical beneficial effect of a GFD reported by athletes is the resolution of abdominal bloating, gas, diarrhea, and fatigue [114]. One of the first surveys conducted on endurance cyclists, by Fritscher K. and colleagues [117], reported that GFD was the most popular "special diet" among this group of athletes since it improved GI symptoms in approximately 80% of survey respondents. A successive and broader survey conducted on 910 athletes spanning various sports and levels, including world and/or Olympic medalists, concluded that 41.2% of NCAs followed a GFD for 50–100% of the time and that most of them were endurance sport athletes (70%) [114]. Interestingly, a successive controlled, randomized, double-blind, crossover study conducted by the same group on thirteen competitive endurance cyclists with no positive clinical screening for CD or history of IBS concluded that a short-term GFD had no overall effect on performance, symptomatology, and inflammation. In this study, athletes, allocated to a 7-day gluten-containing diet (GCD) or GFD, were tested for performance, GI symptoms, well-being, and select indicators of intestinal injury and inflammation, and at the end of the study, clinical and biochemical index results were similar in both groups [118]. Furthermore, it is plausible that a placebo effect could contribute to the symptomatic improvement experienced by athletes. A review by Halson and Martin confirmed that the "belief effect" can contribute to a performance improvement of between 1% and 3%, whether it has ergogenic mechanisms or not [119]. Moreover, following a GFD may increase awareness of food choices and encourage a healthier diet containing more fruit, vegetables, and gluten-free whole-grain, and in turn, these positive dietary changes may influence perceptions of improved health, psychology, or exercise performance [114]. Gluten should not be considered the only culprit of symptoms; amylase-trypsin inhibitors (ATIs) and fructans (rich in FODMAPs), which are all components of wheat and other gluten-containing and non-gluten foodstuffs, may also be responsible for GI disturbances [120,121]. Although gluten and fructans co-exist in cereals, historically, gluten alone has been incorrectly blamed for related GI disturbances and thus is often promptly eliminated from the diet [122–124]. In truth, it is more likely that the other proteins and carbohydrate nutrients are the actual culprits of athletes' symptomatology. In fact, it was widely demonstrated in a series of clinical studies that fructan and not gluten elimination reduced GI symptoms in IBS patients with self-reported NCGS [125,126]. Therefore, athletes following a GFD unknowingly reduce high-FODMAP foods, which may reduce Ex-GIS, and the decrease in FODMAP intake and not gluten itself may be the true reason for improved GI disturbances obtained in a GFD.

This justifies the new dietary strategy to address the multifactorial nature of gastrointestinal disorders in athletes using a "low FODMAP" approach and not a GFD [127]. FODMAPs are a family of fermentable short-chain carbohydrates found in a wide as-

sortment of foods/food constituents [128]. In predisposed individuals, FODMAPs are partially digested, remaining in the intestinal lumen, particularly in the colon, where they are subsequently fermented by the microbiota, releasing gas, recalling water, and leading to exacerbation of the symptoms of IBS [129]. The distension of the intestinal wall initiates a painful visceral response conveyed by the nerve fibers that are present in the intestine. Several controlled clinical trials and meta-analyses have demonstrated the superiority of the low-FODMAP diet (LFOD) over control diets in patients with IBS [129]. As reported above, adverse GI symptomatology during exercise can be analogous to IBS [130]. In strenuous exercise with a subsequent impairment of GI function and integrity (i.e., transporters), undigested food molecules, such as FODMAPs, may increase the osmotic water translocation and fecal volume, with physiological consequences such as loose stool or diarrhea [131]. Furthermore, high-FODMAP foods are common in an athlete's diet [115], especially due to FODMAPs that are contained in certain sports foods specifically formulated for and marketed to athletes or snacks containing dry dates (fructans), fructose, inulin (fructans), honey (fructose), and chicory root (oligosaccharides) [127]. A quantitative recommendation in an LFOD is to reduce FODMAP intake from 15–30 g FODMAP/day to 5–18 g FODMAP/day [132] and specifically less than 0.5 g FODMAP per meal or less than 3 g per day in IBS patients [133]. However, endurance athletes suffering from Ex-GIS consume 2 times more FODMAPs (up to 43 g/day). Considering this, the LFOD is becoming a strategy to reduce GI distress parameters in athletes with a history of non-clinical exercise-associated GI symptoms [109].

Four studies [116,134–136] have evaluated the potential efficacy of an LFOD in Ex-GIS. A case study about a multisport athlete with Ex-GIS showed that a 6-day restriction of FODMAPs (81 $\pm$ 5 g vs. 7.2 $\pm$ 5.7 g FODMAP/day) resulted in a decrease in GI symptoms both during exercise and on resting days of the athlete [136]. Another case report [135] presented the effect of a 4-week LFOD in a female ultra-endurance runner diagnosed with IBS. Apart from severe nausea, minimal GI symptoms including bloating and flatulence were observed throughout the race [135]. Another evaluated a 6-day LFOD or high-FODMAP (HFOD) diet in eleven recreationally competitive runners [116]. The study reported a significant decrease in Ex-GIS, particularly in flatulence, urge to defecate, loose stool, and diarrhea, in 9 of 11 athletes after the low-FODMAP trial [116]. Finally, a crossover study [134] analyzed the effects of a 24 h HFOD or LFOD before exertional heat stress on GI integrity, function, and symptoms. The authors proved that even if an HFOD ameliorates GI integrity, it results in greater carbohydrate malabsorption compared with an LFOD and correlates with more severe Ex-GIS during exertional heat stress compared to an LFOD [134]. In addition, Scrivin et al. [105] recently performed an exploratory study to review the specific self-reported strategies used to manage symptomology amongst endurance athletes who experience Ex-GIS. Avoiding disaccharides (lactose and sucrose) was the most popular strategy to avoid or reduce Ex-GIS, followed by galacto-oligosaccharides, polyols, and fructose. Other popular dietary strategies were dietary fiber reduction and dairy avoidance [105].

We want to emphasize that specific regimens are not only a way to alleviate GI discomfort but should provide specific nutrients and energy intake in an efficient manner. Therefore, after a first exclusion phase, it is recommended to proceed to a reintroduction phase, which should be carefully applied by a trained nutritionist to identify which foods high in FODMAPs cause these symptoms to personalize the diet and maintain a healthy GM [127]. Since long-term outcomes and the safety of low-FODMAP diets remain to be investigated, further studies are required to evaluate their long-term effects on GM, cost effectiveness, and efficacy compared with other regimens [137,138]. Similar considerations also apply to GFDs, which may have potential negative issues in terms of diet restriction with suboptimal nutrient intake, the increased difficulties of, the organization of the diet, the potential impact on GM and increased food costs [139,140]. Unnecessary food restrictions should always be considered a concern for athletes given increased energy requirements and the importance of a balanced diet on general health and performance.

Considering all the aspects addressed in the present work and the results available to date in the literature, we propose a diagnostic–therapeutic algorithm to manage Ex-GIS (Figure 2).

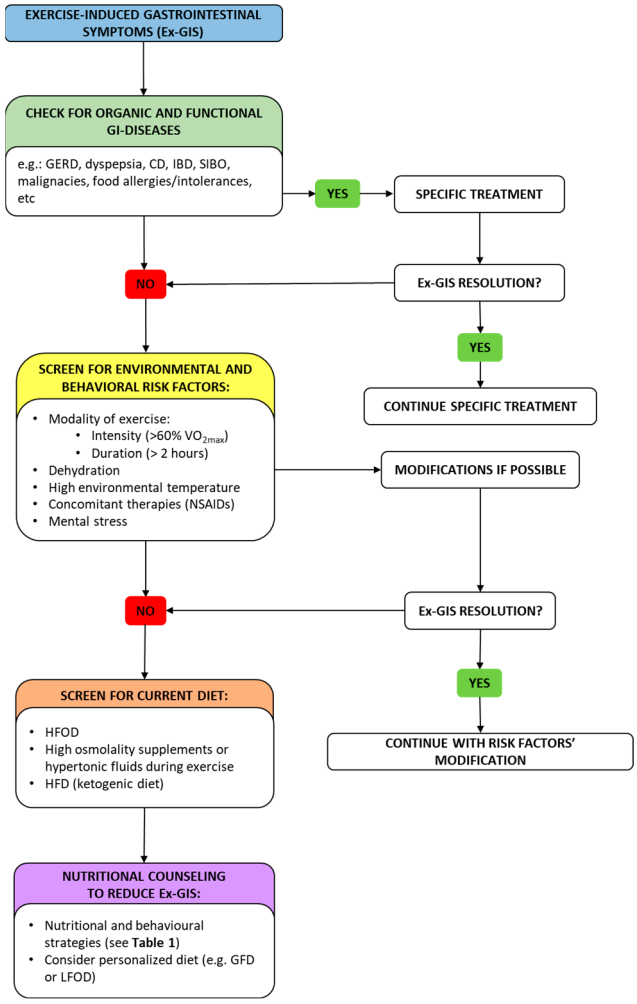

Figure 2. A diagnostic–therapeutic algorithm with suggestions for managing Ex-GIS. In the framework of Ex-GIS, an initial check for organic/functional disease and risk factors is recommended. Exercise modality, state of dehydration, environmental temperature, concomitant therapies, and mental status should be evaluated, and if risk elements are present, an attempt should be made to modify them. If no resolution has been obtained, screening for current diet and nutritional counseling should be advised by a nutritionist. See Table 1 for the possible nutritional strategies to manage Ex-GIS in endurance sports. Abbreviation: Ex-GIS: exercise-induced gastrointestinal symptoms; GERD: gastro-esophageal reflux disease; CD: celiac disease; IBD: inflammatory bowel disease; SIBO: small intestinal bowel overgrowth; VO2max: maximal oxygen consumption; NSAIDs: non-steroidal anti-inflammatory drugs; HFOD: high-FODMAP diet; HFD: high-fat diet; GFD: gluten-free diet; LFOD: low-FODMAP diet.

7. Conclusions

Endurance exercise causes physiological and pathological disturbances that alter GI function and integrity, which eventually results in Ex-GIS. Endurance can cause acute GI symptoms even in a healthy gut through multiple pathological changes associated with hypoperfusion, ischemia, epithelial injury, impaired barrier function, endotoxemia, local and systemic inflammation, impaired nutrient absorption, and altered gastric and intestinal motility. These changes are the result of multifactorial interactions between the gastrointestinal tract and the circulatory, immune, enteric, and central nervous systems,

analogous in some respects to the pathogenesis of IBS, as well as in terms of the symptomatology triggered. Ex-GIS can impact the physical and psychological performance of athletes during competitions and vice versa; the psychological stress to which they are subjected may worsen GI disturbances. Numerous nutritional and behavioral interventions have been investigated to alleviate Ex-GIS; diet is perhaps the principal one and should be personalized and planned by experts to avoid self-managed diets.

In conclusion, although more research is needed to gain insight into gastrointestinal physiology during exercise and to better understand the most appropriate individualized dietary strategies to address the multifactorial nature of GI disorders in athletes, nutritional intervention appears to be a promising tool to manage them.

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