Gastrointestinal Symptoms During Endurance Exercise: a Guideline for Investigation

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Abstract: Gastrointestinal complaints are very common in sport, especially in endurance athletes. Depending on the severity of the symptom, it can cause an athlete to drop out of a race. Besides, people who have gastrointestinal complaints often have this problem constantly and often an accurate diagnosis is not made.
We propose a guideline, where we analyze the 10 main causes of gastrointestinal problems (exercise-induced gastrointestinal syndrome, gastric emptying / intestinal absorption, diet pattern, carbohydrates intake during exercise, supplements, stimulants, small intestine bacterial overgrowth, leaky gut, medications, and other conditions) and the way to deal with those conditions.
Using this approach, this group could identify about 98% of the causes of gastrointestinal problems in athletes

Introduction:

Gastrointestinal symptoms (GIS) during exercise are a very common situation, especially in endurance athletes. This situation affects professionals and amateurs, both genders and all ages. It is responsible for discomfort during exercise, impacting performance, urge to defecate during exercise, and even abandoning a sport event. The recovery can be also compromised, due to the impaired gut nutrients absorption.
The complaints consist of nausea, flatulence, gastroesophageal reflux, dyspepsia, diarrhea (bloody or not), abdominal distension, vomiting, urge to defecate, and abdominal pain. The severity varies from mild discomfort to ischemic colitis[1].

There is a large variation in the report prevalence of GIS in the literature. A trial conducted in the '80s showed that 81% of endurance competitors complained about GIS; upper gastrointestinal symptoms (nausea, vomiting, abdominal pain, dyspepsia, and gastroesophageal reflux) were noticed in 58% of participants and lower gastrointestinal symptoms (flatulence, abdominal distension, diarrhea, and abdominal pain) noticed in 61%, this last tending to be more severe[2]. Also in the '80s, Riddoch et al observed that 83% of Belfast Marathon competitors had gastrointestinal disturbance during or immediately after the competition[3].

Peters et al compare the upper and lower symptoms among runners, cyclists, and triathletes. Runners experienced more lower (71%) than upper (36%) GIS during exercise. Cyclists experienced similar upper (67%) and lower (64%) symptoms. Triathletes experienced during cycling both upper (52%) and lower (45%) symptoms, and during running more lower (79%) than upper (54%) symptoms[4].

Causes of GIS:

1 – Exercise-Induced Gastrointestinal Syndrome:

In rest, the splanchnic organs (stomach, liver, spleen, pancreas, small intestine, and large intestine) receive 20% of the cardiac output, but only consume 10-20% of the available oxygen[5]. In response to exercise the sympathetic nervous system is massively stimulated, increasing splanchnic vascular resistance that may decrease the local blood flow, even with the increased cardiac output[6] while a considerable amount of blood flow is diverted to the working muscles. In maximal intensity exercise, splanchnic blood flow (SBF) can decrease by 80% at an exercise intensity of 70% VO2 máx[7], aggravated by younger ages, exercise intensity and duration, trained status, dehydration, and high temperature. Costa et al and ter Steege et al published articles showing that women are more prone to exercise-associated gastrointestinal symptoms than men[8,9].

Rehrer et al observed a gradual reduction in portal vein flow from 20% after 10 minutes to 80% after 80 minutes when volunteers exercise at 70% of VO_2 max[10]. Kenney et al compared the effects of exercise at 60% VO_2 max at 22°C and 36°C, observing an additional 17% decrease in SBF in the warmer temperature. Younger individuals had a more pronounced decrease of SBF due to the higher production of norepinephin[11]. Van Wijck observed gastrointestinal ischemia in all patients who cycled for 60 minutes at 70% VO^2 max[12] while Nielsen found 6 volunteers in 10 with gastrointestinal ischemia cycling for 30 minutes at a maximal level during the last 5-10 minutes[13].
The increased sympathetic nervous system causes slow gastric emptying and delayed orocecal transit[14]. The intestine ischemia stimulates NF-KB expression within epithelial cells, initiating a local inflammatory cascade by signaling the release of pro-inflammatory cytokines (interleukin 1β, tumor necrosis factor α, and interferon γ)[15]. Consequences of this situation: mucosal damage, nutrient malabsorption, gastrointestinal bleeding, and impaired gut barrier function leading to increased gastrointestinal permeability. All these conditions led to impaired nutrient absorption, which may cause abdominal cramps and osmotic diarrhea. Persistent gastrointestinal permeability (leaky gut) can cause systemic endotoxemia (presence of circulating bacterial lipopolysaccharides, which attach to lipopolysaccharide-binding protein to form immune complexes that initiate a cell-mediated immune cascade[16]) and systemic inflammation. Furthermore, changes in SBF can lead to dysmotility, which causes compression of the microcirculation, causing GIS.

Qamar et al compared the superior mesenteric artery (SMA) blood flow in fasting state, after a 30 minutes exercise test, after a meal and an exercise test after ingestion of a meal. He observed that the exercise test reduced the SMA flow by 43%, whereas the ingestion of a meal increased the SMA flow by 60%. The exercise test after the ingestion of a meal shown increased by 40% of the SMA flow[17].

So, adequate hydration before and during exercise has huge importance to avoid exercise-induced gastrointestinal syndrome. Adequate food intake before exercise has to be evaluated also. This situation can get worse in high temperatures, demanding more careful hydration planning. Moreover, the appropriate intake of carbohydrates during exercise is a protective strategy against exercise-induced gastrointestinal syndrome, because its presence increases its absorption, consequently stimulating nitric oxide production, thus causing vasodilatation, increasing microvascular blood flow in intestinal villi[18]. Vasodilators such as citrulline and arginine, enhance blood flow into the intestinal microvasculature reducing exercise-induced gastrointestinal syndrome, possibly being a good alternative to treat this condition[19,20].

2 – Gastric Emptying/Intestinal Absorption:

When food enters the stomach, its proximal part relaxes to act as a reservoir for the meal. Following this, the gastric muscles begin to push the food against a closed pylorus to begin the process of mechanical digestion. The pylorus then opens to gradually allow the digested chyme through. This process, known as gastric emptying, varies between solid and liquid foods and is under neurohormonal regulation. Gastric fundic tone is maintained by vagal innervation. The presence of food stimulates the vagal sensory afferents and transmits the information to the brainstem, which sends inhibitory signals to the gastric circular muscles to allow accommodation[21]. Delayed gastric emptying is associated with gastric distension and sensation of fullness. The overall rate of availability of ingested fluid and nutrients is determined by a combination of the rates of gastric emptying and intestinal absorption.

The majority of evidence suggests that GE is delayed during strenuous exercise[22,23] and accelerated[24] or unchanged[25,26] during mild to moderate exercise. There is a close relationship between exercise intensity and gastric emptying and oral-caecal transit time. High-intensity exercises (> 70% VO2 máx) are associated with slower gastric emptying while low-intensity activities (< 40% VO2 máx) have minimum gastric emptying alterations[27], although few investigations reported an increased gastric emptying[24,28]. The amount of food ingested also impacts its absorption; high volumes (> 600ml) delay gastric emptying during exercise[29]. Until 600ml, the absorption can be even faster; therefore this is our threshold level. So, if an athlete has to consume 90g of carbohydrates during a sporting event, it is a good idea to make 3 ingestions of 30g carbohydrate in an hour.

Acute intense exercise suppresses ghrelin levels by 16.5% and increases levels of peptide YY by 9%, glucagon-like peptide 1 by 13%, and pancreatic polypeptide by 15%[30]. These peptides have several roles in appetite regulation, including regulation of gastric motility; while ghrelin accelerates gastric emptying[31], peptide YY and glucagon-like peptide 1 inhibit gastric emptying[32]. Ueda et al reported that a period of high-intensity exercise resulted in significantly greater secretion of PYY than did moderate-intensity exercise or rest[33]. Similarly, Deighton et al observed that circulating concentrations of PYY were greater after a high-intensity intermittent exercise protocol than after a steady-state exercise protocol[34]. So, intense exercise per se delays gastric emptying. However, this situation can get worse when certain amounts of fiber, fat, and protein are ingested before exercise.

Fatty food ingestion stimulates hormones production like cholecystokinin, PYY, and GLP-1[21]. The length of the fatty acid acyl chain is an important factor in determining the response in the duodenum as a higher number of carbon atoms (>12) in the chain cause increased levels of cholecystokinin and GLP-1 in the bloodstream and more inhibition of gastric emptying[35]. Protein can also delay gastric emptying, probably due to action of a gastric inhibitory polypeptide, which is released by foods reaching the jejunum, showing a lower response for the first hours after a protein meal, especially a fast absorption protein (isolate/hydrolyzed whey)[36]. In general, dietary fiber increases the fecal mass and accelerates intestinal transit. It also generates more hydrated feces. It affects the metabolism of minerals, nitrogen, and bile acids, excreting more these substances as a result of accelerated transit. The effect of massive dilution is the prime factor causing immediate defecations[37]. This condition is worse in exercise when absorption can be impaired due to exercise-induced gastrointestinal syndrome. Carbohydrates can be consumed in a range of formats during sports, including bars, gels, sports beverages, soft drinks, fruits, and tubers. Guillochon et al compared gastrointestinal symptoms when carbohydrate was consumed in bars, gels, and beverages, observing more complaints with bars[38]. Solid food is more associated with GIS. Choosing the right food is also very important; low FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) is associated with lower gastrointestinal complaints.

Some articles have shown that feeding least than 1 hour before exercising can cause GIS due to delayed gastric emptying or impaired intestinal absorption. Rehrer et al showed that in a half Ironman triathlon distance (1.9km swimming followed by 90km cycling and then 21.1km running), all athletes who vomited while swimming had eaten between breakfast and one-half hour before the start of the race, while only 27% of the athletes without this symptom had eaten in this period time; similarly all of the individuals who vomited had eaten in the last half-hour before the start, while only 14% of those without this complaint had eaten in this period time. All triathletes who experienced intestinal cramps immediately after the race had eaten fiber-rich foods[39]. If the activity is vigorous, athletes should avoid meals 1 hour before exercising.

Another situation related to feeding before exercising is hypoglycemia. Foster et al reported a negative, hypoglycemic response to carbohydrate ingestion directly preceding exercise (< 60 minutes). This situation happens due to rebound hypoglycemia, rising the insulin in consequence of carbohydrate ingestion associated with upregulation of glucose transporter type 4 (GLUT4) due to the beginning of the

exercise, leading to a decrease in blood glucose[40]. One solution to this situation proposed by Moseley et al is to consume carbohydrates only a few minutes before the exercise[41]. In this condition, the rise of catecholamines at the beginning of exercise would decrease the insulin level.

The fiber ingestion must be analyzed not only pre-competition but the total amount of ingestion in a day. Its action isn't acute and an accelerated intestinal transit can happen a few days after lowering fibers ingestion.

3 – Diet Pattern:

Our body tries to adapt itself according to the diet pattern we consume. Usually, an endurance athlete consumes high amounts of carbohydrates. Consequently, his body adapts to absorb this macronutrient, increasing the gut's carbohydrate transporters and glycolytic enzymes. Glucose and galactose are absorbed through sodium-glucose transporter cotransporter 1 (SGLT1) in enterocytes and transported into the blood vessels through GLUT2 transporters. Fructose enters enterocytes through GLUT5 receptors and also goes into blood vessels through GLUT2 transporters[42]. More carbohydrates the athlete consumes, more SGLT1, GLUT2, and GLUT5 will be expressed.

However, among fatty acids, their absorption is different; short-chain fatty acids (< 8 carbon molecules) and medium-chain fatty acids (from 8 to 12 carbon molecules) are absorbed directly to the portal vein. Long-chain fatty acids (from 13 to 21 carbon molecules) and very-long-chain fatty acids (> 22 molecules) are packed into chylomicrons and transported via the lymphatic system.

There are three pathways for the uptake of fatty acids and their transport across the apical membranes of enterocytes:
1) Membrane-associated fatty acid-binding protein (FABP) and CD36 (also referred to as fatty acid translocase) in the enterocytes accepts medium-chain and long-chain fatty acids at the cell surface to increase their local concentrations
2) Medium-chain and long-chain fatty acids are transported by fatty acid transport protein 4 (FATP4)
3) Short-chain fatty acids may traverse the apical membrane by simple passive diffusion and may be absorbed into the mesenteric venous blood and then the portal vein[43]

The presence of these membrane transporters is upregulated by the presence of high amounts of carbohydrate and/or fat. So, an endurance athlete that is used to eating great amounts of carbohydrates has a lot of SGLT1, GLUT2, and GLUT5 transporters in the small intestine. On the other hand, athletes adept at ketogenic diet (high fat) have a lot of FABP, CD36, and FATP4 transporters.
An athlete adept at a ketogenic diet may have GIS during his carbohydrate intake during a sporting event due to the low expression of carbohydrate transporters in the gut. As previously described, an athlete may consume up to 90g of carbohydrate per hour during competition. The decreased number of SGLT1, GLUT2, and GLUT5 transporters can impair the carbohydrate absorption causing GIS. Jeukendrup has shown

that athletes have to train their gut to absorb more carbohydrates, either at rest and during sports activities[42]. Ingestion of small and medium-chain fatty acids during training for adepts to ketogenic diet seems to be more reasonable; however, more studies must be performed.

4 – Carbohydrate Intake During Exercise:

Carbohydrate feeding during exercise can improve time to exhaustion and exercise performance during prolonged exercise[44]. When exercise exceeds 2 hours and 30 minutes, the American College of Sports Medicine (ACSM) advises intake up to 90g of carbohydrate per hour[45], while the International Society of Sports Medicine (ISSN) recommends from 30g to 60g of carbohydrate per hour or 0,7g of carbohydrate per kg per hour[46].

The amount of carbohydrate intake during exercise is independent of an athlete's body mass. An athlete improves his capacity to absorb carbohydrates and avoid GIS by training with relatively large volumes of fluids, training immediately after a meal, with high carbohydrates intake during exercise, and increasing carbohydrate amount of the diet[42]. This is the reason why a 55kgs, 160cm female athlete can absorb 90g of carbohydrate per hour and an 85kgs, 190cm man athlete may not absorb; the female athlete has been training her gut with these approaches previously cited. That is why ACSM and ISSN guidelines are cited as the total amount of carbohydrate and not grams per kg.
Another point to be evaluated is carbohydrate's gel osmolality. A lot of professionals and amateurs consume carbohydrate gels during prolonged sports activities. To facilitate transport during exercise, these gels are very concentrated (high osmolality). Dense carbohydrate formulations lead to hypertonic gastric contents which empty slowly and can cause distension and cramping and delayed absorption of energy. In the gut, a dense carbohydrate formulation can have its absorption impaired and attract fluids into the gut lumen by osmotic pressure causing cramping and urge to defecate. Better absorption of carbohydrates occurs when the solution is isotonic, with an osmolality close to 300 mOsmol/L; however, our gut can absorb fluids up to 750 mOsmol/L without complaints. Zhang et al evaluated 31 carbohydrate gels from 23 different brands demonstrating that only 4 had an osmolality lower than 1000 mOsmol/L and only one was considered isotonic. The average osmolality was 4500 mOsmol/L and 70% of gels samples were higher than 2000 mOsmol/L[47].

So, if an athlete is experiencing GIS during a sporting event, physical exercise gut ischemia and feeding should be evaluated; the gel osmolality should be checked. All gels must be consumed with at least 250ml of water; if the problems persist, replacing with another gel's brand could be a good approach.

Isotonic fluids have from 6% to 8% carbohydrates (13 to 19 grams per 08 ounces). Can this small difference in concentration generate GIS? Shi et al evaluated 36 adults in a double-blind, randomized trial of 6% and 8% carbohydrate-electrolytes beverages during sports activities. He found more GIS when a volunteer consumed an 8% carbohydrate isotonic beverage. In this study, the 6% carbohydrate isotonic beverage had 305 mOsmol/L while the 8% beverage had 434 mOsmol/L[48].

Others may prefer to consume fruits, roots, and tubercles during exercise. Two aspects must be evaluated in this situation: the amount of fibers and level of fermentation. High fiber intake causes GIS as described before. There are many different kinds of fibers, found in a range of plant-based food, with different levels of fermentation, producing more or less gas (mainly hydrogen and methane). So, high-level fermentation food, produces more hydrogen and methane, causing more GIS.
Costill et al evaluated the level of gastric emptying according to the fluid's temperature. The volume of fluid remaining in the stomach was consistently less with the colder solutions (5, 15, 25, and 35°C)[49].

5 – Supplements

Supplements are widely consumed by people adept at sports, especially in endurance. An ultra marathonist or an Ironman triathlete usually consume from 8 to 12g of carbohydrate per kg every day, which is a large amount of food. Supplements may help to achieve these values in a more comfortable tastier way with less volume. However, the competition among supplement brands is intense, as it is a billion-dollar market. The palatability aspect is very important to ensure more consumers. In this way, many manufacturers add large amounts of artificial sweeteners to become the taste of supplements more pleasant. Unfortunately, these artificial sweeteners have adverse effects on the body, particularly to the gut. In 2012 American Heart Association recognized that excessive consumption of artificial sweeteners is associated with a higher risk of coronary heart disease and chronic kidney disease[50]. They can also cause alterations in gastrointestinal motility via their effects on the secretion of incretin hormones, more precisely the glucagon-like-peptide-1 (GLP-1) which decreases motility in the antro-duodeno-jejunal region and inhibits the migrating motility complex[51]. Harpaz et al evaluate six different artificial sweeteners (aspartame, sucralose, saccharine, neotame, advantame, and acesulfame potassium-k) found in ten sports supplements; all were considered toxic to a bacteria present at gut's microbiota[52].

So, artificial sweeteners contained in sports supplements can also cause dysbiosis, thus generating GIS and impairment of nutrients absorption.
On the other hand, replacing artificial sweeteners with sugar (sucrose) is not the solution, even for an athlete who needs high amounts of carbohydrate. Sucrose is composed of glucose plus fructose and, the excessive consumption of this last monosaccharide brings harmful effects to health such as nonalcoholic fatty liver disease, dyslipidemia, insulin resistance[53], and dysbiosis in animal studies[54,55].

Sodium bicarbonate ($NaHCO_3$) has been proposed as a performance enhancer by reducing acidosis during exercise, thus postponing acidosis fatigue. Athletes supplementing $NaHCO_3$ reported GIS including nausea, stomach pain, diarrhea, and vomiting. When sodium bicarbonate mixes with stomach acid, it produces gas[56]. Although the use of $NaHCO_3$ is very common in anaerobic sports activities, many endurance athletes may use it several times during the same event. A road cyclist may ingest $NaHCO_3$ before a competition and periodically every hour or every two hours; it depends on how his gastrointestinal system responds. Hadzic et al in a systematic review evaluated $NaHCO_3$ supplementation is sports lasting less and more than 4 minutes; he concluded that $NaHCO_3$ may be ergogenic in long period sports[57].

6 – Stimulants

Stimulants by definition are substances or agents that produce a temporary increase in the functional activity or efficiency of an organism or any of its parts. Some stimulants not only activate the central nervous system (CNS) but may also increase thermogenesis and are therefore referred to as stimulant thermogenics. Common indicators of CNS stimulatory activity are increases in heart rate and diastolic and systolic blood pressure. Non-stimulant thermogenic agents enhance thermogenesis but do not produce significant stimulation of the CNS and do not produce cardiovascular effects[58].
The sympathetic nervous system (SNS) is responsible for the regulation of energy expenditure, either the increasing use of adenosine triphosphate (ATP) and/or increasing the rate of mitochondrial oxidation with a poor coupling of ATP synthesis leading to increased heat production[59]. SNS activation increases thermogenesis to expend excess energy as heat and it might improve exercise performance. Sympathomimetic drugs such as salbutamol and dobutamine, are agents which in general mimic responses due to stimulation of sympathetic nerves, activating adrenergic receptors or increasing epinephrine and norepinephrine levels.

Thermogenic agents result in activation of UCP1, an integral part of the inner mitochondria membrane which dissipates energy as heat, which is an opposite mechanism to the ATP synthase, which couples the energy inherent in the proton gradient to the synthesis of ATP
A great number of stimulant substances are used by professionals and amateurs because they are quite easy to be found in stores and on the internet, and also because they are not listed in World Anti-Doping Agency (WADA). Da Silva et al has shown that 18% of physical exercise practitioners consume thermogenic substances[60] (women consume 22,2%).

Capsaicin, a chemical compound first isolated from chili peppers, but also found in cayenne, spur, and tabasco pepper, increases thermogenesis by enhancing catecholamines secretion from the adrenal medulla[61]. Two studies demonstrated that the use of propranolol abolished the capsaicin effect[62,63]. The stimulatory effect of pungent principles in spices on oxygen consumption is probably due to the involvement of Transient Receptor Potential Vanilloid receptor 1 (TRPV1), a channel expressed on peripheral sensory neurons, involved in pain sensation[64]. Capsaicin can cause abdominal pain, nausea, vomiting, burning, diarrhea, and rectal hyperalgesia[65].

Green tea extract is produced from the leaves of *camellia sinensis* and contains catechins (which are the predominant form of polyphenols) and caffeine. The main catechins are epigallocatechin gallate (EGCG), epigallocatechin, epicatechin gallate, and epicatechin. EGCG is the most pharmacologically active of the catechins which typically accounts for approximately 50-80% of the catechin content of green tea and also the most potent component[66]. The catechins in green tea may stimulate thermogenesis and fat oxidation through inhibition of catechol O-methyl-transferase, an enzyme that degrades norepinephrine[67] and increases SNS activity acutely[68]. In general, green tea extracts produce mild stimulatory effects that result in clinically insignificant cardiovascular effects[69]. Association of exercise plus green tea ingestion has shown a

significant increase in fat oxidation[70,71]. The tannins present in the green tea increase stomach's acid which may cause stomachache and nauseous feeling. Furthermore, green tea increases bowel peristaltic movements, increasing the risk of urge to defecate[72].

Caffeine belongs to a class of compounds called methyl-xanthines and can be found in coffee, tea, chocolate, cocoa, and in some soft drinks[59]. It is the world's most widely consumed stimulant. Caffeine has two different mechanisms: inhibiting adenosine receptors[73] (A1 and A2a) and acting as a competitive inhibitor of the enzyme phosphodiesterase, which is responsible for the breakdown of 3,5-cAMP, which is responsible for diverse signaling, including those for energetic status (AMP/ATP ratio)[74,75]. However, the thermogenic response caused by caffeine didn't decrease using β-blockers, pointing a mechanism independently from catecholamines[76,77]. The result of caffeine ingestion is an increase in energy metabolism, vasoconstriction, higher heart rate, and higher blood pressure. The most frequent symptom reported is heartburn; however, caffeine also can cause gastro-esophageal reflux, stimulates gastrin release, and increases rectosigmoid motor activity within 4 min after ingestion, causing an urge to defecate[78]. Caffeine withdrawal doesn't need to be complete. Most athletes don't have GIS consuming 3mg/kg before training or competing. Usually, doses of 6mg/kg are associated with a higher risk of GIS. If the athlete still suffers from GIS with a lower dose, the complete caffeine withdraw is indicated.

A lot of different substances are considered stimulants/thermogenic and can cause GIS. Every single different substance must be evaluated. We just don't mention all these substances because it is not the goal of this article.

7 – SIBO

Small Intestine Bacterial Overgrowth (SIBO) is a disease caused by an excessive amount of bacteria in the small intestine. In the proximal small bowel of healthy individuals, gram-positive aerobic bacteria predominate with rare facultative anaerobic. In contrast, the distal small bowel acts as a transition zone with the microbiota consisting mostly of facultative anaerobes and sparse populations of aerobic bacteria, while the colon microbes consisting of a dense population of strict anaerobes[79].

In SIBO, there are a large number of anaerobes bacteria in the proximal small intestine. It has a complex etiology, including anatomical abnormalities (obstruction, fistulas, and diverticular disease), surgical interventions, disturbed gastrointestinal motility causing constipation, and disturbance of defense mechanisms (achlorhydria). So, patients using proton pump inhibitors (some of them for mild symptoms), associated with a low fiber diet are at risk to develop SIBO[80].

Due to the large presence of anaerobic bacteria in the proximal intestine, carbohydrates are fermented, generating hydrogen and methane. SIBO has similar symptoms compared to lactose intolerance. Lactose should be broken into glucose and galactose and absorbed in the small intestine; in lactose intolerance, lactose reaches the colon and

is fermented, causing all the symptoms. In SIBO, anaerobic bacteria are in the small intestine, fermenting carbohydrates in the small intestine, causing the similar condition. SIBO is associated with malabsorption, abdominal distension, flatulence, and gut stasis.

Symptoms can get worse depending on the ingestion of certain kinds of carbohydrates. Although the gold standard exam to detect SIBO is the quantitative culture of a jejunal aspirate, it is invasive, costly, requires endoscopy, and needs an appropriate laboratory. A lactulose breath hydrogen test consists is a reliable non expensive exam to confirm SIBO diagnosis.

A low FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) may help or at least cause small improvement in this condition. It is a diet based on food with fermentation low degree. However the best approach is to identify and manage the cause (if possible) and treat with antibiotics for anaerobes bacteria. Today, around 41% of a non-coeliac athletic population surveyed reported adhering to a gluten-free diet in the belief that this approach reduces gastrointestinal symptoms and enhanced exercise performance; in fact improvements in symptoms and performance are not associated to a gluten-free diet, but possible to a low FODMAP diet that accompanies a gluten-free diet[81,82,83,84].

8 – Leaky Gut

Not a diagnosis, but a consequence of other abnormalities, leaky gut is the increased intestinal permeability, when gut loses their barriers and some undesirable substances (toxins, allergens e pathogens) can reach blood vessels. These barriers are composed of a mucus layer, epithelial layer, the underlying lamina propria, tight junctions proteins (connect the intestinal epithelial cells and regulate the paracellular permeability), immune cells, and anti-microbial peptides[85].
Intestine cells are continued attacked by dietary components, toxins, microbes, drugs, causing possible shortness in cells lifetime depending on personal habits. So, physiological cell proliferation is extremely important and glutamine will be used for this situation. Glutamine is an important energy resource for intestine cells (about 35% of total energy)[86]. In the small bowel mucosa, glutamine is a unique nutrient providing fuel for metabolism, regulating cell proliferation, repair, and maintaining the gut barrier functions[87].

Tight junctions, as cited before, are composed of transmembrane barrier proteins (occluding, claudin) peripheral scaffolding proteins (zonulin, afadin) and microtubules (cingulin, myosins)[88]. Glutamine deprivation and/or low level of serum glutamine concentration reduced the expression of tight junction proteins, possibly causing leaky gut[89,90]. Maes et al demonstrated that glutamine in combination with N-acetyl cysteine and zinc partially restores the tight junction integrity and attenuated gut-derived inflammation[91].

Causes of leaky gut include the use of non-steroidal anti-inflammatory drugs (NSAIDs), western diet (high in animal protein, saturated fatty acid, and sucrose), inflammatory diseases, ulcerating diseases, alcohol, stress, antibiotics, malnutrition. Many authors mention dysbiosis as a cause of leaky gut; however, some dysbiosis does not necessarily result in mucosal damage[92].

Endurance athletes need higher values of glutamine (the most abundant amino acid in the blood) due it depletion under exercise and stress. Glutamine is required in gluconeogenesis during and after exercise. Athletes exercising for long periods and/or above 70% VO2 max increases the gluconeogenesis rate thus decreasing the glutamine body's concentration. Some authors pointed deficit of glutamine as a cause of overtraining syndrome[93,94]. Endurance athletes produce huge amounts of free radicals, due to the prolonged time exercising plus intense sessions and due to the immense quantity of macronutrients utilized to produce energy. To neutralize all these free radicals, our body increases the production of glutathione, an endogenous antioxidant. However, to produce glutathione, glutamine is required. The plasma concentration of glutamine is significantly reduced under the conditions of extraneous exercise[95,96].

Glutamine is a major transporter of nitrogen from the sites of synthesis (skeletal muscle, liver, and lung) to the sites of utilization (kidney, intestine, neuron, and immune cells), including ammonia[97]. Quantitatively, skeletal muscle tissue is the most important place for glutamine synthesis, storage, and release; however, endurance athletes usually don't have large amounts of muscle mass[98]. Ammonia, a product from protein catabolism, should be transport from muscles to the liver by glutamine (glutamate plus ammonia) and then go to the urea cycle, transforming into urea (a less toxic substance). So, increasing gluconeogenesis also increases ammonia production, which uses glutamine (in fact glutamate) for transportation, making it less available to intestine cells. Glutamine is safe when taken up to 40mg per day. It may be harmful to people suffering from hepatic encephalopathy, acting as a trojan horse delivering more ammonia to astrocytes[99].

Leaky gut may cause bloating, flatulence, and abdominal cramps.
Intestinal permeability is most commonly measured indirectly in humans by the fractional urinary excretion of orally ingested substances that cross the intestinal epithelium, enter the bloodstream, are filtered by the glomerulus and excreted in the urine without active reabsorption in the kidney[100]. The most common substances are carbohydrates, such: sucrose, mannitol, rhamnose, lactulose, and sucralose (not metabolized by colonic bacteria). Timing of urinary excretion provides the best way to differentiate regional analyses: 0–2hours reflects predominantly small intestinal permeability and 8–24hours reflects almost exclusively colonic permeability[102]. A frequent association used for the leaky gut diagnosis is lactulose plus mannitol; lactulose is a large molecule and only goes into blood vessels due to leaky gut lesion while mannitol is a small molecule that could cross pore pathways with sodium, water, and other small molecules. Another method for demonstrating intestinal epithelial injury has been by measuring changes in circulating concentrations of the intestinal fatty-acid binding protein (I-FABP), a small (14-kD) cytosolic protein that is rapidly released into circulation upon injury and damage to mature enterocytes[102]. Fecal calprotectin, a marker of mucosal inflammation and fecal blood loss are other marks that depending on the situation, can be useful.

9 – Medications

Non-steroidal anti inflammatory drugs (NSAIDs) use has been linked to gastrointestinal injury and dysfunction, including nausea, regurgitation, dyspepsia, gastrointestinal ulcers, gastrointestinal bleeding, and diarrhoea[103]. Consuming NSAIDs before exercise can increase intestinal injury and permeability marks in response to exercise[104,105]. Antidepressants (mainly selective serotonin reuptake inhibitors), proton bomb inhibitor, metformin, colchicine, angiotensin-converting enzyme, inhibitors, bisphosphonates, and certain kinds of antibiotics may also cause diarrhea. However, more than 700 drugs may cause GIS[106].

10 - Other causes

Irritable bowel syndrome, inflammatory bowel disease (Crohn's disease and ulcerative colitis), celiac disease, rheumatoid disease, intolerances, excess intake of magnesium

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