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Gastrointestinal disorders and leaky gut syndrome in endurance athletes

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Abstract

Gastrointestinal disorders are common in endurance-sport athletes, and can negatively affect physical performance and general health. During long lasting exercises such like ultramarathon, triathlon, marathon a characteristic phenomenon is the increase in the concentration many proinflammatory markers and proteins such like IL-1, IL-6, TNF-alfa, LPS, CK and C-reactive protein. Despite observed biochemical changes on of the typical "side effects" of physical activity is increased intestinal permeability, also called to as leaky gut.

Recent research has demonstrated that even one hour of of intense endurance training note even with a maximum work capacity can lead to leaky gut symptoms and gastrointestinal disorders.

Increased intestinal permeability is accomplished with changes of numerus molecular biomarkers, that indicate presence of this disease state and the degradation of the intestinal mucosa, such like lipopolysaccharides, zonulin, lactulose/rhamnose ratio, occludin and I-FABP, and many other.

The understanding of this processes and understanding of the molecular mechanisms involved in the induction of leaky gut syndrome can lead to funding new methods and means of both avoiding and treating this condition.

Key words: leaky gut syndrome, long distance runners, gastrointestinal disorders,

Słowa kluczowe: zespół nieszczelnego jelita, biegacze długodystansowi, zaburzenia żołądkowo-jelitowe

Introduction

Sports competition in disciplines referred to as "extreme physical efforts" is each time associated with the intensification of the inflammatory response and damage of

many body tissues and organs. A significant increase in the serum level of pro-inflammatory cytokines is observed both after the marathon and ultramarathon, which may directly indicate the harmful effects of this form of sports activity on general health (Mieszkowski et al. 2021).

In addition, long-term running induces an increase in concentrations and/or activity of biomarkers that reflect the physiological stress of organs and tissues ex. skeletal muscles, liver, heart, gastrointestinal tract and other organs (Carmichael et al. 2006; Mieszkowski et al. 2021). Oxidative stress is one of the processes associated with tissue damage. It can be triggered by exercise, especially prolonged physical activity such as marathon running or other more demanding running efforts (Peterson et al. 2003; Nieman et al., 2006).

As a consequence, this process can lead to major changes in markers of tissue damage that are commonly associated with pathological conditions (Changas et al. 2012). An example is the increase in the concentration of cardiac troponin T (cTnT), one of the markers of myocardial damage, which may increase by up to 68% after endurance exercise, reaching values typical of acute myocardial infarction (Jablonski et al. 2011). Similarly, biomarkers of liver damage, such as aspartate aminotransferase (AST), γ -glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), and conjugated bilirubin, are similarly elevated after ultra-long runs (Choi et al. 2013). Changes in the concentration and/or activity of markers of heart and liver damage after marathon running are not observed in all athletes and are usually transient, returning to baseline values within a few days after the end of the competition (Carrillo et al. 2012; Choi et al. 2013).

Unfortunately, changes in tissue blood supply associated with increased blood flow through skeletal muscles during running competition almost always induce ischemic changes in the gastrointestinal tract (de Oliveiry et al. 2014). Such intense physical effort leads to damage to enterocytes in the lumen of the digestive tract, which in almost 90% can lead to an increased inflammatory response and gastrointestinal disorders, causing symptoms such as abdominal pain, colic, bloating, nausea, vomiting or diarrhea (de Oliveira et al. 2014). This condition is also often referred to as intestinal hyperpermeability syndrome or leaky gut syndrome. This has been described as a condition where we see a loosening of the tight junctions in the intestinal epithelial wall and a reduction in the integrity of the protective intestinal barrier. As it progresses, it can lead to the infiltration of bacterial endotoxins from the intestinal lumen into the bloodstream or other body organs, which in itself activates a series of inflammatory

cascades, increasing the likelihood of serious organ and inflammatory disorders. As a result of increased intestinal permeability, lipopolysaccharide (LPS) and pro-inflammatory cytokines can easily pass through the lining of intestinal cells, increasing their concentration in the bloodstream (Brock-Utne et al. 1988; Twardowska et al. 2022). In addition, due to the important immunological role of the gastrointestinal tract, long-term intensive exercise affects the athlete's health (causing post-exercise increased likelihood of illness) and intensifies the inflammatory process (Twardowska et al. 2022). Increased concentration of pro-inflammatory cytokines (interleukin-6, tumor necrosis factor- α , interleukin-1 β) in the blood, combined with the intensification of bacterial infections, leads to an increase in the production of procalcitonin, whose increase in serum concentration very quickly correlates directly with the severity of the infection, and this directly may indicate serious systemic disorders induced by a pathological response from the gastrointestinal tract induced by extreme exercise (Chagas et al. 2012).

The circulatory-gastrointestinal and the neuroendocrine-gastrointestinal pathway are two distinct and communicable pathways that contribute to exercise-induced gastrointestinal syndrome.

Total splanchnic perfusion is decreased by the first pathway's redistribution of blood flow to working muscles and peripheral circulation, whereas the neuroendocrine-gastrointestinal pathway is associated with an increase in sympathetic activation and a corresponding decrease in gastrointestinal functional capacity (Van Wijck et al. 2011; Van Wijck, et al. 2012). Due the specific activity of blood flow in gastrointestinal tract it is thought that intestinal ischemia is the main factor causing vomiting, diarrhea, stomach aches, nauseousness and many other symptoms happening twice as often in runners as in athletes who participate in other endurance sports (De Oliveira et al. 2014)). However, both pathways result in gastrointestinal symptoms with short-term or long-term health issues (Costa et al. 2017). During long lasting exercises deterioration of the gastrointestinal mucosal barrier may also be observed and in most situation this process is increasing intestines permeability causing bacterial endotoxemia, and inducing systemic inflammation response, which in most of the situations affects overall health (Gubert et al. 2020; Mohr et al. 2020).

Gastrointestinal Response During Exercises

Gastrointestinal system is a specific complex built of a different cell, which work together to generate motility, digestion, absorption, and secretion during food

consumption. Normally during gastrointestinal system activity, we observe cooperation of intestinal epithelial cells (IECs), intestinal lumen, lamina propria, smooth muscle, and the myenteric and submucosal plexuses. Thus, the physiological response during intensive exercise affects different cells in several species (van Nieuwenhoven et al. 2014).

Long distance running leads to an increase in the skeletal muscle's energy demand and the organism's adaptation to supply this demand. During this type of physical activity, the sympathetic nervous system affects hemodynamics, reducing and redistributing the blood flow to the exercising muscles (mainly lower limbs). This situation decreases splanchnic blood flow even up to 70–80% of the maximum oxygen consumption (VO_{2max}) during exercises (Van Wijck K et al. 2012). As a consequence of this situation hypoxic changes can be observed, causing local gastrointestinal system ischemia (Oliveira and Burini, 2009). Observed ischemia causes cell damage affecting mainly Paneth cells, goblet cells, tight junction proteins, as a response of ATP synthesis reduction (King et al. 2020; Liu et al. 2018). Moreover, bacterial endotoxins may pass through epithelial cells inducing proinflammatory response which results in a definite state “leaky gut syndrome” (Gill et al. 2015; Stewart et al. 2017). Furthermore, sympathetic system stimuli can also lead to changes in intestinal motility and nutrients absorption (Costa et al. 2017). Observed during prolonged running local ischemia and down-regulated intestinal transporter activity are associated with lower-gastrointestinal symptoms (ex. flatulence, lower-abdominal bloating, urge to defecate, abdominal pain, diarrhea, and bloody stools (Oliveira et al. 2009; Costa et al. 2017).

Molecular Response During Prolonged Exercises

Physical exercises can lead to increase intestinal permeability due to the exercises associated increased expression in inflammation specific proteins. For example, it has been proven that increase IL-1 β induces increase of the Caco-2 TJ permeability and increased transcription of MLCK mRNA (Al-Sadi et al. 2016, Jin et al. 2020). Moreover changes of IL-1 β induces increase in mitogen-activated protein kinase kinase 1 (MEKK1) (Al-Sadi et al. 2010). Similar effect can be observed during increased synthesis of tumor necrosis-alpha (TNF- α) (Al-Sadi et al. 2013).

Long lasting stress exercises almost every time induces inflammation process causing changes in proinflammatory proteins and cytokines such as C-reactive protein, interleukin-6 (IL-6), IL-1 β , TNF- α , and interferon-gamma (IFN- γ) increased (Gill et al. 2015; Mieszkowski et al. 2021).

During prolonged stresses exercises (lasting ≥ 1 h) synthesis of enterocyte-derived intestinal fatty-acid binding protein (I-FABP) is increased. It is a specific marker of intestinal enterocyte damage and prolonged ischemia (Costa et al. 2017). Moreover, during prolonged exercises or training in very hot environment the increase in intestinal permeability leads increased concentration of LPS the bloodstream (Bosenberg et al. 1988; Brock-Utne et al. 1988).

Perspectives of gastrointestinal protection

As it was proven, prolonged, long lasting and energy demanding exercises may affect the gastrointestinal system, inducing changes in the mucosa's integrity, increasing its. This process is associated with the activation of proinflammatory signaling, directly affecting gastrointestinal tract. Moreover, dehydration, bloody diarrhea episodes, abdominal discomfort and many other affects sport results and influence sportsman health. are typical responses in endurance athletes As a result, several strategies have been considered to restore the gastrointestinal mucosa by modulating the gut microbiota. To date, the mutual interaction among exercise, dietary supplementation, and gut microbiota is speculated to be a key strategy to reduce the effects of gastrointestinal distress caused by strenuous exercise and even a game-changer concerning sports performance (Oktedalen et al. 1992). Many workers in heath and sport reserch seek for new methods, form of gastrointestinal protection. The results of recent reports indicate that supplementation with various preparations (vitamin D, glutamate, probiotics) as well as the use of various methods inducing a number of adaptive reactions aimed at increasing tolerance to hypoxemic disorders may be helpful in the case of post-exercise disorders of the digestive system (Rao et al. Samak, 2012; Dattola et al. 2020; Altenhoefer et al. 2004). The correct supply of glutamate may be associated with beneficial changes in the intestinal microbiome, which will directly affect the improvement of intestinal health and homeostasis of the immune system (Camilleri et al. 2012). In addition, it has also been shown that the administration of high doses of vitamin D can induce an interesting and effective anti-inflammatory effect, reducing the synthesis of tumor necrosis factor α and IL-1 β , IL-6 in monocytes. Both TNF α and IL-1, IL-6 are well-known factors affecting intestinal permeability, exacerbating the symptoms of intestinal hyperpermeability. In this way, supplementation with glutamate and/or vitamin D may prove to be one of the valuable methods of preventing post-exercise gastrointestinal disorders and intestinal hyperpermeability. However, amateur runners, due to the specificity of the starting

preparation, may require a variety of methods and measures to protect organ tissues from damage. In addition, administration of high doses of vitamin D or probiotics may not seem advisable in every athlete (high content in blood serum, overgrowth of intestinal microflora). Therefore, in addition to nutritional methods, other procedures inducing adaptive changes that protect body cells, including enterocytes, against the symptoms of ischemia and related damage may prove valuable.

Of particular interest to people treated for ischemic changes are protocols of the so-called hardening of tissues through their transient ischemia. Ischemic episodes caused in this way contribute to an increase in blood flow in their structure. This phenomenon is referred to as blood reperfusion and contributes to the increased tolerance of treated tissues to possible ischemic events (e.g. patients with thromboembolic vasculitis and active coronary artery disease) (Bushel et al. 2002). Recent studies have shown that repeated episodes of ischemia followed by reperfusion (IPC) may contribute to the development of adaptive changes related to both the change in blood flow and the increase in tolerance to ischemia in the future. The adaptive changes observed in this way may concern both the hardened tissues and also translate into a systemic effect.

Mieszkowski et al. (Mieszkowski et al. 2022) proved that the use of the ischemic preconditioning procedure induces a protective effect against post-exercise damage to the heart and liver in long-distance runners, which allows to presume that the secretion of various trophic factors, cytokines, enhanced as a result of the RIPC/IPC procedure and proteins will also indirectly affect the lumen of the digestive tract. This may translate into an increase in tolerance to secondary ischemia, and thus guarantee the intestinal epithelial cells a better chance of survival in conditions of impaired blood supply induced by a decrease in blood flow through the intestine as a result of physical activity.

Conclusions

Physical exercise acts as a modulator of the intestinal activity due the nutritional and oxygen demands of working with great effort skeletal muscle. Long lasting exercises leads to gastrointestinal ischemic response. Moreover, it is mostly associated with the hyperthermia and many other sport specific changes. However, available data about this process are still uncertain and need farther exploration. Moreover, still studies are needed in order to emphasize the role of exercise in intestinal permeability and to pinpoint other variables that may influence this process and how with the nutritional, training and procedural method we can modulate this process

Author's contribution

Conceptualization, IM, and MK; methodology, IM; software, IM; check, IM, MK; formal analysis, IM; investigation, IM, MK; resources, IM; writing - rough preparation, IM, MK; writing - review and editing, IM, MK; supervision, IM, MK; project administration, IM; receiving funding, IM.

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Conflict of Interest Statement

The authors declare no conflict of interest. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

References

Al-Sadi R, Guo S, Ye D, Ma TY. TNF-alpha modulation of intestinal epithelial tight junction barrier is regulated by ERK1/2 activation of Elk-1. *Am J Pathol.* (2013) 183:1871–84. doi: 10.1016/j.ajpath.2013.09.001

Al-Sadi R, Ye D, Dokladny K, Ma TY. Mechanism of IL-1beta-induced increase in intestinal epithelial tight junction permeability. *J Immunol.* (2008) 180:5653–61. doi: 10.4049/jimmunol.180.8.5653

Al-Sadi R, Ye D, Said HM, Ma TY. IL-1 β -induced increase in intestinal epithelial tight junction permeability is mediated by MEKK-1 activation of canonical NF- κ B pathway. *Am J Pathol.* (2010) 177:2310–22. doi: 10.2353/ajpath.2010.100371

Altenhoefer, A., Oswald, S., Sonnenborn, U., Enders, C., Schulze, J., Hacker, J., Oelschlaeger, T. A. The probiotic *Escherichia coli* strain Nissle 1917 interferes with invasion of human intestinal epithelial cells by different enteroinvasive bacterial pathogens. *FEMS Immunology & Medical Microbiology*, 2004, 40(3), 223-229.

Bosenberg AT, Brock-Utne JG, Gaffin SL, Wells MT, Blake GT. Strenuous exercise causes systemic endotoxemia. *J Appl Physiol.* (1988) 65:106–8. doi: 10.1152/jappl.1988.65.1.106

Brck-Unte, JG, Gaffin, SL, Wells, MT, Gathiram, P., Sohar, E., James, MF, Morrell, DF, Norman, RJ. "Endotoxaemia in exhausted runners after a long-distance race." *South African Medical Journal* 1988, 73.9, 533-536.

Brock-Utne JG, Gaffin SL, Wells MT, Gathiram P, Sohar E, James MF, et al. Endotoxaemia in exhausted runners after a long-distance race. *S Afr Med J.* (1988) 73:533–6.

Camilleri, Á., Madsen, K., Spiller, R., Van Meerveld, B. G., & Verne, G. N. Intestinal barrier function in health and gastrointestinal disease. *Neurogastroenterology & Motility*, 2012, 24(6), 503-512.

Carmichael, M.D.; Davis, J.M.; Murphy, E.A.; Brown, A.S.; Carson, J.A.; Mayer, E.P.; Ghaffar, A. Role of brain IL-1 β on fatigue after exercise-induced muscle damage. *Am. J. Physiol.-Regul. Integr. Comp. Physiol.* 2006, 291, R1344–R1348, doi:10.1152/ajpregu.00141.2006

Carrillo, A.E.; Flynn, M.G.; Pinkston, C.; Markofski, M.M.; Jiang, Y.; Donkin, S.S.; Teegarden, D. Vitamin D supplementation during exercise training does not alter inflammatory biomarkers in overweight and obese subjects. *Eur. J. Appl. Physiol.* 2012, 112, 3045–3052, doi:10.1007/s00421-011-2279-3.

Chagas, C.E.; Borges, M.C.; Martini, L.A.; Rogero, M.M. Focus on vitamin D, inflammation and type 2 diabetes. *Nutrients* 2012, 4, 52–67, doi:10.3390/nu4010052.

Choi, M.; Park, H.; Cho, S.; Lee, M. Vitamin D3 supplementation modulates inflammatory responses from the muscle damage induced by high-intensity exercise in SD rats. *Cytokine* 2013, 63, 27–35, doi:10.1016/j.cyto.2013.03.018.

Costa RJS, Miall A, Khoo A, Rauch C, Snipe R, Camoes-Costa V, et al. Gut-training: the impact of two weeks repetitive gut-challenge during exercise on gastrointestinal status, glucose

availability, fuel kinetics, running performance. *Appl Physiol Nutr Metab.* (2017) 42:547–57. doi: 10.1139/apnm-2016-0453

Costa RJS, Snipe RMJ, Kitic CM, Gibson PR. Systematic review: exercise-induced gastrointestinal syndrome-implications for health and intestinal disease. *Aliment Pharmacol Ther.* (2017) 46:246–65. doi: 10.1111/apt.14157

Dattola, A.; Silvestri, M.; Bennardo, L.; Passante, M.; Scali, E.; Patruno, C.; Nistico, S.P. Role of Vitamins in Skin Health: a Systematic Review. *Curr. Nutr. Rep.* 2020, 9, 226-235, doi:10.1007/s13668-020-00322-4.

De Oliveira EP, Burini RC, Jeukendrup A. Gastrointestinal complaints during exercise: prevalence, etiology, nutritional recommendations. *Sports Med.* (2014) 44(Suppl. 1):S79–85. doi: 10.1007/s40279-014-0153-2

de Oliveira GLV, Leite AZ, Higuchi BS, Gonzaga MI, Mariano VS. Intestinal Dysbiosis and Probiotic Applications in Autoimmune Diseases. *Immunology.* 2017, 152:1–12. doi: 10.1111/imm.12765

Gill SK, Teixeira A, Rama L, Prestes J, Rosado F, Hankey J, et al. Circulatory endotoxin concentration and cytokine profile in response to exertional-heat stress during a multi-stage ultra-marathon competition. *Exerc Immunol Rev.* (2015) 21:114–28.

Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases. *Neurobiol Dis.* (2020) 134:104621. doi: 10.1016/j.nbd.2019.104621

Jablonski, K.L.; Chonchol, M.; Pierce, G.L.; Walker, A.E.; Seals, D.R. 25-Hydroxyvitamin D deficiency is associated with inflammation-linked vascular endothelial dysfunction in middle-aged and older adults. *Hypertension* 2011, 57, 63–69, doi:10.1161/HYPERTENSIONAHA.110.160929.

Jin Y, Blikslager AT. The regulation of intestinal mucosal barrier by myosin light chain kinase/rho kinases. *Int J Mol Sci.* (2020) 21:3550. doi: 10.3390/ijms21103550

King DR, Padget RL, Perry J, Hoeker G, Smyth JW, Brown DA, et al. Elevated perfusate [Na(+)] increases contractile dysfunction during ischemia and reperfusion. *Sci Rep.* (2020) 10:17289. doi: 10.1038/s41598-020-74069-x

Liu F, Lu J, Manaenko A, Tang J, Hu Q. Mitochondria in ischemic stroke: new insight and implications. *Aging Dis.* (2018) 9:924–37. doi: 10.14336/AD.2017.1126

Mieszkowski, J., Stankiewicz, B. E., Kochanowicz, A., Niespodziński, B., Borkowska, A. E., Sikorska, K., ... & Antosiewicz, J. (2021). Remote Ischemic Preconditioning Reduces Marathon-Induced Oxidative Stress and Decreases Liver and Heart Injury Markers in the Serum. *Frontiers in Physiology*, 12, 731889.

Nieman, D.C.; Henson, D.A.; Dumke, C.L.; Oley, K.; McAnulty, S.R.; Davis, J.M.; Murphy, E.A.; Utter, A.C.; Lind, R.H.; McAnulty, L.S.; et al. Ibuprofen use, endotoxemia, inflammation, and plasma cytokines during ultramarathon competition. *Brain Behav. Immun.* 2006, 20, 578–584, doi:10.1016/j.bbi.2006.02.001

Oktedalen O, Lunde OC, Opstad PK, Aabakken L, Kvernebo K. Changes in the gastrointestinal mucosa after long-distance running. *Scand J Gastroenterol.* (1992) 27:270–4. doi: 10.3109/00365529209000073

Oliveira EP, Burini RC. The impact of physical exercise on the gastrointestinal tract. *Curr Opin Clin Nutr Metab Care.* (2009) 12:533–8. doi: 10.1097/MCO.0b013e32832e6776

Peterson, J.M.; Trappe, T.A.; Mylona, E.; White, F.; Lambert, C.P.; Evans, W.J.; Pizza, F.X. Ibuprofen and acetaminophen: Effect on muscle inflammation after eccentric exercise. *Med. Sci. Sports Exerc.* 2003, 35, 892–896, doi:10.1249/01.MSS.0000069917.51742.98.

Rao R, Samak G., Role of glutamine in protection of intestinal epithelial tight junctions. *J Epithel Biol Pharm* 2012, 5:47

Ruiz-Iglesias P, Estruel-Amades S, Camps-Bossacoma M, Massot-Cladera M, Castell M, Perez-Cano FJ. Alterations in the mucosal immune system by a chronic exhausting exercise in Wistar rats. *Sci Rep.* (2020) 10:17950. doi: 10.1038/s41598-020-74837-9

Stewart AS, Pratt-Phillips S, Gonzalez LM. Alterations in intestinal permeability: the role of the “leaky gut” in health and disease. *J Equine Vet Sci.* (2017) 52:10–22. doi: 10.1016/j.jevs.2017.02.009

Twardowska, A., Makaro, A., Binienda, A., Fichna, J., & Salaga, M. Preventing bacterial translocation in patients with leaky gut syndrome: Nutrition and pharmacological treatment options. *International journal of molecular sciences*, 2022, 23(6), 3204.

van Nieuwenhoven MA, Brouns F, Brummer RJ. The effect of physical exercise on parameters of gastrointestinal function. *Neurogastroenterol Motil.* (1999) 11:431–9. doi: 10.1046/j.1365-2982.1999.00169.x

Van Wijck K, Lenaerts K, Grootjans J, Wijnands KA, Poeze M, Van Loon LJ, et al Physiology A and pathophysiology of splanchnic hypoperfusion and intestinal injury during exercise: strategies for evaluation and prevention. *Am J Physiol Gastrointest Liver Physiol.* (2012) 303:G155–68. doi: 10.1152/ajpgi.00066.2012

Van Wijck K, Lenaerts K, Van Loon LJ, Peters WH, Buurman WA, Dejong CH. Exercise-induced splanchnic hypoperfusion results in gut dysfunction in healthy men. *PLoS ONE.* (2011) 6:e22366. doi: 10.1371/journal.pone.0022366

Yin, K.; Agrawal, D.K. Vitamin D and inflammatory diseases. *J. Inflamm. Res.* 2014, 7, 69-87, doi:10.2147/JIR.S63898.