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Extreme Endurance Exercise and Colorectal Neoplasia: Potential Links Between Gut Barrier Dysfunction, Microbiota and Inflammation

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Abstract

Background: Regular physical activity lowers colorectal neoplasia risk, but extreme endurance exercise (EEE) may act differently, causing splanchnic hypoperfusion, intestinal injury, permeability increases, endotoxaemia, and systemic inflammation (exercise-induced gastrointestinal syndrome), plus rapid microbiota shifts and transient immune changes. Advanced adenomas reported in young runners raise the question of whether repeated exercise-related stress affects colorectal neoplasia.

Aim. To integrate evidence from sports gastroenterology, exercise physiology, microbiome research, immunology, and oncology into a mechanistic framework linking repeated EEE to colorectal neoplasia.

Material and methods. A narrative literature synthesis on exercise-induced intestinal injury, endotoxaemia, microbiome/immune alterations, and adenoma findings in runners, distinguishing established associations from unproven hypotheses.

Results. Strenuous exercise may cause splanchnic hypoperfusion and ischaemia-reperfusion stress, leading to epithelial injury, permeability changes, and bacterial translocation with inflammation. EEE causes rapid microbiota shifts of unclear significance and transient immune-cell redistribution, not suppression. Inflammation can enhance genotoxic bacteria (colibactin-producing *E. coli*). A prospective study found advanced adenomas in 14/94 runners (15.0%), linked to rectal bleeding; single-arm design precludes causal conclusions.

Conclusions. EEE may cause repeated hypoperfusion, barrier disruption, microbial remodeling, inflammation, and immune perturbation, a plausible framework for studying colorectal neoplasia risk. Evidence does not establish causation, but findings warrant prospective study of athletes' gut health. Rectal bleeding should not be assumed benign.

Keywords: extreme endurance exercise, colorectal adenoma, splanchnic hypoperfusion, exercise-induced gastrointestinal syndrome, gut microbiota dysbiosis, ischemia-reperfusion injury, exercise immunology

1. Introduction

The role of regular physical activity in preventing chronic diseases is a foundational pillar of modern preventive medicine. Extensive epidemiological data, including the comprehensive meta-analysis conducted by Wolin, Yan, and Colditz (which synthesized data from 20 independent studies), consistently demonstrate that physical activity is associated with a statistically significant decrease in the risk of developing colon adenomas [1]. Specifically, their analysis revealed an overall 16% risk reduction for colon adenomas (Relative Risk [RR] = 0.84; 95% Confidence Interval [CI]: 0.77–0.92), with the protective effect being comparable between men (RR = 0.81) and women (RR = 0.87) [1]. Crucially from an oncological standpoint, this inverse association appeared even stronger for large and advanced polyps, where physical activity was linked to a substantial 30% reduction in risk (RR = 0.70; 95% CI: 0.56–0.88) [1]. The recognized biological mechanisms driving this preventive phenomenon primarily include reduced systemic inflammation, decreased hyperinsulinemia, lowered circulating insulin-like growth factors, and a systemic modulation of immune function [1]. Consequently, physical activity is widely recommended by oncological guidelines as a preventive measure.

However, the dynamic evolution of sports medicine has brought attention to a paradox regarding extreme endurance exercise (EEE), such as ultramarathons and Ironman triathlons. While moderate activity is protective, extreme loads provoke physiological, thermodynamic, and neuroendocrine stress that may disrupt normal organ homeostasis. During such events, the gastrointestinal (GI) tract frequently becomes the most vulnerable system, failing to cope with the competing circulatory demands of the working muscles and thermoregulation. Clinical

evidence indicates that exercise-induced gastrointestinal symptoms in endurance sports are not merely rare anomalies, but rather widespread and highly prevalent phenomena [4, 6].

According to a comprehensive review by Ribichini et al., these gastrointestinal disturbances affect up to 70% of all endurance athletes [6]. Athletes routinely experience a broad, debilitating spectrum of upper and lower GI distress, ranging from heartburn, belching, nausea, vomiting, and delayed gastric emptying, to severe abdominal cramping, the urgent need to defecate, explosive watery diarrhea, and acute gastrointestinal bleeding [4, 6]. This clinical presentation, now formally recognized as Exercise-Induced Gastrointestinal Syndrome (EIGS), is driven by a complex pathophysiological interplay. It is triggered not only by altered gut motility and mechanical trauma (the repetitive torso movements and bouncing inherent in running), but also by nutrient malabsorption [4, 6]. Under extreme stress, the unabsorbed, hyperosmolar carbohydrates from sports nutrition draw water into the intestinal lumen, exacerbating osmotic diarrhea and physical distress [6]. Ultimately, these combined forces inflict significant structural mucosal injury, stripping the GI tract of its barrier integrity and transforming transient race-day discomfort into potential systemic inflammatory threat [4, 6].

Although exercise-induced gastrointestinal symptoms have traditionally been viewed primarily as transient consequences of strenuous exercise, emerging evidence suggests that they may reflect more substantial alterations in gastrointestinal integrity, including intestinal injury, increased permeability, and inflammatory responses [6]. Evidence from study by Jeukendrup et al. indicates that prolonged strenuous exercise may be associated with endotoxin translocation into the systemic circulation and a concomitant acute inflammatory response [8]. It has prompted critical reflection on the theoretical cumulative, long-term consequences of these recurrent gastrointestinal insults. The most alarming catalyst for this reflection comes from recent prospective screening studies, which have documented a high prevalence of advanced colorectal adenomas in a cohort of young, otherwise remarkably healthy endurance runners [22]. This startling clinical manifestation raises a fundamental question regarding a potential relationship between years of extreme, repetitive exercise and the accelerated neoplastic process in the colon. To fully comprehend this phenomenon, it is imperative to move beyond isolated symptoms and construct an integrated, mechanistic model. This requires a systematic analysis of the proposed pathophysiological cascade, beginning with exercise-induced splanchnic hypoperfusion [2], progressing through disruption of gut barrier integrity [7] and exercise-associated alterations in intestinal microbiota composition [15], and potentially leading to local adaptive immune surveillance that may influence the persistence and progression of dysplastic lesions [19].

2. Physiology and Pathophysiology of Post-Exercise Splanchnic Hypoperfusion

2.1. Redistribution of Cardiac Output and Organ Metabolic Prioritization

The primary physiological challenge during EEE is meeting the increased demand of working skeletal muscles for oxygen while maintaining thermoregulation [9]. The human body copes with this challenge through a redistribution of blood flow. As detailed by van Wijck et al., during high-intensity exercise, splanchnic blood flow undergoes a reduction, leading to exercise-induced splanchnic hypoperfusion [2, 3]. This compensatory redistribution of blood flow, while crucial for sustaining global physical performance, may lead to intestinal ischemia, including the highly sensitive epithelium of the intestines [2].

2.2. Ischemia-Reperfusion Injury

Hypoperfusion is the first phase of this pathological phenomenon. A second event occurs during the reperfusion phase at the cessation of physical exercise, when oxygenated blood returns to the previously ischemic area [2]. Restoration of splanchnic blood flow following hypoperfusion may contribute to reperfusion-associated oxidative stress, with reactive oxygen species potentially exacerbating epithelial injury [2].

The work of van Wijck et al. demonstrated that exercise-induced splanchnic hypoperfusion was associated with increased plasma Intestinal Fatty Acid-Binding Protein (I-FABP) levels, which correlated with the intestinal epithelial injury. [3].

The pathophysiological mechanisms underlying exercise-induced gastrointestinal damage can be divided into three interconnected processes. First, during the ischemia phase, splanchnic hypoperfusion and a subsequent drop in oxygen levels lead to enterocyte stress and cellular dysfunction [2]. Second, restoration of blood flow following intestinal hypoperfusion may result in reperfusion-associated oxidative stress, with reactive oxygen species potentially contributing to epithelial injury. In the study by van Wijck et al., exercise-induced splanchnic hypoperfusion was associated with increased plasma I-FABP levels, which may indicate intestinal epithelial injury [3]. Third, strenuous endurance exercise may also be associated with gastrointestinal mucosal injury and bleeding, as evidenced by reports of fecal blood loss following marathon running [4, 5].

3. Clinical and Immunological Evolution of Exercise-Induced Gastrointestinal Syndrome (EIGS)

Exercise-induced gastrointestinal syndrome (EIGS) represents a multifactorial spectrum of gastrointestinal disturbances that develops in response to strenuous and prolonged exercise and

encompasses alterations in gastrointestinal integrity, permeability, motility, digestion and absorption. [4, 6]. Current evidence indicates that the clinical manifestation of EIGS evolves with increasing exercise intensity and duration, with prolonged exercise at approximately $\geq 60\%$ VO_2max for ≥ 2 h representing a condition in which clinically relevant gastrointestinal perturbations become increasingly apparent [4]. The initial pathophysiological event is predominantly related to redistribution of blood flow from the splanchnic circulation toward active skeletal muscles and the skin, accompanied by increased sympathetic and neuroendocrine activation. The resulting intestinal hypoperfusion and ischemia may induce epithelial injury, disruption of tight-junction proteins and increased intestinal permeability, subsequently impairing gastrointestinal motility and nutrient absorption [4, 6]. In severe cases, mucosal injury may also manifest as gastrointestinal bleeding; notably, McCabe et al. reported conversion from negative to positive fecal occult blood testing in 23% of marathon runners after the race, demonstrating that exercise-associated gastrointestinal injury may extend beyond transient functional symptoms [5]. The disruption of the intestinal barrier has important immunological consequences because increased permeability facilitates translocation of bacterial products, particularly lipopolysaccharide (LPS), into the systemic circulation. This may activate innate immune pathways, including NF- κ B-dependent inflammatory signaling, and stimulate the release of cytokines such as IL-1 β , TNF- α and IL-6, followed by anti-inflammatory responses involving IL-10 and IL-1ra [4]. In highly trained triathletes, gastrointestinal symptoms were reported by 93% of participants, while mild endotoxaemia was detected immediately after exercise in 68%; this was accompanied by a marked increase in IL-6 and subsequent acute-phase responses, including substantial elevation of C-reactive protein [8]. Importantly, the relationship between endotoxaemia and gastrointestinal symptoms was not strictly linear, suggesting that EIGS reflects the interaction of several processes rather than a single inflammatory pathway [8].

Environmental heat stress may further accelerate this clinical-immunological cascade: compared with exercise in temperate conditions, running in the heat markedly increased intestinal epithelial injury, circulating endotoxin and cytokine responses, while reducing anti-endotoxin antibody concentrations, indicating impaired endotoxin clearance [9]. Prolonged physiological stress may additionally be accompanied by alterations in intestinal microbiota composition and metabolic activity, occurring in parallel with increased intestinal permeability and inflammation, suggesting that the gut microbiome may constitute another component linking acute physiological stress with gastrointestinal barrier dysfunction [7].

Thus, the clinical evolution of EIGS can be conceptualized as a continuum progressing from transient functional disturbances and mild gastrointestinal symptoms to epithelial injury, increased permeability and endotoxaemia, with subsequent activation of local and systemic immune responses. Although these alterations are generally reversible after cessation of exercise, repeated or severe exposure, particularly in the presence of heat stress, may increase the potential for clinically significant gastrointestinal complications [4, 6, 9].

4. From Metabolic Adaptation to Acute Microbial Remodeling

The gut microbiome is a dynamic and highly responsive ecosystem influenced by host physiology, diet, and physical activity [10, 13]. Long-term gut microbiota composition is shaped by dietary habits and physical activity, with these factors influencing the abundance and activity of microbial taxa associated with health and disease [10, 11, 13].

4.1. The Baseline Exercise-Associated Microbiome: Metabolic Adaptation

Studies by Bressa et al. and Monda et al. have shown that individuals with an active lifestyle were characterized by distinct gut microbiota profiles, including greater abundance of several taxa associated with metabolic and intestinal health [12, 13]. Scheiman et al. provided experimental evidence linking *Veillonella* to exercise performance, showing that its abundance increased after marathon running and that a *V. atypica* strain could enhance endurance in mice through lactate-to-propionate metabolism [14].

4.2. Rapid Microbiome Remodeling During Extreme Endurance Exercise

The microbiome profile associated with regular physical activity may undergo rapid remodeling during episodes of extreme endurance stress. Grosicki, Durk, and Bagley documented substantial changes in gut microbiota composition in a world-class ultramarathon runner following a 163-km race [15]. The post-race microbiome was characterized by marked shifts in the relative abundance of several taxa, including a dramatic increase in *Veillonella* and an increase in *Streptococcus*, accompanied by reductions in *Alloprevotella* and *Subdoligranulum* [15].

Such findings raise the possibility that extreme endurance exercise is associated with acute restructuring of the gut microbial community. The pronounced expansion of *Veillonella* is particularly noteworthy, as this genus can metabolize exercise-derived lactate and generate propionate, a pathway associated with enhanced endurance capacity in an experimental mouse model [14]. Nevertheless, the simultaneous redistribution of other bacterial taxa suggests that

the microbiome response to extreme exercise is not limited to a single performance-associated organism but involves broader community-level remodeling [15]. Whether these acute shifts represent an adaptive metabolic response, a transient perturbation of intestinal microbial homeostasis, or, under conditions of repeated physiological stress and intestinal barrier disruption, contribute to a more adverse microbial and inflammatory environment remains unknown. This distinction is particularly important in the context of EIGS, where exercise-induced splanchnic hypoperfusion, epithelial injury, and increased intestinal permeability could theoretically interact with stress-induced microbial remodeling.

Although the inflammatory consequences of these exercise-associated microbial shifts have not been established in endurance athletes, experimental evidence indicates that alterations in the intestinal inflammatory milieu can modify microbial functions relevant to carcinogenesis [21]. This raises the possibility that repeated episodes of exercise-induced intestinal stress and microbial remodeling could, under specific conditions, influence pathways involved in intestinal inflammation and colorectal neoplasia; however, this hypothesis remains to be tested.

5. Immunological Overload: Modulation and Early Biomarkers of Dysfunction

The sustained inflammatory environment associated with EIGS may place additional demands on the host's immune system.

Historically, it was believed that prolonged exertion caused generalized immune suppression; however, modern analyses by Campbell and Turner, as well as Simpson et al., effectively challenge this long-standing hypothesis [16, 17]. Instead of broad immune suppression, exercise induces transient changes in the distribution of immune cells, including their redistribution to peripheral tissues, where they contribute to immune surveillance and regulation [16, 17]. This redistribution should be distinguished from the biomarker-level immune alterations described below, which reflect measurable changes under progressively increasing training load rather than a return to the generalized-suppression model.

Nevertheless, prolonged exposure to progressively increasing training loads may be associated with measurable alterations in immune function. Xu et al., utilizing iTRAQ-based urinary proteomics, demonstrated that four weeks of incremental treadmill training induced measurable changes in immune function in healthy men, reflected by reductions in circulating white blood cells, CD4⁺ lymphocytes, and the CD4⁺/CD8⁺ ratio — changes that the original authors interpreted as consistent with exercise-induced immunosuppression [18], though they may equally reflect the transient redistribution described above rather than true functional suppression. A total of 1,854 urinary proteins were identified, with the number of differentially

expressed proteins increasing substantially at the highest training load, which may reflect an increasing systemic response to exercise-induced physiological stress. Importantly, the urinary abundance of four proteins - semenogelin-1 (SEMG-1), prolactin-inducible protein (PIP), platelet-derived growth factor receptor-like protein (PDGFRL), and nucleoside diphosphate kinase (NDPK) - increased progressively with exercise intensity. Bioinformatic analyses indicated that these proteins are associated with stress-response and immune-related processes, supporting their potential utility as non-invasive indicators of exercise-induced immune modulation. These findings suggest that progressively increasing training loads are accompanied by detectable changes in both conventional immune parameters and the urinary proteome. Urinary proteomic profiling may therefore represent a promising approach for monitoring physiological responses to intensive training and exercise-induced changes in immune function [18].

6. Evolution of Immune Surveillance: The Adenoma-Carcinoma Sequence and the Pre-Invasive Environment

The local immune microenvironment may represent an additional biological link between exercise-associated systemic stress and colorectal neoplasia.

Colorectal carcinogenesis occurs within the adenoma–carcinoma sequence (ACS), during which the immune landscape of neoplastic lesions undergoes dynamic changes. As demonstrated by Freitas et al., colorectal tumor progression is accompanied by a progressive reduction in adaptive immune cell infiltration and the development of an increasingly immune-cold microenvironment [19]. Furthermore, Wallace et al. demonstrated that immune responses within preinvasive colorectal lesions vary according to tumor location and histological characteristics, highlighting the heterogeneity of the immune microenvironment during early colorectal tumorigenesis [20].

In the context of prolonged and strenuous exercise, repeated episodes of exercise-associated endotoxaemia and systemic inflammatory responses [8] together with alterations in immune function observed following intensive training [18], may potentially influence immune surveillance within the gastrointestinal tract. Although direct evidence linking exercise-induced immune alterations to the progression of colorectal precursor lesions is currently lacking, these observations provide a theoretical framework in which repeated physiological stress could modify the local immune microenvironment and potentially influence the persistence or progression of preinvasive colorectal lesions [19, 20].

7. Colibactin-Producing Bacteria as a Potential Link Between Intestinal Stress and Colorectal Neoplasia

To better understand the potential mechanisms linking prolonged endurance exercise to an adverse intestinal environment, changes in the gut microbiota should be considered alongside exercise-induced endotoxaemia and inflammatory responses [8,15]. Important experimental evidence linking intestinal inflammation to the cancer-promoting activity of the gut microbiota was provided by Arthur et al. Using a murine model of colitis-associated colorectal cancer, the authors demonstrated that intestinal inflammation altered the composition of the gut microbiota and promoted the expansion of microorganisms with genotoxic potential. In particular, inflammation favoured the expansion of commensal *Escherichia coli* strains harbouring the polyketide synthase (pks) pathogenicity island, which encodes the biosynthetic machinery for the genotoxin colibactin. In this murine model, pks-positive *E. coli* promoted DNA damage and increased tumour multiplicity and invasion, whereas deletion of the pks island substantially reduced these tumour-promoting effects. These findings support a model in which intestinal inflammation and microbiota-derived genotoxic activity act together to promote DNA damage and colorectal tumorigenesis [21]. Consequently, these intersecting mechanisms raise the hypothesis that repeated exercise-associated intestinal stress and exercise-related alterations in the gut microbiota may, under certain conditions, influence the abundance or activity of potentially genotoxic bacteria. Such changes could potentially contribute to microbiota-mediated DNA damage in the colonic epithelium [8, 15, 21]. However, the findings reported by Arthur et al. were obtained in a murine model [21], and direct evidence linking endurance exercise in humans with the expansion of colibactin-producing bacteria or exercise-induced microbiota-mediated genotoxicity is currently lacking.

8. Clinical Findings from a Cohort of Endurance Runners (Swain et al., 2026)

These proposed mechanisms may provide a possible context for findings reported in recent clinical oncology studies. In a prospective, hypothesis-generating prevalence study, Swain et al. assembled a cohort of young endurance runners to investigate the incidence of pre-neoplastic lesions. The observed data revealed an unexpectedly high prevalence of advanced adenomas among these young, healthy endurance athletes [22]. This is clinically significant because advanced adenomas carry a well-established long-term risk of colorectal cancer progression and cancer-related mortality [23].

Among the 94 participants aged 35–50 years, advanced adenomas were identified in 14 individuals (15.0%; 95% CI, 8.4–23.7%). The lesions were predominantly located in the right

colon, while no cases of colorectal cancer were observed. Although the prevalence of advanced adenomas in this cohort was higher than that reported in historical screening data for average-risk adults aged 40–49 years, this comparison should be interpreted cautiously. The study's single-arm design, inclusion of participants presenting with post-exercise rectal bleeding, and other differences between the study populations may have contributed to the observed discrepancy. Therefore, Swain et al. conclude that these findings should be considered hypothesis-generating and warrant further investigation rather than being interpreted as evidence of an increased population-level risk of colorectal cancer associated with endurance running [22]. In addition, Swain et al. identified a clinical association between post-exercise gastrointestinal bleeding and the presence of advanced adenomatous lesions in these athletes. Post-exercise rectal bleeding was reported substantially more frequently by participants with advanced adenomas, occurring in 57.1% of individuals in this group compared with 16.0% among those with non-advanced adenomas and 25.5% among participants with no adenomas ($P = 0.0191$). Notably, advanced adenomas were also detected in runners who reported no history of rectal bleeding [22].

The clinical findings observed in this endurance cohort may have important implications for preventive medicine. The notably high prevalence of adenomas among young endurance athletes raises the possibility that repeated exposure to strenuous physical stress may influence the colonic environment and, potentially, neoplastic development [22]. Notably, rectal bleeding was highly prevalent and was associated with the presence of adenomas. These findings suggest that rectal bleeding in endurance athletes should not necessarily be attributed to a benign, transient manifestation of EIGS, but may warrant appropriate clinical evaluation to exclude underlying colorectal neoplasia [5, 22].

9. Conclusions

Integrating reports from sports gastroenterology [2, 4, 6], microbiome genomics [14, 15], and oncoimmunology [19] provides a potential mechanistic framework linking prolonged, strenuous physical exertion with biological pathways potentially involved in colorectal neoplasia.

During ultramarathon-distance efforts, splanchnic hypoperfusion [2] and heat stress associated with physical exertion [9] may contribute to intestinal ischaemia–reperfusion injury and compromise intestinal barrier integrity [3, 7]. Increased intestinal permeability may facilitate the translocation of bacterial endotoxins into the systemic circulation, accompanied by an acute systemic cytokine response [8]. Repeated exposure to such physiological stress may

also contribute to rapid alterations in the composition of the human gut microbiota [15]. Simultaneously, exercise-induced immune redistribution and transient changes in immune function [16, 18] could potentially influence immune surveillance within the gastrointestinal tract [19, 20]. Taken together, these mechanisms provide a potential biological framework linking repeated strenuous exercise with alterations in the intestinal environment that may be relevant to colorectal neoplasia.

These potential mechanisms may provide a possible context for the clinical findings reported by Swain et al., including the presence of advanced adenomas in endurance athletes and their association with post-exercise bleeding. These findings underscore the importance of careful evaluation of rectal bleeding in adults and suggest that bleeding associated with physical activity should not be routinely considered a benign manifestation of exercise, particularly given its potential association with underlying colorectal neoplasia [22]. In light of these emerging findings, further research is warranted to better elucidate the relationship between physical activity and the development of advanced adenomas. Future studies should also consider the potential identification of specific subgroups at increased risk of advanced adenoma development among individuals with high levels of physical activity [22]. Such an approach may help to better characterize individual risk profiles and provide a more comprehensive understanding of the factors underlying colorectal neoplasia.

Disclosure

Author Contributions

Conceptualization: Przemysław Piątek, Alicja Kodura, Jan Łozowski

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The authors declare no conflict of interest.

Declaration of Artificial Intelligence Use

The authors declare that artificial intelligence (AI) tools were used exclusively to support language editing and improve the clarity, coherence, and readability of the manuscript. The AI tools did not influence the selection of literature, the critical analysis and synthesis of sources,

the interpretation of findings, or the formulation of conclusions. The authors take full responsibility for the content, originality, and scientific integrity of this narrative review.

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