International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn23201

Major evidence of clinical studies on the triad gut microbiota, ubiquinone and physical exercise: a systematic review

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DOI: https://doi.org/10.54448/ijn23201
Received: 12-14-2022; Revised: 03-10-2023; Accepted: 03-15-2023; Published: 03-16-2023; IJN-id: e23201

Abstract

Introduction: In the scenario of sports practices, the human gut microbiota is currently the focus of convergent interest in many diseases and sports performance. Sports performance studies have also shown interesting and promising results. Supplementation with certain antioxidants such as ubiquinone [Coenzyme Q10 (CoQ10)] is important for physically active individuals to speed recovery from fatigue and prevent exercise damage. **Objective:** It was to demonstrate the influence of the gut microbiota and ubiquinone on the performance of athletes. **Methods:** The systematic review rules of the PRISMA Platform were followed. The research was carried out from September to November 2022 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 104 articles were found. A total of 54 articles were evaluated and 27 were included in this systematic review. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 13 studies with a high risk of bias and 27 studies that did not meet GRADE. Most studies showed homogeneity in their results, with X 2 =97.2% >50%. The composition and activity of the gut microbiota are influenced by many different factors, such as diet and physical activity. Cumulative data indicate that gut bacteria are sensitive to modulation by physical activity, as demonstrated by studies using models of training and hypoactivity. Supplementation with the antioxidant Coenzyme Q10 is important for physically active individuals to accelerate recovery from fatigue and prevent damage caused by exercise, in addition to optimizing training and improving sports performance. Clinical studies have shown that in physical fatigue concerning physical exercise, patients have low plasma concentrations of Coenzyme Q10.

Keywords: Physical exercise. Sports performance. Gut microbiota. Ubiquinone.

Introduction

In the scenario of sports practices, the human gut microbiota (GM) is currently the focus of convergent interest in many diseases and sports performance. The composition and activity of the GM are influenced by many different factors, such as diet and physical activity. Macro and micronutrients influence the composition of the GM [1,2]. Cumulative data indicate that gut bacteria are sensitive to modulation by physical activity, as demonstrated by studies using models of training and hypoactivity. Sports performance studies have also shown interesting and promising results [3].

In this sense, the microbiota of the healthy gastrointestinal system has about 800 species of bacteria. Thousands of these microorganisms live in symbiosis with fungi, archaea, and viruses that characterize every human being with maximum concentration in the colon [2,3]. Thus, the human microbiome has about 3 million genes in the gastrointestinal tract, which corresponds to 150 times more than the human genome [1]. Combining bacterial cells and genes with host cells and genes leads to the design of a "superorganism" [2]. In this scenario, the intestinal microbiota is essential for the host to guarantee digestive and immunological homeostasis [1,2]. However, in the presence of dysbiosis, the malfunction of the epithelial barrier leads to intestinal and systemic disorders [3].

Still, there are many ways in which GM can affect an athlete's health. Undesirable genetic makeup has been associated with local inflammatory changes leading to the permeability of the intestinal wall that may allow greater systemic migration of bacterial material. Alterations in GM can lead to psychological stress in conditions such as chronic fatigue syndrome and post-traumatic stress disorder [2,3].

In addition, supplementation with certain antioxidants such as Coenzyme Q10 (CoQ10) is important for physically active individuals to speed recovery from fatigue and prevent exercise damage. The use of nutritional supplements associated with exercise, to improve health, optimize training, or improve sports performance, is a scientific concern that not only drives many research projects but also generates great expectations in the context of its application in pathology. [4]. In this regard, CoQ10 can be an interesting molecule in health or disease in individuals without pathological deficiency and when used to optimize exercise performance [5]. Furthermore, CoQ10 is part of the electron transport chain in mitochondria, especially in muscle, brain, and heart [6- 12]. However, clinical studies have shown that in physical fatigue concerning physical exercise, patients have low plasma concentrations of CoQ10 [13].

In this regard, the present systematic review study aimed to demonstrate the influence of the intestinal microbiota and ubiquinone on the performance of athletes.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and meta-analysis: //www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to November 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, addressing scientific articles from various eras to the present day. The descriptors (MeSH Terms) were used: "*Physical exercise. Sports performance. Gut microbiota. Ubiquinone*", and using the Boolean "and" between MeSH terms and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and discussion

Summary of Findings

As a corollary of the literary search system, a total of 104 articles were found that were submitted to the eligibility analysis and, then, 27 of the 54 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X 2=97.2%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 13 studies with a high risk of bias and 27 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

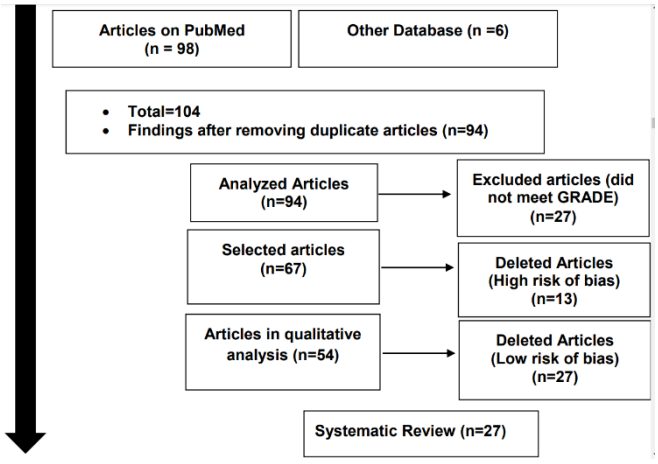
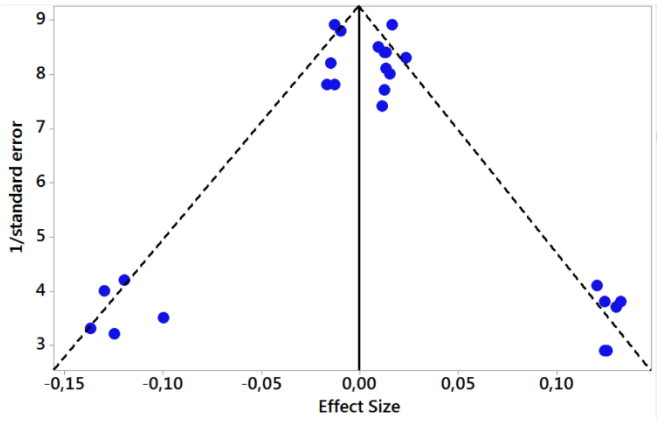


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This chart had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes

(lower precision) that are shown at the bottom of the chart and in studies with large sample sizes that are shown at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=27 studies).



Source: Own authorship.

Main Clinical Results

In the context of intestinal microbiota and physical exercise, the main bacteria that make up the enteric microbiota are beneficial and/or probiotic and harmful. As an example of probiotics, we have Bifidobacteria and Lactobacilli (*Bacteroides spp., Bifidobacterium spp.*, Lactobacillus spp., and for the harmful ones we can mention Enterobacteriaceae and Clostridium spp. Also in the enteric microbiota are *Eubacterium spp., Fusobacterium spp.*, and *Peptostreptococcus spp., Ruminococcus spp*) [1,2].

In most individuals, about 90.0% of the phyla are Firmicutes and Bacteroidetes, the rest being Actinobacteria (Bifidobacteriaceae family) and Proteobacteria (Enterobacteriaceae family). Next, in order of frequency, appear the phyla Synergistetes, Verrucomicrobia, Fusobacteria, and Euryarchaeota, representing a small percentage of our microbiota. The main members of the Firmicutes are the classes Bacilli, Clostridia, and Mollicutes and the Bacteroides are the Bacteroides, Flavobacteria, and Sphingobacterias [6].

In this sense, gut microbiota-derived products induce low-grade inflammatory activation of tissue-resident macrophages and contribute to metabolic and degenerative diseases, including diabetes, obesity, metabolic syndrome, and cancer. Here, we update the potential interaction of host gut microbiome dysbiosis and metabolic diseases. We also summarize advances in fecal, probiotic, prebiotic, symbiotic, and nutritional therapy and small molecule inhibitors of metabolic pathway enzymes as prophylactic and therapeutic agents for metabolic diseases [7-10].

In addition, gut microbiota dysbiosis can promote the occurrence of many diseases related to chronic inflammation. So far, traditionally prescribed probiotics and prebiotics have not shown a significant impact on improving these diseases in general [10-13]. Thus, the development of next-generation prebiotics and probiotics designed to treat specific diseases is much needed. Then, in the condition of gut microbiota dysbiosis, the development of chronic inflammation occurs, resulting in obesity, type 2 diabetes mellitus, liver inflammation, and other diseases such as colorectal cancer, obesity-induced chronic kidney disease, impaired lung immunity, and some brain disorders [14-16].

The mechanism proposed by the inhibition of the 5'-monophosphate-adenosine protein kinase (AMP-Q) pathway, an enzyme activated by adenosine monophosphate (AMP), regulates cellular energy metabolism. When inhibited, this enzyme activates anabolic processes and blocks catabolism. Furthermore, AMP-Q may regulate fatty acid metabolism and appetite glucose [17]. It was observed that germ-free mice, even on a hypercaloric diet, maintained weight, a fact attributed to the increase in AMP-Q activity in the liver and skeletal muscle and the greater oxidation of fatty acids, improving insulin sensitivity. These findings suggest that the presence of the microbiota suppresses the oxidation of muscle fatty acids through mechanisms that inhibit QAMP and, therefore, favor body adiposity and the generation of insulin resistance [17].

In addition, another mechanism concerns the sensitivity of the intestinal epithelium to bacterial products. A recent line of research refers to the impact that the intestinal microbiota can have on eating behavior, to influence the central regulation of appetite and satiety [18].

Furthermore, the human intestine can digest dietary fiber largely due to the synthesis of enzymes by the microbiota. These enzymes allow the metabolization of non-digestible polysaccharides into monosaccharides and short-chain fatty acids (SCFAs) [19]. These SCFAs represent an important source of energy to promote body adiposity. Furthermore, they diffuse into cells passively or via monocarboxylic acid pathway transporters and can act as cellular signals.

Other indirect effects influence intestinal motility and the production of intestinal hormones, playing a role in the regulation of satiety. Short-chain fatty acids can bind to G proteincoupled receptors (GPCR): Gpr41 and Gpr43. Currently, these have been called free fatty

acid receptors (FFAR), FFAR2, and FFAR3, respectively [20]. These receptors are expressed by intestinal epithelial cells in enteroendocrine L cells, which produce peptide YY (PYY), a hormone that acts by inhibiting gastric secretion, gastric emptying, gallbladder contraction, and reduces gastrointestinal transit time. Thus, when activated, these receptors increase the production of PYY, a fact that favors the reduction of intestinal motility and leads to greater absorption of nutrients from the intestinal lumen, mainly short-chain fatty acids, which are substrates for lipogenesis in the liver. [20].

Gut Microbiota and Athlete Performance

There are many routes by which the GM can affect athlete health [1-3]. Undesirable genetic makeup has been associated with local inflammatory changes leading to the permeability of the intestinal wall that may allow greater systemic migration of bacterial material. This can lead to systemic immune and metabolic dysfunctions. These processes are implicated in many chronic diseases. From an immunological standpoint, GM impairment and subsequent immunopathology have also been associated with allergic conditions, as they are common in athletes whose airways are exposed to environmental factors such as cold air or chlorine during water sports [7-10].

In this context, allergic conditions may increase the risk of upper respiratory diseases [10]. Supplementation with probiotics has been shown to reduce the incidence and severity of upper respiratory tract infections in some athletes. Furthermore, gastrointestinal complaints are common in the spectrum of conditions associated with relative energy deficiency in sports and in the female athlete triad. Thus, changes in GM composition occur after a period of energy deficiency [11].

Changes in GM have also been observed after prolonged periods of psychological stress in conditions such as chronic fatigue syndrome and post-traumatic stress disorder [11,12]. Furthermore, there are modifications in the hypothalamic-pituitary axis that are influenced by GM. In addition, this occurrence is related to overtraining syndrome. The investigation of GM in athletes in overtraining states or non-functional over range can help to understand these conditions [13].

GM changes were investigated in chronic musculoskeletal conditions. Studies reveal an important link between GM and rheumatoid arthritis, spondyloarthropathies, and gout [6]. Lowgrade inflammation, gut dysbiosis, and bacterial DNA are also present in degenerative musculoskeletal conditions such as osteoarthritis and rotator cuff tendon degeneration. Chronic tendinopathy is more prevalent in people with metabolic disorders, including type 2 diabetes and dyslipidemia. The change to GM is present in metabolic disorders and the investigation of GM in chronic tendinopathy can provide valuable information [2].

To ensure optimal bone health in athletes, it is important to reduce the risk of injury and aid recovery [3]. GM has a proposed regulatory effect on bone mass by altering the skeletal immune system, influencing hormonal regulation of bone metabolism, and producing bacterial metabolites that act as cellular messengers in bone. GM analysis can provide a biomarker for bone and a health guide for therapeutic manipulation in cases of fracture, stress fracture, and osteoporosis [2,3]. Optimizing GM for athlete health and injury management will yield benefits for athletic performance. Research investigating the performance benefits of GM changes is starting to emerge. Changes in GM can positively alter body composition through several mechanisms [1].

Added to this, the study also demonstrated that variations in GM affect endurance performance in the rodent model. It has been proposed that this occurs through the action of GM on antioxidant enzyme systems. While research into GM's potential in sports medicine is in its infancy, there is definite potential to positively impact health, injury, and ultimately performance, as a greater understanding of the complex microbe-human relationship is developed [1,6].

Another study investigated extreme changes in the dietary patterns of the intestinal microbiota of elite runners, enhancing training and its possible links with athlete performance. Numerous studies with sedentary individuals have shown that diet and/or exercise can exert strong selective pressures on the gut microbiota [14]. Similar studies with elite athletes are relatively scarce, despite the recognition that diet is a major contributor to athletic performance. Stool samples were collected from the cohort at baseline and at the end of a three-week intensified training program, during which athletes were assigned either a high-carbohydrate or ketogenic diet with a high-carbohydrate diet (post-treatment). Microbial community profiles were determined by amplicon sequencing of the 16S rRNA gene.

Microbiota profiles in BL can be separated into distinct "enterotypes", with predominant enterotypes in Prevotella or Bacteroides. While the enterotypes were relatively stable and remained evident after treatment, the high carbohydrate diet resulted in a greater relative abundance of Bacteroides and Dorea and a reduction of Faecalibacterium. Furthermore, an unfavorable relationship was observed between Bacteroides and fat

oxidation and between Dorea and the test economy after the high-carbohydrate intervention [14].

In addition, in studies with regular athletes, it was observed that there were changes in GM associated with exercise. This relationship is also harmed by food. Therefore, one study prospectively looked at healthy, sedentary adults on a short-term exercise regimen with and without a daily intake of whey protein. Reviews based on metagenomics and metabolomics have shown modest changes in GM composition and function after increases in physical activity [15]. In this sense, changes in diet can induce GM imbalance. A randomized trial was conducted in cross-country runners whose diets were supplemented with a protein supplement (whey and beef) (n=12) or maltodextrin (control) (n=12) for 10 weeks. Thus, fecal pH, water content, ammonia, and SCFA concentrations did not change, showing that protein supplementation did not increase the presence of these metabolites. Therefore, long-term protein supplementation may harm GM [16].

In this scenario, events such as fatigue, mood disorders, low performance, and gastrointestinal discomfort are common among athletes, as the psychosocial and physical demands during intense exercise can initiate a stress response. Thus, exercise-induced stress decreased caecal levels of Turicibacter spp and Ruminococcus gnavus, which have well-defined roles in intestinal mucosal degradation and immune function [17]. Studies using probiotics and prebiotics have shown that the microbiota acts as an endocrine organ and can contribute to improving performance in athletes [2,3,17].

Furthermore, based on a recent study, it should be considered that intense exercise is associated with transient suppression of immune function and increased risk of infections, requiring the administration of probiotics in athletes. Thus, thirty-three highly trained subjects were randomly assigned to either the probiotic (PRO, n = 17) or placebo (PLA, n = 16) groups. The probiotics used were Bifidobacterium bifidum, Bifidobacterium lactis, Enterococcus faecium, Lactobacillus acidophilus, Lactobacillus brevis, and Lactococcus lactis or placebo once a day for 12 weeks. After that time, post-exercise tryptophan levels remained unchanged in the PRO group and were altered in the placebo group with a reduction of 11.0% [18].

Coenzyme Q10 and Athlete Performance

Coenzyme Q10 (CoQ10) is fat-soluble and is referred to as 2,3-dimethoxy-5-methyl-6- decaprenyl-1,4-benzoquinone [4,5,19], and is derived from the conjugation of the benzoquinone ring to a hydrophobic chain of isoprenoids and double bonded. In humans, CoQ10 has 10 isoprene units. In addition, CoQ10 exerts an important protective antioxidant action [20]. Formation of CoQ10 occurs through the mevalonate cycle or can be obtained from food.

Based on the protective action of CoQ10, some clinical studies have shown that the low concentration of this protein in human plasma is related to pathologies such as acute myocardial infarction, arterial hypertension, and myopathies induced by statins, physical fatigue inherent to physical exercise, infertility, eclampsia, Parkinson's disease, periodontal disease and migraine [4,21]. In addition, the dose of 2-5 mg/day of CoQ10 that can be obtained from food intake is not sufficient to meet the body's needs, as only 10.0% is absorbed slowly by the intestinal tract due to its high molecular mass index and its low solubility in water [21].

Furthermore, CoQ10 protects the lipids present in cell membranes, as well as plasmatic lipoproteins [21,22], directly impacting the performance of athletes. Thus, one study examined the effects of CoQ10 supplementation for 14 days. Therefore, oral administration of CoQ10 inhibited adverse changes in oxidative stress and rates of liver and muscle damage in the competitive swimming phase [5,23].

Furthermore, another study showed that physical exercise significantly affects the body's biochemistry, with ubiquinol being an emerging molecule in sports nutrition. Thus, this study evaluated the effect of ubiquinol supplementation on biochemical and oxidative stress indices after an intense exercise session [24]. Therefore, ubiquinol supplementation prevented exercise-induced CoQ10 deprivation. Furthermore, ubiquinol supplementation was associated with a significant decrease in cytosolic ROS [5].

In this sense, a review study showed nutritional intervention in chronic fatigue syndrome (CFS), discussing the various immunological, environmental, and nutritional aspects currently investigated in this disease. Some nutrient deficiencies such as vitamin C, vitamin B complex, sodium, magnesium, zinc, folic acid, L-carnitine, L-tryptophan, essential fatty acids, and coenzyme Q10 are directly related to the severity and exacerbation of CFS symptoms [25]. Still, CoQ10 may play a key role in maintaining GM. Therefore, menaquinones function as a growth factor for GM bacteria, suggesting that CoQ10 may stimulate bacterial growth in the human gut as well as modulate GM [26].

Furthermore, most GM studies have been based on metagenomic analysis. Recent work has shown that the main results of the pathway distribution in human GM genomes were consistent with previous reports and with the distribution of quinone-dependent reductases to

electron acceptors. The comparative genomic analysis identified four alternative forms of previously known enzymes for quinone biosynthesis. Thus, these findings provided more information about the biosynthesis of quinones in bacteria and their physiological importance for GM in athletes [27].

Conclusion

The composition and activity of the gut microbiota are influenced by many different factors, such as diet and physical activity. Cumulative data indicate that gut bacteria are sensitive to modulation by physical activity, as demonstrated by studies using models of training and hypoactivity. Supplementation with the antioxidant Coenzyme Q10 is important for physically active individuals to accelerate recovery from fatigue and prevent damage caused by exercise, in addition to optimizing training and improving sports performance. Clinical studies have shown that in physical fatigue concerning physical exercise, patients have low plasma concentrations of Coenzyme Q10.

Acknowledgement

Not applicable.

Ethics approval

Not applicable.

Informed consent

Not applicable.

Funding

Not applicable.

Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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