ABRAN ASSOCIAÇÃO BRASILEIRA DE NUTROLOGIA
International Journal of Nutrology
(Official Journal of the ABRAN - Brazilian Association of Nutrology)

REVIEW ARTICLE

DOI: 10.54448/ijn23109

Sports nutrology and gut microbiota: a systematic review

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DOI: https://doi.org/10.54448/ijn23109
Received: 10-18-2022; Revised: 01-10-2022; Accepted: 01-23-2023; Published: 01-02-2023; IJN-id: e23109

Abstract

Introduction: Many of the established positive health benefits of exercise have been documented by historic discoveries in the field of exercise physiology. Regular physical training associated with nutritional health has broad health benefits for the gut microbiota, acting positively on almost all organ systems of the body. **Objective:** It was to analyze the main metabolic pathways modulated by nutrients, gut microbiota, and physical exercise in muscle regeneration and sports performance. **Methods:** The present study followed a systematic review model (PRISMA). The literary search process was carried out from July to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, with scientific articles from 2004 to 2022. 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. **Results and Conclusion:** We found 132 studies that underwent eligibility analysis, and then 31 of the 52 total studies were selected for this systematic review. According to the GRADE instrument, most studies showed homogeneity in their results, with I^2 =98.9% >50%. The Funnel Plot showed a symmetrical behavior, not suggesting a significant risk of bias in studies with a smaller sample size. A healthy gut microbiota and a positive interaction with the immune system, promoted by diligent nutrological care, can be crucial for the muscle-gut axis and can influence the maintenance of muscle mass and its functionality in athletes. However, dysbiosis resulting from a negative interaction with the immune system can influence muscle wasting disorders. These changes can promote systemic inflammation, with overproduction of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. Future studies should clarify whether gut microbiota dysbiosis and nutrient depletion are pathophysiologically associated with muscle wasting disorders and whether exercise can positively influence this supposed gut-muscle axis.

Keywords: Nutrients. Nutrology. Gut microbiota. Sports. Metabolism. Skeletal muscle.

Introduction

Many of the established positive health benefits of exercise have been documented by historic discoveries in the field of exercise physiology. These investigations generally assess performance thresholds or exercise-induced health benefits **[1]**. Thus, several important findings were informed by the study of athletes. Recent progress has been made concerning gut microbiota (GM), regenerative nutrition, and skeletal muscle metabolism **[1-3]**.

In this context, regular physical training associated with nutritional health has broad benefits for the health of the GM, acting positively on almost all organ systems of the body **[4]**. The mysteries of human physiology and the adaptive response to acute and chronic physical training have been largely elucidated through exercise science. Thus, exercise physiologists have studied the physiological response to physical activity and sports **[5,6]**.

In the context of the triad physical exercise, nutrition, and intestinal microbiota for the process of muscle regeneration, adult stem cells stand out as gut stem cells at the base (crypts) of the intestine and muscle stem cells outside the sarcolemma adjacent to the muscle basement membrane **[7-9]**. The tissue

niche is also able to influence adult stem cells metabolism. Tissue stem cell metabolism has focused on central carbon metabolism, that is, the generation of metabolic building blocks via glycolysis, oxidative phosphorylation, or the pentose phosphate pathway.

Adult tissue stem cells mediate tissue and organ homeostasis and regeneration, making decisions about whether to remain quiescent, proliferate, or differentiate into mature cell types. These decisions are directly integrated with the body's energy balance and nutritional status. Metabolic by-products and substrates that regulate epigenetically and signaling pathways are considered to have an instructive role, rather than an observer, in the regulation of cell fate decisions **[9]**.

In this sense, it is suspected that the quiescent state of stem cells is characterized by an inherently glycolytic metabolism, followed by a transition to favor mitochondrial oxidative phosphorylation during differentiation **[10-13]**. However, increasing evidence suggests that metabolism during quiescence, activation, and differentiation may vary between tissues, integrating signaling cues and metabolic inputs from the niche and the organism as a whole, mainly by signaling nutrients and the gut microbiota. In this scenario, metabolomics provides information on cellular pathways, observing substrates and metabolic products through different pathways **[14,15]**. Along with transcriptomics and proteomics analysis, it is observed that metabolism can affect cell fate (and vice versa) **[16]**.

In the sports practice scenario, both physical exercise and nutrients are modulators of the GM composition, increasing biodiversity and beneficial metabolic functions **[17]**. Overtraining is associated with IM dysbiosis, promoting inflammation and negative metabolic consequences **[17,18]**.

Furthermore, GM can influence the pathophysiology of several distant organs, including skeletal muscle **[19,20]**. The gut-muscle axis can regulate muscle protein deposition and muscle function **[17]**. In older individuals, this axis may be involved in the pathogenesis of muscle wasting disorders through multiple mechanisms, involving transduction of pro-anabolic stimuli from dietary nutrients, modulation of inflammation, and insulin sensitivity **[21]**.

In this sense, the immune system plays a key role in these processes, being influenced by the composition of the microbiome and at the same time contributing to the formation of microbial communities. In this sense, exercise is considered one of the main environmental factors that possibly influence the composition of GM **[21,22]**.

Therefore, the present systematic review study analyzed the main metabolic pathways modulated by nutrients, gut microbiota, and physical exercise in muscle regeneration and sports performance.

Methods

Study Design

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

Search Strategy and Search Sources

The literary search process was carried out from July to September 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, with scientific articles from 2004 to 2022, using the descriptors (MeSH Terms): "Nutrients. Nutriology. Intestinal microbiota. Sports. Metabolism. Skeletal muscle", and using the Booleans "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for 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 (Cohen test (d)).

RESULTS AND DISCUSSION

Summary of Literary Findings

It was found 132 studies that underwent eligibility analysis and, then, 31 of the 52 total studies were selected for the present systematic review (Figure 1), considering in the first instance the level of scientific evidence of studies in study type such as metaanalysis, 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 R2 =98.9% >50%.

Figure 1. Flowchart showing the article selection process.

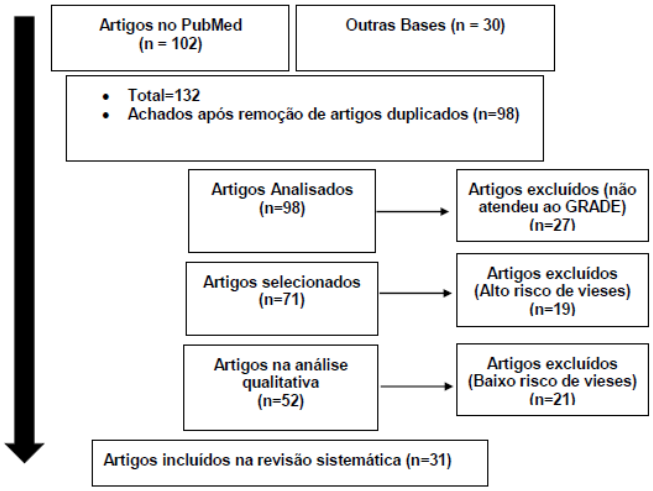
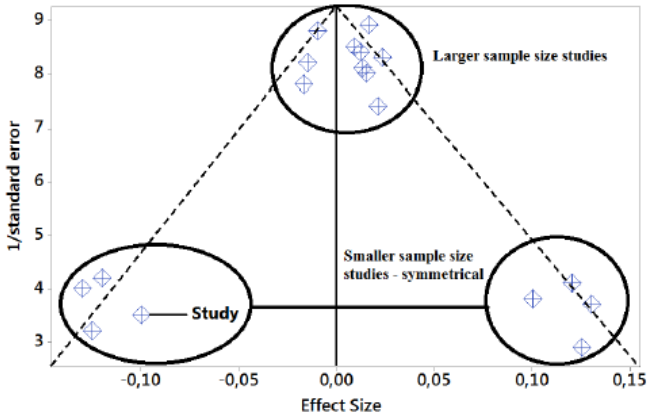


Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented in the upper region.

Figure 2. The symmetrical funnel plot suggests no risk of bias between 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 (NTotal=31 studies evaluated in full in the systematic review).



Metabolic Pathways and Muscle Regeneration

Physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter the fate of the cell by controlling chromatin accessibility and downstream gene expression patterns **[16]**.

Thus, many substrates and cofactors for chromatin-modifying enzymes are derived from metabolic pathways involving the tricarboxylic acid cycle, the methionine cycle, the folate cycle, glycolysis, β-oxidation, and the hexosamine pathway. These metabolites can serve as activators or inhibitors of epigenetic writers, such as proteins containing the Jumonji C domain (JmjC), DNA methyltransferases (DNMTs), histone acetyltransferases (HATs), ten-eleven DNA translocase demethylases (TETs) and histone deacetylases (HDACs). In this sense, metabolites can influence nutrient detection signaling pathways **[16]**.

Thus, the mechanistic target of the rapamycin complex 1 (mTORC1) can be activated by growth factor-induced signaling only when the amino acids arginine and leucine, as well as the cofactor S-adenosyl methionine (SAM), are detected within the cell. Furthermore, the energy balance communicated through the cellular AMP/ADPATP ratio can be detected by AMP-activated protein kinase (AMPK). In addition, transcription factors can be directly regulated by metabolites, for example, the tryptophan kynurenine metabolite is an endogenous agonist of the aryl hydrocarbon receptor and alpha-ketoglutarate (α-KG) binds and activates IKKβ and initiates IKKβ signaling. NFκβ **[16]**.

In this scenario, dietary manipulations and metabolites can affect tissue stem cell fate decisions, as highlighted in the small intestine (intestinal stem cells (LGR5+)), hematopoietic system (hematopoietic stem cells (HSCs), liver, muscle (muscle stem cells/satellite cells) and hair follicles (hair follicle stem cells (HFSCs). For example, in HFSCs, mitochondrial pyruvate carrier 1 (MPC1) and lactate dehydrogenase (LDHA) regulate the balance between telogen and anagen during the hair cycle. In LGR5+, 3hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed while MPC1/2 is expressed at low levels. The ketogenic or glucose-rich diet regulates the balance of selfrenewal of LGR5+ Self-renewal and differentiation of HSC can be regulated by manipulating vitamin C, A, or D levels and valine restriction **[16]**.

Regarding muscle regeneration, a diet rich in nicotinamide riboside can increase muscle stem cell numbers and function in a histone deacetylase (SIRT1) dependent manner. Muscle stem cells, called satellite cells, are responsible for maintaining adult muscle mass and repairing it after injury. Several studies have

demonstrated how changes in innate metabolism interfere with the differentiation of satellite stem cells into mature myocytes [23]. For example, mapping a single cell with histone acetylation showed that acetylation levels tend to be low in quiescent cells.

In this context, one study found that isolated quiescent muscle stem cells express fatty acid oxidation enzymes/transporters, however, as they exit quiescence and enter the cell cycle for proliferation, a metabolic transition occurs to favor glycolysis [24]. In this sense, SIRT1 is a target of increased glycolysis. SIRT1 represses the maturity expression of specific skeletal muscle genes as well as genes involved in mitochondrial biogenesis.

Advanced glycolysis depletes NAD+, an essential metabolic cofactor of SIRT1, reducing SIRT1 activity and promoting downstream activation of these mature muscle-specific genes and differentiation [25].

Physical Activity and Gut Microbiota

In a case-control study, microbial diversity was much greater in a group of professional players than in age, sex, and body-size-matched controls who do not play sports [26]. Recently, metagenomic analyzes of fecal samples from the same groups highlighted that athletes had a different microbial composition also from a functional point of view, with an increased microbial representation of genes involved in carbohydrate and amino acid metabolism, and fatty acid chain production [27].

In another study, the mean abundance of taxa involved in energy and carbohydrate metabolism, including Prevotella and Methano-brevibacter smithii, was significantly higher in professional than amateur cyclists and was correlated with training frequency [28]. However, these studies were unable to fully separate the contribution of exercise and diet in determining the different compositions of the microbiota in different groups, as participants followed a wide range of dietary regimens.

Also, the intensity of training is also important. Light exercise programs induce only slight changes in the composition of the gut microbiota in sedentary individuals [29]. Therefore, findings from studies performed on athletes should not be automatically transferred to all individuals who perform a non-competitive exercise.

According to three different studies, fecal microbiota biodiversity is correlated with cardiorespiratory fitness in adult individuals. However, in one of these studies, performed on 71 premenopausal Finnish women, this relationship was mediated by body composition [29-31]. Another study, performed on 19 actives and 21 sedentary women aged ≤40 years, confirmed that the microbiome abundance of various bacterial taxa was significantly correlated with body fat or lean mass percentage [32]. Thus, the possible association between exercise and microbiota should be further investigated, taking into account possible confounding factors, such as dietary habits, nutrient intake, and body composition parameters [33].

The influence of body composition on the microbiota was also emphasized by the findings of an intervention study, where two groups of sedentary individuals, one lean and one obese, underwent a 6-week structured exercise program, followed by a washout period of 6 weeks. 6 weeks [34]. After exercise training, lean and obese participants experienced a change in gut microbiota composition, but the overall representation of species with known anti-inflammatory properties and the microbiome's ability to produce short-chain fatty acids (SCFA) was greater in lean subjects, highlighting a body mass index (BMI) dependent response to training. However, all changes reverted to the baseline state after the washout period [34].

Furthermore, in healthy, exercised young males undergoing a period of forced inactivity, cessation of the exercise was associated with changes in gastrointestinal physiology (i.e., reduced bowel movements and increased stool consistency) before changes in gastrointestinal GM composition and function could be detected [30-32]. These circumstances suggest that the microbiome is resilient to acute changes in exercise habits and that exercise maintenance is necessary to induce lasting changes in the gut microbiome.

In this aspect, changes in the composition of the gut microbiome induced by exercise can exert beneficial effects throughout the body, modulating pathological processes. For example, changes in the microbiota induced by exercise can attenuate the clinical course and evolution of experimental models of myocardial infarction or chemically induced colitis, mainly by modulating the inflammatory response [35]. The main mediators in these processes may be SCFAs, particularly butyrate, whose production by the gut microbiota has been shown to increase after exercise in humans [34].

Nutrients and Gut microbiota In Muscle Pathophysiology

Several research groups have independently hypothesized that the composition of the gut microbiota may influence the onset of sarcopenia, ie the loss of

muscle mass and function that occurs with aging **[17,19,30,31]**. In this sense, a dysbiotic GM can reduce the bioavailability of dietary proteins and particularly of some amino acids, such as tryptophan, involved in modulating inflammation and promoting muscle protein synthesis **[36-40]**. Gut bacteria are also involved in the synthesis of many vitamins, including folate, vitamin B12, and riboflavin, exerting various beneficial and pro-anabolic effects on skeletal muscle cells, ranging from amino acid biosynthesis to neutralizing oxidative stress during exercise **[41]**.

Furthermore, a healthy GM can effectively transform some dietary nutrients into metabolic mediators that, once absorbed into the systemic circulation, can exert beneficial effects on inflammation, insulin sensitivity, anabolism, and antioxidant capacity. Polyphenols, including resveratrol, and ellagitannins contained in pomegranates and berries represent the most relevant examples of nutrients that, after microbial metabolism, enter the systemic circulation and exert beneficial effects on the muscle **[42,43]**. Resistance training appears to increase the bioavailability of dietary polyphenols, likely through their beneficial modulations of GM **[44]**.

In addition, age-related changes in GM composition, occurring regardless of the level of physical training, may promote intestinal mucosal dysfunction, with increased permeability. This phenomenon can result in the systemic absorption of microbial byproducts and toxins, including LPS. In skeletal muscle cells, circulating LPS may contribute to activating Toll-Like Receptors (TLR) 4 and 5, promoting the activation of the NF-kB pathway, with reduced insulin sensitivity, increased protein catabolism, and inflammatory cytokine production **[17]**. In aging humans, TLR4 activation is associated with metabolic endotoxemia, decreased insulin sensitivity, and reduced quadriceps muscle strength and volume.

In this context, the most studied mechanism involved in the gut modulation of GM by physical exercise is the bacterial production of metabolic mediators, including bile acids and SCFA **[18]**. A healthy GM can produce secondary bile acids, which are wellknown activators of the farnesoid X receptor stimulating myocyte anabolism. SCFA and particularly butyrate, are generally synthesized by a large number of intestinal bacteria, including Faecalibacterium, Butyricimonas, and Succinivibrio, highly represented in healthy individuals, but reduced in older individuals. These mediators have several beneficial metabolic activities, influencing skeletal muscle protein deposition by modulating the systemic anabolic/catabolic balance **[18]**.

Also, dietary polyphenols exert several beneficial effects on sports performance, demonstrated in vivo and in human studies. The health-related mechanisms of polyphenols mainly concern the modulation of mitochondrial biogenesis and stimulation of stress-related enzymes or transcription factors, as well as a nutritional deficiency, which regulates gene expression of essential antioxidant proteins (SOD, Catalase, Glutathione system, etc.). They have also been shown to modulate inflammatory processes and the immune system response (Th1/Th2 balance). Furthermore, some polyphenols favor vascular regulation and endothelial function in humans, increasing endothelial synthesis of nitric oxide **[45]**.

Overall, these mechanisms promote athletic performance by improving cardiometabolic functions, reducing recovery times and post-exercise pain, maintaining a low degree of oxidative stress, and preventing dysregulated inflammatory processes. Thus, polyphenols are able, through their interaction with the intestinal microbiota, to favor the proliferation of bacterial genera of great importance for metabolic and cognitive functions, such as Akkermansia, Lactobacilli, and Bifidobacteria. The microbiota, on the other hand, metabolizes polyphenols in the colon to produce small bioactive molecules that exert epigenetic mechanisms in biochemical pathways modulating gene expression. Polyphenols have multiple biological effects, and future exercise studies should be designed appropriately and specifically to determine the physiological interactions between exercise and the selected supplement, rather than just considering performance **[46]**.

Gut-Muscle Axis

Intestinal muscle communication in human pathophysiology can be bidirectional, with GM making a true weave between epigenetic factors, physical exercise, and skeletal muscle **[17]**.

In healthy individuals who regularly perform physical activities, a homeostatic balance between GM and skeletal muscle is present, promoting a healthy GM composition. However, this balance between GM and skeletal muscle can be disrupted by a sedentary lifestyle or excessive exercise, resulting in GM dysbiosis. Other factors that promote dysbioses, such as medications or acute illness, may also be associated with reduced muscle mass and function. Dysbiosis influences intestinal permeability, systemic inflammation, anabolism, and nutrient availability. All these mechanisms are involved in muscle physiology and represent the substrates of the gut-muscle axis **[17]**.

Thus, the gut-muscle axis may be bidirectional, with GM influencing muscle and exercise contributing to shaping the composition of the microbiota. The intensity and frequency of exercise can be of great importance in determining the prevailing axis and its pathophysiological consequences.

Besides, a healthy GM plays a key role in shaping the local and systemic immune response to intestinal bacteria throughout life, favoring the maintenance of tolerance towards commensal antigens and activation against pathogen antigens **[41]**. The gut with microbiological dysbiosis favors the loss of immune tolerance to commensals, the deficiency of epithelial barrier function, and an imbalance in the activation of antiinflammatory Treg, lymphocytes, and pro-inflammatory Th17. These phenomena may contribute to the onset of inflammatory and autoimmune diseases, including inflammatory bowel disease, type 1 diabetes, and multiple sclerosis **[47,48]**.

Furthermore, the immune system is indeed capable of influencing the composition of GM at various levels. Both innate and adaptive immunity are involved. Possible mechanisms include the production of antimicrobial peptides from intestinal cells, mucus secretion, activation of immunoglobulin A (IgA), similar to TLR receptor activation, lymphocyte transfer, and differentiation, and the presence of natural T cells (iNKTC) **[42,49]**.

Thus, whatever mediators are involved, the balance between the immune system and GM can be strongly influenced by epigenetic factors. Positive modulators of GM composition, including regular exercise, can induce a beneficial balance with the immune system, aiding in the maintenance of health **[50-52]**.

Conclusion

It was concluded that a healthy gut microbiota and a positive interaction with the immune system, promoted by diligent nutrological care, can be crucial for the muscle-gut axis, and can influence the maintenance of muscle mass and its functionality in athletes.

However, dysbiosis resulting from a negative interaction with the immune system can influence muscle wasting disorders. These changes can promote systemic inflammation, with overproduction of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6. Future studies should clarify whether gut microbiota dysbiosis and nutrient depletion are pathophysiologically associated with muscle wasting disorders and whether exercise can positively influence this supposed gut-muscle axis.

Acknowledgement
Not applicable.

Funding
Not applicable.

Ethics approval
Not applicable.

Informed consent
Not applicable.

Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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