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REVIEW ARTICLE

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Gut microbiota and skeletal muscle axis in sports performance through nutrological activation of irisin and microRNAs: a systematic review

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Abstract

Introduction: Several discoveries have accumulated evidence regarding gut microbiota, regenerative nutrition, and skeletal muscle metabolism. Exercise volume and intensity have been shown to influence gastrointestinal health status, including the role of growth factors, signaling pathways, oxidative stress, metabolic factors, irisin, and microRNAs. **Objective:** To present, through a systematic review, the main approaches and outcomes of clinical studies of the gut microbiota and skeletal muscle axis in sports performance through the nutritional activation of irisin and microRNAs. **Methods:** The PRISMA Platform systematic review rules were followed. The research was carried out from January to April 2024 in the 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:** 121 articles were found. A total of 40 articles were evaluated in full and 19 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 25 studies that did not meet GRADE. It was concluded that exercise-induced stimulation of irisin (bioactive cytokines), through muscle-bone-fat crosstalk, increases muscle anabolism, bone formation, mitochondrial biogenesis, glucose utilization, and fatty acid oxidation and Attenuates chronic low-grade inflammation. A current focus in the field of sports and metabolism is the investigation of how specific metabolites and nutrients affect the progression and treatment of muscle injuries. Nutrients can also regulate normal homeostatic processes by altering the decisions of muscle stem and satellite cells. MicroRNAs have emerged as important players in the regulation of gene expression, being involved in most of the biological processes examined to date, given that microRNAs are mainly involved in the cell's stress response making them ideal candidates for mediating the skeletal muscle response to changes in contractile activity. Identifying and validating target genes will help understand the molecular mechanism through which microRNAs regulate skeletal muscle in response to exercise.

Keywords: Athletes. Gut microbiota. microRNAs. Irisina. Sports performance.

Introduction

In the context of sports performance, several discoveries have accumulated evidence regarding gut microbiota, regenerative nutrition, and skeletal muscle metabolism **[1,2]**. In this context, regular physical training associated with nutritional health has broad benefits for the health of the gut microbiota, acting positively on almost all organic systems of the body **[3,4]**.

In this scenario, metabolomics provides information on cellular pathways, observing metabolic substrates and products through different pathways **[1,5]**. With transcriptomic and proteomic analysis, it is observed that metabolism can affect cell fate (and vice versa). Previous studies suggest that exercise can promote tissue regeneration and repair in various organs. There are several well-known effects of physical training on intestinal physiology. The volume and intensity of exercise have been shown to influence gastrointestinal health status **[6,7]**.

In this sense, training reduces the transit time of feces in the gastrointestinal system, thus reducing the prolonged contact of pathogens with the gastrointestinal mucus layer. Furthermore, moderate exercise is associated with reduced levels of cecal cancer, while exhaustive endurance exercise has been associated with gastrointestinal disturbance because of toxic effects induced by reduced local blood flow and bacterial translocation into the bloodstream **[8-10]**.

Although there is no consensus on which symptoms or biomarkers, such as microRNAs and exosomes, define stress, some common signs widely accepted in the scientific literature include clinical, hormonal, and other symptoms such as fatigue, decreased performance, insomnia, change in appetite, loss of weight, and mood disorders such as irritability, anxiety, loss of motivation, lack of concentration and depression, as well as inflammation and immunosuppression. Appropriate nutritional choices have been recommended to reduce the risk of gastrointestinal discomfort in elite athletes by ensuring rapid gastric emptying, water, and nutrient absorption, and adequate perfusion of the splanchnic vasculature before competition **[2,3]**.

In this context, optimizing the gut microbiota for athlete health and injury treatment can produce benefits for athletic performance. Thus, changes in the gut microbiota can positively alter body composition and muscle recovery **[11]**. The protective function of exercise-induced stem cell activation is one of the main targets, whose main molecular mechanisms involved in exercise-induced tissue regeneration include the role of growth factors, signaling pathways, oxidative stress, metabolic factors, irisin, and microRNAs **[3,12]**.

Based on this context, the present study aimed to present, through a systematic review, the main approaches and outcomes of clinical studies of the gut microbiota and skeletal muscle axis in sports performance through the nutritional activation of irisin and microRNAs.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 03/15/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 03/15/2024.

Data Sources and Research Strategy

The search strategies for this systematic review were based on the keywords (descriptors in health sciences: DeCS/MeSH): *"Athletes. Gut microbiota. microRNAs. Irisina. Sports performance"*. The research was carried out from January to April 2024 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. Furthermore, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Quality of Studies and Risk of Bias

According to GRADE recommendations (available at: https://www.jclinepi.com/article/S0895-4356(10)00332-X/fulltext. Accessed on 03/15/2024), the quality of scientific evidence in studies covered was classified as high, moderate, low or very low, according to the risk of evidence bias, sample size, clarity of comparisons, precision, and consistency in the effects of the analyses. High-quality evidence was assigned using four criteria: 1) Randomized or prospective controlled clinical trials; 2) Retrospective clinical trials; 3) Sample size greater than 20 participants; 4) Studies with statistically well-designed results; 5) Studies published in indexed journals and with a significant impact factor; 6) descriptive validity (identification of studies that clearly showed the results and follow-up of participants), interpretative (identification of advantages and disadvantages), theoretical (credibility of the methods)

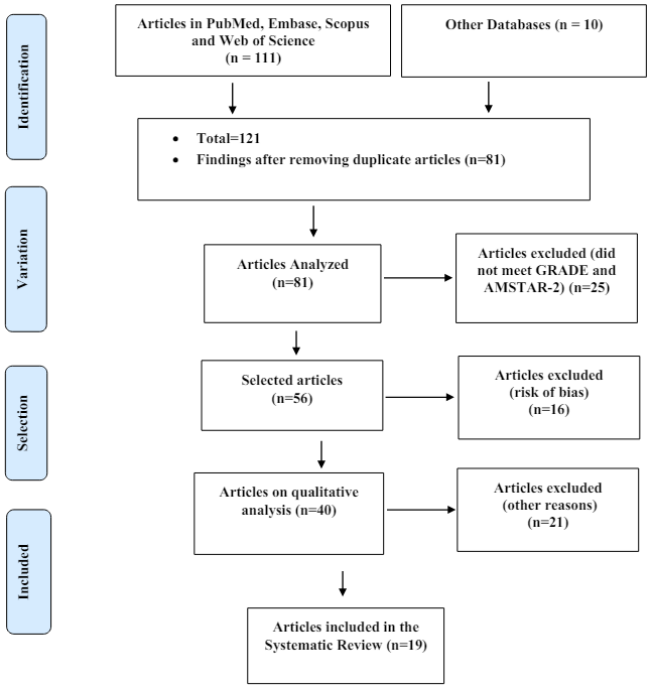
and pragmatic. The low quality of evidence was attributed to case reports, editorials, and brief communications. The risk of bias was analyzed according to the Cochrane instrument (Available at: https://sites.google.com/site/riskofbiastool/. Accessed on 03/15/2024) through analysis of the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 121 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was carried out, removing articles that did not include the topic of this article, resulting in 81 articles. A total of 40 articles were evaluated in full and 19 were included and developed in the present systematic review study (Figure 1). Considering the Cochrane tool for risk of bias, the overall assessment resulted in 16 studies with a high risk of bias and 25 studies that did not meet GRADE.

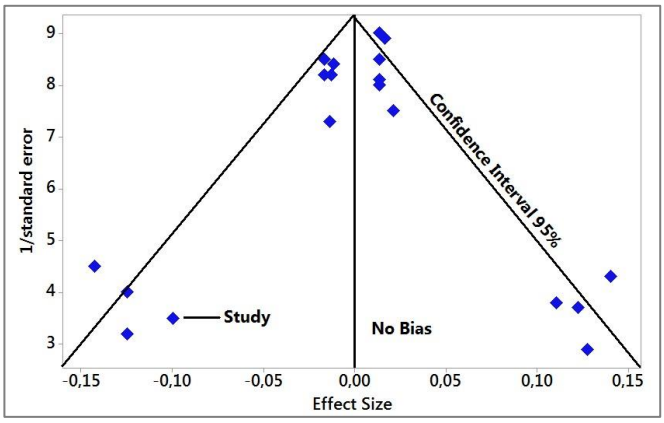
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

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

Figure 2. The symmetric funnel plot suggests no 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 (NTotal= 19 studies evaluated in full in the systematic review).



Source: Own authorship.

Major Considerations and Clinical Findings (N=19 studies)

Metabolism encompasses the interactions between diet, gut microbiota, and cellular enzymatic processes **[2,13,14]**. High rates of intestinal self-renewal are enabled through intestinal stem cells (LGR5+) at the base of intestinal crypts **[15]**. Cells in the intestine can communicate through metabolic signals, with differentiated Paneth cells secreting lactate to support the LGR5+ function. In this context, physical activity, endogenous metabolites, and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications to DNA and histone proteins alter cell fate by controlling chromatin accessibility and downstream gene expression patterns. HSC self-renewal and differentiation can be regulated by manipulating vitamin C, A, or D levels and valine restriction **[10]**.

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 **[16]**.

One study showed 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 **[17]**. In this sense, SIRT1 is a target of increased glycolysis. SIRT1 represses the maturity expression of skeletal muscle-specific 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 **[18]**. In this aspect, epigenetic signaling and transcription pathways are affected by changes in nutrient levels.

In this regard, the individual response to nutrients and non-nutritive molecules can be largely affected by three important biological layers. The gut microbiome can alter the bioavailability of nutrients and other substances, the genome can influence the kinetics and dynamics of molecules, while the epigenome can modulate or amplify the properties of the genome. The composition of each athlete's microbiome influences sports performance both directly by acting on energy metabolism and indirectly through modulating the availability of nutrients or non-nutritive molecules that ultimately affect the individual epigenome and genome **[10,17,18]**.

At the genetic level, two nutritional fields analyze the intricate relationships between nutrients, genes, and biological systems such as nutrigenetics and nutrigenomics. Nutrigenetics aims to understand how our genetic background can modulate the absorption, distribution, metabolism, and elimination of nutrients, affecting the response to diet. Genetic factors are responsible for approximately 50% to 80% of the interindividual variation in body mass, and this has an essential impact on the muscle growth response. Furthermore, endocrine functions, the composition of muscle fibers, psychological aspects, and nutrition may have differences associated with the genotype and influence athletic performance **[10,18]**.

In this context, irisin is an exercise-induced myokine/adipokine (bioactive peptide) that promotes the transformation of white adipose tissue into brown adipose tissue, increasing thermogenesis and energy expenditure **[3]**. Furthermore, irisin has been associated with favorable effects on metabolic diseases, including obesity, type 2 diabetes mellitus (T2DM), lipid metabolism and cardiovascular disease (CVD), non-alcoholic fatty liver disease (NAFLD), polycystic ovary syndrome (PCOS), and bone diseases. In patients with T2DM, NAFLD, and CVD, most observational studies reported lower irisin levels in patients than in controls. Concerning metabolic bone diseases, irisin is positively associated with bone mineral density and strength in athletes and inversely associated with osteoporotic fractures in postmenopausal osteoporosis **[19]**.

Also, irisin has an anabolic effect on bone. A study carried out by Buccoliero et al. (2021) **[20]** used an in vitro-controlled 3D cell model to mimic the bone microenvironment aboard the International Space Station. Irisin treatment in microgravity has been shown to prevent downregulation of the transcription factors Atf4, Runx2, and Osterix, as well as collagen Proteins I and Osteoprotegerin, crucial for osteoblast differentiation under physiological conditions. The action of irisin has also been investigated in humans, where it correlates with the state of bone health, supporting its physiological importance also in human bone, both in healthy individuals and in patients suffering from diseases related to bone metabolism, such as hyperparathyroidism and type 1 diabetes. Also, low levels of circulating irisin have been found in postmenopausal women affected by hyperparathyroidism. Besides, irisin is positively correlated with bone strength in athletes and bone mineral density in football players.

Moreover, irisin is induced by multiple tissues and organs, with exercise and exposure to cold being the main inducers of its secretion. In this sense, many studies on irisin are accumulating scientific evidence regarding physiological functions for health promotion, prevention, treatment, and rehabilitation of chronic diseases, as well as mechanisms associated with improving energy metabolic balance, improving cellular homeostasis, optimizing autophagy, promoting mitochondrial quality, reducing the production of reactive oxygen species (ROS) and attenuating inflammatory responses **[21]**.

In this regard, an experimental study analyzed the effect of irisin on the healing of bone fractures. Thus, closed fractures of the mid-diaphyseal femur were produced in 8-week-old C57BL/6 mice. Irisin was administered intraperitoneally every other day after surgery, fracture healing was assessed using X-rays. Greater callus formation, mineralization, and harder fracture healing were observed in the irisin-treated group than in the control group, indicating better fracture callus healing due to irisin treatment. The vessel surface and vessel volume fraction of the callus also increased in the irisin-treated group. The expression of BMP2, CD31, and VEGF in the callus was increased in the irisin-treated group. In mouse bone mesenchymal stem cells, irisin promoted the expression and mineralization of ALP and increased the expression of osteogenic genes, including OSX, Runx2, OPG, ALP, OCN, and BMP2 **[22]**.

Added to this, the biochemical crosstalk of muscle tissue occurs through the endocrine system, orchestrated by a family of cytokines (myokines) and osteokines, as well as adipose tissue and the secretion of adipokines. The myokines IL6, irisin, IGF-1, BDNF,

myostatin, and FGF2 exert anabolic/catabolic effects on bone, while the osteokines osteocalcin and sclerostin have been shown to induce anabolism and muscle catabolism, respectively. Adipokines such as leptin, resistin, adiponectin, and TNFα can also modulate muscle and bone metabolism. Exercise-mediated release of lipolytic myokines (IL6, irisin, and LIF) stimulates thermogenesis by promoting browning of adipocytes. Myokines, osteokines, and adipokines exert autocrine/paracrine effects locally, as well as through the endocrine system, to regulate muscle, bone, and fat metabolism. Reduced physical activity and increased energy intake, both associated with aging, lead to adipocyte hypertrophy and the recruitment of immune cells (macrophages). In turn, this releases pro-inflammatory adipokines that induce chronic low-grade inflammation, a key factor in the pathology of several diseases **[23]**.

In this scenario, some relevant myokines are interleukin-6 (IL-6), IL-8, IL-15, irisin, myostatin, fibroblast growth factor 21 (FGF21), leukemia inhibitory factor (LIF), neurotrophic factor derived from brain (NFDB) and insulin-like growth factor-1 (IGF-1). They are related to playing a positive or negative role in muscle function and metabolic homeostasis, as well as being associated with the regulation of glucose and lipid metabolism, the deposition of fat in adipose tissue, and the "browning" of white adipose tissue **[24]**.

A study evaluated whether overtraining syndrome (OTS) and its biochemical markers are associated with plasma irisin levels in athletes. A total of 7 severely overtrained athletes (OA) and 10 healthy control athletes (CA) were recruited and examined at diagnosis (baseline) and after 6 and 12 months of follow-up. Training volume and intensity were initially restricted but progressively increased in OA as OTS symptoms were alleviated. CA continued his normal training routine. Before exercise testing, irisin levels tended to be lower in OA than in CA at baseline (154.5 ± 28.5 vs. 171.7 ± 58.7 ng/mL). Resting irisin concentration correlated positively with a marker of oxidative stress, malondialdehyde, and negatively with a marker of antioxidant protection, and oxygen radical absorbance capacity **[25]**.

Furthermore, microRNAs have emerged as critical regulators of numerous biological processes, modulating gene expression at the post-transcriptional level. MicroRNAs are important regulators of gene expression regulatory mechanisms in muscle. Many mechanistic problems that occur during regeneration and repair after skeletal muscle injury can be better understood through knowledge of irisin and microRNAs. It has become increasingly clear that regeneration of skeletal muscle development involves regulation by microRNAs. In recent years, the field has seen a rapid expansion of our knowledge of microRNAs in skeletal muscle regeneration **[26]**.

In this sense, microRNAs play a role in the stress response of skeletal muscle to changes in contractile activity. Exercise has accumulated responses and is a potent activator of gene expression. Furthermore, resistance exercise results in the activation of several signaling cascades that promote an increase in protein synthesis. These changes in gene expression can be attributed to changes in the levels of microRNAs. These fluctuations in microRNA levels can enhance training adaptations by regulating specific genes **[27]**.

In addition to striated muscle, exercise alters the expression of microRNAs within the circulation. Plasma samples taken from human subjects showed that an acute bout of resistance exercise elevated circulating levels of miR-146a, miR-222, miR-21, and miR-221. After a 90-day training period, the basal level of these microRNAs remained elevated in addition to miR-20a. Even after the training period, the circulating levels of these microRNAs still showed a transient effect after an acute exercise session **[28]**.

One study looked at whether there was any relationship between circulating levels of microRNAs and aerobic capacity. The authors reported that individuals with low aerobic capacity (VO_2max) had elevated levels of miR-21, miR-210, and miR-222; however, elevated levels of these microRNAs in circulation have not been shown to correlate with risk factors associated with cardiovascular disease **[29]**. Furthermore, the authors Uhlemann et al. (2012) **[30]** found that circulating levels of miR-133a were elevated after an exercise session designed to damage skeletal muscle, while miR-126 was elevated after exercise that would damage the endothelial layer within the vasculature.

A possible mechanism may involve the release of microRNAs from vesicles (exosomes) by active skeletal muscle, thus acting as a paracrine factor that influences the activity of other tissues. A better understanding of how exercise, whether acute or chronic, is capable of altering the expression of microRNAs will provide a more complete picture of the molecular mechanisms underlying exercise-induced adaptations. Furthermore, microRNAs themselves may represent therapeutic targets that can be manipulated to enhance training adaptations **[3]**.

Conclusion

It was concluded that exercise-induced stimulation of irisin (bioactive cytokines), through muscle-bone-fat crosstalk, increases muscle anabolism, bone formation, mitochondrial biogenesis, glucose utilization, and fatty acid oxidation and Attenuates chronic low-grade

inflammation. A current focus in the field of sports and metabolism is the investigation of how specific metabolites and nutrients affect the progression and treatment of muscle injuries. Nutrients can also regulate normal homeostatic processes by altering the decisions of muscle stem and satellite cells. MicroRNAs have emerged as important players in the regulation of gene expression, being involved in most of the biological processes examined to date, given that microRNAs are mainly involved in the cell's stress response making them ideal candidates for mediating the skeletal muscle response to changes in contractile activity. Identifying and validating target genes will help understand the molecular mechanism through which microRNAs regulate skeletal muscle in response to exercise.

CRediT

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