

Regular exercise shapes healthy gut microbiome

Abstract

The gut microbiota is the collective microbial community colonized within the lumen of the intestinal tract of the host. A growing body of evidence has demonstrated that the microbiome is capable of responding to environmental, dietary, pathological and genetic factors. Particularly of interest is novel research into the response of the gut microbiota to exercise stimulus as a potential therapeutic mechanism for exercise on metabolic diseases. Although experimental studies investigating the mechanisms governing the exercise-induced changes in the microbiota have been limited, preliminary data from animal and human studies implicate the microbiota in a wide range of host metabolic pathways that are modulated by exercise. This review outlines some of these findings and frames the microbiota within the context of energy metabolism, exercise and disease.

Keywords: exercise, dysbiosis, microbiota, obesity, metabolic diseases, *Tenericutes* phylum

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Introduction

A recent dietary, cultural and behavioural shift, accompanied with the increased availability of calorie-rich foods has led to the development of an obesogenic lifestyle. Obesity is currently ranked as the most prevalent preventable health related disorder the world over. Estimates suggest that there are approximately 2.1 billion people in the world who are either categorized as overweight or obese, a statistic that has risen substantially in the last few decades.¹ Classically, obesity was viewed in a paradigm of energetics, where it was the product of caloric intake against energy expenditure. However, obesity is now recognized as a multifactorial phenomenon resulting from complex and interconnected factors including environmental, social, physiological, genetic and neural.² The gastrointestinal tract represents the first interface between ingested nutrients and the host metabolism. Recent research has implicated the gut microbiota, the entirety of the microbial community residing with the intestinal lumen, in the development of metabolic diseases.³⁻⁷ Currently under-examined by the literature is the relationship between exercise and metabolic diseases understood through the lens of changes in gut microbiota. This narrative review seeks to outline key concepts and developments in the role gut microbiota in metabolism, immunity and pathogenesis, the effects of exercise on the intestinal composition and the therapeutic benefits of exercise in changing the characteristics and properties of the gut microbiota.

Exercise-induced changes in gut microbiota

Exercise has long been recognized as a useful therapy for a wide host of pathologies and diseases including diverse cancers, cardiovascular disease, diabetes, anxiety, depression and systemic inflammation. The mechanisms through which exercise mediates its therapeutic effects on these disease states are both numerous and interconnected. One such, albeit largely unexplored, mechanism might be exercise-mediated manipulation of the gut microbiome. Following the seminal work by Bäckhed et al.,⁸ the researchers later established a potential role for the gut microbiota in the regulation of metabolism in skeletal muscle.⁹ This putative muscle-microbiota axis has undergone limited further investigation, albeit initial findings in animal models

and a study in humans have revealed promising results. In a study examining the effects of exercise on the diversity of the microbiota, researchers observed a change in over two thousand bacterial taxa between mice undergoing exercise and their sedentary counterparts.¹⁰ In particular, exercise has been demonstrated to increase the prevalence of the *Lactobacillales* order and reduce bacteria from the *Tenericutes* phylum within the microbiota.^{10,11} This finding was corroborated by a reported increase in the *Lactobacillus* genus in obese rats having undergone exercise.¹² Studies in both humans and animals have also elucidated that exercise induces an increase in microbial diversity within the gut.¹³⁻¹⁶ In the only available study carried out on humans to date, athletic rugby players were compared against healthy controls to determine microbiota composition. Athletes demonstrated approximately twice as many phyla, families and genera of bacteria than their non-athletic counterparts, suggesting a role for exercise in increasing microbiota diversity. It is worth noting that the role of exercise could not be conclusively established given the inability to control for diet, a factor with known consequences on the microbiome.¹⁶⁻¹⁸ Evans et al.,¹³ established that exercise not only counteracted the changes in the microbiota caused by a high-fat diet, but also induced significant shifts in the major phyla in the same direction and order of magnitude as changes caused by the high-fat diet.^{13,19} In another study, exercise increased the percentage of *Bacteroidetes* and decreased *Firmicutes* phyla, irrespective of the diet involved. The researchers also found an inverse correlation with the amount of exercise performed and the ratio of *Bacteroidetes* to *Firmicutes*,¹³ although results by Kang et al.,¹⁹ seem to contradict this finding. It has also been reported that the metabolic state of the individual may be an important factor in determining exercise-induced changes in the microbiota, given that diabetic 9 mice reported different microbiota shifts than non-diabetic mice.²⁰ The interaction between the gut and the microbiome appears to be bidirectional as findings by Hsu et al.,²¹ implicate the composition of the gut with exercise performance. Mice monocolonized with *Bacteroides fragilis* had different performance on a regime of strenuous exercise.²¹ Mechanisms explaining the interactions between the gut microbiota and exercise have been the subject of limited research. Nevertheless, potential mechanisms for the microbiota-muscle axis are discussed below.

Exercise-induced changes in AMPK and FIAF

In the work by Bäckhed et al.,⁸ the researchers noted two mechanisms by which the microbiota interacts with skeletal muscle. First, AMPK, an enzyme previously discussed for its role in energy homeostasis, fatty acid oxidation and glucose uptake in muscles, was found in elevated concentrations in the muscular tissue of GF mice compared to their conventional littermates. In other words, the presence of the microbiome reduced fatty acid oxidation and glucose uptake in skeletal muscle tissue.^{9,22,23} Secondly, the presence of the microbiota suppressed the expression of FIAF, an inhibitor of lipoprotein lipase peroxisomal proliferator which is implicated in fatty acid oxidation in muscle, in an AMPK independent mechanism. Bäckhed et al.,⁸ also previously reported increased locomotion in GF animals, though the cause of this activity is unclear.⁸ Further research is necessary to elucidate the mechanisms that govern this interaction.

Modification of bile acids profile

Numerous studies have demonstrated that an increase in physical activity is inversely correlated with the amount of bile acids within the feces.^{24–26} Bile acids are generally antimicrobial in nature. However, this antimicrobial effect differentially applies pressure to the microbiota species depending on the acid profile. For example, in rats taking dietary cholic acid supplementation, the microbiota demonstrated changes in diversity and composition, with a decrease in the *Bacteroidetes*:*Firmicutes* ratio.²⁷ Other researchers have highlighted unique bile acids pathways that influence energy metabolism such as farnesoid X receptor,^{28–30} and cyclic-AMP-dependent thyroid hormone-activating enzyme type 2 iodothyronine deiodinase.³¹ The exact role of these mediators is unknown to date, requiring further research to identify whether or not they contribute to the exercise-induced changes in the microbiome.

Short-chain fatty acids (SCFAs)

The existence of a microbiota-muscle axis has further been supported by research demonstrating that exercise has a profound effect on the SCFA profile. SCFAs have already been discussed for their vital role in governing energy homeostasis by means of the microbiota. For example, Matsumoto et al.,³² found that running exercises increased fecal levels of butyrate, a change associated with an uptick in butyrate-producing bacteria within the gut.³² Interestingly, butyrate has been linked with gene regulation, oxidative stress, intestinal barrier function and intestinal motility.³³ Ultimately, SCFAs play a vital role in regulating satiety and energy homeostasis, as previously described, which may present a mechanism by which exercise may induce changes in the microbiome.

The influence of exercise on mucosal immunity and inflammation

Another potential mechanism of gut microbiota mediated effects on skeletal muscle is via TLR activation by bacterial components. Muscles express both TLR-4 and TLR-5, which may be activated by LPS and flagellin, respectively, trans-located from the gut lumen into circulation.³⁴ These molecules may then initiate the production of proinflammatory cytokines from muscle cells. In fact, the activation of TLR-4 by LPS injections led to muscle atrophy.³⁵ Moreover, a study by Oliveira et al. found that physical exercise, whether acute or chronic, induced a significant suppression in the TLR4 signaling pathway in the liver, muscle, and adipose tissue, reduced LPS serum levels, and improved insulin signaling and sensitivity.³⁶ Other immu-

nological effects of exercise include the upregulation of IL-6, IL-4, IL-10, TGF- β , TNF- α and IL-12 expression while the gene expression of IL-2 was downregulated in the duodenum of exercised mice.^{37,38} Other putative mechanisms that have been investigated in the literature include the role of myokines, such as interleukin-6,^{39–42} gut transit time^{43–45} and the hypothalamic-pituitary-adrenal axis.⁴⁶

Conclusion

The overwhelming consensus within the literature confirms a therapeutic role for exercise in promoting good health. However, if this beneficial effect is mediated, even partially, by the gut microbiota, there is limited research to substantiate it. The mechanisms by which the gut microbiota exerts control over the host's energy metabolism and satiety are being continually elucidated in animal and human models of obesity. A number of mediators identified in these pathways are also modified by exercise-induced changes, including inflammatory mediators, cytokines, short chain fatty acids, and other regulators of energy homeostasis. It remains unresolved as to whether or not the therapeutic effect of exercise can be explained via the microbiota. Until further studies with germ free or gene knockout models can be performed, putative mechanisms remain largely theoretical. Moreover, study findings have reported discrepancies that may arise from variations in exercise type and duration, diet, metabolic state and genetics of the animal strains. Nevertheless, manipulation of the gut microbiota may present a powerful tool to prevent or treat a number of metabolic diseases and pathologies in the future.

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Conflict of interest

The author declares no conflict of interest.

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