Impact of Physical Exercise on Gut Microbiome, Inflammation, and the Pathobiology of Metabolic Disorders

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Abstract

BACKGROUND: The gastrointestinal tract (GIT) harbors a complex and diverse microbial composition that outnumbers our own body cells and their gene contents. These microbes play a significant role in host metabolism and energy homeostasis. Emerging evidence suggests that the GIT microbiome significantly contributes to host health and that impairments in the microbiome may cause the development of metabolic diseases. The microbiome architecture is shaped by several genetic and environmental factors, including nutrition and physical activity. Physical exercise has preventive or therapeutic effects in respiratory, cardiovascular, neuroendocrine, and muscular diseases. Yet, we still have little information of the beneficial effects of physical exercise on GIT health and microbial composition. Furthermore, we are not aware whether exercise-derived benefits on microbiome diversity can beneficially influence other tissues and body organs. OBJECTIVES: The aim of this article is to review the available literature on exercise-induced microbiome changes and to explain how these changes may induce inflammatory, immune, and oxidative responses that may contribute to the improvement of metabolic disorders. METHODS: A systemic and comprehensive search of the relevant literature using MEDLINE and Google Scholar databases was conducted during fall 2018 and spring 2019. The search identified sixty-two research and review articles that discussed exercise-induced microbiome changes. RESULTS: The review of the relevant literature suggests that exercise-induced microbial changes affect the host’s immune pathways and improve energy homeostasis. Microbes release certain neuroendocrine and immune-modulatory factors that may lower inflammatory and oxidative stress and relieve patients suffering from metabolic disorders. CONCLUSIONS: Exercise-induced changes in microbial diversity are able to improve tissue metabolism, cardiorespiratory fitness, and insulin resistance.

Keywords: diabetes · exercise · microbiome · microbe · inflammation · immune response · obesity · oxidative stress

1. Introduction

During the last century the mortality index indicated a gradual shift from infectious diseases towards non-communicable diseases (NCDs) [1]. Simultaneously, the importance of healthy lifestyle has been emphasized. Besides genetics, diet and lifestyle are the two most important factors associated with the risk of obesity-related metabolic disorders (ORMDs). Consumption of a calorie-rich diet and sedentary lifestyle have contributed to the rising incidence of ORMDs in industrialized countries. In particular, cardiovascular diseases, diabetes, and obesity have been associated with sedentary lifestyle. Research on the gastrointestinal tract (GIT) microbiome has increased our understanding of the bi-directional communication between host...
and microbiome which is carried out through neuroendocrine signals and genetic transfer, and increased knowledge on “microbiome perturbations” in the pathogenesis of ORMDs [2]. Cumulative evidence suggests that the GIT microbiome is an essential mediator between different factors such as genetics, diet, exercise, and environment and the pathophysiology of the ORMDs [3]. Genetics, dietary habits, and host environment may influence the microbiome and eventually affect host metabolism. While this interaction has been studied extensively in diet-induced microbiome perturbations and host physiological and pathological processes [4], little attention has been given to other factors such as physical exercise.

GIT microbiome research has emerged as a potential exploratory field with special focus on ORMD pathogenesis. Microbiome dysbiosis (dysregulations in microbial ecology) in ORMDs has been reported [5]. Because of the presence of highly diverse microbial populations, the GIT represents the primary site of immunological activity. Lifestyle and physical activity may act as important factors to reshape gut microbiome and immunological responses [6], and provide the opportunity to influence disease development by therapeutic measures.

Therefore, in this article, we collected information on the impact of exercise on GIT microbiome and discussed how this information may relate to major NCDs, such as obesity and diabetes. We have previously reported changes in microbiome diversity in a type 1 diabetes rat model [7], and we have outlined the changes in microbiome architecture in diabetes and obesity [8]. In this review, we also analyzed exercise-associated changes in the microbiome that are able to modify body physiology and homeostasis.

2. Methods

The review of the literature was intended to identify taxonomic and community changes in the GIT microbiome in response to physical exercise. We explored exercise-mediated alterations in gut microbiome and metabolites that could be related to systemic inflammation, oxidative stress, and impaired immune responses. A systematic and comprehensive search of MEDLINE and Google Scholar was conducted between fall 2018 and spring 2019 to find relevant research articles published from 2000 to 2019. The following keywords were used in different combinations to retrieve all relevant research articles published in the English language:

- Exercise
- Physical activity
- Microbiome
- Metabolic disorders
- Inflammation
- Immunity
- Obesity
- Diabetes

References and bibliographic lists in published and review articles were also reviewed to identify relevant studies that may have been overlooked during database searches. All original research articles that presented data on intestinal microbiome, exercise, and/or metabolic disorders in humans and animals were included in the study. The literature search was not restricted to:

- Pattern, intensity, or duration of exercise
- Participants’ gender or age
- Sampling pattern or
- Study design

We retrieved 51 original articles and 10 review papers published during 2008-2019 (Figure 1). The research articles were divided into the following two categories:

1. Articles that studied exercise-induced microbiome diversity.

Abbreviations:

- AMPK 5 AMP-activated protein kinase
- BRFSS Behavioral Risk Factor Surveillance System
- BWG body weight gain
- CFU coliform unit
- GABA γ-aminobutyric acid
- GIT gastrointestinal tract
- GLP-1 glucagon-like peptide-1
- GPR G protein receptor
- GPR G-protein-coupled receptor
- HFD high-fat diet
- HPA hypothalamus-pituitary-adrenal
- IL interleukin
- LDL low-density lipoprotein
- LPS lipopolysaccharides
- NCD non-communicable disease
- NF-κB nuclear factor kappa light-chain enhancer of activated B cells
- ORMD obesity-related metabolic disorder
- PYY peptide YY
- SCFA short-chain fatty acid
- SGLT1 sodium-glucose cotransporter 1
- Th cell T helper cell
- TLR toll-like receptor
- Treg cell T regulatory cell


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2. Generic articles that linked exercise-induced microbiome changes with ORMDs.

For each study, we retrieved data on exercise pattern, microbiome diversity, metabolic responses, and immune-inflammatory markers. The primary outcome of this effort was in the form of a database on the following aspects:

- GIT microbiome taxonomy and metabolic profile
- Immune-inflammatory responses
- Oxidative stress

A few studies discussed the molecular mechanisms involved in exercise-mediated alterations of the microbiome and systemic inflammation and immunity [9, 10], while the majority of studies simply described phylogenetic changes observed in response to exercise. To pursue the objective of this review, namely to find out more about the relation between microbiome changes and exercise with respect to metabolic diseases, we further explored review articles and mechanistic studies that related systemic inflammation and immunity to microbiome and exercise.

3. The microbiome as a virtual body organ

Most body surfaces of mammalians harbor a robust microbial colonization that is established to protect the body against potential pathogens; it is collectively called the microbiome. The microbiome is composed of archaea, bacteria, eukaryotes, viruses, and their genetic material. Both cell number and genetic material of the microbiome outnumber our own body cells and their genetic materials [11]. The host's genetics and several habitual and environmental factors act together in shaping host microbiome (Figure 2). Beyond genetics, a number of habitual and environmental factors contribute to shaping the host microbiome, including mode of delivery at birth, breastfeeding as opposed to formula feeding, adult dietary habits, hygiene, physical activity, antibiotics or xenobiotics exposure, and geographical location [12-14].

The microbiome has essential structural, protective, metabolic, and endocrine functions that include food digestion, pathogen displacement, and nutrient synthesis [15, 16]. The GIT is the primary site of interaction between our body's largest component of the immune system and microbial colonization. The commensal microbes not only tune and train this local immunity, they also impact systemic immunity. Microbes interact with the nervous and endocrine system through glucagon-like peptide 1 (GLP-1) and peptide YY (PYY) that are produced in enteroendocrine L-cells, even though the exact mechanisms involved in this communication are not fully understood [17].

The endocrine activities of the microbiome are very heterogeneous. Frequently, the metabolic products of the microbiome, such as short-chain fatty acids (SCFAs), histamine, monoamines, and γ-aminobutyric acid (GABA), act as second messenger molecules or neurotransmitters [18-20]. These molecules mediate gut-brain and endocrine communications and contribute to the micro-
biome’s systemic functions. Gnotobiotic rodent models and probiotic supplementation studies have highlighted the significance of the microbiome. The poor microbial composition in gnotobiotic rats is explicated by averted hypothalamic-pituitary-adrenal (HPA) responses to psychological or environmental stressors [21, 22]. This neuroendocrine containment within the microbiome influences behavior and learning aptitude through biosynthesis of microbial neurochemicals either directly or by bi-directional transfer of genetic information between host and microbiome [23].

SCFAs are the main metabolic products of microbiome fermentation. These molecules act as signaling ligands for G-protein-coupled receptors (GPRs) on enterocytes for chemosensation, appetite regulation, and peripheral nutrient disposal [24]. Acetate, butyrate, and propionate are the main SCFAs that are produced by bacterial fermentation. Acetate and propionate enhance the expression of GPR-43 in immune cells to regulate immune-inflammatory responses [25]. Furthermore, these metabolites improve intestinal barrier function and display potent immunoregulatory properties through T cell proliferation and cytokine production [26].

4. Microbial dysbiosis and aberrant energy homeostasis: the prodrome of metabolic syndromes

Obesity is the consequence of genetic predisposition, chronic energy imbalance, and lack of...
proper physical activity. Extensive diet restriction as well as lifestyle, surgical, and pharmacological interventions have been implemented to treat obesity. These efforts are targeted at losing weight, but they have demonstrated insufficient, unsafe, and inconsistent results in most of the cases [27-29]. In recent years, significant progress has been made in the understanding of the GIT microbiome, suggesting a crucial intermediate role in energy homeostasis.

The basic functions of the gut microbiome are to digest dietary fibers and provide energy to the host. Changes in GIT microbiome composition alter digestive efficiency and consequently host metabolism [30]. Several studies have demonstrated substantial changes in microbiome composition in obese subjects compared with healthy controls, and these changes were associated with ORMDs. Palleja et al. observed that weight loss interventions are associated with beneficial changes in bacterial diversity and improvements in metabolic functions [31]. Furthermore, fecal microbiome transplant from lean donors recapitulates the functional metabolic phenotype and improves insulin sensitivity in the obese recipients [32].

Consumption of energy-rich food or antibiotics can induce microbiome perturbations and promote the incidence of metabolic syndromes. For example, prolonged antibiotic treatment, or antibiotic consumption during early life may induce microbial dysbiosis and promote obesity and diabetes [33, 34]. Hicks et al. observed a positive correlation between microbial dysbiosis, antibiotic consumption, and metabolic syndrome [35]. The authors performed a retrospective analysis using major data pools, including USA population data, American Community Survey, Area Resource File data, and the Behavioral Risk Factor Surveillance System (BRFSS) data obtained from Centers for Disease Control and Prevention. They found that the obese portion of the American population has the highest antibiotic prescription rate.

While these studies suggest an association between microbiome and host energy homeostasis, most of them lack a mechanistic explanation of the impact of microbiome changes on host energy cycle. It is still unknown whether these microbiome changes are cause or effect of obesity. We present the most discussed microbiome-energy homeostasis pathways below.

Recent evidence suggests bi-directional communication, through neuroendocrine signals, between gut microbiota and host cell energy homeostasis [36]. Several high-Impact studies link SCFAs production in gut fermentation to host energy homeostasis [37, 38]. Furthermore, microbiome composition is a key regulator of non-digestible carbohydrate and fiber digestion capacity. Cani et al. have discussed the microbiome’s capacity to digest fibers, the production of SCFAs, and host energy homeostasis in symbiotic relationship [39]. In brief, SCFAs promote mitochondrial function, lipolysis, neoglucogenesis, beige adipogenesis, and release of GLP-1 and PYY. Conversely, these intestinal hormones influence food intake by modulating the activity of brain feeding centers. Furthermore, as revealed by germ-free mice experiments, microbial fermentation products stimulate the production of leptin in adipocytes that promote hepatic lipogenesis and surplus energy storage [40].

5. Exercise as a modulator of gut microbiome

There is compelling evidence to suggest that long-term exercise has a positive effect on energy homeostasis and plays a preventive role against various ORMDs. The most important physiological adaptations that occur in response to exercise are mitochondrial biogenesis, muscular hypertrophy and angiogenesis, cardiovascular fitness, better organized energy supply chain, and activation of the HPA axis. Exercise-induced activation of the HPA axis improves energy balance and better regulates immune-inflammatory responses [20]. Exercise promotes the cholinergic anti-inflammatory pathway and reduces tumor necrosis factor α (TNF-α) release. Lowder et al. reported that continuous moderate exercise is able to prevent influenza infection in rats by enhancing the production of anti-inflammatory cytokines (IL-10 and IL-4) and by lowering the secretion of pro-inflammatory cytokines (TNF-α, IL-1, interferon-γ) [41].

Since 2008, more than 50 research articles have been published on the impact of exercise on gut microbiome diversity. Effects of exercise on GIT health, though not fully explained, have emerged as a key interest in cancer and metabolic disease research. Endurance exercise may modulate GIT immune-inflammatory and redox responses, GIT permeability, motility, and stool transit time and consistency [42-44]. Hoffmann et al. reported that acute and continuing exercise regimes of varying intensities could increase antioxidant capacity, lymphocyte turnover, and expression of anti-inflammatory cytokine in the intestinal wall [43]. In the initial stages of intense exercise, GIT hypoxia and hypoperfusion may increase gut perme-
permeability and thus to cope with physiological

novel strategy to prevent increases in intestinal
targeting the intestinal microbiota may provide a
flammation markers are linked to gut permeability
These changes in microbiome, metabolites, and in-
profile and decreased colon inflammation [54].

transplanted from exercising mice to gnotobiotic
studies. Allen et al. reported an increased production of

physical exercise has positive effects on GIT mi-
microbiome biodiversity, as observed in several ani-
mal and human studies [10, 50, 51]. Several au-
authors suggest that these changes in microbiome diver-
sity are associated with cardiorespiratory fit-
ness and GIT microbial metabolic profile [49, 52, 53]. People with better cardiorespiratory fitness have better microbial diversity and chemotaxis ac-
tivity with decreased lipopolysaccharide (LPS) bio-
synthesis [52]. This improvement in microbial di-
versity and cardiorespiratory fitness in exercising
subjects may be attributed to higher abundance of
butyrate-producing bacteria by the Clostridiales,
Erysipelotrichaceae, Lachnospiraceae, and Rose-
buria families.

microbiome involvement in metabolic diseases is
perhaps most vividly portrayed in gnotobiotic ro-
dents and probiotic/prebiotic supplementation
studies. Allen et al. reported that microbiome transplanted from exercising mice to gnotobiotic
mice improved bacterial diversity and metabolite
profile and decreased colon inflammation [54].
These changes in microbiome, metabolites, and in-
flammation markers are linked to gut permeability
during scenarios of physiological stress. Therefore,
targeting the intestinal microbiota may provide a
novel strategy to prevent increases in intestinal
permeability and thus to cope with physiological
stress [55]. Exercise started in early life is more
effective in correcting microbiome (increasing Bacteroidetes to Firmicutes ratio) and in de-
veloping stable lean body mass [56]. An increase in
Firmicutes to Bacteroidetes ratio, characterized by
microbiome enrichment with Firmicutes or deple-
tion of Bacteroidetes, is recognized as an obesog-
enic trait and is often found in obese children [57].
Furthermore, an increase in butyrate-producing
bacteria influences the metabolic pathways in-
volved in fat accumulation and prevents obesity. Estaki et al. reported an increased production of

SCFAs and reduced biosynthesis of LPS by gram-
negative bacteria in exercising subjects, suggesting a protective role of exercise in immune-
inflammatory inhibition of ORMDs [52]. Similarly, Hsu et al. observed that probiotic Bacteroides
fragilis supplementation improved exercise toler-
ance and swimming performance in gnotobiotic
mice [58]. The improvement in exercise tolerance
was also associated with improvements in liver,
muscle, brown fat weight, and the antioxidant en-
zyme production system [58]. Although the initial
response to intense exercise regimes constitutes an
increase in gut barrier permeability, continuing
exercise for longer duration may improve GIT mi-
crobial diversity which attenuates production of
the cytokines involved in tissue regeneration [54].

Jarke et al. reported conformational changes in
microbiome diversity in high-performance rugby
player’s stool, particularly, a decrease in Firmi-
cutes to Bacteroidetes ratio [59], which has im-
plications for the pathogenesis of obesity and dia-
betes [8]. Data from the American Gut Project re-
vealed that adopting moderate exercise (from
ever to daily) increases species diversity among
Firmicutes phylum and promotes healthier gut
environment [60]. Habitual moderate to intense
physical activity improves microbial diversity and
immune functions and reduces inflammatory dis-
ees [61]. Petersen et al. performed shotgun me-
tagonomics and metatranscriptomic analysis of
competitive cyclists, and reported changes in mi-
crobiota diversity and an upregulation in carbohy-
drate metabolism and energy production [62].

Similarly, Welly et al. reported that exercise-
induced microbiome changes in rats were associ-
ated with low insulin resistance, adipose tissue in-
flammation, and better exercise tolerance [63].

In most of the published studies, exercise-
induced microbiome changes are investigated at
the holistic level, while very few studies describe
specific taxonomic associations between exercise
and GIT microbiome. However, a few rodent exer-
cise studies have associated weight loss with an
increase in the Bacteroidetes/Firmicutes ratio [64, 65]. Furthermore, investigators observed a positive
correlation between Lactobacillus and Bifidobacte-
rium spp. and serum leptin levels in exercising
rats. Although we assume that an increase in the
Bacteroidetes/Firmicutes ratio is beneficial for
metabolic health, as has been observed in several
studies [57, 59, 64-66], there are also contradictory
findings, suggesting exercise-induced health bene-
fits in association with increased Firmicutes diver-
sity and depletion in Bacteroidetes populations
[60, 67]. These differences in observations may be
attributed to different exercise interventions, dietary patterns, or different genetic background of the host. The members of the Firmicutes phylum are most responsive to exercise-associated microbiome changes. However, it is hard to identify specific bacteria genera that create beneficial health responses or that lead to systemic inflammation.

Most of the studies reviewed here reported that the changes in microbiome diversity are associated with improvements in health status. Perhaps, most of these studies describe dissimilar taxonomical changes in microbiome in response to exercise, and generally present more global changes at phylum level (e.g., changes in Bacteroidetes/Firmicutes ratio) or in terms of alpha and beta diversity (species richness and diversity). These inconsistent taxonomical observations may be due to different experimental settings, such as differences in subjects’ age, sex, disease state, supplementation regime, and exercise pattern. Although, similar exercising patterns may have different results in different ages [56] or diet groups [64]. Allen et al. reported that different exercising patterns (voluntary wheel running vs. forced treadmill running) may also affect microbiome differently [68]. Therefore, the only conclusive observations in almost all of these studies are that exercise increases microbial species’ richness and evenness (alpha diversity), and results in distinct clustering patterns (beta diversity), and that there is no single microbial taxon or group of bacteria that can be associated with such variation, as reported elsewhere [9, 10, 58].

Furthermore, most of the reviewed studies recapitulate enhanced production of SCFA, particularly butyrate [53, 64, 69], which are produced by microbial fermentation of fibers and non-digestible starch. This discussion endorses a significant role of physical exercise in microbial metabolism and energy cycles. Perhaps, further mechanistic experimentation is required to elucidate host energy homeostasis in the framework of mode and duration of training that imprints positive effects on microbial community and its functional containment. The future goals of research on exercise-induced microbiome changes should include molecular evaluation of immune-inflammatory pathways or neuroendocrine mediators in gut and metabolic tissues.

6. Metabolic disorders in the view of exercise-induced microbial diversity

Patients with metabolic disorders are characterized by excessive release of pro-inflammatory cytokines from bone marrow-derived monocytes, NF-κB, and chemoattractant protein 1 that disturb the blood-brain barrier and induce neuroinflammatory responses [70, 71]. Inactive lifestyle enhances fatigability and acts as mediator of the development of obesity, hypertension, dyslipidemia, and insulin resistance [72]. In a sedentary rat model of metabolic syndrome, Feng et al. observed that exercise rectified immune-inflammatory markers of obesity and immune-inflammatory responses [73]. These changes in ORMD markers were coequally associated with an exercise-induced improvement in microbiome diversity.

Recently, Dalton et al. reviewed the effects of exercise on the gut-brain axis and microbiome diversity [74]. The authors proposed that exercise-induced improvements in mood and psychological disorders are linked with changes in microbial diversity [75]. Increase in microbiome diversity in response to continuous aerobic exercise has been shown to stabilize GIT barrier function and lower symptoms of irritable bowel syndrome [76]. Probiotic supplementation and aerobic exercise may improve the diversity and abundance of genera from the Firmcutes phylum [76]. This may be explained as a neuroendocrine link between the positive effects of exercise on GIT and brain to prevent or treat psychological distress through the microbiome-gut-brain axis [74]. This neuroendocrine containment within the microbiome influences behavior or learning aptitude through biosynthesis of microbial neurochemicals either directly or through bi-directional transfer of genetic information between host and the microbiome [23].

Allen et al. observed that at baseline, the fecal microbiome, microbiome metabolic profile, and cardiorespiratory fitness level of obese subjects were different from those of lean subjects, and exercise training was positively correlated with these parameters [77]. However, when the rats were returned to a sedentary lifestyle, these changes also reverted to baseline values. Furthermore, exercise-induced microbiome changes reduced fatigue and depression, and improved exercise tolerance, motivation, and cardiorespiratory fitness. Similarly, Feng et al. showed that pre-operative exercise minimizes postoperative weight-gain, neuroinflammation, and cognitive decline and corrects the microbiome in rats [78]. Carbajo-Pescador et al. studied the effects of exercise training on the functionality of gut microbiota, intestinal barrier integrity, and hepatic steatosis in high-fat diet rats [9]. Exercise lowered body weight, mitigated metabolic syndrome and hepatic steatosis, and improved intestinal barrier function.
These exercise-induced metabolic changes were associated with an increased population density of Bacteroides, Flavobacterium, and Parabacteroides genera. These microbial genera have been recognized previously for their protective role against obesity, liver steatosis, and anti-inflammatory capacities [79, 80]. Denou et al. reported that exercise could improve the Bacteroidetes/Firmicutes ratio, metabolic rate, and tricarboxylic acid pathway genes in high-fat diet fed obese mice [66]. In general, overabundance of phylum Firmicutes is associated with obesity, whereas increase in Phylum Bacteroidetes is associated with weight loss in obese individuals. Similarly, higher species richness and diversity of the GIT microbiome corresponds to improved metabolic markers and energy balance, whereas low bacterial diversity is correlated with insulin resistance, obesity, and dyslipidemia (Figure 3) [81]. Since continuous physical exercise is known to prevent or treat these metabolic diseases, these findings may suggest that exercise-associated changes in the GIT microbiome may support the host’s metabolic health. Furthermore, enhanced microbiome diversity in endurance performers can also improve antioxidant capacity, which is crucial in lowering insulin resistance and preventing ORMDs [58, 82].

Another plausible mechanism that may impart exercise-induced changes in the microbiome in ORMDs is the change in microbiome metabolic profile. The microbiota-produced SCFA activate the 5′ AMP-activated protein kinase (AMPK) pathway to control lipids and glucose metabolism and act as a sensor for cellular energy status [83].
Table 1. Summary of exercise-induced gut microbiome changes observed in different metabolic syndrome conditions

<table>
<thead>
<tr>
<th>Study format</th>
<th>Exercise format</th>
<th>Clinical features and major findings</th>
<th>Microbiome changes</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical exercise decreased weight gain in rats</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise decreased food intake and weight gain, and increased cecal weight and size</td>
<td>Increased butyrate-producing bacteria SM 7/11 and T2-87</td>
<td>[67]</td>
</tr>
<tr>
<td>Exercise corrected toxicity-induced microbial dysbiosis in mice</td>
<td>Volunteer wheel running, aerobic</td>
<td>--</td>
<td>Exercise increased bacteria abundance and diversity</td>
<td>[45]</td>
</tr>
<tr>
<td>Diet restriction- or exercise-induced microbiome changes in rats</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise and anorexia decreased body weight and leptin secretion and increased ghrelin secretion</td>
<td>Exercise and anorexia increased Bacteroides, Prevotella, Lactobacillus, and Bifidobacterium population sizes</td>
<td>[63]</td>
</tr>
<tr>
<td>Microbiome changes in rats following to diet vs. exercise</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise more effectively reduced adiposity, adipose inflammation, insulin resistance, and LDL cholesterol</td>
<td>Exercise more effectively increased the Streptococcaceae family and reduced the Rikenellaceae family</td>
<td>[61]</td>
</tr>
<tr>
<td>Exercise altered microbial composition and increased lean mass in juvenile rats</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise lowered body weight in adult rats and increased body weight in juvenile rats compared with the sedentary counterpart groups</td>
<td>Juvenile runners had higher Bacteroides to Firmicutes ratio</td>
<td>[54]</td>
</tr>
<tr>
<td>Microbiomes of professional or amateur cyclists</td>
<td>Professional or amateur cyclists, aerobic cycling</td>
<td>--</td>
<td>Bacteroides, Prevotella, Eubacterium, Ruminococcus are the dominant bacteria in all cyclists</td>
<td>[60]</td>
</tr>
<tr>
<td>Specific microbiome structure improved exercise performance</td>
<td>Exhaustive anaerobic swimming</td>
<td>--</td>
<td>Microbiome split into three clusters dominated by either Bacteroides, Prevotella, or a mix of many microbes in all cyclists</td>
<td>[60]</td>
</tr>
<tr>
<td>Active participation in athletics lowered anxiety and improved oral immunity</td>
<td>Professional soccer and hokey players, both aerobic and anaerobic training</td>
<td>Active athletes had higher cardiorespiratory fitness and oral immunity, and lower anxiety.</td>
<td>Active athletes had lower oral bacteria- colony-forming units (CFU)/ml, particularly for Streptococi</td>
<td>[87]</td>
</tr>
<tr>
<td>Exercise altered microbiome and SCFA concentration</td>
<td>Both volunteer wheel and forced treadmill running</td>
<td>--</td>
<td>Exercise increased SCFA diversity</td>
<td>[88]</td>
</tr>
<tr>
<td>Exercise altered the microbiome of obese and hypertensive rats</td>
<td>Controlled treadmill training at 12 to 20 m.m-1 speed, aerobic</td>
<td>--</td>
<td>Exercise increased alpha diversity and changed clustering pattern</td>
<td>[89]</td>
</tr>
<tr>
<td>Exercise improved postoperative rehabilitation</td>
<td>Treadmill training at 20 m.m-1 speed, aerobic</td>
<td>Preoperative exercise prevents postoperative neuroinflammation and improves cognition in metabolic syndrome rats</td>
<td>Exercise improved microbiome alpha diversity</td>
<td>[76]</td>
</tr>
<tr>
<td>Exercise prevented weight gain and altered the microbiome in rats</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise lowered body weight and insulin resistance in high-fat diet rats</td>
<td>Exercise decreased Bacteroides to Firmicutes ratio</td>
<td>[62]</td>
</tr>
<tr>
<td>Exercise changed the microbiome of diabetic and control mice</td>
<td>Treadmill running at 2 to 4 m.m-1 speed, aerobic</td>
<td>Exercise decreased Bacteroides to Firmicutes ratio in both diabetic and control rats</td>
<td>Exercise increased alpha diversity and changed clustering pattern</td>
<td>[65]</td>
</tr>
<tr>
<td>Exercise changed microbial composition and influenced cardiac function in mice</td>
<td>Treadmill running at 12-15 m.m-1, aerobic</td>
<td>Exercise inhibited decline in cardiac output and stroke volume in the mouse model for surgical myocardial infarction</td>
<td>Exercise increased Butyrivimonas, Prevotella, and Akkermansia compared with the control</td>
<td>[90]</td>
</tr>
<tr>
<td>Exercise corrected HFD-induced bone loss and microbial dysbiosis in rats</td>
<td>Volunteer wheel running, aerobic</td>
<td>Exercise prevented BWG, bone loss, bone marrow adiposity</td>
<td>Exercise decreased Firmicutes to Bacteroides ratio and increased Bifidobacteriaceae population</td>
<td>[91]</td>
</tr>
<tr>
<td>Exercise improved cardiorespiratory fitness in elderly women</td>
<td>Brisk walking, trunk muscles, aerobic</td>
<td>Exercise increased cardiorespiratory and energy expenditure</td>
<td>Exercise increased Bacteroides, decreased Clostridium populations</td>
<td>[92]</td>
</tr>
<tr>
<td>Exercise lowered BWG and insulin resistance in HFD rats</td>
<td>Treadmill running, both aerobic and anaerobic</td>
<td>Exercise lowered oxidative stress, inflammation, insulin resistance, and liver damage</td>
<td>HFD rats had a higher Firmicutes to Bacteroides ratio that was partially reverted by exercise</td>
<td>[7]</td>
</tr>
<tr>
<td>Exercise had limited effect on HFD-induced dysbiosis in mice</td>
<td>Treadmill running, 20 m.m-1, aerobic</td>
<td>Exercise failed to improve HFD-induced decrease in exercising capacity and aerobic power</td>
<td>Exercise decreased abundances of Proteus and Vagococcus genera</td>
<td>[93]</td>
</tr>
<tr>
<td>Intense exercise improved glycemic index and adipose tissue loss in Zucker rats</td>
<td>Treadmill running, 10 to 18 m.m-1, aerobic</td>
<td>Exercise decreased inflammation and adiposity and improved glycemic control in obese rats</td>
<td>Exercise did not affect the abundance of major bacteria taxa</td>
<td>[94]</td>
</tr>
</tbody>
</table>


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GIT microbiome is critical for sodium-dependent glucose transporter 1 (SGLT1) and G-protein-coupled receptor (GPR) expression on colon epithelial cells. However, it has been observed that antibiotic-induced GIT microbiota depletion in rats results in impaired muscle function in endurance running performance. Furthermore, decrease in microbial diversity is also associated with loss in muscle glycogen levels and insufficient metabolic performance because of SGLT1 and GPR depletion [84]. However, SCFA-regulated GPR stimulation controls size and function (expression of Foxp3 and IL-10) of the colonic T regulatory (Treg) and T helper (Th) cells in intestinal inflammation [85, 86]. Therefore, a decrease in the richness of bacteria species, as observed during antibiotic therapy, may suppress SCFA production, which eventually results in decreased Treg cell production and activation of pro-inflammatory and autoimmune pathways.

Furthermore, exercise increased fecal abundance of arabinose and carnosine metabolites, which are promising candidate for therapies to combat diabetes and obesity [87]. These microbes and metabolites prevent LPS influx, TLR-4-mediated NF-κB activation, and inflammatory cytokine production. Eventually, downregulation of TLR-2, TLR-4, and the NF-κB pathway resulting from exercise may improve insulin sensitivity [88].

In brief, exercise-induced changes in GIT microbiome and metabolome help to maintain intestinal wall integrity and downregulate both local and systemic immune-inflammatory pathways that may contribute to the prevention of ORMDs [51].

As discussed in the above sections and shown in Table 1, most of the literature available provides only common diversity or phyllum level taxonomic changes in microbiome in response to exercise, both in health and metabolic diseases. It is therefore reasonable to assume that exercise-induced changes in microbiome diversity could improve host metabolic profile by:

- Decreasing lipid production and storage in visceral organs
- Correcting chronic low-grade inflammation
- Decreasing insulin resistance

We have attempted to establish a link between exercise-induced phylogenetic changes in microbiome and metabolic disorders that associate microbiome changes with predictive immune-inflammatory pathways. Eventually, this may provide a mechanistic understanding of the beneficial effects of physical exercise in metabolic disorders through microbiome changes.

7. Conclusions

The observations reviewed here suggest a plausible microbiome basis for exercise-induced prevention of metabolic diseases, and provide an opportunity to explore novel avenues to prevent metabolic diseases in critically lethargic subjects who are incapable of voluntarily exercise to manage their weight. Although, most of the favorable health outcomes are independent of microbiome-host interactions, there is also evidence to indicate that some of the benefits may be mediated by exercise-induced adaptations in gut microorganisms.

Reciprocal associations between immune-inflammatory mediators and exercise-induced microbiome/metabolome corrections may engage several cellular energy sensors and trigger adipokine and myokine activation that monitor energy balance and tissue metabolism. Although abundant evidence is available on the role of the microbiome in metabolic disorders, no significant clinical findings are available to prevent or correct these disorders. Extensive work is needed on metagenomics beyond taxonomic diversity profiling. More mechanistic research is required to connect exercise with microbiome, body metabolism, and energy homeostasis.

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Physical Exercise and Gut Microbiome


