

Exploring the association between physical activity and gut microbiota composition: a review of current evidence

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Abstract

The gut microbiota is implicated in digestive, metabolic and immune processes of the host. The physiological and pathophysiological functions of the intestinal microbiota depend of its composition, and several individual or external factors may be associated with the presence of some categories, phyla or species of microorganisms in the gut. In particular, two bacterial phyla - Firmicutes and Bacteroidetes - are predominant in the human gut and their relative concentrations seem to be related with age, gender, diet habits and weight status. In the last decade, several studies have tried to characterize the possible role of physical activity in determining qualitative and quantitative composition of the intestinal microbiota. This review is aimed at exploring the current evidences regarding the association between physical activity and gut microbiota composition in animal models and in the humans. Further studies are needed to clarify the mutual relationships among exercise, diet, nutritional supplements/doping agents and gut microbiota.

Introduction

The human gut microbiota is the totality of the microorganisms that populate the intestine of the humans and are implicated in digestive, metabolic and immune processes of the host (1, 2). Microbiota is involved in mucosal homeostasis, biosynthesis and absorption of nutrients, maintenance of epithelial integrity, interaction with the immune system, competitive inhibition of possible

invasion and colonization by pathogenic microorganisms (3, 4). In addition, the gut microbiota plays an important role in drugs and xenobiotics metabolism through a series of microbial enzymatic reactions which can activate, inactivate or alter the systemic bioavailability of certain substances, so as different molecules, not only antibiotics, may alter the composition of the gut microbiota in a manner that is detrimental for health (5, 6). The gut dysbiosis is the disruption of the

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equilibrium in the intestinal ecosystem and is associated with many human diseases, including autoimmune and allergic diseases, colorectal cancer, metabolic diseases, and bacterial infections (7, 8). A lot of studies have recently highlighted that the physiological and pathophysiological functions of intestinal microbiota depend of its composition, while other evidences have suggested that several factors may be associated with the presence of some categories, phyla or species of microorganisms in the gut (3, 9, 10). In the healthy adult population, two major bacterial phyla are predominant: Gram-positive *Firmicutes* (ranging from 60% to 80%) and the Gram-negative *Bacteroidetes* (ranging from 20% to 40%), nevertheless intestinal microbiota is different, in variety and quantity, from one person to another and it is influenced by endogenous and exogenous determinants, such as anagraphic, geographic or behavioral factors (11-14). Moreover, seven bacterial divisions constitute the gut microbiota, e.g. *Firmicutes*, *Bacteroides*, *Proteobacteria*, *Fusobacteria*, *Verrucomicrobia*, *Cyanobacteria*, and *Actinobacteria*. The gut microbiota performs essential functions in maintenance of health, including having protective, structural, and metabolic roles. Table 1 shows the main functional activities of gut microbiota; although the reported informations are not exhaustive, they indicate the multiple connections between intestinal microflora and essential activities of human homeostasis (9, 15-29).

Relative proportions of *Bacteroidetes* and *Firmicutes* seem to influence health and are influenced by host characteristics; indeed, these proportions have been observed to change with age, gender and body mass index (30-32). Also, geographical residence seems to play an important role. For example, among the members of the *Bacteroidetes*, two genera dominate: *Bacteroides* and *Prevotella*; they are antagonist and the first is more abundant in the gut of Western people, while *Prevotella* is more common

in the gut of non-Westerners, even though this difference may also partially correlate with the type of diet (32). Indeed, a lot of evidences have demonstrated the existing relationship between gut microbiota composition and diet: a high fiber diet, including fruits, vegetables, legumes, and whole-wheat grain products, has been shown to increase the microbial diversity (20, 33). In obese people and in persons with type 2 diabetes or altered blood glucose the relative proportion of *Bacteroidetes* is decreased so as the microbiota diversity (34-36).

Furthermore, in the last decade some studies have tried to characterize the possible role of physical activity - including exercise and sport - in determining the animal or human gut microbiota composition (37, 38).

This narrative review is aimed at exploring the current evidences regarding the association between physical activity and gut microbiota composition.

Search and selection methods

The literature search was carried out on Pubmed. Search terms used were “Gut Microbi*” AND “Exercise” OR “Sport” OR “Physical Activity”. No time restrictions were applied. Editorials, commentaries, discussion papers and conference abstracts, and non-English papers were excluded.

On a total of 21 articles selected, 10 were focused on animal models and 9 on the humans, while two papers reviewed studies on both animals and humans: all of them were included in the following review.

Physical activity and gut microbiota in animal models

The results of studies carried out on gut microbiota of animal models are often conflicting. Some researchers have shown that exercise may lead to an increase of

Table 1 - Main beneficial roles of the gut microbiota for human health grouped in five principal macro-functions.

	Macro-functions	Bacteria	Implications	Ref
Metabolic function	Production of Short Chain Fatty Acid (SCFA) such as acetate, butyrate and propionate	<i>Bacteroides</i> , <i>Roseburia</i> , <i>Bifidobacterium</i> , <i>Fecalibacterium</i> , <i>Enterobacteriaceae</i> , <i>Lachnospiraceae</i> , <i>Ruminococcaceae</i> , <i>Negativicutes</i> , <i>Clostridium</i> , <i>Prevotella</i> , <i>Blautia</i> , <i>Coprococcus</i> , <i>other Firmicutes and Verrucomicrobia</i>	Acetate: the principal short-chain fatty acid in the colon and the substrate for cholesterol synthesis; central appetite regulation. <u>Butyrate</u> : reduce of the accumulation of toxic products; energy source for epithelial cells; potential anti-tumour activity. <u>Propionate</u> : reduces cholesterol levels; energy source for epithelial cells; role in gluconeogenesis	13-16
	Bile acid bio-transformation	<i>Bacteroides intestinalis</i> , <i>Bacteroides fragilis</i> , <i>Escherichia coli</i> , <i>Enterobacteriaceae</i> , <i>Clostridium</i> , <i>Lactobacillus</i> , <i>Veillonella</i>	Microbial enzymes have implications for cholesterol and glucose metabolism	13, 17
	Activation of protein kinases	<i>Bacteroides thetaiotaomicron</i> , <i>Lactobacillus innocua</i>	Some bacteria induce the oxidation of non-esterified fatty acids and greater energy yield of food ingested	13
	Carbohydrate degradation and salts/water absorption	<i>Bacteroides</i>	Ability to help to metabolize several energy sources in human colon	18
	Production and vitamins/amino-acids biosynthesis	<i>Firmicutes</i> , <i>Actinobacteria</i> , <i>Fusobacteriaceae</i> , <i>Proteobacteria</i>	e.g. Biosynthesis of Vitamins of B group	19, 20
	Energy source	<i>Bacteroides thetaiotaomicron</i>	Lipolysis increasing	13
	Fermentation of non-digestible substrates and mucus/antimicrobial secretion	<i>Lactobacillus rhamnosus</i>	Production of soluble proteins implicate in epithelial growth factor (EGFR) and protein kinase C (PKC) pathway. Increasing of the antimicrobial activity of the host lysozyme	13
	Colonization resistance and sites and nutrients competition	<i>Bacteroides</i> , <i>Propionibacterium</i>	Commensal organisms prevent pathogenic colonization by competing for attachment sites, nutrients, and antimicrobial secretion	21, 22
	Innate and adaptive immunity activation	<i>Bacteroides</i> , <i>Akkermansia</i> and <i>Gram-negative bacteria</i>	B and T cell development	13
	Inflammatory cytokine regulation	<i>Bacteroides</i> and <i>Propionibacterium</i>	Activation of pattern recognition receptors initiates nuclear factor- κ B pathways, mitogen-activated protein kinase, and caspase dependent signalling cascades	13
Structural and protective function	Immune system and lymphatic systems developments	<i>Bifidobacterium</i> , <i>Streptococcus salivarius</i> , <i>Lactobacillus reuteri</i> , <i>Clostridia</i>	Association with cytokine responses and may affect susceptibility to the disease	7, 23-25
	Barrier fortification and mucus layer protectives	<i>Bacteroides thetaiotaomicron</i> , <i>Campylobacter jejuni</i> , <i>Clostridium difficile</i> , <i>Escherichia coli</i> , <i>Lactobacillus</i> and some <i>Lachnospiraceae</i>	Increased expression and secretion of mucins, trefoil factors, and antimicrobial peptides secretion	23
Histological function	Epithelial cell growth and differentiation regulation	<i>Bacteroides fragilis</i> , <i>Clostridium</i> , <i>Lactobacillus</i>	Synthesis of conjugated linoleic acid known to be anti-obesity, anti-carcinogenic, anti-atherogenic, anti-diabetogenic, immunomodulatory, apoptotic, osteo-synthetic, and to increase muscle mass	26, 27
	Other structural and histological function	<i>Bacteroides</i> , <i>Clostridium</i> , <i>Lactobacillus</i>	Intestinal villi micro-vascularization and crypts development, tight junctional permeability	13

Firmicutes/Bacteroidetes ratio, while others reported a reduction in this ratio related to exercise (39-44). Similar phylum variations were lacking in some studies involving mouse models (45, 46), or they were observed only with certain conditions such as age, diet or type of physical activity (39, 40, 47).

In 2008, a study carried out by Matsumoto et al. showed that, in rats, voluntary running exercise determines a variation in microbiota composition, an increase in the cecum diameter and in butyrate concentration, which protects against colon cancer and inflammatory bowel disease (IBD) playing a role in mucin synthesis and gut epithelium protection (45). These effects were in part explained by other studies which demonstrate that exercise determines an increase in some bacterial species, such as bacteria producing lactic acid (e.g. *Bifidobacteria* and *Lactobacillus*), which modulate mucosal immunity and prevent pathogens invasion, or *Blautia coccoides* and *Eubacterium rectale* which convert lactate into butyrate (48, 49). Another study carried out by Allen et al. reported different effects of voluntary and forced training on changes in mice gut microbiota during an inflammatory insult such as ulcerative colitis; these changes may be related to gut immune function and involved in the pathogenesis of IBD (47). Other researches showed that exercise may prevent induced weight gain and obesity changing the percentage of *Bacteroidetes* and *Firmicutes* in mouse models (39, 46). Conversely, in 2013 Queipo-Ortuño et al. reported that exercise associated with food restriction may result in a decrease of beneficial bacteria in the gut, favoring mucosal barrier disorders (49). Moreover, it has been showed that exercise starting in juvenile period may produce more positive effects in microbiota composition respect to adult exercise, leading to an increase in lean body mass through adaptive changes in the rat metabolism (40). Another study by Petriz et al. reported exercise-induced

changes in gut microbiota composition of obese rats, suggesting a possible therapeutic role of physical activity in obesity treatment (41). Furthermore, Kang et al. investigated the effects of high fat diet and exercise on gut microbiota diversity and their influence on cognitive and psychological functions. They found that diet and exercise influence independently anxiety and cognition modulating the concentration of specific bacterial species in the gut of mice (42).

Physical activity and gut microbiota in humans

Several studies have shown that exercise can determine changes in qualitative and quantitative microbial microbiota composition in humans and that athletes have greater microbiota biodiversity.

In 2014, Clarke et al. reported the results of an investigation carried out among professional rugby players and two control groups composed by sedentary individuals having a BMI ≤ 25 and a BMI > 28 respectively. The study showed an enhanced diversity of the athletes' microbiota, with 22 phyla detected, respect to both control groups (11 and 9 phyla detected); this diversity correlated with exercise and dietary protein consumption (50). It should be noted that athletes and the low BMI group had significantly higher proportions of the genus *Akkermansia*, which is a mucin-degrading bacterium that resides in the mucus layer and whose abundance inversely correlates with obesity and associated metabolic disorders in mice and humans (51, 52). Similar results were found by Bressa et al. in active women compared with sedentary controls (53). By analyzing the bacterial and fungal communities in gut microbiota of 186 healthy Slovenian adults, Mahnic and Rupnik found that higher levels of physical activity were positively related with higher total fungal diversity and lower abundance of

S. cerevisiae, while no significant differences were detected in bacterial composition (14). Two studies have tried to analyze the gut microbiota composition as a function of cardiorespiratory fitness: Estaki et al. showed that individuals with higher levels of cardiorespiratory fitness have enhanced microbiota diversity and higher concentrations of butyrate-producing taxa regardless of diet, while Durk et al. found that a higher ratio of *Firmicutes* to *Bacteroidetes* ratio is significantly correlated with maximal oxygen uptake (54, 55).

In 2018, Allen et al. explored the effects of exercise on gut microbiota providing a 6-week supervised endurance exercise program to 32 sedentary adults lean or obese (56). They found that exercise may alter the abundance of several taxa and species depending on BMI status: exercise increased *Faecalibacterium* species and decreases *Bacteroides* species in lean subjects while the contrary was registered in obese subjects; butyrate-producing taxa were also increased in lean subjects, but these effects were transient and vanished in the subsequent sedentary washout period. In the same year, Cronin et al. explored the effects of a short-term aerobic and resistance exercise program with or without protein supplementation on gut microbiota of overweight and obese adults (57). Even if their results did not show any significant microbiota changes related to exercise, the Authors concluded that a fitness enhancement in sedentary individuals may lead to modest but detectable changes in gut microbiota composition.

A further research published by Munukka et al. showed that a 6-week endurance exercise program resulted in an increase of *Akkermansia* and a decrease in *Proteobacteria* among previously inactive overweight women (58). In addition, several studies have demonstrated that gut microflora has a role in structural and histological function of human body and is involved in muscle fibers and epithelial cells growth and differentiation

and can encourage the reversion of cells to a non-neoplastic phenotype (59, 60). These findings suggest that exercise influences the human gut microbiota independently of diet, fostering specific microbial profiles, and that the microbiota of lean individuals may be more responsive to exercise than that of overweight or obese individuals. This is in line with the evidence-based ongoing configuration of physical activity as a fundamental tool in the prevention of multifactorial diseases and underlines the need for public health strategies focused on the exercise (61, 62).

Conclusions

Current evidences show that gut microbiota, physical activity and eating habits/weight status interact with a complex relationship. However, further studies, especially longer longitudinal investigations, are required to confirm and clarify these findings. In particular, it is necessary to explore in depth how specific diet, foods, nutrients or supplements may modulate the possible influence of exercise on microbial diversity in the gut. Considering that the practice of exercise or sport is frequently associated with the assumption of dietary supplements or doping agents, the possible role of gut microbes in the metabolism of these substances as well the influence that these drugs may have on gut microbiota composition should be characterized. Improving knowledge about the effects and the interactions of these factors can offer new opportunities to maintain health, reduce risk of diseases and develop personalized therapeutic approaches.

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Riassunto

Associazione tra attività fisica e composizione del microbiota intestinale: una revisione delle attuali evidenze scientifiche

Il microbiota intestinale è implicato nei processi digestivi, metabolici e immunologici dell'ospite. Le funzioni fisiologiche e patofisiologiche del microbiota intestinale dipendono dalla sua composizione, e diversi fattori individuali o esterni possono essere associati alla presenza di alcune categorie, phyla, generi o specie di microrganismi nell'intestino. In particolare, due phyla batterici - *Firmicutes* and *Bacteroidetes* – sono predominanti nell'intestino umano e le loro concentrazioni relative sembrano essere correlate con l'età, il genere, le abitudini alimentari e lo stato ponderale. Negli ultimi anni numerosi studi hanno provato a caratterizzare il possibile ruolo dell'attività fisica nel determinare la composizione qualitativa e quantitativa del microbiota intestinale.

Questa revisione analizza le attuali evidenze circa l'associazione tra attività fisica e composizione del microbiota intestinale in modelli animali e nell'uomo. Risultano necessari ulteriori studi per chiarire le interazioni tra esercizio fisico, dieta, assunzione di supplementi nutrizionali o sostanze dopanti e microbiota intestinale.

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