

The Impact of Diet and Physical Activity on the Human Gut Microbiota

Xiaoyue Shang

Institute of Human Nutrition, Columbia University Irving Medical Center, New York, USA

xs2541@cumc.columbia.edu

Abstract. The human gut microbiota is a crucial regulator of nutrient metabolism, immune function, and even influences psychological status through gut-brain communication. Strategies targeting gut microbiota as adjunct approaches to aid in conventional pharmacotherapy, while supplements such as prebiotics and probiotics are gaining markets due to consumer's growing awareness on the health benefits of desirable gut microbiota pattern. This paper summarizes the effects of leading lifestyle factors, dietary intake and physical activity, on the composition and function of human gut microbiota. It addresses the need for standardized research designs to improve cross-study comparability and consensus. Dietary patterns and nutrient sources have profound influences on gut microbiota composition through supporting substrate and introduction of new species. The mechanisms of physical activity impacting gut microbiota composition are not well-understood, while the synergistic effects with diet should be acknowledged. Personalized lifestyle interventions targeting the gut microbiota are recognized as a compelling strategy to address precision health. Since diet and physical activity are crucial modulators of the human gut microbiota, understanding their independent effects and interactions provide a foundation for developing microbiota-targeted lifestyle interventions and guiding personalized approaches to improve health outcomes.

Keywords: Gut microbiota, diet, physical activity, lifestyle interventions, nutrient metabolism.

1. Introduction

The human gut microbiota is defined as a community of microorganisms residing in the gastrointestinal tract in a symbiotic relationship with the host, including bacteria, archaea, lower eukaryotes and viruses. The high diversity and redundancy of this community underpin its crucial functions in nutrient metabolism, energy homeostasis, immune regulation, and the defense of potential pathogens. Although the gut microbiota exhibits considerable resilience, its composition is shaped by various factors, such as lifestyle, delivery method at birth, age, activity levels, antibiotic use, genetics and environmental factors. Many of these factors can induce the disruption of gut microbiota, also referred as dysbiosis. This condition leads to numerous health conditions not limited to the gastrointestinal (GI) system, including inflammatory bowel disease (IBD), allergies, non-alcoholic fatty liver disease (NAFLD), immune disorders, metabolic disorders, and even neurological disorders [1].

The link between gut microbiota and host health has drawn increasing attention in therapeutic strategies targeting gut microbiota to enhance balance and promote GI health. Fecal microbiota transplantation (FMT) is a treatment of transferring fecal material from the donor to restore a balanced gut microbiota community and gut functions. Live biotherapeutics (LBPs) are similar but novel medications that directly apply live microorganisms to gut microbiota to target specific diseases and dysbiosis-related conditions. Alongside their therapeutic uses, microbiome-related products like prebiotics and probiotics have also gained global popularity in recent years. Probiotics are living microorganisms that are thought to provide beneficial health outcomes to the host, while prebiotics are fibers to feed the beneficial microbes in the gut. Their validated applications include inhibiting infection and recurrence, GI issues, and supporting diabetes management. Nowadays, consumers have realized the health effects of these products. The current global market for probiotics reaches a market size of \$220 billion, and the expected to achieve a 14% compound annual growth rate (CAGR) over the next 5 years [2]. A similar trend is observed in the research activity of probiotics, with the number of published articles indexed from PubMed spiking from 2254 to 7139 over the last decade.

Despite the extensive research on host-microbiome interactions, there is currently no defined ideal pattern of gut microbiota. Due to the large variation of gut microbes at the individual-level, it appears that a functional definition of the gut microbiome community is more feasible than a universal taxonomy for all populations. Thus, it is essential to investigate the impact of diet and exercise on gut microbiome to develop lifestyle interventions.

Although diet and physical activity have profound influences on gut microbiota, the mechanisms of their influence remain unclear. To explore this relationship, it is necessary to have a consensus on measurable biomarkers to define a “healthy” gut microbiota. Common indicators of microbial status are metabolites of microbiota, such as short-chain fatty acids (SCFAs), tryptophan metabolites, trimethylamine N-oxide (TMAO) and bile acids (BAs). In fact, the correlation between these metabolites and the host’s physiological status has not been established. The Firmicutes/Bacteroidetes ratio is another popular indicator of gut health with contradictory outcomes. The results are highly variable across individuals and studies due to the weak association and even inverse correlation. This paper will explain the regulation of dietary components and physical activity on the human gut microbiome and describe the potential pathways of their synergistic regulation. It will also illustrate the core gaps in current research and outline future research directions to provide theoretical support for personalized lifestyle strategies.

2. Common Biomarkers of the Gut Microbiota

The most commonly used biomarkers reflecting gut microbial function and the host status are usually metabolites of human gut microbiota, such as SCFAs, secondary bile acids, tryptophan metabolites, and even specific strains. The gut-derived short-chain fatty acids, primarily acetate, propionate and butyrate are fermented products from dietary fiber that are known to influence host health locally and systemically. These SCFAs support the gut epithelial integrity, regulate immune cell differentiation, and modulate gut-hormone signaling. Bile acids are products from the liver to aid in fat absorption. The gut microbiota then transforms them into secondary bile acids, which can modulate the appetite, energy balance, systemic metabolism, immune function, and neuroinflammation [3]. Similarly, the tryptophan metabolites are crucial signaling molecules of the immune function and the central nervous system [3].

Taxonomic indicators are also used to assess the gut microbiota and its health outcomes. The Firmicutes/Bacteroidetes ratio (F/B ratio), or sometimes the Bacteroidetes/Firmicutes ratio and SCFA producers, such as *Faecalibacterium* and *Akkermansia*, are frequently analyzed due to their well-defined roles in host health status [4]. The core of the debate regarding the F/B ratio lies in whether it can function as a universal biomarker of gut health. It is proposed that the F/B ratio in the population with obesity is higher than that of the non-obese population, which is positively correlated to the risk of developing metabolic disorders. On the other hand, various studies propose that the F/B ratio can be affected by individual baseline microbiota, age, medication use, and feeding time, and there is no universal standard for the “healthy ratio range” across different populations. Even the fluctuation of the ratio in the same population at different intervention stages is not directly associated with health outcomes. Therefore, the essence of the controversy is the applicability of “taxonomic biomarkers” rather than the detection reliability of the ratio itself.

3. Diet

3.1. Diet Regulation of Gut Microbiota

Dietary pattern is the major modulator of gut microbiota composition, diversity, and functionality. Even short-term dietary changes, as little as seven days, can induce compositional changes to healthy female athletes, whose gut microbiota are generally more resistant than those of the sedentary population. Long-term interventions are able to induce clinically significant health effects, such as functional reprogramming of microbial metabolism. Dietary fiber promotes gut motility and serves

as the substrate for SCFAs production, which makes it the most influential dietary component shaping gut microbiome. Through fermentation of dietary fiber, the gut microbiota can produce butyrate to feed the colonocytes, upregulate tight junction proteins, and enhance the gut barrier [5]. Other SCFAs, propionate and acetate, contribute to the regulation of glucose and lipid levels and act as ligands for G-protein-coupled receptors to regulate gut hormones [5]. Furthermore, the anti-inflammatory effect is caused by their inhibition of the histone deacetylase activity, which reduces the NF- κ B activation and the release of subsequent proinflammatory cytokines [5]. In addition to indigestible carbohydrates, the type of protein source also modifies the composition of gut microbiome. A study of fermented soy protein products applied to mice reported positive changes, such as an increase in gut microbial diversity and nutritional values [6]. However, there are negative impacts of plant-based proteins on gut microbiota, including lower digestibility and a higher content of antinutritional factors compared to animal proteins. The undigestible protein builds up and undergoes fermentation in the colon, hence the detrimental compounds like indole and ammonia are produced [7]. Given the distinct properties of two protein sources, the effects of dietary protein on gut microbiota must consider both the quantity and source of protein intake. Omega-3 fatty acids (FAs) can serve both as an energy source and a regulator of gut microbiota. For instance, it can support the increase of desirable species and repress the potential pathogens [8]. The above changes enhance the need to track nutrient sources in dietary research.

3.2. Effects of Typical Dietary Patterns on Gut Microbiome Diversity and SCFA-Producing Taxa

The Mediterranean diet (MD) is defined by an emphasis on plant-based foods consumption, including fruits, vegetables, legumes, nuts, and whole grains, with extra virgin olive oil (EVOO) and a pattern of fish rich in omega-3 fatty acids as the major fat sources, while consumption of animal products like red meat and dairy products is limited. Across human studies, MD intervention has been associated with enriched beneficial bacteria involved in SCFA production, energy metabolism, and anti-inflammatory processes. The taxa repeatedly increased in response to the MD interventions include Erysipelotrichaceae, Peptostreptococcaceae, Veillonellaceae, and key butyrate-producing species Ruminococcaceae and Lachnospiraceae.

The ketogenic diet (KD) is a dietary pattern of very low carbohydrate and high fat intake to promote the ketone body production. Accumulating evidence from human studies shows that a diet of high-fat intake is associated with decreased beneficial taxa due to ketone bodies. This dietary pattern also has positive impacts on the gut microbiome by reducing pro-inflammatory species and increasing SCFA production. Clinical studies have found an increase in certain SCFA-producers following KD. These include *Ruminococcus bromii* and *Phascolarctobacterium faecium*, as well as some species of the Bacteroidetes. A lack of fiber substrate can result in a decrease of other SCFA-producing bacteria, including *Bacteroides eggerthi*, *Dialister succinatiphilus*, and other members of Firmicutes. The conflicting outcomes of KD highlight the complexity of its role in reshaping gut microbiota functions and health outcomes, suggesting the need for further research

3.3. Functional Foods and Controversies

Unlike the macronutrients discussed above, functional foods impact the gut microbiome through supplementing bioactive compounds, increasing diversity, and adjusting pH levels. In addition to prebiotics and probiotics, functional foods have other categories, including dietary fiber, fermented products, and fortified products. Each of these categories has distinct influences on microbial composition and metabolic activity. Fermented products are natural sources of lactic acid bacteria (LAB) that lower the pH to defend against pathogens and supply metabolites to the cross-feeding network. Pre- and probiotics are products promoted for benefits to gut health and metabolism. In fact, their effects on healthy individuals are uncertain, and the evidence behind health claims fails to ensure their safety and efficacy [9]. More importantly, the sudden introduction of exogenous strains may

induce transient shifts in the gut microbiome, causing gastrointestinal discomfort such as gas, flatulence, and watery stool [9].

3.4. Gaps and Future Directions

The duration of various studies on dietary intervention spans a wide range from less than a week to months. Although short-term dietary changes can alter gut microbiome composition, these changes can hardly induce clinically significant outcomes. Since many long-term microbial outcomes are summarized from short-term interventions, it is necessary to define a standardized minimum duration for studies on dietary interventions. Another confounding factor is the specificity of records on dietary intake. Many studies did not address the dietary components with profound and distinctive effects on gut microbiota composition and function, such as the type of protein source, the amount of omega-3 FAs, and the type of fiber.

4. Physical Activity

4.1. Physical Activity Regulation of the Gut Microbiota

Physical activity is another factor that can reshape the environment of GI system. General PA is found to increase the diversity of gut microbiota overall, and its effects on gut microbiota are influenced by the type, duration, and activity load. For instance, aerobic training has a deeper influence on the gut microbiota compared to resistance training [10]. A higher intensity and duration are associated with a higher diversity in pro-inflammatory taxa [10]. Long-term effects of physical activity are usually observed in professional athletes. Their gut microbiome is more resistant to changes compared to individuals with moderate or sedentary activity levels. Recent findings suggest that the link between PA and gut microbiome is bidirectional [10]. For instance, endurance training can enrich *Veillonella atypica* in athletes, while supplementing *Veillonella* can improve their performance and inflammatory state [11]. These findings emphasize the potentials of systemic health effects of gut microbiota through PA.

Despite the existing observations above, the mechanisms of how PA changes gut microbiota are still not well-understood. One hypothesis is the supplementation of substrates, such as lactate metabolizing species. Bile acids are another possible bioactive compound group that can have significant interactions with gut microbiota [10]. PA is known to impact the metabolic profile and homeostasis of the bile acid pool, which has antimicrobial effects to selectively change the species in gut microbiota [12]. Thirdly, the gut transit time indirectly but significantly affects the gut ecology after PA, especially endurance training [13]. This connection can be explained by the decreased blood flow to the gut during exercise, which alters the microenvironment in the gut: substrate availability, pH, and metabolic output, ultimately shifting favored microbial taxa [14]. Lastly, neuroendocrine factors from the gut-brain axis are also found to modulate gut microbiota. The intense exercise will activate the stress systems, cause hormones including cortisol and catecholamines to be released and directly act on the gut environment, which alters microbial populations [15].

4.2. Gaps and Future Directions

Physical activity can apparently alter the gut microbiota, but the specific mechanisms are not clearly understood. First and foremost, the primary confounder that is not broadly discussed in current studies is the lack of control over other modifiable variables influencing gut microbiota. Regarding the research of PA interventions, dietary intake is not consistently tracked, despite its potent and direct impact on the gut microbiota composition. Secondly, athletes have lifestyle highly different from those of the general population. Their diets are designed to support their training load and enhance performance. Supplements such as whey protein, prebiotics, and probiotics are also commonly used depending on the types of exercise and training seasons. The complex combination of effects from PA and dietary factors together shapes their unique pattern of gut microbiota. Lastly, the methodologies in different studies are inconsistent in the trials of physical activity interventions. The

forms of information on physical activity include data from accelerometers, monitored single-movement activities, combinations of multiple activities, and even training camps with controlled diets. As a result, the gut microbial changes across studies are hardly comparable and cannot be used to isolate the effects of type, duration, and intensity.

5. Synergistic Effects of Diet and Physical Activity

The effects of modifiable lifestyle factors, including diet composition, meal timing, physical activity, and circadian rhythm, are interconnected on the gut microbial community. The dietary pattern and physical activity modulate gut microbiota through shared pathways, such as the increase of SCFA-producing species. Diets high in fiber can provide fermentation substrates for SCFA-producing bacteria, *Faecalibacterium* and *Veillonella*, which can be enriched by exercise as well. Likewise, exercise can improve the fermentation efficiency of SCFA-producing bacteria on dietary fiber by regulating intestinal transit time. This creates a favorable intestinal environment (pH and oxygen concentration), thereby improving SCFA production. At the same time, PA can modify the composition of bile acid pool to promote the microbial decomposition of dietary fat. Despite synergistic effects of diet and PA on gut microbiota regulation, the result interpretation is limited by a lack of standardization in the study design. The insufficient control over diet and PA is the primary confounder to study their independent effects. Since the data of dietary intake and PA are self-reported through questionnaires or software for research purposes, adherence cannot be guaranteed, which may weaken the accuracy of results and the dose-response relationship. Another challenge of cross-study comparison lies in the differences in target cohort selection. The common baseline cohort for the studies of lifestyle intervention would contain prediabetic children, non-diabetic adults with or without obesity, and professional athletes. This would decrease the comparability of observed microbiota responses and weaken the power of intervention effects.

6. Conclusion

Diet and physical activity are two daily aspects, but their potent and relatively safe lifestyle effects on gut microbiota regulation are usually overlooked. Each factor can raise significant changes in gut microbial composition, functionality, and host health status. Combined together, these factors can even work synergistically through shared mechanisms based on recent findings. Also, the interpersonal variability in the baseline gut microbiota composition highlights the need for personalized approaches. Without a universal and “ideal” gut microbial pattern, future interventions should involve personalized dietary and physical activity recommendations to match the microbial conditions and lifestyle patterns. It is essential to establish an individualized framework that turns lifestyle interventions targeting gut microbiota into successful and safe strategies to improve human health.

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