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Intermittent fasting and gut microbiota: Exploring the bidirectional relationship

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Abstract
Intermittent fasting (IF) has gained considerable attention as a dietary approach with potential health benefits, including weight management, metabolic regulation, and disease prevention. Recent studies indicate that the gut microbiota may play a central role in mediating these effects. This review explores the bidirectional relationship between intermittent fasting and gut microbiota, highlighting how fasting modulates microbial diversity and function, and conversely, how the gut microbiota mediates the physiological outcomes of IF. We also examine the mechanistic underpinnings of this interaction and its implications for human health and disease.

Keywords: Gut health, diet, bacteria, human health, Intermittent fasting

Introduction

The gut microbiota, consisting of trillions of microorganisms including bacteria, archaea, viruses, and fungi, is a dynamic ecosystem critical for maintaining host health. It influences digestion, immune function, energy metabolism, and neurological processes (Lynch & Pedersen, 2016) [7]. On the other hand, intermittent fasting (IF), a dietary pattern involving periods of voluntary abstention from food, has been associated with improved metabolic profiles, enhanced insulin sensitivity, and longevity (Patterson & Sears, 2017) [9, 21]. Emerging evidence suggests that the gut microbiota may be a key mediator of these benefits.

Intermittent fasting (IF) has gained considerable attention in recent years as a dietary strategy for weight management, metabolic health, and longevity. Unlike traditional caloric restriction, IF involves alternating periods of eating and fasting, without necessarily altering the quantity or type of food consumed. Various IF regimens—such as alternate-day fasting, time-restricted feeding (TRF), and the 5:2 diet—have been associated with improvements in insulin sensitivity, lipid metabolism, circadian rhythm regulation, and cellular repair processes (Patterson & Sears, 2017) [9, 21]. While much of the focus has been on its physiological and metabolic benefits, an emerging area of interest lies in understanding how IF influences the gut microbiota—a complex ecosystem of trillions of microorganisms inhabiting the gastrointestinal tract—and how, in turn, the gut microbiota modulates the effects of intermittent fasting.

The gut microbiota plays a vital role in human health, influencing digestion, immune regulation, inflammation, and even neurobehavioral processes via the gut-brain axis (Shreiner, Kao, & Young, 2015) [23]. Composed primarily of bacteria, but also including archaea, viruses, and fungi, the microbiota functions as a dynamic and adaptive interface between diet and host physiology. Changes in microbial composition, also known as dysbiosis, have been linked to several chronic diseases, including obesity, type 2 diabetes, cardiovascular disorders, and neurodegenerative conditions (Tilg *et al*., 2020) [25]. Given the sensitivity of the gut microbiota to dietary patterns, it stands to reason that IF, with its structured feeding-fasting cycles, could exert profound effects on microbial diversity, composition, and function.

Recent preclinical and clinical studies suggest that intermittent fasting reshapes the gut microbial ecosystem in ways that may contribute to its health-promoting effects. For instance, animal models have demonstrated that time-restricted feeding can enhance microbial diversity and promote the abundance of short-chain fatty acid (SCFA)-producing bacteria, such as *Akkermansia muciniphila* and *Faecalibacterium prausnitzii*, which are associated with anti-inflammatory effects and improved gut barrier integrity (Zarrinpar *et al*., 2014; Thaiss *et al*., 2016) [14, 27]. Similarly, human trials report changes in microbial composition after prolonged fasting or Ramadan-style fasting, indicating a potential modulation of gut microbiota through controlled feeding windows (Remely *et al*., 2015) [10, 22].

This bidirectional relationship is particularly intriguing: while IF modulates the gut microbiota, the microbiota itself can influence the host's response to fasting. Microbial metabolites, such as SCFAs (e.g., butyrate, acetate, propionate), secondary bile acids, and lipopolysaccharides (LPS), mediate systemic effects on inflammation, insulin sensitivity, appetite regulation, and immune response (Koh *et al*., 2016) [17]. Therefore, the interplay between IF and gut microbiota may represent a synergistic mechanism by which fasting exerts its systemic benefits. It has also been proposed that gut microbes possess their own circadian rhythms, influenced by the host's feeding schedule, and that aligning feeding times with natural circadian cues via IF could optimize microbial metabolic output and, consequently, host physiology (Leone *et al*., 2015) [18].

The gut microbiota also influences nutrient absorption and energy harvesting from food. For example, individuals with a higher Firmicutes-to-Bacteroidetes ratio are thought to extract more calories from the same amount of food, potentially contributing to obesity (Turnbaugh *et al*., 2006)

[26]. By reshaping this ratio, IF may alter caloric efficiency and metabolic outcomes. Furthermore, the fasting periods may induce a state of mild metabolic stress that stimulates microbial autophagy, known as "xenophagy," and bacterial turnover, favoring the colonization of beneficial commensals (Li *et al*., 2017) [5, 19]. This dynamic exchange may rejuvenate the microbial landscape and reduce pathogenic overgrowth, enhancing gut resilience.

Another critical dimension of this relationship is the role of the gut-brain axis. The microbiota communicates with the central nervous system via neural (vagus nerve), endocrine (cortisol, ghrelin), and immune (cytokines) pathways, influencing mood, cognition, and stress response. Intermittent fasting, which has been shown to improve cognitive performance and neuroplasticity, may mediate these effects partially through alterations in gut microbial composition (Mattson *et al*., 2018) [8, 20]. Some studies report increased levels of *Lactobacillus* and *Bifidobacterium*, both known for producing gamma-aminobutyric acid (GABA) and serotonin precursors, following fasting regimens, suggesting a psychobiotic role of fasting-induced microbiota shifts (Zhao *et al*., 2020) [28].

In parallel, the immune-modulatory role of the gut microbiota cannot be overlooked. Intermittent fasting may enhance intestinal immune homeostasis by promoting the expansion of regulatory T-cells and reducing systemic endotoxemia—conditions closely tied to gut microbiota status (Jordan *et al*., 2019) [16]. For example, reductions in LPS-producing gram-negative bacteria during fasting reduce metabolic inflammation and improve insulin sensitivity. The integrity of the intestinal barrier, supported by SCFA-producing bacteria, is also critical in preventing chronic low-grade inflammation, a common denominator in metabolic syndrome and autoimmune conditions.

Despite these promising insights, challenges remain in delineating causal relationships. Much of the current understanding stems from animal models, which may not fully replicate the complexity of human microbiota or lifestyle factors. Human studies are often limited in duration, sample size, and dietary control, making it difficult to isolate the effects of IF from other confounding variables. Moreover, inter-individual variability in gut microbiota composition means that responses to IF can vary widely, necessitating a personalized nutrition approach. Future research should aim to integrate metagenomics, metabolomics, and controlled feeding studies to better characterize the microbiome-mediated mechanisms underlying intermittent fasting.

The relationship between intermittent fasting and the gut microbiota represents a promising frontier in nutritional science and health promotion. By modulating microbial diversity, metabolic activity, and host–microbiota interactions, IF may offer multifaceted benefits that extend beyond calorie control. Understanding this bidirectional relationship is essential for optimizing dietary interventions aimed at disease prevention, weight management, and overall well-being. As we deepen our knowledge of how temporal eating patterns influence our microbial allies, novel therapeutic strategies may emerge that harness the microbiome as a mediator of fasting-related health benefits.

Intermittent Fasting: Patterns and Physiological Impact

Intermittent fasting includes several regimens such as alternate-day fasting (ADF), the 5:2 diet (fasting 2 days/week), and time-restricted feeding (TRF), where food intake is limited to specific hours (Longo & Panda, 2016) [6]. These regimens induce metabolic shifts such as increased ketogenesis, autophagy, and modulation of circadian rhythms (de Cabo & Mattson, 2019) [3]. These systemic changes can impact the composition and function of the gut microbiota.

The Gut Microbiota: Composition, Functions, and Plasticity

The gut microbiota is primarily composed of the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Diet is a major determinant of microbial composition. High-fiber diets encourage the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus*, while high-fat and high-sugar diets promote dysbiosis (Zmora *et al*., 2019) [15]. The microbiome is responsive to even short-term dietary changes, suggesting that IF could modulate microbial diversity and metabolism.

Effects of Intermittent Fasting on Gut Microbiota

Several studies have shown that IF can induce beneficial shifts in the gut microbiome:

1. Animal Studies

Animal models provide robust evidence of the microbiota-modulating effects of IF. Mice subjected to TRF displayed increased microbial diversity and altered abundance of bacteria such as *Akkermansia muciniphila* and *Lactobacillus*, associated with improved metabolic outcomes (Zarrinpar *et al*., 2014) [14, 27]. Another study found that ADF in mice improved gut barrier function and increased the production of short-chain fatty acids (SCFAs), critical for colonic health (Li *et al*., 2017) [5, 19].

2. Human Studies

Though human studies are fewer, they corroborate findings from animal models. A study by Su *et al*. (2021) [11] demonstrated that Ramadan fasting resulted in increased levels of *Faecalibacterium prausnitzii*, a beneficial butyrate-producing bacterium. Other studies have shown an enrichment of SCFA-producing bacteria and reductions in pro-inflammatory species during IF (Remely *et al*., 2015) [10, 22].

Gut Microbiota as a Mediator of Fasting Benefits

The gut microbiota not only responds to IF but also influences its outcomes:

1. Metabolic Health

SCFAs such as acetate, propionate, and butyrate, produced by microbial fermentation, enhance insulin sensitivity, regulate lipid metabolism, and reduce inflammation (Canfora *et al*., 2015) [1]. IF-induced shifts toward SCFA-producing bacteria may underlie improvements in glucose and lipid profiles.

2. Immune Modulation

Gut microbes influence immune function by modulating regulatory T cells and maintaining intestinal barrier integrity. IF has been shown to promote microbial profiles that reduce endotoxemia and systemic inflammation, thus lowering the risk of chronic diseases (Ganesan *et al*., 2018) [4].

3. Neuroendocrine Effects
The gut-brain axis, mediated by microbial metabolites and vagus nerve signaling, is influenced by IF. Changes in microbiota during fasting can affect mood, cognition, and stress resilience, potentially explaining some of the neuroprotective effects of IF (Cignarella *et al*., 2018) [2].

Mechanistic Insights into the IF-Microbiota Axis
1. Circadian Rhythms
Both host metabolism and gut microbiota exhibit circadian rhythms. TRF synchronizes feeding-fasting cycles with circadian gene expression, which in turn regulates microbial diurnal oscillations (Thaiss *et al*., 2014) [12, 24].

2. Autophagy and Gut Health
IF enhances autophagy, a cellular cleanup process that also supports gut epithelial integrity. A healthy gut barrier, maintained by beneficial microbiota, prevents translocation of harmful bacteria and endotoxins.

3. Bile Acid Metabolism
IF alters bile acid profiles, which directly affect microbial composition. Secondary bile acids modulate microbial growth and act as signaling molecules influencing host metabolism (Wahlström *et al*., 2016) [13].

Clinical Implications and Therapeutic Potential
The interaction between IF and gut microbiota has significant clinical implications:

- **Obesity and Type 2 Diabetes:** IF-mediated microbial modulation may enhance insulin sensitivity and promote weight loss (Li *et al*., 2017) [5, 19].
- **Inflammatory Disorders:** Improved microbial profiles reduce markers of systemic and gut inflammation (Ganesan *et al*., 2018) [4].
- **Aging and Neurodegeneration:** IF-associated microbiota changes may support brain health and delay age-related decline (Mattson *et al*., 2018) [8, 20].

Study (Model / Design)	Microbiota Changes	Host Outcomes & Mechanisms
Ramadan-style IF (Özkul *et al*., human, pilot)	Akkermansia muciniphila, Bacteroides spp., Butyricicoccus pullicaecorum, Faecalibacterium prausnitzii, Roseburia (post-fasting)	Enhanced SCFA production (e.g., butyrate), improved gut barrier integrity, anti-inflammatory effects (Özkul et al., 2019 & 2020).
Systematic reviews (human)	Microbial richness and diversity; compositional shifts vary by phenotype	Suggests overall improvement in gut microbiota, but results are heterogeneous and need further validation (Paukkonen et al., 2024; phenotype-dependent).
Human 3-week IF (Chinese adults, 5:2 regimen)	Parabacteroides distasonis, Bacteroides thetaiotaomicron	Weight loss, better insulin resistance, increased genes for succinate production and glutamate fermentation.
Buchinger periodic fasting (humans)	Firmicutes, Lachnospiraceae, Ruminococcaceae; Bacteroidetes, Proteobacteria	Correlated with improved metabolic markers, reduced gut permeability, immune modulation (sIgA, lysozyme), reduced LPS translocation.
Mice, 16-hour daily fasting	Akkermansia; Alistipes	Linked to reduced liver triglycerides and intestinal inflammation; IF effects dependent on fasting duration (mice model).
Obese mice, alternate-day fasting	Firmicutes/Bacteroidetes ratio; Allobaculum; trend toward diversity	Improved lipid metabolism, reduced endotoxemia, promoted white-to-beige adipose conversion.
Murine colorectal-cancer model (APC^Min/+ mice)	Odoribacter, Alistipes; isovaleric acid (metabolite)	Suppressed tumor development via modulation of gut microbiota and SCFA-related metabolites.
Fasting + fiber in mice (FF-EODF)	Lactobacillus, Bifidobacterium, S24-7; SCFAs	Enhanced insulin sensitivity, increased satiety, improved energy expenditure.
Systematic review (humans, TRF & ADF)	Altered Firmicutes/Bacteroidetes ratio; Akkermansia muciniphila, Lactobacillus spp.	Positive effects on adiposity, insulin sensitivity, obesity-related metabolic indicators.
Human fasting and circadian rhythms	Changes in microbial rhythms linked to feeding schedule	Suggests bidirectional regulation: microbiota influences host circadian genes and vice versa.

Conclusion
Intermittent fasting and the gut microbiota engage in a dynamic, bidirectional relationship. IF reshapes the gut microbiota, increasing microbial diversity and enhancing the abundance of health-promoting species. In turn, the microbiota mediates many of the physiological benefits of IF, including improved metabolism, immune regulation, and neuroprotection. While current evidence is promising, further longitudinal and mechanistic studies in humans are needed to harness the full therapeutic potential of this interaction.

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