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Review Article

Intermittent fasting - a potential approach to modulate the gut microbiota in humans? A systematic review

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Abstract. Research on gut microbiota has increased in popularity over the past decade, with evidence associating different dietary habits with changes in the makeup of the rich ecosystem of microorganisms that performs a variety of functions and induces a range of health effects, within and well beyond the gastrointestinal tract. Similarly, intermittent fasting (IF), an umbrella term describing various regimens of periods of voluntary abstinence from food and drink, has classically been associated with favourable impacts on cardiovascular risk factors, body weight, circadian biology, and, more recently, the gut health..The objective of this PRISMA systematic review was to summarize the peer-reviewed literature of clinical trials related to the impact of IF regimens on the gut microbiota. A MEDLINE search was conducted using PubMed and the keywords "intermittent fasting", "gut microbiota", "microbes", and others. Whilst the field is still in its infancy, an emerging body of evidence suggests beneficial effects of IF on the health of the gut through increasing the microbial diversity and abundance, with possible clinical implications related to improving the immune function and ameliorating the metabolic status. Further research in larger clinical trials is warranted before practical recommendations for the public health can be made.

Keywords: Intermittent fasting, periodic fasting, alternate-day fasting, whole-day fasting, time-restricted feeding, gut microbiota, microbes

1. Background

Both human and animal studies demonstrate a beneficial impact of intermittent fasting (IF), a term describing several regimens of periods of voluntary abstinence from food and drink, on various aspects of health. IF regimens can be categorized into fasting for up to 24 hours once or twice a week with ad libitum food intake for the remaining days, known as periodic prolonged fasting (PF) or intermittent calorie restriction (ICR) [1]; eating for 8 hours then fasting for the other 16 hours of the day (time-restricted feeding, TRF); and alternating between feasting and fast days (alternate-day fasting, ADF) [2, 3] (Table 1). IF has classically been recognized to ameliorate obesity [2], insulin resistance [4], dyslipidemia [5], blood pressure [4] and inflammation [6]. More recently, IF has been shown to also benefit the gut microbiota [7], a term describing the trillions of microorganisms (bacteria, viruses, protozoa, and fungi),which are present in the human gut and are involved in

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Table 1
Comparison of different types of intermittent fasting

Type of IF	Description	Metabolic states involved
Alternate day fasting	Alternating feast (ad lib intake) and fast days (≤ 25% of energy needs)	Fed, post-absorptive, fasting (short duration, likely < 36 hours between meals)
Time- restricted fasting	Eating only during certain time periods (i.e., 8 hours), then fasting for remaining hours of the day	Fed, post-absorptive (maximum duration between meals is usually < 16 hours)
Periodic fasting	Fasting for up to 24 hours once or twice a week with ad lib intake on the remaining days	Fed, post-absorptive, fasting (up to 48 hours between meals depending on whether fast days are consecutive)

virtually all aspects of health [8, 9]. This is a vast and complex microbial community, with over 1000 bacterial species identified and approximately 160 species found in the gut of any one person [10], and the most abundant bacterial phyla in the adult gastrointestinal tract are Firmicutes and Bacteroidetes [11, 12].

The gut microbiota provides many benefits to the host, such as the biosynthesis of certain vitamins and essential amino acids, and the generation of short-chain fatty acids (SCFAs) as metabolic by-products from undigested food components [13]. SCFAs, including butyrate, propionate, and acetate are a major source of energy for the intestinal cells and may strengthen the intestinal barrier [14] and improve the gut integrity [15], which is paramount in promoting optimum colonic health and function; resulting in better immunity [16]. SCFA production is influenced by gut microbiota composition and diet, with primarily butyrate and acetate decreasing the inflammatory response, whilst increasing the anti-inflammatory response of the adaptive immune system [17]. In addition, butyrate methylates promoter regions, thus influencing gene expression in enterocytes, macrophages and immune cells; deficient SCFA can disrupt these processes, which can lead to an autoimmune response and disease [17]. Furthermore, SCFA and butyrate specifically controls the function and size of the regulatory T cell network by stimulating the induction and fitness of regulatory T cells in the gut [18–20]. In addition, the microbiota is involved in many critical functions to ensure that optimum immune responses can be produced, including aiding development and maturation of lymphoid structures and potentiation of the function of innate immune cells [21]. Whilst, the microbiota is critical for maturation of the immune system, in return, the latter determines the composition of the microbiota. As such, disrupted microbial composition has been associated with several diseases in humans. However, the intricate immune/microbial interactions make it difficult to determine whether dysbiosis, the imbalance of gut microbiota, is a cause and/or a consequence of immune dysregulation and disease initiation or progression [21].

Diet is reported as a major factor influencing gut microbiota and several studies have investigated the impact of different dietary components, including carbohydrates, predominantly fibre, and plant-based diets, on the gut microbiota [22–26]. Nuts and other plant-based foods that are abundant in polyunsaturated and monounsaturated fats and, occasionally, polyphenols and other phytochemicals have been shown to increase bacterial diversity, as well as the beneficial butyrate-producing bacteria revealing a positive metabolic effect [27–28].

With rapidly advancing screening used to analyse and differentiate complex ecosystems, the role of microbiota in a significant number of gastrointestinal diseases has become increasingly clear [29, 30]. Dysbiosis may contribute to the pathogenesis of a vast range of such diseases, including inflammatory bowel disease (IBD), celiac disease, colorectal cancer, *Clostridium difficile* infection, and obesity [31]. For instance, studies [32–35] have found IBD patients to have less bacterial diversity in the gut and reduced numbers of Bacteroidetes and Firmicutes, potentially leading to decreased concentrations of butyrate that is, along with other SCFAs, believed to have a direct anti-inflammatory effect [33, 36, 37]. Greater diversity in the microbial community has also been associated with a healthier gut microbiome [38–40]; a diverse array of bacteria promotes microbiome capability, and is imperative for a healthy host–microorganism balance to ensure optimal metabolic and immune function.

For this reason, the gut microbiome has become a promising target for prediction, prevention and treatment of diseases [8]. Given that it is evident that diet is a significant modulator of the gut health and microbiota diversity [22–26], and that dietary restrictions such as IF may also contribute to such effect [9], the objective of this review was to summarize the peer-reviewed literature of clinical trials related to the impact of IF regimens on the gut microbiota.

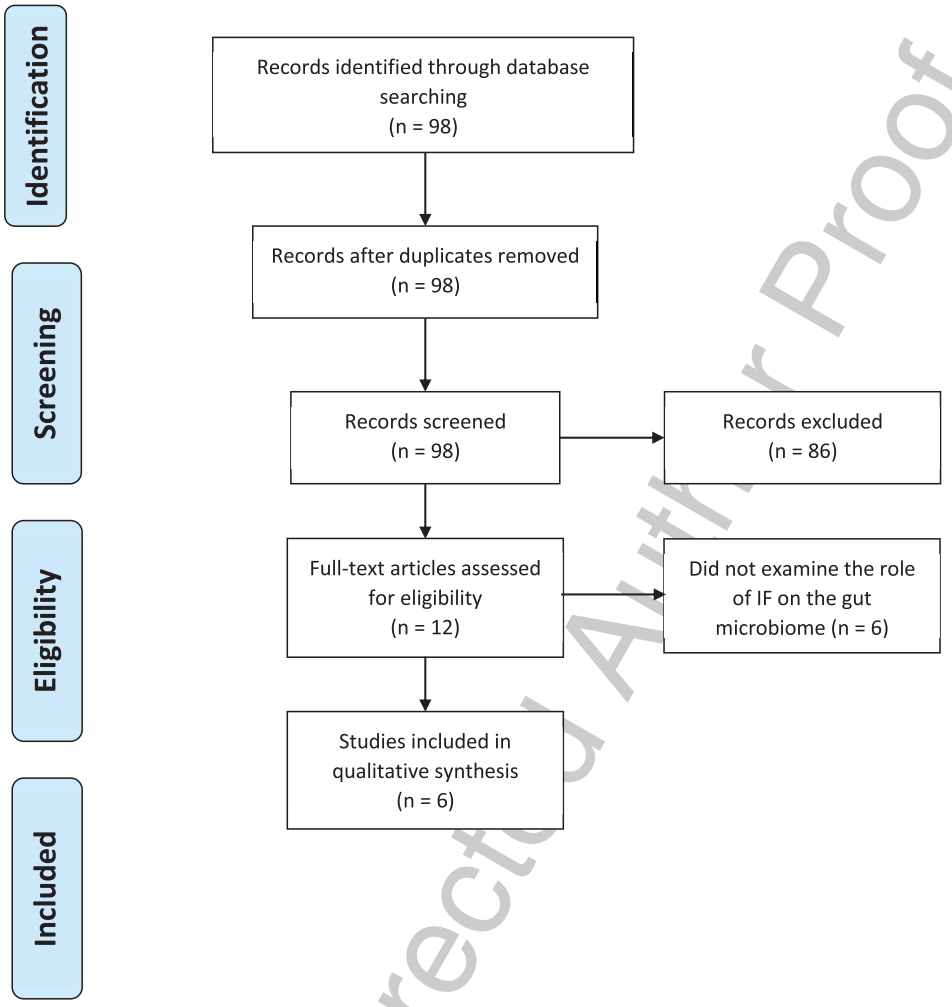

Fig. 1. PRISMA 2009 Flow Diagram.

2. Methods

The design of the study is a qualitative systematic review in line with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist (Fig. 1). A literature review was performed independently by two reviewers, KLW and MA using PubMed. Search criteria included clinical trials published in English between January 2000 and April 2020 with the keywords "intermittent fasting", "periodic fasting", "time-restricted", "alternate-day fasting", "whole day fasting", "gut microbiota", and "microbes". References were reviewed from seminal papers to identify additional articles.

3. Results and discussion

Based on the inclusion criteria, 98 clinical studies were identified and six articles were included in this review [8, 41–45] (Fig. 1). Other studies were excluded as they did not specifically examine the role of IF on the gut microbiota. The excluded articles investigated the effect of alternative nutrients'

Table 2
Summary of studies included in the present review

Reference	Participants (n)	Duration and type of fasting	Comparison group	Change in microbial Composition
He et al. (2019) [8]	Healthy adults aged 18–40 years ($n=16$)	1 week: water-only fasting ($n=6$)	1 week: juice fasting ($n=10$)	↓ *Fusobacterium* water-only fasting ↔ *Akkermansia* water-only fasting ↔ juice fasting
Remely et al. (2015) [41]	Overweight ($n=13$)	CR and PF/TRF (non-traditional fasting regimen) (600–800 kcal)	None	↑ *Lactobacillus* ↑*Enterobacteria* ↑ *Akkermansia*
Cignarella et al. (2018) [42]	Adults with MS ($n=16$)	15 days: ADF	15 days: ad libitum	↑ *Bacteroides* ↑ *Lactobacillus* ↑ *Prevotella (*fasting group)
Özkul et al. (2019) [43]	Healthy adults aged 31–56 years ($n=9$)	29 days: Ramadan fasting /TRF	None	↑ *Bacteroides* ↑ *Akkermansia*
Gabel et al. (2020) [44]	Obese adults ($n=14$)	12 weeks: TRF	None	↔
Özkul et al. (2020) [45]	Healthy adults ($n=9$)	29 days: Ramadan fasting /TRF	None	↑ *Bacteroides* ↑ *Butyricicoccus* ↑ *Faecalibacterium* ↑ *Roseburia* ↑ *Allobaculum* ↑ *Eubacterium* ↑ *Dialister* ↑ *Erysipelotrichi*

Abbreviations: ADF, alternate-day fasting; CR, calorie restriction; MS, multiple sclerosis; PF, periodic fasting; TRF, time-restricted feeding; ↑, statistically significant increase ($p<0.05$); ↔, no change.

or foods such as gluten, yogurt, high-fat and/or high-sugar diet on the gut microbiota. Main microbiota-related findings of studies included in the present review are summarized in Table 2 and are discussed below.

Cignarella et al. 2008 [42] initiated a 15-day randomized controlled pilot trial to multiple sclerosis (MS) subjects experiencing relapse; where seventeen subjects were equally randomized to ADF vs ad libitum diet. No bacteria were significantly different at day 15 between the two groups, but the abundance of *Faecalibacterium, Lachnospiracea_incertae_sedis* and *Blautia* showed an increasing trend after 15 days of IF [42]. *Faecalibacterium* and *Blautia* belong to the *Clostridia clusters XIV* and *XIVa* (in the Firmicutes phylum) and have been shown to increase regulatory T cell (Treg) accumulation in the colon [46]. These bacteria are important as they produce acetate and have been observed to be decreased in MS subjects [47]. As such, the increase in the *Clostridia clusters XIV* and *XIVa* with IF may function to counterbalance the dysbiosis usually observed in MS [42].

In a 2019 study of sixteen healthy subjects aged 18–40 years and have BMI >18.5 kg/m^2, six individuals were allocated to a water-only fast and ten were assigned a juice fast for one week [8]. Daily stool sample collection, prior to and post fasting, started from two weeks before fasting until four weeks after. The authors hypothesized that water only fasting may be a potential therapeutic strategy in reducing *Fusobacterium*, which has been shown to promote colorectal cancer [8]. However, the differential abundance findings suggest that the impact of fasting on individual microbial taxa is unique and personalized. Despite this individualized effect, relative abundance of *Fusobacterium* was decreased across all participants in group 1 ($P<0.05$) when compared with pre-fasting controls. This finding was not reported in group 2 ($P>0.05$), however pre-fasting relative abundance of *Fusobacterium* was increased in group 1 compared with group 2 participants. In all participants, post water-only fasting *Fusobacterium* remained consistently reduced. In addition, eight out of ten subjects were not affected by juice fasting, with no increased homogeneity between subjects. These findings suggest that water-only fasting may have a long-lasting effect on the microbiota and a more homogenous microbial community; indicating

increased homogeneity and alterations in microbiota demonstrated in water-only fasting may not be necessarily due to the absence of solid food [8]. The authors anticipated relative abundance of *Akkermansia* in the water-only fast participants since *Akkermansia* uses mucin as a sole substrate [48]. However, they observed no increase in the relative abundance of *Akkermansia* after fasting. This suggests that there could be other bacteria that utilize mucin, which compete with *Akkermansia* in the gut during water-only fasting.

There are a limited number of small-scale human studies that consider the role of *Akkermansia muciniphila,* a species of bacteria reported to thrive when undergoing fasting conditions [43, 45], and which may represent 3–5% of the healthy gut microbiota [49-50]. One small intervention study of obese patients demonstrated significant improvement in microbiota diversity and showed a significant increase in *A. muciniphila* after a week of mild fasting (Remely et al, 2015) [41]. This pilot study [41] assigned thirteen overweight subjects to a non-traditional fasting regimen that involved a limited period of abstinence from solid food and natural stimulants. The fasting regimen was low in energy with an intake of 2.5 L/day of calorie-free liquid (water, herbal tea) or vegetable broth (600–800 calories/day) followed by a probiotic formula. Microbiota diversity was shown to increase due to fasting and probiotic intervention between the time points *T1* (before fasting), *T2* (during fasting) and *T3* (after 6-weeks of probiotic intervention ($P = 0.05$), and between the time points *T2–T3* ($P = 0.02$) [41]. In addition, the authors reported a significant increase in *Akkermansia* between the time points (T1–T3: $P = 0.03$, T1–T2: $P = 0.47$, T2–T3: $P = 0.47$).

In a pilot study by Özkul et al., [2019] [43], 9 subjects were included in a fasting protocol involving a 17 h fast/day for 29 days during the month of Ramadan. A significantly increased abundance of *A. muciniphila* and *B. fragilis* group was observed in all subjects after fasting when compared with baseline levels ($P = 0.004$ and 0.008, respectively). A similar Ramadan-based study involving nine subjects by Özkul et al., [2020] [45] demonstrated increased microbial richness ($P = 0.016$) and differing microbiota composition after 29 days vs before fasting ($P = 0.025$). *Butyricicoccus pullicaecorum* ($P = 0.002$), *Faecalibacterium prausnitzii* ($P = 0.003$), and *Roseburia* ($P = 0.02$) were the major species that showed a significant increase after the end of Ramadan fasting. *A.muciniphila* ($P = 0.005$) and *Bacteroides* spp ($P = 0.02$) were also significantly increased post fasting. This finding is similar to that of Remely et al., 2015 [41] in which the authors reported increased *A.muciniphila* in overweight subject post fasting. *Roseburia* has the ability to metabolise dietary components, generate SCFAs and influence the integrity of the intestinal epithelial barrier, whilst supporting immunity with its anti-inflammatory capabilities [51]. *F. prausnitzii* is an anti-inflammatory commensal bacterium that also produces SCFAs [52], whilst *B. pullicaecorum* has recently been shown to be one of the main butyrate-producing bacterial species with the ability to promote intestinal epithelial barrier integrity with its anti-inflammatory capabilities. Furthermore, in a 2018 study [53] in an antibiotic-disrupted microbiota, depleted *B. pullicaecorum* was observed.

Finally, in a 12-week pilot study by Gabel et al. 2020 [44], 14 obese adults were allocated to daily 8-hour feeding/16-hour fasting TRF intervention. At baseline, the two most common phyla were Firmicutes and Bacteroidetes, at 61.2% and 26.9%, respectively, of total abundance. The authors hypothesized that the proportion of Firmicutes would decrease and the proportion of Bacteroidetes would increase with TRF, and that these improvements would be associated with weight reduction. Whilst the results indicated that TRF reduced body weight ($P < 0.05$), TRF did not significantly alter the diversity or overall gut microbiota composition, with no significant changes in the abundance observed at the end of the trial [44]. These findings are contradictory to what has generally been observed with caloric restricted diets [54–56], which have all reported beneficial changes in gut microbiota composition and/or diversity. The authors concluded that in view of these previous findings, it is possible that the weight reduction (2%) and caloric restriction (20%) produced in their study was not sufficient and subsequently, did not impact the gut microbiota composition beneficially [44].

4. Conclusion

Chronic calorie restriction (CR) has been reported to elicit metabolic changes, including shaping the gut microbial community in humans [57] and mice [58]. Fecal microbiota of subjects exercising long-term CR may also be more diverse and richer than in individuals consuming Western-style diets [59–61]. Data suggests that chronic CR is, however, difficult

to adhere to [62] and thus IF could be a more feasible method for compliance. Although, it still needs to be established whether individuals can maintain IF for long terms or obtain the similar IF benefits observed in animal studies [63–65]. Furthermore, it is still not known which individuals would benefit the most from IF, which form of IF is the most effective, whether there are sex-based differences, or variations between healthy individuals and those present with certain disease. In addition, all the relevant studies have small sample sizes, a drawback that limits the generalizability of the observed effects. Therefore, future research should take these limitations into consideration for better understanding of the role of IF on gut health.

In conclusion, whilst current research is still in its infancy stage, findings of the available human studies, thus far, suggest that IF may play a potentially beneficial role in enhancing changes in gut microbiota composition and diversity. Fasting has been demonstrated to increase the abundance of protective, beneficial microbial families, such as Bifidobacteriaceae, Lactobacillaceae and Akkermanisaceae. The initial findings may be promising for the use of fasting to beneficially influence and alter the gut microbiota. However, further confirmation is warranted, with larger clinical trials with longer observation timeframes needed to replicate the available findings before clinical recommendations may be made on the role of IF in the gut health.

Conflicts of interest

KLW conceived the review idea and wrote the first draft of the manuscript. MA contributed to the article search and revision of the manuscript. The authors have no proprietary, financial, professional or other personal interest of any nature in any product, service or company. The authors alone are responsible for the content and writing of the paper.

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