Review Article

Association between *Faecalibacterium prausnitzii* Reduction and Inflammatory Bowel Disease: A Meta-Analysis and Systematic Review of the Literature

Yuan Cao, Jun Shen, and Zhi Hua Ran

*Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai Institution of Digestive Disease, Shanghai Inflammatory Bowel Disease Research Center, Shanghai 200127, China*

Correspondence should be addressed to Zhi Hua Ran; zhihuaran@vip.163.com

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Background. Laboratory data suggests a reduction of *Faecalibacterium prausnitzii* (*F. prausnitzii*) is confirmed both in fecal samples in inflammatory bowel disease (IBD) patients. Numerous observational studies have suspected dysbiosis, an imbalance between protective and harmful bacteria to be relevant to the etiology and pathogenesis of IBD.

Methods. Medline, EMBASE, Pubmed, and others were searched by 2 independent reviewers. Of 48 abstracts reviewed, 11 studies met our inclusion criteria (*N* = 1180). Meta-analysis was performed with Review Manager 5.2. Results. The bacterial count of *F. prausnitzii* in IBD patients was significantly lower (6.7888 ± 1.8875 log10 CFU/g feces) than healthy controls (7.5791 ± 1.5812 log10 CFU/g feces; *P* < 0.0001). The Standardization Mean Difference of *F. prausnitzii* in IBD patients was −0.94 (95% confidence interval [CI]: −1.07−−0.80). Subgroup analyses revealed a trend toward a greater effect for CD (SMD: −1.13, 95% CI: −1.32−−0.94) when compared to UC (SMD: −0.78, 95% CI: −0.97−−0.60). Conclusions. The abundance of *F. prausnitzii* was decreased in IBD patients compared with healthy controls. Furthermore, the reduction of *F. prausnitzii* and misbalance of the intestinal microbiota are particularly higher in CD patients with ileal involvement.

1. Introduction

IBD is suspected to arise from the interaction between the host’s genetic background, mucosal immunity, and the resident bacterial flora [1]. Genome-wide association studies (GWAS) have identified more than 160 host genetic variants. Many are related to human gut microbiota [2]. In patients with inflammatory bowel diseases (IBD), the composition and diversity of the microbiota are always altered [3]. The imbalance between potentially “beneficial” and potentially “harmful” bacteria, also called dysbiosis, plays a role in the pathogenesis of chronic mucosal inflammatory lesions of IBD [4].

*F. prausnitzii* belongs to the phylum of Firmicutes and is the major bacterium of the *Clostridium leptum* group. The Meta-analysis of the Human Intestinal Tract project have shown that *F. prausnitzii* is one of the most abundant anaerobic bacteria in the human gut microbiota, with a proportion of around 5% of total bacteria in faeces [5]. *F. prausnitzii* plays an important role in providing energy to the colonocytes and maintaining the intestinal health [6]. Furthermore, there is emerging laboratory evidence illustrating a strong anti-inflammatory effect of *F. prausnitzii* both in vitro and in vivo. And deficiency of *F. prausnitzii* might provoke and enhance inflammation [7]. Specially, a significant inverse correlation between disease activity and the count of *F. prausnitzii* was found in UC patients, even with quiescent disease [8]. The depletion of *F. prausnitzii* was observed in patients with untreated CD but not in the patients with chronic diarrhea, suggesting a relationship in the pathomechanisms of CD [9]. Finally, a diminished prevalence and abundance of *F. prausnitzii* are revealed in the fecal samples of patients with...
IBD. The F. prausnitzii level was much lower when the disease activity increased [10].

To further investigate the possible association between F. prausnitzii reduction and IBD, we conducted a meta-analysis and systematic review to estimate the relative risk of F. prausnitzii reduction in patients with and without IBD. Given the laboratory data previously cited, we hypothesized a relationship between F. prausnitzii reduction and IBD.

2. Materials and Methods

2.1. Search Strategy. This review was performed according to the standard guidelines for meta-analyses and systematic reviews of observational studies [11]. To find relevant articles for this review, we searched the following databases (from inception to November 2013): EMBASE, MEDLINE, Google Scholar, Pubmed, ACP Journal Club, the Cochrane Central Register of Controlled Trials, CMR, DARE, and HTA. The search strategy used free-text words to increase the sensitivity of the search. The following search terms were used: “inflammatory bowel disease,” “Crohn’s disease,” “ulcerative colitis,” “IBD,” “UC,” “CD,” “Faecalibacterium prausnitzii,” “F. prausnitzii,” and “FP” Boolean operators (AND, OR, NOT) were used to widen and narrow the search results. The titles and abstracts from the search results were examined for potential inclusion. Also, the references from selected articles were examined as further search tools.

2.2. Study Selection. For inclusion in the systematic review, a study had to meet the following criteria established by the study team: (1) F. prausnitzii counts measured by polymerase chain reaction-denaturing gradient gel electrophoresis (PCR-DGGE), terminal restriction fragment length polymorphism (T-RFLP), or fluorescence in situ hybridization (FISH), (2) studies of human, (3) inclusion of a control group, (4) IBD and control groups were similar in age and sex and from the same catchment area, and (5) data were reported that were sufficient to calculate F. prausnitzii reduction in both the IBD and control groups. Studies were excluded if they used data from a previously published study.

2.3. Data Extraction. To reduce reporting error and bias in data collection, 2 independent reviewers extracted data from selected studies using standardized data extraction forms. These forms, created by the study team, included the (a) title, (b) authors, (c) journal, (d) year of publication, (e) study design, (f) inclusion and exclusion criteria, (g) methods by which IBD was diagnosed, (h) methods by which F. prausnitzii reduction was diagnosed, (i) number of patients with ulcerative colitis (UC), (j) number of patients with Crohn’s disease (CD), (k) number of patients in the control group, (l) reported previous use of antibiotics, probiotics, or prebiotics in the IBD and control groups, and (m) reported previous use of steroids, 5-aminosalicylates (5-ASAs), and tumor necrosis factor-alpha (TNF-α) antibody medications in the IBD group. Studies were excluded if participants had used steroids, 5-ASAs, TNF-α antibody antibiotics, probiotics, or prebiotics in the last month preceding fecal sampling as this could influence the intestinal microbiota. If needed, authors were contacted regarding specific questions relating to their study. The independent reviewers conferred after data extraction was complete, discrepancies were identified, and review of the relevant article led to consensus.

2.4. Statistical Analysis. The primary outcome of this analysis was the Standardization Mean Difference (SMD) of F. prausnitzii counts in IBD versus controls. Std. mean difference was used to describe the counts of the F. prausnitzii in IBD patients versus the controls. We calculated the SMD with a 95% confidence interval (CI) based on a random-effects model as described by Mantel-Haenszel. Meta-analysis was performed with the Review Manager 5.2. Analysis with a funnel plot used to assess publication bias. An F statistic was used to measure the proportion of inconsistency in individual studies that could not be explained by chance. Any heterogeneity identified would prompt subgroup analysis in an attempt to explain these findings.

2.5. Assessment of Study Quality. Each study chosen for review was carefully assessed for study quality by the study team. Study quality was assessed using the following criteria: (1) study design, (2) method of IBD diagnosis, (3) method of patient enrollment (consecutive versus selected), (4) method of F. prausnitzii counts measurement, and (5) whether F. prausnitzii reduction was the primary or secondary outcome of the study.

3. Results

3.1. Search Results. Our initial search strategy yielded 58 potential articles for inclusion. After detailed analysis of selected articles, 27 articles were reviewed in detail. Subsequently, 16 articles did not meet inclusion criteria [1, 21–35]. The reasons for exclusion included: 12 studies did not provide data on F. prausnitzii counts [1, 21–23, 25, 29–35]. 2 studies...
Table 1: Characteristics of the included studies.

| Author            | Year | Location | Single versus multicenter | \( n \), total | \( n \), IBD (CD/UC) | \( n \), control | Control composition | Mean age, IBD (CD/UC) | Mean age, control |
|-------------------|------|----------|----------------------------|----------------|---------------------|----------------|---------------------|---------------------|------------------|
| Machiels et al.   | 2013 | Belgium  | Single                     | 214            | 0/127               | 87             | Healthy controls    | 43                  | 41.5             |
| Varela et al.     | 2013 | Spain    | Single                     | 176            | 0/116               | 31             | Healthy controls    | 40                  | 32               |
| Swidsinski et al. | 2008 | Germany  | Single                     | 422            | 82/105              | 32             | Healthy controls    | 35/41               | 40               |
| Dörffel et al.    | 2012 | Germany  | Single                     | 171            | 50/0                | 25             | Healthy controls    | 39                  | 48               |
| Vermeiren et al.  | 2012 | Belgium  | Single                     | 12             | 0/6                 | 6              | Healthy controls    | Not reported         | Not reported      |
| Joossens et al.   | 2011 | Belgium  | Single                     | 207            | 68/0                | 55             | Healthy controls    | Not reported         | Not reported      |
| Wang et al.       | 2013 | China    | Single                     | 76             | 21/34               | 21             | Healthy controls    | Not reported         | Not reported      |
| Jia et al.        | 2010 | UK       | Single                     | 73             | 20/14               | 18             | Healthy controls    | Not reported         | Not reported      |
| Sokol et al.      | 2009 | France   | Single                     | 133            | 22/13               | 27             | Healthy controls    | 37/40               | 36               |
| Andoh et al.      | 2012 | Japan    | Multicenter                | 188            | 67/0                | 121            | Healthy controls    | 30                  | 32               |
| Willing et al.    | 2009 | Sweden   | Single                     | 20             | 6/0                 | 6              | Healthy controls    | Not reported         | Not reported      |

IBD: inflammatory bowel disease; CD: Crohn’s disease; UC: ulcerative colitis.

Table 2: Quality assessment of the included studies.

| Author            | \( F. prausnitzii \) counts | IBD diagnosis | Study type | Patient enrollment | Outcome | Samples |
|-------------------|-------------------------------|---------------|------------|--------------------|---------|---------|
| Machiels et al.   | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Varela et al.     | RT-PCR                        | Colonoscopy and histology | Retrospective | Not reported       | Primary | Stools  |
| Swidsinski et al. | FISH                          | Colonoscopy   | Retrospective | Not reported       | Primary | Stools  |
| Dörffel et al.    | FISH                          | Colonoscopy   | Retrospective | Not reported       | Primary | Stools  |
| Vermeiren et al.  | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Joossens et al.   | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Wang et al.       | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Biopsies|
| Jia et al.        | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Sokol et al.      | RT-PCR                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Andoh et al.      | T-RFLP                        | Not reported  | Retrospective | Not reported       | Primary | Stools  |
| Willing et al.    | RT-PCR                        | Colonoscopy   | Retrospective | Not reported       | Primary | Biopsies|

only provided data for pediatric patients [24, 28]. 2 studies were animal studies [26, 27]. Therefore, 11 studies [8, 9, 12–20] with 1180 patients fulfilled the inclusion criteria for the review (Figure 1). 3.2. Study Characteristics. The characteristics of the included studies are summarized in Tables 1 and 2. The results of each study are in Table 3. \( F. prausnitzii \) counts were expressed as log10 values per gram feces. The largest and earliest study examining the relationship between \( F. prausnitzii \) reduction and IBD was conducted in Germany by Swidsinski et al. [13]. The authors investigated sections of paraffin-embedded punched fecal cylinders using fluorescence in situ hybridization (FISH). \( F. prausnitzii \) with high concentration was counted within a \( 10 \times 10 \mu m \) area of the microscopic field representative of the region of interest. \( F. prausnitzii \) with uneven distribution or overall low concentrations was enumerated within larger areas of \( 100 \times 100 \mu m \).

8 of the included studies confirmed the differences in the presence or intensity of \( F. prausnitzii \) counts after denaturing gradient gel electrophoresis (DGGE) by real-time PCR (RT-PCR) [8, 12, 14–18, 20]. \( F. prausnitzii \) cannot be cultured owing to its requirement for a complex anaerobic environment [19]. By RT-PCR, they were able to amplify, clone, and sequence the bacterial 16S ribosomal RNA genes and analyze the fecal samples individually to avoid the possible error [36]. Three of the included studies commented on the activity of IBD and \( F. prausnitzii \) counts. Wang et al. found sharply decreased \( F. prausnitzii \) in the feces of active CD and UC patients [16]. Sokol et al. and Andoh et al. reported lower counts of \( F. prausnitzii \) in active CD patients compared to CD patients in remission [18, 19].
1 of the included studies examined the *F. prausnitzii* counts before and after treatment by an elemental diet [17]. It suggests recovery following elemental diet is attributed to lower levels of gut flora.

1 of the included studies reported the relationship between the maintenance of clinical remission and the recovery of the *F. prausnitzii* population after relapse Varela et al. found low counts of *F. prausnitzii* were associated with less than 12 months of remission and more than 1 relapse/year [12].

### 3.3. Meta-Analysis of SMD

Overall, the bacterial count of *F. prausnitzii* in IBD patients was significantly lower (6.7888 ± 1.8875) log10 CFU/g feces than healthy controls (7.5791 ± 1.5812) log10 CFU/g feces; *P* < 0.0001. The SMD of *F. prausnitzii* in IBD patients was −0.94 (95% confidence interval [CI]: −1.07−−0.80) (Figure 2). Subgroup analyses revealed a trend toward a greater effect for CD (SMD: −1.13, 95% CI: −1.32−−0.94) when compared to UC (SMD: −0.78, 95% CI: −0.97−−0.60). There was significant heterogeneity in the included studies (I² = 96%). Furthermore, analysis of the funnel plots for publication bias suggested a possible bias against small studies demonstrating high SMD (Figure 3).

### 4. Discussion

Our systematic review and meta-analysis of the literature has identified recent studies examining the relationship between *F. prausnitzii* reduction and IBD. The majority of recent studies find a higher rate of *F. prausnitzii* reduction in IBD patients as compared to controls. All of the 11 included studies found significantly lower *F. prausnitzii* counts in IBD patients versus controls. Our meta-analysis suggests a possible link with the reduction of *F. prausnitzii* and misbalance of the intestinal microbiota and IBD patients, especially CD patients with ileal involvement. The levels of *F. prausnitzii* were extremely low in two studies [19, 28]. Wang et al. took biopsies samples from active CD patients and found extremely lower *F. prausnitzii* counts compared to stools [28]. Andoh et al. demonstrated a difference in gut microbiota of the Japanese population, suggesting that environmental factors such as sanitation, diet, hygiene, and ethnicity were important for shaping the gut microbiota [19]. However, significant heterogeneity and the possibility of publication bias limit our certainty in this association. Furthermore, Hansen et al. challenged the current model of a protective role for *F. prausnitzii* in CD [24]. They reported an increase in mucosal *Faecalibacterium* in pediatric CD patients compared with controls, which suggested a more dynamic role for this organism than previously described in adult IBD. It is possible that the microbial signature of pediatric IBD is distinct from adult disease. Furthermore, the early host and microbiota response to IBD may induce proliferation of *F. prausnitzii* to reverse the inflammatory change, which still remains to be explained.

Mechanistic theories of microbial etiopathogenesis between the possible protective benefit of *F. prausnitzii* against IBD have been proposed. Duncan et al. demonstrated that the major end products of glucose fermentation by *F. prausnitzii* strains are substantial quantities of butyrate [37]. Butyrate plays a major role in gut physiology, protection against pathogen invasion, and modulation of immune system [38]. Butyrate is the primary energy source for intestinal epithelial cells, which are fundamental elements for the maintenance of barrier integrity [26]. Therefore, butyrate may contribute to the anti-inflammatory effect. Additionally, butyrate may inhibit inflammatory response through inhibition of histone deacetylase activity, resulting in suppression of NF-κB activity and hyperacetylation of histones [12]. Furthermore, Himmel et al. found that *F. prausnitzii* could induce relatively low amounts of IL-12 and large amounts of IL-10 and Tregs in epithelial and PBMC models to restrain the progression of inflammation [39]. While Sokol et al. reported that *F. prausnitzii* led to significantly lower IL-12 and IFN-γ production levels

### Table 3: Study results.

| Author          | IBD patients (CD/UC) log 10 copies/g | Healthy controls (CD/UC) log 10 copies/g | *P*   |
|-----------------|--------------------------------------|------------------------------------------|-------|
| Machiels et al. [8] | 0/(10.95 ± 1.41)                     | 11.72 ± 1.08                            | <0.0001 |
| Varela et al. [12] | 0/(8.02 ± 0.57)                      | 8.90 ± 0.37                             | <0.0001 |
| Swidsinski et al. [13] | (9.75 ± 7.97)/(10.14 ± 10.02)        | 10.17 ± 9.65                            | <0.0001 |
| Dörfl et al. [9]     | (9.06 ± 9.33)/0                      | 10.21 ± 9.94                            | <0.001  |
| Vermeiren et al. [14] | 0/(5.56 ± 0.83)                      | 6.63 ± 0.95                             | 0.07   |
| Joossens et al. [15] | (9.44 ± 1.85)/0                      | 10.97 ± 1.25                            | <0.0001 |
| Wang et al. [16]     | (0.03 ± 0.06)/(0.23 ± 0.51)          | 1.40 ± 1.06                             | <0.0001 |
| Jia et al. [17]      | (5.71 ± 5.34)/(5.93 ± 5.87)          | 5.93 ± 5.83                             | <0.05  |
| Sokol et al. [18]    | (8.81 ± 0.52)/(8.70 ± 0.63)          | 10.4 ± 0.2                              | 0.0004 |
| Andoh et al [19]     | (0.40 ± 0.09)/0                      | 0.81 ± 0.04                             | <0.0001 |
| Willing et al. [20]  | (0.40 ± 0.89)/0                      | 8.72 ± 2.49                             | <0.001  |
and higher secretion of IL-10 in vitro peripheral blood mononuclear cells [26].

The data on the incidence of F. prausnitzii reduction and IBD found in the literature has several limitations. Most of the studies did not comment on the participants’ previous history of treatment such as antibiotics, probiotics, or prebiotics, which may influence the intestinal microbiota. It is therefore possible that study participants had been treated for dysbiosis prior to entering the study, thereby producing a false F. prausnitzii reduction. Additionally, we did not evaluate confounding factors including diet and smoking in our study, even though these factors might reduce F. prausnitzii levels and faecal butyrate values [40]. Furthermore, some of the included studies did not clearly identify the criteria for the IBD diagnosis. Few commented on personal review of the endoscopic findings or histology. Also we did not relate the differences in microbiota to geography and ethnicity. Lastly, most studies were performed at a single medical center.

Future studies should address these limitations. After confirming the diagnosis of IBD through the endoscopic and histological findings, PCR-DGGE, T-RFLP, or FISH for F. prausnitzii counts would be initiated. In patients found to have F. prausnitzii reduction, probiotics or prebiotics may be used to restore the “ecological balance” of intestinal microbiota. Dörffel et al. reported rifaximin was associated with an increased level of F. prausnitzii [9]. Other specific treatments such as infliximab and a high-dose cortisol therapy were shown to reverse the depletion of F. prausnitzii [13]. The mechanism for the inverse association between F. prausnitzii reduction and the initiation and perpetuation of inflammatory bowel disease has yet to be defined. Healthy controls who are age- and sex-matched to the IBD group would be selected from the same area as the IBD group and tested for F. prausnitzii by the same method. In both groups, a thorough history examining previous treatment such as antibiotics, probiotics, or prebiotics, steroids, 5-aminosalicylates (5-ASAs), and tumor necrosis factor alpha (TNF-α) antibody would be obtained. Prideaux et al. reported that regardless of ethnicity or geography, Crohn’s disease resulted in reduced bacterial diversity. However, in ulcerative colitis, diversity was reduced in Chinese subjects only. It suggested that ethnicity might also play an important role in the pathogenesis of IBD [41].
5. Conclusions
In summary, our meta-analysis and systematic review suggest a possible protective benefit of *F. prausnitzii* against the development of IBD. However, significant variation among the studies and the possibility of publication bias limit the certainty of this association. Therefore, further treatment such as probiotics or prebiotics to increase the levels of *F. prausnitzii* in IBD lead to attempts. If *F. prausnitzii* is found to indeed protect against IBD, we can approach the treatment such as supplementing the microorganisms that produce butyric acid.

Conflict of Interests
The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors’ Contribution
All of the authors contributed equally to the study.

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