Gut Microbiome in the Populations

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The gut microbiota is emerging as a promising target for the management or prevention of inflammatory and metabolic disorders in humans. Many of the current research efforts are focused on the identification of specific microbial signatures, more particularly for those associated with obesity, type 2 diabetes, and cardiovascular diseases. The Firmicutes/Bacteroidetes ratio is frequently cited in the scientific literature as a healthy hallmark. The aim of the present review was to discuss the validity of this potential marker, based on the great amount of contradictory results reported in the literature. We re-analyzed the 16S rRNA gene sequence data from nine published studies to allow direct comparisons among their Firmicutes/Bacteroidetes ratio. We observed that the relative abundance of the Firmicutes and Bacteroidetes phyla is highly variable between subjects from a same population. This is probably due to many lifestyle-associated factors including diet, physical activity, food additives and contaminants, antibiotic consumption, physical activity, among others that influence the composition of the microbiota in the gastrointestinal tract. This could explain the contradictory results observed when comparing the microbiota between normal-weight and obese subjects, making it difficult to associate the Firmicutes/Bacteroidetes ratio with a determined health status.

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1. Introduction

To assess the relevance of the Firmicutes/Bacteroidetes ratio as a taxonomic signature of healthy, we used data from microbiota composition from nine published studies carried out in seven countries (USA, United Kingdom, India, Pakistan, Chile, Argentina, and Colombia) and including 728 healthy subjects. High-throughput 16S rRNA gene sequence data from previous studies, corresponding to V3–V4 or V4 hypervariable regions and generated by the Illumina MiSeq Platform, were collected (Table 1). To allow direct comparisons among sequences from different studies, all the reads were filtered using the DADA2 pipeline, then aligned and trimmed to the same length (80 bp) using Mothur, followed by the taxonomic identification using the DADA2 pipeline based on the identification of Exact Sequence Variants [1].

2. Heterogeneity

We considered that a sequence length of 80 bp was adequate for analyzing the microbial communities at the Phylum level (less than 0.02% of the reads were not assigned). Using a unique pipeline and reads generated by a same sequencing platform, we expected to eliminate all bias generated by sequencing and bioinformatic tools, as commented above. Subsequently, we analyzed the relative abundance of Firmicutes and Bacteroidetes and their ratio. Overall, the data indicate that the abundance of Firmicutes in the gut microbiota of healthy individuals varies between 11% to 95% and that of Bacteroidetes between 0.6% to 86.6% (Figure 1). Considering this variability, it seems difficult to observe significant changes for these two phyla in obese people. In their meta-analysis, Finucane et al. observed that the variations for both Firmicutes and Bacteroidetes abundance were much larger among studies than between lean and obese individuals within any study [2]. In agreement with these findings, we recently observed a high variability of both Firmicutes and Bacteroidetes, between 25%–67% and 4%–64% respectively, in the fecal microbiota of young healthy Chilean volunteers, despite rigorous inclusion criteria including the control of anthropometrical and biochemical markers, biomarkers of systemic and colonic inflammation (plasma IL-6 and high sensitivity C-reactive protein and fecal calprotectin, respectively), and dietary intake [3]. Again, the heterogeneity of the diet is probably the main factor explaining such variations in the healthy population and this might eventually make difficult the identification of specific microbial signatures. For example, on the one hand, Wu et al. showed in 100 healthy individuals with known dietary habits that the microbiota from those consuming protein and fat-based diets were enriched with Bacteroides whereas that from those consuming carbohydrate-based diets were enriched with *Prevotella* [4], results from which these authors formulated the concept of “enterotype”. On the other hand, Balamurugan et al. compared the gut microbiota from a tribal population (Malayalis) living in the northern part of Tamil Nadu (India) that consumed a restricted diet due to cultural and religious beliefs, with that from healthy villagers from the same region as controls. Both populations exhibited a high abundance of Firmicutes (85.9% and 63.5%, for the Malaiyalis and controls, respectively) and low abundance of Bacteroidetes (2.65% and 0.45%, respectively), resulting in very high Firmicutes/Bacteroidetes ratio (34.0 and 92.9, respectively), though the individuals from both populations were lean [5]. Although the Malaiyalis population had a restricted, homogenous diet, a high variation in the proportions of both Firmicutes and Bacteroidetes was observed, confirming that factors other than diet influence this ratio.

Table 1. Description of studies considered in this study for evaluating the variability of the Firmicutes and Bacteroidetes.

Country	Accession Number	Effective &	Age (Years)	BMI (kg/m^2)	Sequencing Platform	Hypervariable region	Ref
							[6]
USA	PRJNA290926	68		22.0 ±1.9		V4 region	

			53.1 ±10.8		MiSeq Illumina		
UK[1]	PRJEB6702	230	61.2 ±10.1	22.4 ±1.8	MiSeq Illumina	V4 region	[7]
UK[2]	PRJEB6705	189	60.0 ±9.5	22.3 ±1.8	MiSeq Illumina	V4 region	[7]
Pakistan	PRJNA554535	20	37.7 ±12.1	22.1 ±3.1	MiSeq Illumina	V3–V4 region	[8]
India	PRJEB28290	80	Range 18–55 *	23.9 ±3.2*	MiSeq Illumina	V3–V4 region	[9]
Colombia	PRJEB33360	83	52.1 ±18.6	25.1 ±3.9	MiSeq Illumina	V3–V4 region	[10]
Chile	PRJEB16755	32	25.0 ±3.9	22.5 ±1.6	MiSeq Illumina	V3–V4 region	[3]
Argentin[1]	PRJNA503303	28	35.2 ±8.3*	23.9 ±3.4*	MiSeq Illumina	V3–V4 region	[11]
Argentin[2]	Personal data**	28	40.2 ±4.4	22.6 ±2.0	MiSeq Illumina	V4 region	Personal data

[&] Effective obtained after the bioinformatic processing; * Data obtained from publishing data (not-recalculated due to the lack of individual data); ** Data submitted for publication, provided by Susan Pesoa, co-author of this work; UK [1], UK [2], Argentina [1] and Argentina [2] are studies reported in the Figure 1.

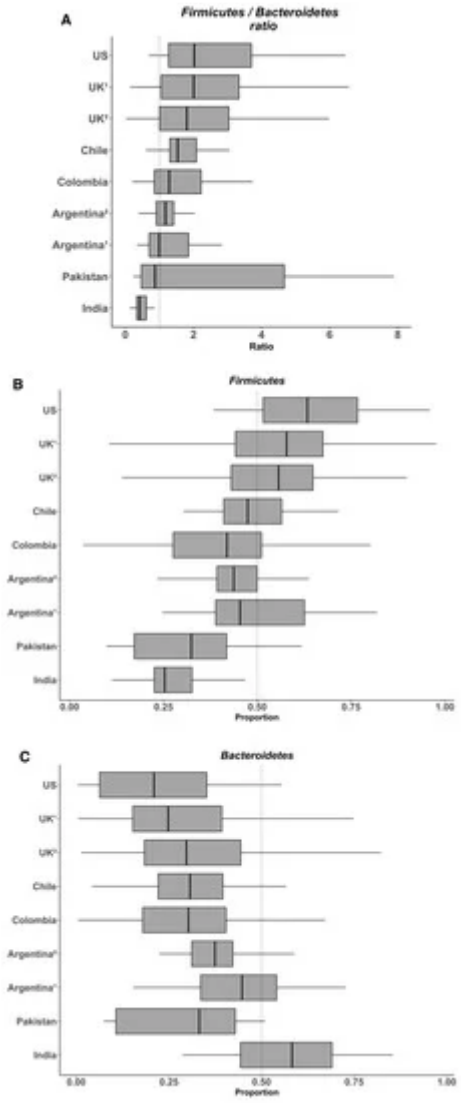

Figure 1. Variability in the Firmicutes/Bacteroidetes ratio (**A**) and the relative abundances of Firmicutes (**B**) and Bacteroidetes (**C**) in the gut microbiota from several healthy populations. Box plots were constructed using R. In the box and whisker plots, the line shows the median; the box, the interquartile range; and the whiskers, the highest and lowest values.

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