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Original Article

An Analysis of Gut Dysbiosis in Obesity, Diabetes, and Chronic Gut Conditions

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Abstract

Introduction: Gut dysbiosis is an imbalance in the microbial communities of the intestine and has been associated with numerous chronic diseases. **Objectives:** We aimed to compare gut dysbiosis within and across various disease states (Crohn's disease [CD], colorectal cancer [CRC], irritable bowel syndrome [IBS], and type 2 diabetes mellitus [T2DM], and obesity). **Materials and Methods:** Assessing comparative studies which examined levels of bacterial phyla in cases and controls. PubMed and Web of Science were searched to identify relevant studies, in which human fecal samples were used to analyze microbial flora. **Results:** Twenty-one studies were included, which met inclusion and exclusion criteria. Three studies were included assessing IBS, which found a decrease in *Bacteroidetes* in the IBS population, but inconsistent findings for other phyla. Six studies were included assessing obesity, and no consistent patterns emerged. Five studies were included examining T2DM, which found a consistent decrease in the *Firmicutes*/*Bacteroidetes* ratio in cases as compared to controls. No patterns were found for other phyla. Three studies were included examining CD, and five examining CRC. **Conclusions:** No consistent patterns were found for either of these diseases. While some patterns were found in bacterial phyla distribution, there were few commonalities, even in same-system disorders. However, uncovering underlying dysbiosis patterns shows great promise in furthering the understanding of disease pathogenesis and the potential for new therapeutic and diagnostic interventions. Further systematic reviews and well-controlled studies are warranted.

Keywords: Diabetes, dysbiosis, gastrointestinal microbiome, gut dysbiosis, microbiota, obesity

Introduction

The gastrointestinal (GI) tract, home to a diverse ecosystem of over one hundred trillion bacteria, viruses, fungi, and archaea, is the most colonized organ of the human body.[1] The gut microbiome, consisting of all microbes inhabiting the intestines,

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has been well characterized in recent years. Improved sequencing methods such as 16S rRNA gene-based approaches and analytic techniques have revealed a complex and diverse array of microbial functions related to human health, as well as tremendous interindividual and intraindividual variations in the composition of the gut microbiome.[2] This makes it difficult to precisely define a "healthy" microbiome. Indeed, the richness and diversity of the microbiome, as opposed to the presence or absence of particular species, has been associated with better overall health.[3-5] Despite this variability, the gut microbiome has been consistently demonstrated to serve a variety of important developmental and physiological functions, including defense against pathogenic colonization, immune regulation, maintenance of epithelial barrier integrity, and metabolism.[1]

Given the importance of the intestinal microbiome to human health, dysbiosis – a deviation in microbial composition from a healthy state – has been associated with a variety of diseases, including Crohn's disease (CD), irritable bowel syndrome (IBS), type 2 diabetes mellitus (T2DM), obesity, colorectal cancer (CRC), and many others. However, it remains unclear whether dysbiosis plays a causal role in disease pathogenesis or results from it. As such, this relationship has been a recent focus of research attempting to better understand factors related to disease development and progression.

Context

Dysbiosis and Crohn's disease

CD is a type of inflammatory bowel disease that can cause chronic and relapsing inflammation anywhere in the GI tract. Although the etiology of CD is likely a complex and multifactorial combination of genetic and environmental factors, intestinal dysbiosis has been linked to its pathogenesis.[5] Specifically, a dysregulated response to commensal gut microbes is believed to contribute to the proinflammatory state of Crohn's GI tract.[5] Several studies have reported decreased microbial diversity in CD patients compared to healthy controls, particularly within the *Firmicutes*.[5-7] Frank *et al.* also noted decreased abundance of *Firmicutes* and *Bacteroidetes* compared to controls.[8] However, research investigating a potential causal role for dysbiosis in CD has been inconclusive, and no clear pathogenetic mechanism related to the microbiome has been elucidated.[3]

Dysbiosis and irritable bowel syndrome

IBS is a common functional intestinal disorder characterized by recurring bouts of abdominal pain or discomfort, as well as changes in stool form and frequency.[9] While the etiology of IBS remains largely unknown, the gut microbiome has recently been proposed to play a pathogenic role.[10] This has been supported by studies documenting symptomatic relief of IBS following antimicrobial treatments such as antibiotics.[9] Studies of the fecal microbiome of IBS patients have also shown it to be significantly different to that of healthy controls, with studies reporting decreases in *Bacteroidetes* and *Actinobacteria*, as well as increases in *Firmicutes* and *Proteobacteria* compared to controls.[11] However, while an association between intestinal dysbiosis and IBS has been demonstrated, associated compositional changes have not been consistently characterized.

Dysbiosis and type 2 diabetes mellitus

T2DM is a metabolic disorder characterized by insulin resistance and associated with obesity. Recent advances concerning the role of the gut microbiome in metabolism and control of body weight, particularly related to obesity, have implicated intestinal microbial dysregulation as a potential etiological factor for T2DM. Dysbiosis leading to increased intestinal monosaccharide uptake has been associated with the development of insulin resistance[12] and an increased ratio of *Bacteroidetes* to *Firmicutes* has been significantly correlated to reduced glucose tolerance.[13] Furthermore, studies have linked increased amounts *Bacteroidetes* and *Proteobacteria* to lipopolysaccharide-induced endotoxemia[14] which is involved in the development of T2DM.[15] A clear association between T2DM and the intestinal microbiome has been demonstrated[13] but more research is necessary to determine the exact nature of this relationship.

Dysbiosis and obesity

Obesity is now considered a global health epidemic by the World Health Organization,

affecting >500 million people worldwide.[3] Dysbiosis has been implicated in the development of obesity, particularly due to the role of the intestinal microbiome in metabolism. Studies conducted in obese mice[16] and humans[17] have demonstrated increases in *Firmicutes* and proportionate decreases in *Bacteroidetes*; increases in *Bacteroidetes* were also associated with weight loss.[17] While an increased *Firmicutes*/*Bacteroidetes* ratio has been associated with obesity by Ley *et al*. [16,17] others, such as Duncan *et al*.,[18] reported contradictory findings. However, rodent studies have induced weight gain through the transfer of feces from genetically obese (ob/ob) mice,[19] demonstrating a clear role for the composition of the gut microbiome in obesity.

Dysbiosis and colorectal cancer

CRC is a highly common form of cancer that causes approximately 500,000 deaths worldwide every year[20] and has been linked to intestinal dysbiosis. Diet, particularly consumption of foods high in saturated fat such as red and processed meat, has been identified as a significant risk factor[21] for the development of CRC. Diet has also been demonstrated to affect the composition of the gut microbiome, leading to shifts that could potentially influence CRC risk.[22] Shifts in microbial composition associated with the aging process have also been implicated in CRC pathogenesis; older age is associated with reduced numbers of anti-inflammatory bacteria such as *F. prausnitzii* and *Roseburia intestinalis* that are protective against CRC.[23]

With the recent development of metagenomic sequencing technologies, the specific compositions of the gut microbiome in both healthy and pathological states have been characterized. However, although the nature of dysbiosis within several diseases has been previously characterized, few studies have directly compared changes in microbial composition across several disease states. As such, the purpose of this study was to compare and contrast the intestinal microbial composition in various disease states to determine whether there were any dysbiosis patterns associated with particular pathological states.

Materials and Methods

This is a narrative review of the literature and comparative analysis. PubMed and Web of Science were searched, using keywords/search phrases such as "bacterial composition (disease)," "microbiome composition (disease)," "gut microbiome (disease)" etc., Inclusion criteria were as follows: (1) conducted in humans, (2) determined bacterial composition from fecal samples, and (3) reported percentage compositions of bacterial phyla. Exclusion criteria were as follows: (1) Use of mucosal biopsies, (2) studies lacking a control group, and (3) pediatric studies. Studies using mucosal biopsies to determine microbial composition were excluded as variability in the biopsy source makes comparisons difficult due to differences in bacterial composition throughout the GI tract.[4] Pediatric studies were excluded due to the potential for differences in bacterial composition related to age as opposed to the disease state.[4] Bacterial compositions were noted and described in terms of phyla, and if genera were reported, percentages were converted to phyla.

Results

After applying the inclusion/exclusion criteria, 21 studies were ultimately included in the final analysis. Key characteristics of each included study, including findings, are summarized in Tables 1-4 and appraised below.

Changes within disease states

Obesity

Six studies were included investigating changes in fecal microbiota in obesity.[24-29] Schwiertz *et al*.[25] found a significant decrease in *Firmicutes* in obese patients. Regarding Bacteroidetes, three studies found a decrease in obese patients [24,26,28] and Schwiertz *et al*.[25] found an increase. Actinobacteria were found to be increased in the obese population by Turnbaugh *et al*.[24] [Table 1].

Type 2 diabetes mellitus

Five studies were included which investigated fecal microbiota changes in T2DM.[29-33] Regarding *Firmicutes*, Larsen *et al*.[30] found a decrease in T2DM cases, whereas Sedighi *et al*.[32] found an increase. Sedighi *et al*.[32] was the only study to report for Actinobacteria for which they found a

Table 1: Study characteristics and key findings in obesity, prediabetes and diabetes

Author (year of publication)	Disease studied (cases/controls)	Findings
Turnbaugh *et al*. (2009)	Obesity (54/54)	Bacterial abundance by phylum: Case/control: *Firmicutes*: 84.6%/83.5%, Bacteroidetes: 7.58%/11.44% (P<0.05), *Actinobacteria*: 4.418%/2.78% (P<0.05). F/B: 11.16/7.30 Also found a significant reduction in diversity in obese patients
Schwiertz *et al*. (2009)	Obesity (33/30)	Bacterial abundance by phylum: Case/control: *Firmicutes*: 51%/73.1% (P<0.05), *Bacteroidetes*: 45%/22.9% (P<0.05), F/B: 1.13/3.19
Kasai *et al*. (2015)	Obesity (33/23)	Bacterial abundance by phylum: Case/control: *Firmicutes*: 48.74%/49.5% NS, *Bacteroidetes*: 23.28%/35.44% (P<0.05), *Proteobacteria*: 0.91%/1.2%, *Fusobacteria*: 1.58%/0.07%, *Actinobacteria*: 3.55%/5.02%, F/B: 2.09/1.40 (P<0.05)
Louis *et al*. (2016)	Obesity (16 pre/post intervention)	No significant changes were detected at the phylum level before and after weight-loss intervention (numbers not reported), F/B ratio higher in obese patients with some metabolic syndrome compared to "healthy" obese (P<0.05)
Armougom *et al*. (2009)	Obesity (20/20)	Copies/gram feces: Case/control: *Bacteroidetes*: 0.4E10/2.6E10 (P<0.05) No statistically significant change in Firmicutes overall
Furet *et al*. (2010)	Obesity (23/13) & T2DM (7/13)	No differences overall at phylum level, only for specific genera (both obesity and T2DM)
Larsen *et al*. (2010)	T2DM (10/10)	Bacterial abundance by phylum: Case/control: *Firmicutes*: 36.91%/56.4% (P<0.05), Bacteroidetes: 43.8%/33.2%, Proteobacteria: 3.54%/3.54%, F/B: 0.84/1.11
Wu *et al*. (2010)	T2DM (28/17)	Bacterial abundance by phylum: Case/control: *Firmicutes*: 10.8%/17.7%, *Bacteroidetes*: 82.1%/76.5%, *Proteobacteria*: 3.6%/5.9%, *Actinobacteria*: 3.6%/0%, F/B: 0.13/0.23. Statistical significance not reported
Sedighi *et al*. (2017)	T2DM (18/18)	Copy numbers/gram of stool: Case/control: *Firmicutes*: 6.65E+06/1.22E+06 (P<0.05), *Actinobacteria*: 1.82E+07/5.24E+08 (P<0.05), *Bacteroidetes*: 1.01E+07/7.66E+06, *Fusobacteria*: 6.81E+06/6.78E+06 (P<0.05)
Lambeth *et al*. (2015)	T2DM (14 diabetes/20 prediabetes/15 control)	Bacterial abundance by Phylum: Diabetic/pre-diabetic/control Firmicutes: 34.3%/38.2%/39.7%, Bacteroidetes:53.5%/59%/53.9% F/B: 0.64/0.65/0.74. No significant differences were found at the Phylum level

T2DM: Type 2 diabetes, NS: Not significant

decrease in T2DM cases. Wu *et al*.[31] did not report statistical significance for bacterial abundances, making their results difficult to interpret. All studies had a reduced F/B ratio in cases as compared to controls, but statistical significance was not always available [Table 1].

Irritable bowel syndrome

Three studies were included investigating fecal microbiota changes in patients with IBS.[34-36] Bacteroidetes were found to be significantly decreased in the IBS population by Jalanka-Tuovinen *et al*.[36] and Rajilic-Stojanovic *et al*.[35] Jalanka-Tuovinen *et al*.[36] found also found a significant decrease in Actinobacteria in the IBS population, which was not reported by other studies [Table 2].

Colorectal cancer

Five studies reported changes to bacterial composition in CRC.[37-41] Regarding Bacteroidetes, Wang *et al*.[37] found a decrease in the CRC population, whereas Zeller *et al*.[40] found an increase. *Firmicutes* were found to be increased in the CRC population by Zeller *et al*.[40] and Allali *et al*.[39] Proteobacteria were found to be increased in the CRC population by Allali *et al*.[39] and Wang *et al*.,[37] while Zeller *et al*.[40] found a reduction in *Proteobacteria* [Table 3].

Crohn's disease

Three studies were included which investigated bacterial changes in CD.[42-44] Two of these studies did not report statistical significance at the phylum level,[42,43] and Wills *et al*. did not find any differences in the abundance of bacteria between remission and exacerbation[44] [Table 4].

Changes across disease states

Decreases in *Firmicutes* were noted in studies of CD, and one study in obesity. However, while there were no opposing results found for these diseases, other studies did not find any statistically significant changes in *Firmicutes*, making these findings very uncertain. While some studies reported concordant increases or decreases in various phyla, no consistent pattern of dysbiosis emerged across the various disease states.

Table 2: Study characteristics and key findings in studies involving irritable bowel syndrome

Author (year of publication)	Cases/controls	Findings
Chung *et al*. (2016)	28/19	Bacterial abundance by phylum: Case/control, *Firmicutes*: 40.7%/38.3%
		Bacteroidetes: 41.3%/45.8%, *Proteobacteria*: 15.4%/7.1%, *Fusobacteria*: 0.6%/2.9%, *Actinobacteria*: 1.1%/4.8%, F/B: 0.99/0.83
		Findings were not statistically significant
Rajilic-Stojanovic *et al*. (2011)	62/46	Bacterial abundance by phylum: Case/control: *Firmicutes*: 89.7%/83.2% (P<0.05), *Bacteroidetes*: 6.5%/11.2% (P=0.001), *Proteobacteria*: 0%/0%, *Fusobacteria*: 0%/0%, *Actinobacteria*: 3.8%/3.1% (P<0.05), F/B: 13.8/7.42 (P<0.05)
Jalanka-Tuovinen *et al*. (2013)	34/11	*Bacteroidetes* species had a 6-fold increase in the IBS population (P=0.001)
		Clostridiales as a measure of *Firmicutes* had a 16.8-fold increase in the IBS population (P<0.05)

IBS: Irritable bowel syndrome

Table 3: Study characteristics and key findings of studies in colorectal cancer

Author (year of publication)	Cases/controls	Findings
Wang *et al*. (2012)	46/56	Bacterial abundance by phylum: Case/control: Firmicutes: 63.1%/57.2%, NS, Bacteroidetes: 22.7%/32%, P<0.05
		Proteobacteria: 4.68%/ 2.81%, P<0.05, Fusobacteria: 1.59%/2.2%, NS
		Actinobacteria: 4.55%/2.22%, NS, F/B: 2.78/1.79, NS
Ahn *et al*. (2013)	47/94	Bacterial abundance by phylum: Case/control: Firmicutes: 74%/80.3%, Bacteroidetes: 16.2%/9.9%, Proteobacteria: 2.1%/2.1%, Fusobacteria: 0.9%/0%, Actinobacteria: 4.4%/5.2%, F/B: 4.57/8.11
		Statistical significance at phylum level not reported
Alliali *et al*. (2018)	11/12	Bacterial abundance by phylum: Case/control: Firmicutes: 50.5%/28.4% (P<0.05), Bacteroidetes: 35.1%/62.6%, Proteobacteria: 9.5%/6.8% (P<0.05), Fusobacteria: 0.1%/0% (P<0.05), F/B: 1.44/0.45
Zeller *et al*. (2014)	53/61	*Firmicutes*: Increased abundance in CRC cases by 5.59E-02
		Bacteroidetes: Increased abundance in CRC cases by 9.49E-02
		Proteobacteria: Increased abundance in healthy controls by 1.77E-03; *Fusobacteria*: Increased abundance in CRC cases by 1.33E-05
		Actinobacteria: Increase abundance in healthy controls by 4.58E-02
		All findings were statistically significant (P=0.001)
Wang *et al*. (2017)	15/12	Bacterial abundance by phylum: Case/control: *Firmicutes*: 44%/44.9%; *Bacteroidetes*: 35.6%/47.1%. No statistically significant differences were detected

CRC: Colorectal cancer

Table 4: Study characteristics and key findings in studies in Crohn's disease

Authors (year of publication)	Cases/controls	Findings
Perez-Brocal *et al*. (2015)	20/20	Bacterial abundance by phyla: Case/control: *Firmicutes*: 37.8%/51.6%, *Bacteroidetes*: 41.8%/45.4%, *Proteobacteria*: 14.3%/1.3%, *Fusobacteria*: 2.6%/0%, *Actinobacteria*: 2.3%/0.131%, F/B: 0.90/1.14. Significance not reported at the phylum level
Wills *et al*. (2014)	10*	No differences were found in the relative abundances of any Phyla between cases and controls
Halfvarson *et al*. (2017)	49/28	Log2 fold change: Case over control: *Firmicutes*: −8.65; *Bacteroidetes*: −7.94

*During remission and exacerbation

Discussion

We did not find highly consistent changes in the microbial composition of the intestine within or between disease states. While some studies within diseases were concordant for increases or decreases within a phylum, the magnitude of changes often differed, and no two studies reported the same changes in all phyla. As such, while some shifts in the microbial composition may recur within studies of a particular disorder, there do not seem to be common dysbiosis changes between diseases. However, this variability may be accounted for when considering the heterogeneity of included studies, as well as variations in the characteristics and environmental exposures of study participants.

Diet has been shown to modify the composition of the gut microbiome in several studies [22,45] with some demonstrating differences at the phylum level between those consuming a typical Western diet compared to one based primarily on plant

carbohydrates.[45] Included studies were conducted in a variety of Eastern (e.g., China, Japan, Taiwan) and Western (USA, Spain, Germany, Denmark, Finland) countries, such that different dietary habits may have affected the type of dysbiosis present in a particular disease state. For example, the three studies investigating intestinal dysbiosis in IBS were conducted in China, Finland, and England such that differences in dietary habits and the associated modifications to the microbiome composition could have potentially confounded any changes related to IBS, or influenced the response of the microbiome to a particular disease state. In fact, examining only the studies by Jalanka-Tuovinen *et al*.[36] and Rajilic-Stojanovic *et al*.[35] (England and Finland, respectively) shows concordant findings for *Firmicutes* and *Bacteroidetes*, while Chung *et al*.[34] (China) found no statistically significant changes for any phyla. Indeed, Duncan *et al*. noted that discrepancies in the findings between various studies may be due to host physiology or dietary habits[18] making the determination of true dysbiosis patterns more difficult if they do exist. Schwiertz *et al*.,[25] who found a decrease in the F/B ratio that contradicted our other included studies[24,26] as well as previous findings,[16,17] also noted that uncontrolled dietary and lifestyle factors such as exercise habits or body mass index (BMI) (in studies unrelated to obesity/T2DM) could potentially limit the conclusions drawn from studies undertaken with unrestricted human volunteers.

Age is another factor that could potentially be associated with the variations in microbial compositions. While it has been proposed that the adult gut microbiome remains relatively stable between the ages of 30 and 70,[46] the proportion of *Firmicutes* tends to decrease. Furthermore, the elderly tend to have more variable intestinal microbiomes than younger individuals.[46] In the included study by Kasai *et al*.,[26] cases were significantly older than controls ($P = 0.001$), such that shifts in the microbiome due to aging could have confounded any compositional changes. Furthermore, several included studies[25,30,35,37,42] reported using participants of various ages, potentially leading to variation in bacterial compositions among cases and controls that is unrelated to the disease state.

Differences in disease severity or other comorbidities between studies could also potentially account for some of the variation in microbial composition. For example, Kasai *et al*.[26] used BMI ≥25 as their benchmark for obesity, whereas most literature considers obesity to be defined as a BMI ≥0.30. Furthermore, they report that only one of their participants had BMI ≥30, which could account for some of the discrepancies noted in their data compared to the others. However, while many studies have found differences in the gut microbial compositions of obese compared to lean participants,[13] it is notable that Schwiertz *et al*.[25] did not find significant differences in the microbiome compositions of obese and overweight (BMI 25–30) participants. As such, the effect of differing degrees of obesity in included studies is unclear. However, patient BMI is another factor that could affect reported findings. Larsen *et al*.[30] for example, included both cases and controls with a range of BMIs in their study, with average BMIs of 30 and 28, respectively. While obesity and T2DM are closely related,[47] the degree of obesity could affect compositions reported between studies. Furthermore, 3 of the studies investigating CRC[37,40,41] included patients with Stages I-IV and Wang *et al*.[38] included patients with stages II-IV; however, none of them investigated the effect of disease severity on microbiome composition. While different bacteria may be related to different aspects of cancer progression, it is still unclear how this may change or whether intestinal dysbiosis is a cause or effect of CRC.

Characterizing dysbiosis in various disease states is of both diagnostic and therapeutic importance. Attempts have been made to use the microbiome as a potential biomarker of disease,[19] and a better understanding of the relationship between microbiota and disease may be used to develop targeted treatments.[48,49] However, the inconsistency of our present findings suggests that compositional changes are variable between diseases, potentially due to factors unrelated to disease states such as participant characteristics, environmental exposures, and lifestyle factors.

To the best of our knowledge, this is the first attempt of comparing changes in the composition of the gut microbiome across multiple disease states. However, it has several limitations. Only 21 studies were included across five disease states in this small, exploratory review; as this was not a systematic review, our findings may be subject to selection bias. Moreover, the included studies were variable and may have been subject to issues of internal validity such as uncontrolled confounders or comorbidities and inadequate study populations, as well as different methods of sequencing and data analysis that limit their potential for comparison. Furthermore, we looked exclusively at stool specimens, which have been shown to differ from mucosal-associated microbiota,[50] as well as the microbiome of more proximal regions in the GI tract.[4] As such, it is possible that patterns of compositional changes in the investigated diseases may not be reflected by the microbes present in collected specimens. Therefore, the findings of this review warrant further exploration into microbiome compositional differences in various disease states in proximal GI regions as well as in mucosal-associated microbiota, and exploration of any associations which may exist between these different sampling methods. This work also highlights the limitations associated with studies determining microbiome composition in uncontrolled human population-future studies should attempt to control for variables such as diet, age, and lifestyle as possible.

Conclusions

The composition of the gut microbiome in CD, obesity, T2DM, IBS, and CRS as compared to healthy controls, suggests that common changes to bacterial genera in these chronic disorders do not exist. However, uncovering patterns of dysbiosis associated with disease state highlighted the promising implications for better understanding their pathogenesis, as well as the potential for novel diagnostic and therapeutic interventions.

Authors' contributions

The authors were assigned specific sections to draft, these were developed into a single manuscript which was reviewed and approved by all authors. First and second authors made equal contributions.

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Conflicts of interest

There are no conflicts of interest.

Compliance with ethical principles

Not applicable. None of the authors reported human or animal studies.

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