Gut Microbial Profile Differences in Autoimmune Diseases

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Abstract

The human gut microbiota has been widely studied due to the possibility of high-throughput sequencing. Humans are distinctly inhabited by normal flora and symbiotic microbial flora, with bacteria accounting for the vast bulk of the component microorganisms. These organisms can be found in a variety of locations throughout the body, including the oral cavity, vagina, skin and stomach. Microbe types and abundance vary in different organs of the same person, but they may also differ between persons. They are very important for human health and also affect the immune system by altering its metabolism and behavior. Conditions such as malnutrition, Crohn’s disease, inflammatory bowel disease and colon colitis, in addition to metabolic disorders including type II diabetes and obesity, have all been associated with the gut microbiota. Several studies in recent years have emphasized the relevance and involvement of commensal bacteria in the development of a variety of disorders, including autoimmune diseases. Autoimmune diseases, Such as Graves’ disease, systemic erythematous lupus (SLE), and irritable bowel syndrome (IBS), are commonly known for their loss of self-tolerance, a hyperactive reaction against the body’s own tissue. Autoimmune diseases are triggered by the immune system targeting self-tissues, and their global frequency is estimated to be between 3 and 5%. This review reaffirms the links between autoimmune disorders and gut bacteria. The precise pathophysiology is unknown; however, environmental factors (such as lifestyle, diet, medications, and infections) and specific genetic conditions have been expected. The gut microbiota is important in autoimmunity because changes in microbial composition can trigger immunological tolerance loss.

Keywords: Human Gut Microbiota, Autoimmune Diseases, Graves’ Disease, Systemic Erythematous Lupus (SLE), Irritable Bowel Syndrome (IBS)

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INTRODUCTION

The human body is thickly inhabited by normal flora and symbiotic microbes, with bacteria accounting for the vast bulk of the component microorganisms. These organisms are found in several parts of the body, including the stomach, skin, vagina, and oral cavity. Microbe kinds and abundance vary in various organs of the same individual, but they may also differ between people. They are very important for human health and also affect the immune system by altering its metabolism and behaviour.¹

Conditions such as malnutrition, Crohn’s disease, inflammatory bowel disease and colon colitis, in addition to metabolic disorders including type II diabetes and obesity, have all been associated with the gut microbiota.² Recent research has underlined the importance of commensal microorganisms in the development of a number of conditions, such as autoimmune diseases.¹

Autoimmune diseases, such as Graves’ disease, Systemic erythematous lupus (SLE), and Irritable bowel syndrome (IBS), are commonly known for their loss of self-tolerance, a hyperactive reaction against the body’s own tissue. It has been hypothesized that the increased incidence of such diseases stems from modern dietary plans and the wide use of antibiotics.¹ Graves’ disease (GD) is an autoimmune hyperthyroidism caused by an autoantibody against the thyrotropin receptor (TSH receptors). “Hyperthyroidism” is a condition in which the thyroid gland produces then secretes excessive amounts of free thyroid hormone. Systemic lupus erythematous (SLE) is a chronic, systemic condition with times of aggravation, referred to as flares, and remissions of disease activity.³ Irritable bowel syndrome (IBS) is a prevalent and frequently severe chronic functional gastrointestinal condition that, despite its impact on quality of life and prevalence, has an unknown origin. However, it is now clear that microbial factors play important roles in the pathophysiology of IBS. This review paper aims to compare and contrast different studies with regard to the correlation between microbiome composition and autoimmune exacerbating episodes of SLE, IBS, and Grave’s, along with the impact of therapeutic manipulations via lifestyle modifications of diet and medication.³

The relationship between gut microbiota and autoimmune illness has been an intriguing issue in recent years, with some suggesting that by changing the gut microbiota, some of these diseases might be treated or even avoided. Changes in (i) diet, (ii) (iii) prebiotics whose compounds support the growth of specific microflora; (iv) synbiotics, which are combinations of probiotics and prebiotics, and non-viable microorganisms to elicit specific biological responses; Product postbiotics are an example of these manipulations. Antibiotics (v) and (vi) as well as faecal microbiota transplantation (FMT), which involves transferring gut microbes from healthy donors to patients.⁴

Acquiring microbiome and its correlation with immunity

During childbirth, the infant is exposed to the mother’s mucosal (vaginal delivery) or skin (cesarean-section) normal flora of the birth canal, where they acquire species like Lactobacillus, or staphylococcus, respectively. However, the gastrointestinal tract is still to be accustomed to the known microbiota of the adults.¹ The gut microbiota matures during the first three years after birth and becomes inhabited by more than 2000 different bacterial species that belong to four main phyla Bacteroides, Firmicutes, Actinobacteria and Proteobacteria. With the first suckle of mother’s milk (“colostrum”), to the infant is considered the first vaccination the infant receives, as it’s filled with immunoglobulins, live microbes (such as; Bifidobacterium) and many immune cells that help protect the infant from the inside.⁵ IgA coming from the maternal milk aids in blocking bacterial entrance through the epithelial barrier. Any defects in mucosal immunity may lead to an inflammatory response. According to a study done on germ-free mice, it was found that such mice have an underdeveloped immune system (from lymph nodes to lymphocytes), which indicates the cruciality of microbiota in immune system development.¹

The significance of the gut microbiota in autoimmune diseases:

Autoimmune illnesses are caused by an individual’s immune system attacking self-tissues,
and their global prevalence is believed to be between 3-5%. The precise pathophysiology is yet unknown; however, environmental variables (such as lifestyle, nutrition, medicines, and infections) and particular genetic backgrounds have been postulated.\(^6\)

The gut microbiota is important in autoimmunity because changes in microbial composition can trigger immunological tolerance loss.\(^6,7\) It has been stated that in a seventy kg individual, the microbiota weighs two kg.\(^7\)

Schmidt et al. identified four main factors that influence microbiota composition, including inherent factors of the microbiome, environmental factors, lifestyle factors and host genetic factors.\(^8\)

Dysbiosis (alteration of microbiota) occurs when there is an imbalance of the gut microbiota, leading to a reduction in its diversity compared to normal (normobiosis) and colonization of opportunistic pathogens.\(^9\)

**From Physiological Immunity to Autoimmunity:**
The microbiome and microbial products are crucial components that aid in the formation, function, and control of the immune system.\(^1\) Many mechanisms are involved, such as: decreasing the inflammatory signaling cascade, and stimulation of regulatory T cells.\(^10\)

Autoimmunity ranges from a low level required for immune system regulation and homeostasis to moderate levels indicated by the presence of circulating autoantibodies without clinical symptoms, to pathogenic autoimmunity.\(^11\)

An important question to ask: what shifts the immune system from its normal physiological function to be reactive and cause autoimmune diseases? It is thought that all autoimmune diseases are caused by the imbalance of functional and regulatory mechanisms. Autoimmune diseases are also believed to arise from various environmental factors, genetic factors, or a combination of both.\(^11\) An example of major environmental factors initiating autoimmunity are microorganisms such as viruses and bacteria.\(^9\)

Environmental factors can cause autoimmunity in a variety of ways, including molecular mimicry, self-antigen alteration, and bystander activation. Molecular mimicry occurs when the sequence or structure of the foreign antigen is similar to that of the endogenous antigen. When pathogens stimulate specific receptors on antigen-presenting cells, proinflammatory intermediaries are generated and cause tissue damage.\(^12,13\)

**Graves’ disease (GD)**
Graves’ disease (GD) is an autoimmune hyperthyroidism caused by an autoantibody of the thyrotropin receptor (TSHR). “Hyperthyroidism” is a condition in which the thyroid gland produces and secretes abnormally large amounts of free thyroid hormone. It is the most common organ-specific autoimmune disease, affecting 2-5% of the world’s population.\(^14\) A study in 2013 showed that the prevalence of Graves’s Disease is approximately 0.5% worldwide, and its incidence has increased significantly in recent years.\(^15\) According to a Saudi study, 76.6% of Graves’ disease patients were female, and her average age was 54.5 years.\(^16\) GD is the most common cause of hyperthyroidism, showing an annual incidence of 20-50 cases per 100,000 subjects with an age peak between 30 and 50 years.\(^17\)

Clinicians have long recognised that high levels of free thyroid hormones are linked to gastrointestinal symptoms and thyroid illness. To assess the overall composition of the gut microbiota, PCR denaturing gradient gel electrophoresis (DGGE) using universal primers targeting the V3 region of the 16S rRNA gene was used and some excised gels were used. Bands were cloned for hyperthyroid and healthy human representative sequencing. In addition, real-time quantitative PCR was used to identify *Lactobacillus, Clostridium, Bifidobacterium, Enterococcus, and Enterobacteria* from stool samples from hyperthyroid and healthy individuals. There was a substantial variation in DGGE profiles between hyperthyroid and healthy persons. Real-time PCR revealed a significant drop in *Bifidobacterium* and *Lactobacillus* (both considered probiotics) and an increase in Enterococcus in the hyperthyroid group, but no statistical significance in *Enterobacterales* in either group.\(^2\)

Another study looked at the quantitative changes in the intestinal microbiota using Real-time PCR for bacteria such as *Lactobacillus, Bifidobacterium* and *Bacteroides vulgatus* in 27 Graves’ disease patients and 11 healthy people.\(^15\)
Patients had lower mean value assessment index displays in \textit{Lactobacillus} and \textit{Bifidobacterium} when compared to healthy persons. At the family taxonomic level, patients had considerably greater relative abundances of \textit{Prevotellaceae} and \textit{Pasteurellaceae}, whereas healthy persons had significantly lower relative abundances of \textit{Enterobacterales}, \textit{Veillonellaceae}, and \textit{Rikenellaceae}. At the genus level, 194 distinct genera were sequenced, and the four most common genera in GD patients were: \textit{Prevotella} (40.60%), followed by \textit{Bacteroides} (11.71%) & \textit{Haemophilus} (11.09%). This finding suggests that thyroid patients, such as GD, have hollow organs due to poor stomach acid production. When autoimmune-related gastritis is added to this, intestinal motility is enhanced, causing diarrhea. It appears that GD induces physiological changes in the gut that may further influence the microbial configuration in the gut.\textsuperscript{18}

Moreover, gut microbiota may be involved in the pathogenesis of GD, nine distinct genera of \textit{Lactobacillus} showed significant correlations with certain thyroid function tests. Moreover, after functional prediction, it revealed that \textit{Blautia} may be an important microbe in certain metabolic pathways that occur in the hyperthyroid state.\textsuperscript{19}

These results are inconsistent, which may be related to individual differences in samples, number of samples, course of patients with GD, and sequencing platforms and sequencing depths in each study (Table 1).\textsuperscript{15}

\begin{table}[h]
\centering
\caption{Highlights of significant findings in previous literature concerning Graves’ disease}  
\begin{tabular}{lccc}
\hline
\textbf{Study} & \textbf{Increased} & \textbf{Decreased} & \textbf{Comments} \\
\hline
Zhou, Lei, et al.\textsuperscript{2} & \textit{Enterococcus} & \textit{Bifidobacterium} & Done by PCR-denaturing gradient gel electrophoresis (DGGE) with universal primers targeting V3 region of the 16S rRNA gene. \\
Ishaq, Hafiz Muhammad et al.\textsuperscript{15} & \textit{Prevotellaceae} & \textit{Lactobacillus}, \textit{Bifidobacterium}, \textit{Enterobacteriaceae}, \textit{Veillonellaceae} & Done by Real-time PCR \textit{Lactobacillus}, \textit{Bifidobacterium}, \textit{Bacteroides vulgaris} and \textit{Clostridium leptum}. \\
Jiang, Wen et al.\textsuperscript{19} & \textit{Bacteroidetes}, \textit{Bacteroides} & \textit{Firmicutes}, \textit{Blautia}, \textit{Eubacterium}, \textit{Anaerostipes}, \textit{Collinsella}, \textit{Dorea}, \textit{Peptostreptococcaceae}, and & Done by 16S ribosomal RNA (rRNA) V3–V4 DNA regions of microbiota that were obtained from faecal samples. \\
\hline
\end{tabular}
\end{table}

Gut microbial composition and the effect of the antithyroid drug

A recent study aimed to find out whether the antithyroid drugs (Methimazole and Propylthiouracil) can cause gut microbiota dysbiosis in GD patients. The patients were divided into The Methimazole (MMI) group and the Propylthiouracil (PTU) group. Each group received daily doses of the Antithyroid drugs (ATDs).

When comparing the gut microbiota composition of the two groups, MMI and PTU, it revealed a higher proportion of \textit{Firmicutes} was shown in the MMI group than in the PTU group, while \textit{Bacteroidetes} were more prevalent in the PTU group. \textit{Enterobacteriaceae}, was more prevalent in the MMI group, whereas \textit{Bacteroidaceae} was more prevalent in the PTU group. At the genus level, \textit{Blautia} and \textit{Escherichia-Shigella} were enriched in the MMI group, while \textit{Bacteroides}, \textit{Lachnospiraceae} and \textit{Lachnoclostridium} were enriched in the PTU group.

In conclusion, the results show that there is dysbiosis in both the MMI and PTU groups, but the MMI group has greater dysbiosis than the PTU. That proved to be consistent with the study of Huo...
D et al. Methimazole intake altered the intestinal microbiota in ecological and evolutionary aspects while improving thyroid function in patients with GD.\textsuperscript{20}

The effects of probiotics on GD patients

Considering that the change in gut microbiota may affect the mechanisms of immune tolerance in GD patients, taking probiotics supplements, which contain live microorganisms, can modify the composition of the gut microbiota.

A randomized trial by Salvi M et al. investigated the effects of the probiotic’s supplements LAB4 (two Lactobacillus acidophilus strains plus Bifidobacterium bifidum and Bifidobacterium animalis var. lactis). Thirty patients untreated or within 4 weeks of antithyroid therapy (ATD) receive an LAB4 or placebo for 6 months orally while treated with ATD. They found out that patients who take LAB4 seem to relapse less at 6 months after ATD therapy and affect the systemic immunological status by reducing IgG and IgA. But this can’t be the last conclusion because of the limited number of patients, must be confirmed in a larger clinical trial.\textsuperscript{21}

Moreover, a study by Huo D et al. determined that by taking Bifidobacterium longum probiotics with MI treatment the clinical thyroid indexes TRAb reduced.\textsuperscript{20}

Taking traditional medicine such as MI, could be a short-term course but the new therapeutic manipulations may play an important role in convalescing TRAb to healthy levels, by taking probiotics and supplements. Iron (Fe) and zinc (Zn) are minerals that are reported to support thyroid function. It has been shown that thyroid dysfunction is linked to abnormal levels of these minerals. Studies have reported that mothers with goiters have lower iodine, Se, and Fe serum levels than healthy controls.

Further mechanistic exploration implied that the consumed probiotic regulated the intestinal microbiota and metabolites. These metabolites impacted neurotransmitter and blood trace elements through the gut-brain axis and gut-thyroid axis, which finally improved the host’s thyroid function.\textsuperscript{20}

Systemic Lupus Erythematosus (SLE):

In the Kingdom of Saudi Arabia, the prevalence of Lupus was estimated to be 19.28 per 100,000 population,\textsuperscript{22} and an increase in trend has been demonstrated ever since. SLE is a systemic chronic, autoimmune disorder with a female predominance. From modest symptoms to illnesses that pose a serious risk of death, SLE’s clinical presentations are noticeably diverse. Through molecular mimicry, interference with the host metabolism axis, and activation of type I interferon pathways, environmental factors can start and advance SLE.\textsuperscript{22} It’s known that autoimmune diseases are more prevalent in females, and the reason behind these phenomena is attributed to the hormonal profile of females; Estrogen has been proven to show a promoting effect on T-cell and B-cell immune response as well as increase the cytotoxicity of Natural Killer (NK) cells which ultimately backfires and leads to females being more susceptible to autoimmunity.\textsuperscript{23}

Testosterone, on the other hand, had a down regulatory effect on NK cells. Characterised by autoantibody production, autoreactive inflammatory lymphocytic recruitment and abnormal production of proinflammatory cytokines.\textsuperscript{24}

Knowing that women of childbearing age are at higher risk of developing lupus, Zhang et al.,\textsuperscript{24} found that female mice exhibit accelerated disease progression and noted a reduction in Lactobacillaceae, with an increase in Lachnospiraceae. According to the findings of a comparative study done in Virginia, USA, comparing control and lupus-prone mouse groups, control females had significantly higher Lactobacillaceae and Streptococcaceae levels and lower Lachnospiraceae and Clostridiceae levels than male mice of the same category. Female mice in the lupus-prone group had higher levels of Lachnospiraceae and Bacteroidetes and lower levels of Bifidobacterium and Erysipelochraceae. Moreover, investigations have established a link between the presence of Lachnospiraceae in the gut microbiota and illness severity, including renal and lymphoid diseases.\textsuperscript{24} In addition to these findings, it was shown that males had larger amounts of Bifidobacterium. These organisms, like Lactobacilli, have an anti-inflammatory impact, which helps to reduce lupus symptoms in men.\textsuperscript{25} So it has been claimed that utilizing probiotics to try to restore normal Lactobacillaceae levels helps
reduce lupus flares by lowering proinflammatory responses by raising interleukin-10 and regulatory T cells, but a convincing association has yet to be demonstrated. A study by Guo et al. analyzed oral microbiota of SLE and SLE-naive groups to examine the alteration of the microbiome in relation to disease activity and found that as disease activity grew, so did Abiotrophia and Lactobacillales, but Phyllobacterium and unclassified Micrococcusaceae declined.22

According to a study done on MRL/lpr mice (mouse MRL lymphoproliferation strain), the compositions of microbiota change in lupus-prone mice between episodes of lupus progression and exacerbation where All-trans Retinoic acid helped reduce lupus nephritis by restoring Lactobacillaceae that was previously less in number as discussed above. While Vitamin A retinoic acid, on the other hand, increased the numbers of Lachnospiraceae, worsening the symptoms (Table 2).24,27

Table 2. Highlights of significant findings in previous literature concerning Systemic lupus erythematosus

<table>
<thead>
<tr>
<th>Study</th>
<th>Increased</th>
<th>Decreased</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhang et al.24</td>
<td>Lachnospiraceae</td>
<td>Lactobacillaceae</td>
<td>Restoring normal levels of Lactobacillaceae helps ameliorate lupus flares.24,26</td>
</tr>
<tr>
<td></td>
<td>Lactobacillaceae &amp; Streptococcae</td>
<td>clostridium</td>
<td>In healthy male and female mice.</td>
</tr>
<tr>
<td>Christou et al.28</td>
<td>Lachnospiraceae &amp; Bacteroidetes</td>
<td>Bifidobacterium &amp; Erysipelotrichaceae</td>
<td>Males had higher levels of Bifidobacterium, which exerts an anti-inflammatory effect thus attenuating lupus symptoms in males.25</td>
</tr>
<tr>
<td>Lopez et al.25</td>
<td>Bacteroidetes</td>
<td>Firmicutes (clostridium)</td>
<td>IFN-γ levels correlated negatively with Bacteroidetes whilst positively with Firmicutes.</td>
</tr>
<tr>
<td>Guo et al.22</td>
<td>Prevotella and Veillonella</td>
<td>Streptococcus and Porphyromonas</td>
<td>Furthermore, when disease activity grew, so did Abiotrophia and Lactobacillales, but Phyllobacterium and unclassified Micrococcusaceae declined.</td>
</tr>
</tbody>
</table>

*IFN-γ is a major effector in disease progression

**Irritable Bowel Syndrome (IBS)**

With a frequency of 22.9% in Saudi Arabia, it is one of the most frequent chronic diverse gastrointestinal illnesses, which means that there is a combination of diverse risk factors contributing to IBS, (Genetic, physiological, psychological, environmental and behavioral).30

In the absence of any organic gastrointestinal disorders, it is distinguished by recurring stomach pain/discomfort, bloating, bowel habit alteration, and changes in stool characteristics.31,32 Altered mucosal secretion, dyspepsia, food intolerance, impaired bowel motility and visceral hypersensitivity.33,34

It’s noticed that these symptoms are exaggerated in patients with psychological stress.32 The immune system and minor inflammation have a great role in IBS pathogenesis, both systemically and at the mucosal level. It may cause a compromised mucosal epithelial barrier and altered intestinal permeability as observed in IBS patients.32 In IBS, mast cells, eosinophils, and intraepithelial lymphocytes dominate the mucosal inflammation.32 It is stated as IBS with constipation; diarrhea, or mixed based on the nature of the stool.31 Patients who meet the investigative conditions for IBS and then have abnormal bowel movements that cannot be identified are classed as (IBS-U).33 IBS diminishes health-associated quality of life by SF-36 to a greater extent than diabetes mellitus or end-stage renal disease. This demonstrates the disease’s prominence and significance.36

**IBS in relation to microbiota**

GI microbiotas have a significant role in maintaining gastrointestinal homeostasis and diverse beneficial physiological functions such as maintaining the integrity of the epithelial barrier, intestinal motility, and intestinal immune system.
by interacting with immune cells resulting in the downregulation of proinflammatory genes, and upregulation of anti-inflammatory genes.\textsuperscript{30,32-34,37} In particular, certain gut bacteria, such as \textit{Bacteroides thetaiotaomicron}, \textit{Faecalibacterium prausnitzii}, and \textit{Ruminococcus} spp., were shown to affect the mucus layer thickness and composition.\textsuperscript{38}

Furthermore, via interacting with CD209, the microbiota can moderate the immune system of the host by eliciting a tolerogenic reply through dendritic cells.\textsuperscript{39} It also modulates the mucus layer, which acts as a barrier between the lumen and the epithelial cells, preventing pathogens from reaching the epithelial surface. In IBS patients with increased GI tract permeability, which leads to inflammatory reactions, powerful antigen-presenting cells, such as muscle macrophages (MM), assist in maintaining tissue homeostasis by scavenging and engaging in immune responses. MMs have been found in animal experiments to be susceptible to microbiome alterations.\textsuperscript{30}

The GI microbiota supplies important amino acids, vitamins (B and K), and short-chain fatty acids (SCFAs). SCFAs reduce colonic pH by breaking down undigested carbohydrates, reducing pathogen development, and boosting the production of certain epithelial tight junction proteins.\textsuperscript{30,33,36}

Additionally, it has been discovered that the action of the GI microbiota on bile acid metabolism creates antimicrobial bacteriocins (compounds with a bactericidal effect). Thus, changes in the GI microbiota are strongly linked to IBS symptoms and pathogenesis.\textsuperscript{31} GI microbiota can be influenced by a variety of conditions, including gastroenteritis and antibiotic usage.\textsuperscript{37}

\textbf{Gram-positive \textit{Firmicutes} (64\%)} (as \textit{Lactobacillus}), \textit{Actinobacteria} (3\%) (as \textit{Bifidobacteriae}), Gram-negative \textit{Bacteroides} (23\%) (as \textit{B. Fragilis}), and \textit{Proteobacteria} (8\%) (including \textit{Escherichia coli}, \textit{Salmonella} etc.) dominate the microbiota. It also contains a large number of viruses, protozoa, archaea, and fungi.\textsuperscript{32,34} \textit{Faecalibacterium prausnitzii}, a member of the \textit{Firmicutes} phylum, is a prominent butyrate generator, which has been associated with remission maintenance in inflammatory bowel disease.\textsuperscript{32} In addition, butyrate induces the differentiation of regulatory T cells, thereby preventing an excessive immune response and autoimmunity. Furthermore, a substantial number of studies have shown a lower abundance of butyrate-producing bacteria from the genus \textit{Faecalibacterium}, mainly \textit{F. prausnitzii}.\textsuperscript{38}

The most prevalent dysbiosis in IBS is an increase in \textit{Streptococcus} spp.,\textsuperscript{32} a pathogenic bacterium that produces elevated levels of IL-6,\textsuperscript{34} (counterbalanced by a drop in \textit{Lactobacillus} spp.) and a decrease in \textit{Bacteroidetes},\textsuperscript{32} \textit{Bifidobacteria} depletion, increased \textit{Firmicutes} known to extracellular proteases, abundance of \textit{Ruminococcus torques} (which are considered mucin degraders,\textsuperscript{10} correlate to symptoms,\textsuperscript{37} profusion of proinflammatory bacterial species, such as \textit{Enterobacterales} with a matching reduction in \textit{Lactobacillus} and \textit{Bifidobacterium},\textsuperscript{39} increased \textit{Actinobacteria}.\textsuperscript{40} Methane has been related to slower intestinal transit and is inversely related to IBS severity.\textsuperscript{39} As a result, methane production is higher in IBS-C and lower in IBS-D.\textsuperscript{34}

\textbf{The order \textit{Methanobacteriales}} is the most prevalent methane generator in the human microbiome.\textsuperscript{34,35} The discovery of \textit{Methanobacteriales} is linked to microbial richness within the enterotype \textit{Clostridiales}, which is likewise linked to delayed transit.\textsuperscript{39}

Because methanogens convert hydrogen to methane, hydrogen is retained in the colon of IBS patients with low methanogen levels, causing flatulence.\textsuperscript{34}

\textit{Ex vivo} fermentation tests indicated that the IBS microbiota generated much less butyrate while producing significantly more sulphide. Hydrogen sulfide is a neurotransmitter that contributes to intestinal distension hypersensitivity. IBS patients had larger numbers of \textit{Enterobacterales} and sulphate-reducing bacteria, as well as higher levels of caecal sulphide and hydrogen generation.\textsuperscript{41}

The fermentation of dietary substrates by the microbiota creates hydrogen, carbon dioxide, methane, and hydrogen sulphide gas, all of which are important in IBS.\textsuperscript{33}

Gases and SCFAs produced by colonic bacteria, such as acetate, propionate, and butyrate, may influence bowel movement and gut permeability.\textsuperscript{36} Butyrate has been shown to have anti-inflammatory and barrier-improving effects.\textsuperscript{37}
SCFA producers (such as *Bifidobacterium* genus, *Clostridiales* order, *Ruminococcaceae*) have been reported to be decreased in IBS patients, especially in IBS-D and IBS-M (Table 3).

### Table 3. Highlights of significant findings in previous literature concerning IBS

<table>
<thead>
<tr>
<th>Study</th>
<th>Increased</th>
<th>Decreased</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Bhattarai et al.</td>
<td>Firmicutes, <em>Streptococci</em>, &amp; <em>Ruminococcus</em> species</td>
<td>Lactobacilli &amp; <em>Bifidobacteria</em></td>
<td>Firmicutes are extracellular proteases. Ruminococcus torques are considered as mucin degraders.</td>
</tr>
<tr>
<td>Raskov et al.</td>
<td><em>Streptococcus</em> spp</td>
<td><em>Lactobacillus</em> spp &amp; <em>Bacteroidetes</em></td>
<td>Enterobacteriaceae is proinflammatory</td>
</tr>
</tbody>
</table>
| Rodino-Janeiro et al. | *Enterobacteriaceae*                                                   | *Lactobacillus* & *Bifidobacterium* & *Erysipelotrichaceae*               | *Lactobacillus* & *Bifidobacterium* secrete bacteriocins compounds that exert, *in vitro*, a bactericidal effect against pathogens. |}
| Pimentel et al.  | *Actinobacteria*                                                          | *Bifidobacterium* & *Lactobacillus*                                       |                                                                                           |
| Major et al.     | *Enterobacteriaceae*                                                     | *Bifidobacterium* & *Lactobacilli*                                        | *Bifidobacteria* & *Lactobacilli* are considered as Lactate utilizing Bacteria.         |

### Effect of diet on IBS

Dietary intolerance is common in IBS subjects, due to the fact that dietary variations have a significant impact on microbes in the gut, GI motility, sensitivity, and barrier function, all of which could lead to IBS symptoms. Long-term dietary changes are known to influence the gut microbial composition. Long-term protein and animal fat intake, for example, is associated with an increase in *Bacteroides*, whereas long-term carbohydrate intake is associated with an increase in *Prevotella* spp. Furthermore, dietary components cause the production of metabolites such as organic acids, ammonia, methane, and hydrogen sulfide, which may contribute to IBS symptoms by supporting a dysbiotic microbiota with the expansion of *Gammaproteobacteria* members and suppressing the growth of healthy gut microbiome.

A strong connection between amino-acid metabolism and (PI)-IBS microbial indicators suggests a link between protein metabolism and gut microbiota. During inflammation, one of the detrimental protein metabolic byproducts is hydrogen sulfide, which is converted to thiosulfate and subsequently oxidized to tetrathionate. Tetrathionate growth benefits Salmonella and other tetrathionate using infections from the *Gammaproteobacteria* class, which have been related to IBS symptoms. Fat and digested proteins increase bile acid secretion, which has been linked to bacterial changes in the bowel, such as bacterial suppression, and hence contribute to many IBS symptoms.

Low FODMAPS (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diets are one of the most popular nowadays. They are indigestible carbohydrates that are fermented by microbes in the intestine, subsequently leading to rise in gas production and osmotic effect affecting small intestinal motility and contributing to visceral hypersensitivity, pain, and other IBS symptoms in a susceptible individual.

Low FODMAP diets have been associated with lower *Bifidobacterium* counts and overall bacterial abundance. Other studies show a...
significant decrease in pro-inflammatory IL-6 and IL-8 serum levels, including fecal Faecalibacterium prausnitzii, Actinobacteria and Bifidobacterium, higher Diversity of Clostridium cluster XIV, and the mucus-associated Akkermansia muciniphila, reduced Ruminococcus torques. Besides this gut microbiota plays an important role in the metabolism of environmental chemicals. The microbiota of healthy patients is unaltered by FODMAPs, demonstrating a significant link amid food, dysbiosis, and IBS symptoms.

Positive effect of low FODMAPS diet

In 70% of patients, there was a substantial drop in IBS symptom severity levels for abdominal bloating, pain, and diarrhea, as well as a significant improvement in quality of life scores. A low FODMAPS diet, on the other hand, may lower the number of commensal microbes. Because of the diet’s substantial limitations, it requires skilled dietitian supervision to avoid improper weight reduction and nutritional gaps.

Therapeutic Manipulations of IBS

The first line of IBS management is diet and lifestyle modifications, such as establishing a regular meal pattern, and avoiding large meals and eating late at night, as well as ensuring good hydration and performing a regular physical activity. IBS therapeutic treatments include a variety of techniques aimed at treating and relieving symptoms.

If there is no improvement, several therapeutic options can be used, such as Probiotics: Probiotics are living bacteria that, when provided in sufficient quantities, provide health benefits to the host. They help to maintain mucosal integrity by maintaining epithelial tight junctions, as well as defend the mucosa from toxins, allergens, and pathogens by competing with them, producing antimicrobial compounds, and interfering with intestinal mucosal adhesion. Furthermore, they may impair the microbiota’s fermentation ability. As a result, the microbiota is rebalanced, visceral hypersensitivity is reduced, and IBS symptoms such as bloating, stomach distension, and irregular bowel habits are all eased. Bifidobacteria, Lactobacillus, and Saccharomyces boulardii are the most frequent bacteria found in probiotics. IBS symptoms improved significantly after using Bifidobacter infantis.

L. rhamnosus lessens the severity and frequency of stomach discomfort, but L. boulardii increases bowel frequency. Probiotics exert their effects through a variety of mechanisms, including proliferation, replacement of a ‘missing part’ of the commensal microbiota, production of anti-inflammatory cytokines, cytoprotection, anti-apoptosis, cell migration and down-regulation of pro-inflammatory pathways, which normalizes the inflammatory profile.

Prebiotics

Prebiotics are non-digestible disaccharides, oligosaccharides, and polysaccharides that increase the development or activity of helpful bacteria like Bifidobacteria while suppressing the growth of pathogenic bacteria like Bacteroides, Clostridia, and Coliforms. Prebiotics are resilient to digestion till they access the large intestine, where they are fermented by non-pathogenic colonic bacteria, resulting in the production of metabolic end products of microbes such as SCFAs, which fix to ‘metabolite-sensing’ G-protein-coupled receptors responsible for gut homeostasis, thereby alleviating IBS symptoms.

Lactulose, one of the first synthetic prebiotics created, boosts gut flora and improves water retention in feces. Inulin-type fructans and galacto-oligosaccharides have the most evidence for prebiotic benefits. Prebiotics have been shown to dramatically reduce IBS symptoms including bloating and gas.

Fecal microbiota transplant

Fecal microbiota transplantation (FMT) has recently become popular as a novel method for modulating gut microbiota in gastrointestinal diseases, such as IBS. Many studies have assessed the gut microbiota composition and found it to be changed after FMT. Larger clinical trials are needed to clearly assess the efficacy of FMT, identify the optimal route of administration and factors predicting a favorable response to FMT, as well as to assess the risk for serious side effects.
CONCLUSION

Finally, there is emerging evidence linking autoimmune diseases to changes in gut microbial profiles. Inflammatory bowel illness, rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis have all been associated with the gut microbiota. Researchers have observed alterations in microbial diversity, imbalances between beneficial and harmful microbes, and distinctive microbial fingerprints in persons suffering from autoimmune illnesses throughout these studies.

However, it is crucial to highlight that the precise processes behind these relationships are yet unknown. It is uncertain if changes in the gut microbiota are the cause or outcome of autoimmune diseases, or if they contribute to disease development. Furthermore, individual variability in gut microbial composition, as well as the complex interplay of genetics, environmental factors, and the immune system, make establishing clear causal links challenging.

Nonetheless, studying the gut microbiota in autoimmune diseases has the potential to provide light on disease processes and, perhaps, lead to the development of innovative therapeutic options. Targeted alterations of the gut microbiota include probiotics, prebiotics, and fecal microbiota transplantation. By better comprehending the gut-microbiota-immune system axis, researchers expect to create novel strategies for regulating autoimmune diseases in the future. There is emerging evidence that prebiotics and probiotics can help cure autoimmune diseases.

It is crucial to emphasize that research on gut microbiota and autoimmune diseases is rapidly developing, and new findings may emerge that improve our knowledge of these complex connections.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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All datasets generated or analyzed during this study are included in the manuscript.

ETHICS STATEMENT

Not applicable

REFERENCES


42. Cosma-Perlu A, Loghin F, Miere D. Diet in irritable bowel syndrome: What to recommend, not what to forbid to patients! *World J Gastroenterol.* 2017;23(21):3771-

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