Dysbiosis of the Gut Microbiota Being a Contributing Factor to Parkinson's Disease: A Literature Review

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Abstract

Parkinson's disease (PD) is a prevalent neurodegenerative disorder characterized by symptoms such as tremors, dementia, and bradykinesia. Early non-motor signs, including constipation and hyposmia, suggest a potential connection between PD and the gut. The loss of dopaminergic neurons in the substantia nigra is a hallmark of PD, with unknown causes. While current treatments provide symptom relief, there are no therapies to slow the progression of the disease. The gut microbiota plays a role in inflammatory and immune responses and has been implicated in neurological disorders. The connection between gut microbiota and neurodegenerative disease remains unclear. In this review, we explored the potential link between gut microbiome dysbiosis in PD, focusing on constipation, an early disease symptom. Our review examined the evidence suggesting that chronic intestinal inflammation may contribute to the development of PD and implicate further connections to other neurodegenerative diseases.

Introduction

Parkinson's disease (PD) comes second to Alzheimer's disease as one of the most prevalent neurodegenerative disorders in the United States (U.S.). PD is characterized by notable symptoms such as tremors, dementia, and bradykinesia. However, the early unique non-motor signs are hyposmia and gastrointestinal disorders, such as constipation, which could indicate a potential for this disease to arise outside the central nervous system (CNS) (1). The pathology of PD is characterized by the loss of dopaminergic neurons in the substantia nigra, and the precise causes are not yet known. Current treatments alleviate PD symptoms; the most effective is carbidopa-levodopa, but no currently available therapies slow the progression of PD-related neurodegeneration (2). Levodopa (L-Dopa) is a natural chemical converted to dopamine in the brain. The drug must be combined with carbidopa to ensure that levodopa would not convert to dopamine outside of the CNS to ensure proper efficacy.

Our literature review investigated the potential contribution of gut microbiome dysbiosis to PD, with constipation being one of the early-onset symptoms. The dysregulation in the composition of the gut microbiota and their metabolites can lead to intestinal inflammation and disrupt the communication and integrity of the blood-brain barrier (BBB). Specifically, gut dysbiosis is believed to be a potential cause of developing a "leaky gut," leading to alterations in the BBB and subsequent neuroinflammation (3). IFNγ and TNFα have shown a correlation with the altered gut microbiome among the various cytokines. The elevated levels of proinflammatory cytokines and chemokines, such as IL-6, TNF, IL-1B, and IL-2, may indicate peripheral manifestations of PD, leading to the deterioration of the intestinal barrier.

Consequently, this allows for systemic exposure to bacterial products like lipopolysaccharides (LPSs) found in the outer membrane (3, 4). This can induce an acute inflammatory response and trigger the production of several inflammatory cytokines in various cell types. In this context, Zonulin and alpha-1-antitrypsin are 2 factors that contribute to the promotion of increased gut permeability. α-synuclein (αSyn) is a protein in PD that affects neuronal function and communication by damaging dopaminergic neurons responsible for movement. The propagation of αSyn from the gut to the brain is thought to contribute to the development of PD. Due to intestinal inflammation and increased gut permeability, the

accumulated αSyn moves from the enteric nervous system (ENS) to the CNS through the vagus nerve, leading to synucleinopathies impacting motor function (2, 5, 6, 7, 8).

Methods

Electronic searches were conducted using the following databases: PubMed, ScienceDirect, and the National Institute of Health (NIH) online library. Additionally, reference lists of selected studies were used as a source. The search strategy included keywords such as "Parkinson's disease," "Immunology," "gut microbiome dysbiosis," and "gut microbiome." Searches were conducted from April to May of 2023. All identified articles were cross-referenced among group members to ensure comprehensive coverage and minimize redundancy. Some articles were excluded from our review due to redundancy, limited accessibility, outdated information, or lack of scientific rigor. Redundant studies presented findings that closely mirrored those of the papers we analyzed, offering no additional insight. Articles behind paywalls were also excluded if no alternative access was available, as this restricted our ability to thoroughly evaluate their content. Additionally, studies with outdated data or conclusions that had been refuted by more recent research were not included to ensure our review reflected the most current understanding of the topic. Furthermore, articles with small sample sizes, weak methodologies, or insufficient statistical analyses were unfavorable, as they lacked the robustness necessary to contribute meaningful evidence. Studies that did not focus specifically on gut microbiota's role in PD or that examined unrelated neurodegenerative disorders without clear relevance were also excluded. This selection process ensured that only the most relevant, high-quality, and evidence-based articles were considered in our review.

Discussion

The gut-brain axis represents a reciprocal communication pathway linking the gastrointestinal (GI) tract and the CNS. Notably, the vagus nerve plays an essential role in establishing this connection. Ongoing investigations have proposed that the gut microbiota influences the axis, potentially contributing to the pathogenesis of PD. Experimental studies utilizing rodent models have elucidated the ability of αSyn to disseminate from the gut to the brain via the vagus nerve (8, 9, 10). Furthermore, cohort studies have revealed a reduced incidence of PD among individuals who have undergone vagotomy. These findings underscore the alleged involvement of the gut-brain axis in the etiology and progression of PD.

The gut microbiota, comprising various microorganisms, is crucial in maintaining normal physiological function and impacting human health. Age, diet, genetics, antibiotics, probiotics, and stool transplants can alter the gut microbiota composition (11, 12). A typical early symptom of PD, constipation, contributes to gut dysbiosis. Pivotal bacteria such as *Prevotella*, *Akkermansia*, short-chain fatty acid (SCFA)-producing bacteria, and *Bacteroides* in the gut microbiota support the pathogenesis of PD. Decreased SCFA levels can increase endotoxin and neurotoxicity, affecting microglial activation and neuronal function (9, 10, 11, 12, 13, 14).

Bacteroides species may contribute to inflammation in PD, while *Akkermansia's* increased levels can disrupt intestinal integrity and promote αSyn formation (10, 14). Reduced levels of *Prevotella* may lead to gut inflammation and oxidative stress, triggering neuroinflammation and neurodegeneration (15). As manifested by their associations with disease duration, cognitive impairment, and potential implications for therapeutic advancements, these findings highlight the gut microbiota dysbiosis as a potential biomarker and therapeutic target for PD.

Lastly, researchers are investigating the potential of diets, such as the Mediterranean diet (MEDI) and ketogenic diets, as an intervention for individuals with PD (16, 17). Probiotic dietary supplementation and fecal microbial transplantation (FMT) have shown initial promise in clinical trials, particularly in alleviating PD-related symptoms (18, 19). Overall, these interventions can potentially manage PD symptoms and warrant further investigation in clinical settings.

Dopamine in PD

PD is caused by the loss of dopaminergic neurons in the substantia nigra, a midbrain dopaminergic nucleus, resulting in decreased dopamine production (20). The substantia nigra is involved in the control of movement, cognition, and the limbic system (20). The substantia nigra is divided into the pars compacta and pars reticulata (20). The pars compacta is the region of the substantia nigra that contains dopaminergic neurons (20). The pars reticulata

consists of GABAergic neurons (20). The substantia nigra pars compacta appears dark due to the elevated levels of neuromelanin pigment within the cell bodies of the dopaminergic neurons (20). The nigrostriatal pathway, extending from the substantia nigra to the putamen, contributes to the motor deficits associated with PD (20).

Dopamine synthesis begins with the precursor L-dihydroxyphenylalanine or L-Dopa, which can be synthesized via a direct or indirect pathway (21). Following a direct synthesis pathway, L-Dopa can be synthesized from tyrosine, a non-essential amino acid (21). The indirect synthesis of L-Dopa utilizes phenylalanine, an essential amino acid, which will be the pathway discussed for synthesizing dopamine (21). L-phenylalanine is converted to L-tyrosine by the enzyme phenylalanine hydroxylase in the liver. Phenylalanine hydroxylase utilizes oxygen, iron, and tetrahydrobiopterin as cofactors, essential for catalysis (21). L-tyrosine is then transported to the dopaminergic neurons in the brain via an active transport mechanism (21). Once in the brain, L-tyrosine is converted into L-Dopa by hydroxylation of the phenol by tyrosine hydroxylase. A further decarboxylation reaction then converts L-Dopa into 3,4-dihydroxy phenethylamine (dopamine) via the enzyme L-3,4-dihydroxyphenylalanine decarboxylase at the pre-synaptic terminal (21). Dopamine metabolism follows a few various pathways. One pathway resulting in dopamine metabolism is the conversion of dopamine to 3-methoxytryramine catalyzed by catechol-O-methyl transferase or COMT (21). Monoamine oxidase (MAO) then converts 3-methoxytryramine to 3-methoxy-4-hydroxyacetaldehyde. Aldehyde dehydrogenase then oxidizes the aldehyde in 3-methyoxy-4-hydroxyacetaldehyde into a carboxylic acid yielding homovanillic acid (21).

Deficits in dopamine release involve several mechanisms that include defective synaptic vesicle exocytosis, impaired dopamine synthesis, and defective dopamine release (22). The release of dopamine is facilitated by calcium-dependent exocytosis. In a normally functioning dopaminergic axon, the SNARE complex is formed on the plasma membrane (22). The formation of the SNARE complex on the plasma membrane allows for direct interaction with PD proteins such as αSyn and LRRK2, resulting in changes in the expression of the SNARE complex (22). LRRK2-dependent phosphorylation of the Snapin

protein coding gene inhibits SNAP25, which results in defective exocytosis of dopamine (22). Mutations in these complexes lead to mitochondrial dysfunction, leading to insufficient axonal energy to produce an action potential and resulting in synaptic loss. This synaptic loss disrupts the release of dopamine in dopaminergic neurons (22). In models with PD mutations in the SNCA gene, which encodes for αSyn inhibit the release of dopamine. The aggregation of αSyn in the synapse results in impaired dopamine release by blocking protein function (22).

αSyn in Parkinson's

αSyn is a neuronal protein encoded by the *SNCA* gene that plays a physiological role in the pathogenesis of PD (23, 24, 25). Abnormal accumulation and aggregation of αSyn results in the degeneration of dopaminergic neurons associated with PD (26). Although the exact function of αSyn remains unknown, convincing evidence supports the involvement of a-synuclein in synaptic plasticity and neurotransmitter release (26). To better understand the connection between neuronal activity and αSyn, researchers used cultured neurons and living mice (27). Studies conducted by both Prashun et al. and Yamada et al., each in separate papers, hypothesized that neuronal activity regulates the release of αSyn from neurons (8, 27). Researchers concluded that depolarization of neurons led to increased exocytosis of pre-synaptic vesicles, which is important in a-synuclein release (27).

The underlying genetics contribute to the pathogenic role of αSyn in PD which include point mutations, duplication of *SNCA*, and polymorphic variants (26). Under native conditions, αSyn exists in a state between an unfolded monomer and folded tetramer, which prevents aggregation (26). A decrease in the tetramer-to-monomer ratio leads to an increased level of αSyn in the unfolded monomer state, favoring aggregation (25, 26). As a result of conformational change, αSyn adopts a ß-sheet-rich structure facilitating aggregation of the protein and accumulation in Lewy Bodies (25, 26, 27). αSyn undergoes post-translational modification with phosphorylation being a significant pathological marker of PD. Evidence revealed a relationship between phosphorylation and αSyn degradation. Increased phosphorylation of αSyn due to inhibition of the ubiquitin-proteasome system suggests regulation of αSyn degradation (26). Failure to inhibit the ubiquitin-proteasome system can prevent phosphorylation of αSyn and dysregulation of αSyn

degradation allowing for the accumulation of αSyn in Lewy bodies (26, 27).

αSyn propagation from the gut to the brain contributes to the etiology of PD (28). The connection between pathological αSyn and the gut-brain axis follows Braak's hypothesis. Braak's hypothesis suggests progressive PD results from pathogens entering the nasopharyngeal cavity and migrating from the gastrointestinal tract to the brain resulting in loss of dopaminergic neurons (5, 28, 29). The gut microbiota imbalance promotes intestinal inflammation and impairment in the mucosal barrier (6). The endotoxins from the entering pathogens cause misfolding and accumulation of αSyn resulting in inflammation (6). The accumulated αSyn spreads from the enteric nervous system and migrates to the central nervous system via the vagus nerve spreading synucleinopathies from the brainstem to the substantia nigra causing motor dysfunction that contributes to the clinical manifestations of PD such as delayed gastric emptying and severe constipation (5, 6, 29).

In recent research conducted, researchers aimed to investigate three different aSyn species including oligomer αSyn (OSyn) and phosphorylate αSyn (PSyn) (6). OSyn was found to display toxic effects on the nervous system and contribute to the pathogenesis of PD (6). Researchers found that αSyn resided in both PD and control groups with variations in distribution within intestinal mucosa, while OSyn excretion occurred from the mucosal layer (6, 7). Enteroendocrine cells lining the intestinal tract aid in the propagation of defective αSyn (7). OSyn is an abnormal aggregate of αSyn (6). Increased excretion of Osyn from the mucous layer into the gut causes toxic protein accumulation and exhibits a correlation between the gut-brain axis retrograde theory (30). In PD patients, the increased production of Osyn in the gut and propagation to the brain via the vagus nerve leading to motor dysfunction and severe constipation (6, 31).

Gut-Brain Axis

The gut-brain axis has a reciprocating relationship with the CNS, sympathetic nervous system (SNS), ENS, hypothalamic-pituitary-adrenal (HPA) axis, and gut microbiota (12, 32). These systems combined contribute to the altered gut, production of neuromodulatory components, vagus nerve activation, and immune pathways. They are probiotic strains

that induce changes in neurotransmitter pathways, including serotonin, dopamine, and norepinephrine (32). A well-maintained and consistent composition of the gut microbiota is vital for preserving intestinal barrier integrity and reducing inflammation in healthy individuals (3). This, in turn, positively influences brain development and behavior through the intricate network known as the microbiota-gut-brain axis (3). Multiple pathways exist connecting the brain and the intestine, with the vagus nerve facilitating the most direct route (2). The vagus nerve originates from the dorsal motor nucleus in the medulla oblongata and extends throughout the abdominal region, innervating the visceral organs (2). When stimulation within the intestine occurs, the stimulus can initiate afferent signaling via the vagus nerve. This signaling process is crucial in neuroimmune inflammatory reflex circuits, vital for maintaining peripheral immune regulation (2). Additionally, emerging evidence suggests that the vagus nerve may serve as a direct pathway through which substances and signals from the intestine can be transmitted to the brain (2). This highlights the potential bidirectional communication between the gut and the CNS mediated by the vagus nerve (2).

Given the bidirectional communication between the CNS and ENS, there is a postulation of whether the onset of PD is due to "body-first" or "brain-first" (2, 14). One would automatically think of the "brain-first" aligning with the pathology of PD since it would indicate that the misfolded αSyn would arise in the CNS and inevitably impact the dopaminergic neurons present in the substantia nigra, and eventually descend towards the rest of the body, causing subsequent symptoms such as motor impairments and constipation. On the other hand, the body-first phenomenon would indicate that an external pathogen would enter the gastrointestinal system and initiate the αSyn misfolding, suggesting that the progressive neurodegeneration could be peripheral (14). Then, this misfolding would continue to occur until it would progress into the dorsal motor nucleus of the vagus nerve to the medulla oblongata, eventually reaching the cerebral cortex (14). Another way an external pathogen may enter the host is through the olfactory bulb, which suggests a 2-hit hypothesis that would trigger the onset of PD more substantially (14). Returning to the gastrointestinal tract obtaining a pathogen, the chronic inflammation that could be associated with it will eventually cause dysbiosis of the gut and lead to increased intestinal permeability. Since

intestinal permeability will increase, it increases the chances of other bacteria and toxins crossing the ENS, potentially causing αSyn misfolding (14).

Notably, abnormal accumulation of αSyn, an essential constituent of Lewy bodies, has been identified within the ENS (10). A study on healthy rodents involved injecting human αSyn fibrils into the gut tissue, which induced αSyn to spread to the vagus nerve and brainstem (10). Furthermore, some studies involved the targeted expression of human αSyn in the vagus nerve by injecting adeno-associated viral vectors to which αSyn aggregates spread progressively from the medulla oblongata to other brain regions (8). In addition, a rodent study revealed that dysbiosis of the gut has effects preceding the formation of αSyn in mouse brains (9). These findings support that the vagus nerve is a conduit for transmission from the GI tract to the brain (8). Additionally, cohort studies performed in Northern Europe yielded compelling outcomes revealing that individuals who underwent truncal vagotomy had a lower risk of developing PD compared to the control group that was age and gender-matched (8). Furthermore, experimental manipulations in mice showed that cervical vagotomy performed before the injection of αSyn into the gastric wall prevented αSyn formation in the vagus's dorsal motor nucleus (8). As supported by the experimental evidence, these findings substantiate that αSyn can propagate from the gut to the brain, providing clarity on crucial aspects of this pathological process (8, 10).

Studies have highlighted that the gut microbiota can regulate the gut-brain axis through endocrine, immunological, and direct neuronal processes, contributing to the idea that PD is a pathological condition that extends from the gut to the brain (8,10). Aligning with the occurrence of gastrointestinal dysfunctions that precede the typical motor symptoms in individuals with PD, it becomes progressively apparent that the impact of microbiota community changes on the interactions within the gut-brain axis is also implicated in PD development (3). During the pathogenesis of PD, gut microbiota dysbiosis can elicit persistent inflammation within the intestinal epithelium, which could inevitably induce neuroinflammation through the microbiota-gut-brain axis (3). These inflammatory responses and fluctuations between the population levels of some bacteria contribute to microbiota dysbiosis, which will disrupt the integrity of the intestinal barrier, referred to as the "leaky gut" (3). Since there is increased

permeability of the intestinal barrier, this will promote the entry of pro-inflammatory byproducts such as lipopolysaccharides (LPSs) and cytokines into the systemic circulation (3). Consequently, these molecules breach the BBB, accessing the substantia nigra (SN), contributing the neuroinflammation, and potentially leading to the demise of dopaminergic neurons, which is a hallmark feature of PD (3).

Gut Microbiome and PD

The gut microbiota contains a collection of microorganisms, such as bacteria, viruses, fungi, and archaea, that live in a symbiotic relationship with the host. These microorganisms have many crucial functions, such as promoting normal motility, developing the gastrointestinal epithelium and ENS, and contributing to the development of priming the immune system to maintain a barrier towards pathogenic bacteria and digestion of nutrients. Its composition can be altered throughout one's lifetime from various factors such as diet, genetics, use of antibiotics or probiotics, energy intake, and stool transplants (11, 12). Normal physiology and the host's vulnerability to illnesses are impacted by the metabolic processes and interactions of the gut microbiota (33). At the bacterial level, unique differences are caused by changes in pH, immunological factors, and digestive enzymes. The microbiota directly impacts human health through the production and release of diverse components, including vitamins, essential amino acids, and lipids (33). This ecosystem is susceptible to changes in one's external environment, such as diet, sleep, chronic noise, and sedentary behaviors. These behaviors could contribute to the onset of several neurodegenerative diseases, such as PD. One of the predominant contributing factors that is also correlated with the inevitable dysbiosis of the gut is aging (32). Throughout aging, there is a potential for a decrease in bowel motility, a sign of constipation (32). Constipation is one of the early symptoms presented in PD. Chronic constipation could result in low-grade inflammation of the intestines, causing a leaky gut, ultimately leading to changes in the blood-brain barrier and neuroinflammation. A study conducted on PD and control groups utilized the Wexner Constipation Scoring System to evaluate constipation severity (15). The results revealed a significant association between the two groups, indicating a statistically significant positive correlation (15). This study confirmed an increased prevalence of constipation among PD patients, particularly in severe grades, thereby

establishing a link between constipation and the severity of PD symptoms (15). These findings suggest that individuals experiencing severe constipation are more susceptible to developing PD, accentuating the potential utility of constipation as a preclinical biomarker (15). Several bacterium levels, persistently noted across studies, have been associated with PD, highlighting the critical role of the gut microbiota in the pathogenesis of the disease (4, 10, 14, 15). Such bacterium includes decreased *Prevotella* and short-chain fatty acid (SCFA)-producing bacteria and increased *Bacteroides* and the Verrucomicrobiaceae genus, *Akkermansia* (1) (see Table 1).

Prevotella, a gram-negative bacterium, is thought to maintain mucosal integrity and produce neuroprotective short-chain fatty acids (SCFAs) that have the potential to exert a protective influence on dopaminergic neurons, shielding them from degradation (15). Additionally, *Prevotella* is involved in the protection of dopaminergic neurons via the secretion of hydrogen sulfide (15). Hydrogen sulfide is a gaseous neurotransmitter in the gut (15). One consistent finding across studies is a decreased abundance of the bacterium *Prevotella* in PD patients across various populations (1, 9, 10, 11, 13, 14, 15, 33). The mean abundance of *Prevotella* was reduced by 46.6% in PD patients compared to healthy controls (4). Decreased levels of *Prevotella* could increase inflammation and oxidative stress in the gut, which would inevitably trigger neuroinflammation and neurodegeneration in the brain. Moreover, *Prevotella* has been found to correlate with the occurrence of REM sleep behavior disorder (RBD) along with the progression of motor symptoms in PD over two years (10). In a separate study, individuals with an increased abundance of *Prevotella* exhibited lower rates

of constipation, indicating a decreased probability of experiencing subthreshold parkinsonism (10) (see Table 1). Subthreshold parkinsonism refers to the presence of mild Parkinsonian features that do not meet the criteria for a proper PD diagnosis (10). These significant findings could suggest that a reduction in *Prevotella* abundance could serve as a biomarker for PD diagnosis and a target for disease-modifying interventions (15) (see Table 1).

Studies have consistently demonstrated reduced short-chain fatty acid (SCFA)-producing bacteria, including *Faecalibacterium prausnitzii* and *Roseburia* from the Lachnospiraceae family in PD patients (9, 13, 14). Acetate, propionate, and butyrate are the three principal SCFAs produced by gut bacteria (12). They typically cause activities such as anti-tumorigenic, anti-inflammatory, and anti-microbial effects, change gut integrity, induce reactive oxygen species, and change cell proliferation and function.

Gut Microbiota	Function	Potential Contribution/Impact on PD
Prevotella	Maintains the integrity of the mucosal lining and produces neuroprotective substances, including short-chain fatty acids (SCFAs) and hydrogen sulfide, which is a gasotransmitter.	Reduced levels are linked to greater inflammation, oxidative stress, neuroinflammation, and neurodegeneration. These lower levels are associated with constipation and the progression of motor symptoms. Decreased levels may act as a potential biomarker for the diagnosis of PD.
Faecalibacterium prausnitzii (Lachnospiraceae family)	SCFA-producing bacterium that maintains epithelial integrity, and has anti-inflammatory properties.	Reduced levels in PD patients may contribute to impaired gut motility and increased inflammation, potentially triggering neurodegeneration and gastrointestinal issues like constipation.
Roseburia (Lachnospiraceae family)	SCFA-producing bacterium that maintains gut integrity and promotes gastrointestinal motility.	Increased abundance in PD, particularly in the non-tremor subtype, is linked to more rapid disease progression. May contribute to neuroinflammation through LPS-mediated immune activation, exacerbating PD pathology and promoting αSyn aggregation.
Bacteroides genus	Produces pro-inflammatory neurotoxins such as lipopolysaccharides (LPS) and toxic proteolytic peptides. Stimulates immune cells.	Increased abundance in PD, particularly in the non-tremor subtype, is linked to more rapid disease progression. May contribute to neuroinflammation through LPS-mediated immune activation, exacerbating PD pathology and promoting αSyn aggregation.
Verrucomicrobiaceae family (*Akkermansia*)	Maintains intestinal integrity, aids in mucus digestion, and plays a role in immune function.	Increased levels of *Akkermansia* in PD lead to increased intestinal permeability and inflammation, exposing the intestinal neural plexus to toxins like LPS. This exposure may promote αSyn aggregation and Lewy body formation, contributing to neuroinflammation and PD progression. It is also linked to IFNγ production.

Table 1: Table 1. Functional Roles of Gut Microbiota and Their Associations with Parkinson's Disease. This table summarizes key gut microbiota species, their functional roles within the body, and their potential associations with PD pathology. Abbreviations: SCFA, short chain fatty-acids; LPS, Lipopolysaccharides. (Adapted from 1, 4, 9, 10, 11, 13, 14, 15, 33, 35).

SCFA-producing bacteria function to maintain epithelial integrity, possess anti-inflammatory properties, and promote gastrointestinal motility while regulating ENS function (10). Several ways could lead to the depletion of this bacteria, including diet, physical activity, sleep, antibiotics, and exposure to environmental toxins such as metals. The decrease in SCFA levels may lead to an increase in endotoxin and neurotoxic occurrence, which have been linked to the onset of PD (10). Recent studies implicated that SCFAs can promote microglia's maturation and inflammatory capabilities (34). Microglia does not express the SCFA receptors. However, they express the associated responsive genes, such as histone deacetylases, which could modulate the gene expression (34). Increased microglia activation and the production of pro-inflammatory cytokines could alter neuronal function and increase cell death in PD patients (34). Moreover, decreased SCFA levels may contribute to the emergence of gastrointestinal motility disorders, including constipation in PD, since one of these bacterium's functions is to promote gastrointestinal motility (10). There is a significant association in PD patients that low SCFAs are substantially correlated with poor cognition and lower BMI, and these individuals were found to have poorer postural instability-gait disorder scores as well (10) (see Table 1).

The *Bacteroides* genus, which falls within the Bacteroidetes phylum, exhibited an exceptional abundance among patients diagnosed with the non-tremor subtype of PD (4). It is worth emphasizing that PD is a clinically heterogeneous disorder. Individuals with the non-tremor subtype experience more rapid disease progression and display heightened αSyn pathology in the ENS neurons compared to those with the tremor subtype (4). Specific genera within the Bacteroidetes phylum can produce diverse pro-inflammatory neurotoxins, including lipopolysaccharides (LPSs) and toxic proteolytic peptides (4). Consequently, this suggests a potential role for *Bacteroides* species in contributing to the inflammatory processes observed in PD. Furthermore, an intriguing positive correlation was observed between the abundance of *Bacteroides* and the plasma levels of the pro-inflammatory cytokine TNFα in PD patients (4). Notably, *Bacteroides* have been demonstrated to stimulate immune cells, such as macrophages and monocytes, to release TNFα through LPS-mediated pathways (4) (Table 1).

Akkermansia, which is a bacterium that is a member of the Verrucomicrobiaceae family, predominantly gram-negative, primarily inhabits the mucus layer of the large intestine, where it plays a vital role in maintaining intestinal integrity and facilitating the digestion of the intestinal mucus (35, 10). *Akkermansia* has been linked to certain health benefits such as improved immune function, accelerated wound healing, and protection against obesity (10). The degrading feature must accompany the pro-inflammatory pathways since the gut barrier's breakdown would increase resident immune cells' exposure to pathogens, causing abnormal aggregation of αSyn formation in the ENS. Increased levels of *Akkermansia* increase intestinal permeability and intestinal inflammation, which would expose the intestinal neural plexus to toxins such as lipopolysaccharide (LPS), which would lead to the abnormal aggregation of αSyn and generation of Lewy bodies (10). Furthermore, a study revealed a modest correlation between the abundance of Verrucomicrobia and IFNγ. IFNγ is a pro-inflammatory cytokine derived from type I helper T cells (4). The dysregulation of the gut microbiota has been associated with abnormal immune responses within the gut and throughout the body, which would lead to the excess production of inflammatory cytokines in the bloodstream, and that would trigger motor impairments and neurodegeneration by inducing neuroinflammation in a PD mouse model with the overexpression of αSyn (4). Therefore, since increased levels of *Akkermansia* are pronounced in PD, this could indicate the contribution to the disorder's progression.

These crucial bacteria strongly suggest the active involvement of gut microbiota in the pathogenesis of PD, as evidenced by their correlations with disease duration, cognitive impairment, and potential implications for treatment development. It is imperative to conduct further research to investigate the specific microbiota differences and their functional roles that contribute to the progression of PD. To gain comprehensive insights, the design of a longitudinal study aimed at monitoring disease progression and characterizing alterations in the taxonomic composition of the gut microbiome would prove highly advantageous. Such an approach would provide valuable information regarding the dynamic relationship between the gut microbiota and PD, enabling a deeper understanding of the disease mechanisms and potentially paving the way for targeted therapeutic interventions.

Immune System and the Gut Microbiota

The gut microbiome is a dynamic environment that balances the immune system. Regulating immune homeostasis is one critical benefit gut microbiota provides to the organism (36). When changes occur within the body, homeostatic balance becomes disrupted, and similar results occur with alterations to gut microbiota (36). Various gut microbiota cytokine interaction patterns have been discovered and are specific to a stimulus or cytokine specificity (37). Microbial metabolic pathways link together specific microbiota species and various cytokine levels. Differences in cytokine levels are associated when more significant or lesser percentages of bacteria are present (37). Such taxonomic associations include the typical gut microbiota, *Dorea formicigenerans*, where higher levels correlate to greater levels of IFNγ. The opposite is seen for Dorea species which negatively correlates to IFNγ response. Taxonomic associations are generally associated with bacterial-induced inflammatory cytokine response (38). Such microbiota changes and cytokine immune responses are correlated with symptoms of PD (39). Changing gut microbiota in PD patients is associated with varying concentrations of IFNγ and TNFα (39). Such changes in cytokine levels were thought to contribute to irregular immune responses and enhance inflammatory processes in PD patients (39).

Gut microbiotas produce metabolites that play critical roles in inflammatory signaling. When such changes occur, disrupting the balance of the gut, alterations to the immune response follow (40). The reciprocal host-gut microbiota axis describes the relationship between gut microbiota and immune responses (41). The axis' primary defense is innate immunity, which correlates to gut microbiota taxis (41). Gut-associated Lymphoid Tissue (GALTs) is critical in establishing a connection between gut microbiota and innate immune homeostasis (42). When gut microbiota is disturbed, GALTs structure is altered, interfering with the local immune responses. Although the mechanism is not entirely understood, one theory is based on the pro-inflammatory cytokines produced by GALTS derived from different gut microbiota. Such cytokines can lead to greater susceptibility to autoimmune disorders (42). The microbiota-gut-brain axis connects gut, immune, and brain functions. Gut dysbiosis and increased pro-inflammatory cytokines are said to improve intestinal and BBB permeability leading to an accumulation of misfolded proteins and axonal damage

(43–45). It is through damaged protein buildup that the pathogenesis of neurodegenerative diseases occurs, including PD (43). PD patients with high levels of Enterobacteriaceae displayed increased levels of lipopolysaccharides within the blood, which acts as a neurotoxin (43–45). Serum LPS may induce the pro-inflammatory cytokine response, which disrupts the blood-brain barrier leading to the degradation of dopaminergic neurons and substantia nigra (43–45).

Studies show that changes in an individual's gut microbiota result in many symptoms. How these changes to the gut microbiome occur varies by patient. Alterations to the gut microbiota composition may be due to environmental factors, stress, and diet. Such changes result in changes in epileptiform activity (46). Modifications within the gut microbiota associated with neuroinflammation are also common symptoms of aging. As one ages, gut microbiota decreases, affecting the gut-brain axis (47). Such environmental factors would trigger T-cell infiltration and immune-mediated neural damages that coincide with symptoms of PD (48). Aging supports a pro-inflammatory microenvironment and, when coupled with a decrease in gut microbiota diversity, can result in increased progression of neurodegeneration (49). Both increase and decrease in specific genera of bacteria, including enriching *Lactobacillus*, *Akkermansia*, and *Bifidobacterium*, as well as depleting Lachnospiraceae family, are some of the most displayed alterations in PD patients (50). The GI tract is the primary communication site between the host immune system and the gut microbiota, highlighting the importance of the relationship (51). Dysregulation of the relationship results in disorders like that of PD. Understanding the variations of gut microbiota and its relationship with the inflammatory immune response will help to advance the treatment of patients with PD.

PD Treatments

Most clinically approved treatment modalities for PD center around treating PD symptoms and do not address underlying pathophysiology in the brain or gut. Current first-line pharmacological treatment for PD symptoms includes dopamine replacement therapies such as levodopa (L-Dopa) and combination levodopa-carbidopa (52–54). L-Dopa is regarded as the standard gold treatment for early-stage PD, administered to replenish the loss of striatal dopamine (54–56). It has a long history of use in alleviating the primary motor effects of PD, namely Parkinsonian tremors.

However, these effects can be limited (57). Prolonged high-dose L-Dopa treatment is complicated by the onset of characteristic involuntary motor movements referred to as levodopa-induced dyskinesia (LID) (54, 58). LID symptom onset occurs in approximately 40% of PD patients on L-Dopa therapy lasting four or more years (58, 59). Clinical data has established a positive correlation between L-Dopa dose and LID manifestation (60, 61). Alternatives to L-Dopa seek to achieve similar efficacy without LID but are still targeted toward symptom management. Preliminary clinical data suggest levodopa-carbidopa administered to the jejunum as a long-acting gel can increase LID-free periods associated with off-peak L-Dopa blood levels by approximately two h (95% CI -3.05 to -0.76]; p=0.0015) but requires surgical placement of jejunostomy, an effective and invasive procedure (62). Research continues to seek methods to improve long-term L-Dopa efficacy, reduce LID-associated complications, or serve as less invasive, effective alternative interventions.

As interest in the gut-brain axis's involvement in PD pathophysiology has grown, so has the concurrent interest in gut-brain axis-mediated prevention and intervention. Investigations that have reached clinical trials include nutritional therapy via diet modification and direct gut microbiome modulation via pre-, post-, and probiotic means (16, 63, 64). Thus far, these treatment avenues remain experimental and have not been widely adopted in the clinic.

A growing body of research has identified diet as a factor that can be protective against PD (64,65). Specifically, the study finds the Mediterranean (MEDI) diet, rich in olive oil, fresh fruit and vegetables, fish, poultry, beans, and pulses, is protective (66–69). Data from a 2019 Greek cohort study suggest adherence to the MEDI diet is associated with a modest 2% lower probability of developing prodromal PD symptoms, defined as gut motility issues, depression, and cognitive decline (p < 0.001) (66). A 2021 analysis from the Rotterdam Cohort Study (n = 9414) finds adherence to a MEDI-like diet has a protective effect against PD with a hazard ratio of 0.89 (95% CI 0.74–1.07) (67). Conversely, a 2009 study from Japan concludes diets high in consumption of animal fats, specifically cholesterol intake, were positively associated with PD risk finding an odds ratio (OR) of 2.09 (95% CI 1.21-3.64) —further suggesting a connection between diet and PD (70). These data suggest dietary modifications, exceptionally minimal

consumption of red meat, animal fats, and alcohol, and increased adherence to a MEDI-like diet can protect against PD.

Beyond preventive benefits, researchers have begun investigating diet as an intervention for those already diagnosed with PD, focusing on the MEDI diet and the related Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet (16, 66, 67). The MIND diet differs from the MEDI diet in food prioritization, with the MIND diet emphasizing more leafy green vegetable consumption instead of MEDI's broader emphasis on fresh vegetable consumption (16, 66). Regardless, data suggests both diets may serve as nutritional therapy for PD patients. 2022 data from the ongoing Modifiable Variables in Parkinsonism study found patients adhering to a MIND diet reported 52.9 points lower on the patient-reported outcomes in PD (PRO-PD) tool — a self-report survey consisting of 32 sliding scale questions to assess PD symptom severity and frequency (17, 68). On average, patients adhering to a MEDI diet reported 29.6 points lower in the same metric (68). Similarly, a 2017 cross-sectional analysis using PRO-PD metrics found patients adhering to diets like MEDI and MIND were associated with slower progression of PD symptoms (p < 0.05), while patients reported adhering to diets high in refined sugars, fried foods, and full-fat dairy products were associated with more rapid progression of PD (p < 0.05) (17). Further differentiation in dietary factors also shows diet modification as a promising intervention. A small 2020 randomized control trial (RCT) of 47 PD patients concludes low fat and specifically ketogenic diets improve nonmotor and motor daily living experiences by 41% (p < 0.001) in patients already prescribed L-Dopa as reported using the Movement Disorder Society's Unified Parkinson's Disease Rating Scale MDS-UPDRS (71).

Recent research has sought to move beyond associative measures and establish a causal relationship between diet interventions, gut microbiome changes, microbial metabolite changes, and disease states. This has led to experimental treatment avenues that directly modulate microbiome and microbial metabolites, such as short-chain fatty acid SCFA levels in PD patients (72, 73). An 86-subject 2020 case-control study not only confirmed gut microbial dysbiosis between healthy subjects and PD-diagnosed subjects, but further concluded adherence to an ovo-lacto vegetarian diet and the addition of a bowel cleansing regimen in PD subjects

currently treated with L-Dopa significantly improves MDS-UPDRS part III motor evaluation scores. It is associated with elevated levels of beneficial Ruminococcaceae microbial taxa known to metabolize dietary components to SFCAs (pooled $p < 0.01$) (72). The benefit of such intervention may be ascribed to the dual effect introduction of SCFA precursors via an ovo-lacto vegetarian diet and a beneficial change in gut microbiota that generates more SCFAs via a bowel cleansing regimen (72). Further, the 2021 open-label trial (RESIST_PD) of 87 subjects concluded that altering bowel SCFA levels via prebiotic dietary supplementation of resistant starches, i.e., starches that undergo digestion only by gut microbiota, results in less gut dysbiosis, increased colonic SCFA levels as measured by fecal butyrate levels ($p = 0.029$), and improvement of non-motor related PD symptoms on the Non-Motor Symptom Questionnaire (NMSQ) ($p = 0.001$) (73).

Future Research

Dietary intervention trials and RESIST-PD prebiotic trials have shown promise in the clinic as stand-alone and supplementary interventions to prevent the onset of PD and reduce symptoms associated with it (73). Research is ongoing to understand better how gut-brain axis-mediated interventions can treat or reverse PD symptoms.

Research into probiotic dietary supplementation has shown preliminary promise in clinical trials for PD-associated symptoms, mostly constipation (74, 75). Data from a 2016 120-subject RCT suggests probiotic dietary supplementation with fermented milk containing probiotic microbial strains and prebiotic fiber significantly increases reported complete bowel movements in PD suffering from PD-associated constipation with a mean difference of mean difference in movements of 1.1 (95% CI 0.4-1.8; $p = 0.002$) (74). A smaller 46-subject 2022 RCT also concludes probiotic supplementation, including defined probiotic microbial strains, improves PD-associated constipation symptoms (75). The study further concludes probiotics can partially restore beneficial microbial taxa that are often observed to be reduced or absent from PD patient gut microbial populations (75). More research will be needed to connect probiotics and their modulatory effect on the gut microbiome to PD symptoms.

Another growing area of interest is using fecal microbial transplantation (FMT) to mitigate microbial dysbiosis and alleviate PD symptoms. Recent studies demonstrate that restoration of gut microbial diversity is linked to reducing pro-inflammatory signals and protective effects against PD symptoms (18, 19.) A 2018 study concludes FMT reduces gut dysbiosis, suppresses pro-inflammatory TLR4 and TNFα signaling, and significantly PD PD-associated motor symptoms in murine models of PD (18). A similar 2021 study supports and expands on this model, concluding that FMT restores gut microbial diversity and barrier integrity, reduces pro-inflammatory TLR4 and NFkB signaling, and restores motor function in rotenone-induced PD mouse models (19). This pre-clinical data shows promise and a roadmap for future human trials.

Conclusion

The significance of the gut-brain axis in neurodegenerative disorders is clear and warrants further investigation to understand the underlying pathophysiology of these diseases better. Dysregulation of the gut microbiome contributes to neuroinflammation by modulating immune responses and altering gut permeability, ultimately promoting αSyn aggregation and neurodegeneration. Understanding the connection between the gut microbiome and immune response, we can develop targeted treatments to restore gut microbiome diversity and inflammatory cytokines, thereby preventing neurodegeneration.

A consistent pattern of gut microbiota shifts has been observed in PD patients, with notable reductions in *Prevotella*, *Faecalibacterium prausnitzii*, and *Roseburia*, all of which play key roles in maintaining gut homeostasis and anti-inflammatory signaling. Notably, *Prevotella* levels are significantly reduced in PD patients, potentially contributing to neuroinflammation and neurodegeneration. This suggests that *Prevotella* could serve as a potential biomarker for PD. Similarly, *Faecalibacterium prausnitzii* and *Roseburia*, both members of the Lachnospiraceae family, exhibit lower abundance in PD, which may lead to decreased anti-inflammatory SCFA production, resulting in neuroinflammation. Their depletion may contribute to increased neuroinflammation through decreased SCFA production.

In contrast, an increase in *Bacteroides* has been observed, potentially exacerbating neuroinflammation through increased lipopolysaccharide (LPS) production, leading to more rapid disease production.

Additionally, the Verrucomicrobiaceae family is often elevated in PD patients, which may be linked to altered gut barrier function exposing the gut neural plexus to toxins leading to an accumulation of αSyn aggregation and Lewy body formation, increasing the progression of PD. These microbial alterations are strongly associated with increased circulating cytokines, disrupting the BBB and accelerating neurodegenerative processes. Homeostatic gut microbiome disruptions and innate immune response are closely associated with the motor and non-motor symptoms present in PD. Numerous studies have identified a consistent pattern of gut microbiota dysbiosis in PD, with specific bacterial taxa playing a key role. These shifts in key gut microbial populations may contribute to PD pathophysiology through gut permeability, neuroinflammation, and microbial metabolite production mechanisms.

Given these findings, targeted modulation of gut microbiota presents a promising therapeutic approach. Restoring microbial diversity through prebiotics, probiotics, or dietary interventions could reduce inflammatory cytokines, enhance gut barrier function, and potentially slow PD progression. Further research is essential to establish transparent causal relationships and identify specific microbiota that could serve as diagnostic biomarkers or therapeutic targets. Understanding the direct communication mechanisms between the gut microbiome, immune responses, and the brain could pave the way for novel microbiome-based interventions, potentially transforming the treatment of neurodegenerative diseases.

Disclosures

The authors have declared no conflicts of interest relevant to this study. Ethical approval was not required for this study, as it is a systematic review of existing literature. The data supporting this work were obtained from multiple published sources, as referenced in the manuscript. MG, TG, LW, and AT were responsible for the study concept, primary literature search, and manuscript drafting. They also contributed equally to interpreting the primary literature data and revising the manuscript. All authors reviewed and approved the initial draft. BP supervised the project, reviewed the manuscript for further modifications, and approved the final version for submission.

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