The Gut Microbiome and Their Alterations in Parkinsons Patients: Recent Literature Based Review

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ABSTRACT

The microbiome and the host have complex hormonal, metabolic, neurological, and immunological associations. In regulating many physiological processes this molecule cross-speech is critical. Changes in gut microbiome composition or function can have profound negative or positive consequences for the host. Cohort studies comparing well-healthy, diseased patients' gut microbiome profiles found a relationship between many conditions and one individual's intestinal microbiome. Dysbiosis is often referred to as a change in the microbiome linked to a disease. In most cases, determining whether dysbiosis is a reason or disease action is difficult, and further research (e.g., intervention and longitudinal strategies) is needed to establish cause-effect. Another significant discovery is that no two people, even identical twins, have the same microbiome. In reality, the gut microbiome profiles of healthy people of similar age and demographic are significantly different. Our attempts to define what a "healthy" microbiome has so far failed. A "Healthy" stomach is assumed to have high levels of taxonomic variety (richness), as well as the lack of harmful species. Alterations in gut microbiota are associated to Parkinson's disease, while the functional importance of these changes is uncertain. A lot of attention has recently been paid to faecal metabolomics, which provides a functional readout of microbial activity.

KEY WORDS: PARKINSON'S, DISEASE; MICROBIOTA, INTESTINAL. MICROBIOTA.

INTRODUCTION

Microorganisms are responsible for essential fermentation mechanisms, as well as for infectious diseases "germs theory". These incidents have tainted the public's opinion of microbes. Because of their association with diseases and food spots, microorganisms were commonly regarded as antagonistic throughout much of the twentieth century. In the next change, it will take another century before we realize the major roles microbes have in each day life. Advances in DNA sequencing technology have made it routine in research institutions all around the world in the previous decade. Scientists may identify and describe huge microbial ecosystems in and on corpses by using next-generation sequencing (NGs) technology (dubbed human microbiome). Our human microbiome contained 1,000 distinct species of prokaryotes, archaea, eukaryotes, and viruses, according to NGs measurements. In addition, both microbial and human cells make up a typical human individual (Sender et al., 2016).

Microbial genes amount in the human microbiome may signify the phylogenetic variety and vast metabolization potential of the human microbiome. The human microbiome has roughly three million (non-redundant) genes, despite the fact that human genome has approximately 20,000 genes. Babies are inoculated with their first microbiota upon delivery. According to studies, different delivery strategies (e.g., vaginal vs. caesarian) result in distinct microbiota patterns in the kid. Infants were traditionally thought to be sterile in pregnancy, but germs were detected in nearly a third of placental samples in 2013 research. Infant's gut microbiota constituents are affected by their diet (Qin et al., 2010; Stout et al., 2013; Goedert et al., 2014).

Human breast milk, for example, contains oligosaccharides, which a child cannot understand but which may be digested by particular bacteria in the gut. As a result, human breast milk evolved to support the gut microbiome of both the child and the infant. Early development of the baby gut microbiome is critical for the creation and operation of the

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adaptive and innate immune systems. The gut microbiome is thought to make up around 75% of the immune cells in the body, and there's growing evidence that it's where autoimmune illnesses like inflammatory bowel disease start and are controlled (Furness et al., 1999; Frese, 2017; DeWeerdt et al., 2018).

In developed countries, the prevalence of allergy and autoimmune illnesses has increased considerably during the previous four decades. According to "hygiene hypothesis" or "microbial exposure hypothesis," this increase is due to developing countries' raising sanitary lifestyles. The relationship between human microbiome and its effect on immune system growth and function has been carefully investigated in two recent publications, "Missing Microbes" and "Dirt is Good," both published by notable academics. Human microbiome has been an underestimated and understudied target for new illness detection and treatment options until recently. Irritable bowel syndrome, colorectal cancer, chronic idiopathic constipation, and obesity are linked to a shift in gut microbiota (Okada et al., 2010; Isolauri, 2012; Russel, 2013; Khan, et al., 2014; Christodoulides et al., 2016; Gilbert et al., 2017; Roca-Saavedra et al., 2018).

Obesity is a complex condition with numerous causes, one of which may be linked to gut microbiome contents. The transplantation of faeces from obese and non-obese twins into mice was one of the most impressive gut microbiomes works produced by obesity research. Following that, the mice were served a high-fat diet; those who received the lean microbiome stayed that way, whereas those who received the obese microbiome gained weight. In comparison to genetics and other modifiable risk factors, dietary modifications are thought to have a five-fold effect on gut microbiota compositions (Zhang et al., 2010; Ridaura et al., 2013; Jeffery et al., 2013; Duncan et al., 2013; Roca-Saavedra et al., 2018).

Though short-term dietary modifications resulted in transitory changes in gut microbiota composition, long-term dietary alterations resulted in significant alterations. It's been difficult to fully comprehend or monitor human diets to judge the effect of their daily food, which is why animal models and small feeding trials, as well as supplementation studies, have been used extensively. Dietary diversity and food quality are crucial predictors of gut microbiome composition; with higher-quality meals leading in a 47 percent more diverse and likely healthier gut microbiota (Walker et al., 2011; O'Connor et al., 2014; Holscher, 2017).

This is particularly true of plant-based diets, which contain a wide variety of dietary fibres; the more fibres available, the more diversified the microbiota grows. Frailty, inflammation, and poor health outcomes have been linked to elders' lack of food diversity and consistency since moving into residential care (Claesson et al., 2012; Perez Martinez et al., 2014; Holscher, 2017; Roca-Saavedra et al., 2018). A microbial culture is a group of microorganisms living together. Multi-species assemblages of (micro) organisms that interact in a continuous habitat are more aptly described as microbial communities. The microbiome is the microbial community in a well-developed ecosystem with different physio-chemical features which result in the establishment of distinct ecological niches. On the other hand, there have been plethoras of microbiome descriptions published. A community of commensal, symbiotic, and pathogenic microorganisms residing inside a body area or other habitat is referred to as a microbiom. Marchesi and Ravel described genomes, microbial (and viral) gene expression patterns, and proteomes in a particular habitat, as well as the biotic and abiotic components that were present at the time (Whipps et al., 1988; Lederberg et al., 2001; Konopka, 2009; Marchesi, 2015; Berg et al., 2020).

The microbiome is a living, breathing micro-ecosystem that evolves over time and across multiple scales. Due to technological limitations, particularly in examining non-cultivable bacteria of interest and a lack of population-scale data displaying microbiota compositions and activities, the properties of the human microbiome and host–microbiota interactions were essentially unknown until recent decades (Berg et al., 2020). Meanwhile, advances in sequencing technology and large-scale sequence-based microbiome projects, such as the Human Microbiome Project (HMP) consortium funded by the National Institutes of Health (NIH) and the Meta HIT (Metagenomics of the Human Intestinal Tract) consortium funded by the European Commission, have ushered in a new era of sequencing-based microbiome research. These large-scale studies aim to characterize the human microbiome and its activities in health and illness, with Meta HIT focused exclusively on the gut microbiome. To taxonomically characterize microbial communities, 16S ribosomal RNA (rRNA) was sequenced. To taxonomically characterize microbial communities, 16S ribosomal RNA (rRNA) was sequenced.

To taxonomically characterize microbial communities, 16S ribosomal RNA (rRNA) was sequenced. To taxonomically characterize microbial communities, 16S ribosomal RNA (rRNA) was sequenced. A type of RNA present in ribosomes is 16S ribosomal RNA. Whole genome shotgun (WGS) metagenomic sequencing of body-site specific whole community DNA, followed by reference genome mapping, metagenomic assembly, gene cataloguing, and metabolic reconstruction, as described by Methé et al. (2012); and 16S ribosomal RNA (rRNA) sequencing to taxonomically characterise microbiota communities, to facilitate maximum capture of organismal and functional information (The Human Microbiome Project Consortium, 2012).

Human Microbiome and Its Functions: The human microbiome is unparalleled in its diversity and quantity. Bacteria are the most common members of this group, having the highest density in the gut, especially the colon. Bacteroidetes and Firmicutes are the most prevalent bacterial phyla, followed by *Actinobacteria, Proteobacteria, Verrucomicrobia*, and *Fusobacteria*. A "heart" human microbiome has been established in most computational analyses in most human subjects tested, that described by a collection of common genes present in certain habitat (as

skin, oral mucosa, stomach, and vagina) (Huttenhower et al., 2012; Le Chatelier et al., 2013, Ding et al., 2014; Ding et al., 2014; Ursell et al., 2012; Lloyd-Price et al., 2017).

Microbiome affects human physiology in ways that go beyond gut function, inspite the fact that the human GI tract has most diverse microbial community. This is accomplished by a range of immunologic, homeostatic, and metabolic processes; however, due to the enormous number of microbial species, distinguishing which strain is responsible for each trait can be challenging. The fact that germ-free (GF) animals born and housed without exposure to microbes exhibit a number of systemic abnormalities, including an underdeveloped immune system and gastrointestinal tract, highlights the significance of microbiota-host interactions. After recolonization, some of these shortcomings, such as better gut immunity, can be recovered in GF animals (Umesaki et al.,1999; Smith et al., 2007; Smith et al., 2007).

The gut microbiota is required for the production, regulation, and differentiation of intestinal epithelium in the small and large intestines, as well as modulating GI motility and enhancing normal ENS development, regulates the integrity and fortification of mucosal barrier, and stimulates angiogenesis. Microbiota's close association with the host resulted in the establishment of a variety of molecular pathways that allow host's defense system to learn to accept commensal population while continuing to function normally. Both innate and adaptive responses are affected and programmed by microbiota. Innate immune system, for example, has evolved a system of protein receptors that recognize common microbe-associated molecular patterns (MAMPS), as bacterial cell wall components (lipopolysaccharide and peptidoglycan) and flagellin, which are similar across bacterial species (Hooper et al., 2001; Anitha et al., 2012, Brun et al., 2013, Collins et al., 2014; Goto et al., 2014; Thaiss et al., 2016).

Defense initial line against invading pathogens is the quality of this receptor family, which contains transmembrane proteins. Because the intestinal mucosa is closely related to ENS, TLRs are vital for gut homeostasis and neurochemical communication with it. In mice, knocking down TLR2 or TLR4 disrupts the morphological and functional integrity of the intestinal mucosa, changes gut movement, and decreases myenteric neurons numbers and neurotrophic factor output. Gut microbiota has an impact on B cells ability to generate and secrete IgA. Connections could be mutualistic, communalistic, or pathogenic. The genomic materials of organisms (microbiota) that live in a specific location of the human body make up the human microbiome (Anitha et al., 2012, Brun et al., 2013; Furusawa et al., 2013; Wesemann et al., 2013; Kawasaket al., 2014; Berg et al., 2020).

Microorganisms can be found in a variety of locations, including the skin, mucosa, gastrointestinal system, respiratory tract, urogenital tract, and mammary gland. They create a distinct, dynamic ecosystem that adapts to the niche's particular environmental conditions. Following birthing, a long-term association (symbiosis) develops between human body and its native microbiota. For total enjoyment and health, these connections are necessary. Co-evolution has allowed microbiota species to actively adapt to their habitats and live in niches within the human body (Grice et al., 2011, Yilmaz et al., 2014; Whitesid et al., 2015).

These species are known as body parts because of their biological roles, which cause a wide range of changes from conception to death. As a result of the host's influences, the human microbiome is always changing. At any one time, age, diet, lifestyle, hormonal swings, inherited genes, and underlying disease all have an effect on the human microbiome. Dysbiosis, on the other hand, is a shift in human microbiota composition that can cause life-threatening disorders. The importance of a healthy microbiome in maintaining good health can't be overstated. The stomach is where the human microbiome is most dense. These animals are essential for human health preservation and maintenance. Changes in the immunological environment have been linked to a dysbiotic gut flora in previous researches on human microbiome project (Whitesideet al., 2015).

Dybiosis has also been linked to life-threatening illnesses like cancer, bowel inflammatory disorders, cardiovascular diseases, and antibiotic-resistant bacterial infections. Mutualistic, communalistic, or pathogenic connections are all possible. The human microbiome is made up of the genomic material of species (microbiota) that live in a specific area of the human body. Microorganisms can be found on the skin, mucosa, respiratory tract, gastrointestinal system, urogenital tract, and mammary gland, among other areas in the body. They establish a dynamic and unique ecosystem that responds to the niche's unique environmental conditions. Microbiota species have actively adjusted to their special circumstances and exist in niches inside human body due to coevolution (Whiteside et al., 2014; Hoeppli et al., 2015; Pascal et al., 2018).

Due to their biological activity, these species are recognized as part of body, resulting in a variety of alterations from conception to death. In response to host cues, the human microbiome is continually developing. Healthy microbiome is essential for maintaining good health. The stomach is where the human microbiome is most dense. These animals play an essential role in human health preservation and maintenance. According to prior researches on human microbiome project, alteration in immunological environment can be associated with dysbiotic gut flora. Dybiosis has been related to life-threatening health conditions such as cardiovascular diseases, cancer, bowel inflammatory disorders, and resistance bacterial infections, all of which are associated to antibiotic resistance (Morgan et al., 2012; Whiteside et al., 2014; Pascalet al., 2018; Ogunrinola et al., 2020).

Microbiome and the Gut-Brain Axis: Changes in gut integrity and microbial development can have an impact on brain function. Gut–brain axis is a two-way communication system that communicates between CNS and gut through neuronal, endocrine, and immunological signals. Vagal or spinal innervation is supposed to transmit neural

knowledge. Microbiota deliver multiple signals to the CNS and ENS, either directly or indirectly, through the creation of neurotransmitters or neurochemical-like precursors in ENS. Bifidobacterium infant is boosted tryptophan levels in the circulation, which is a precursor to serotonin and SCFAs also enhance the serotonin formation by intestinal cells (Desbonnet et al., 2010, Yano et al., 2015, Dinan et al., 2017; Miraglia et al., 2019).

Control microglia maturation in the CNS, influence ENS activity via G-protein coupled receptors like GPR41 and GPR43, and mediate epigenetic change via histone deacetylation. Microbiome of the human stomach has multiple effects on brain health. Lipopolysaccharides, for example, are structural bacterial components that stimulate innate immune system in a low-grade tonic manner. Systemic and/or CNS inflammation is caused by excessive stimulation from bacterial dysbiosis, small intestine bacterial overgrowth, or enhanced intestinal permeability. Adaptive immune system failure is caused by bacterial proteins reacting with human antigens. D-lactic acid and ammonia are neurotoxic metabolites produced by bacterial enzymes. Short-chain fatty acids, which are beneficial metabolites, may be neurotoxic (Venteret al., 2001; Qin et al., 2010; Soret et al., 2010; Nohr et al., 2013; Surjyadipta, 2013; Jacquemin, 2014; Erny et al., 2015).

Human-like hormones and neurotransmitters can be created by gut microbes. Microbial growth and pathogenicity are affected by bacterial receptors for these hormones. Gut bacteria excite afferent neurons in the ENS, prompting the vagus nerve to transmit messages to the brain. The architecture of sleep and the stress reactivity of the hypothalamic-pituitary-adrenal axis are both influenced by gut microorganisms via these several pathways. They have an impact on memory, mood, and cognition, and are important in the treatment of alcoholism, chronic fatigue syndrome, fibromyalgia, and restless legs syndrome (Hooper, 2004; Galland, 2014).

Gut Microbiota and Central Nervous System Disorders: Human cells account for nearly half of all cells and 1% of all unique genes in our body, with rest originating from microorganisms such as archaea, bacteria, fungus, and viruses. These bacteria make up the human microbiota, with the majority colonizing the gut. The identification of these bacteria and the examination of their contribution to neurological health has been made possible by recent technology developments, open access data repositories, and the use of high throughput sequencing. Alterations in gut microbiota associated with neurological illness risk, activity, and progression, according to new research. Despite substantial clinical and biological research, many neurological illnesses' aetiology, development, and effective therapy remain unknown. The aetiology of these diseases is complex.

The gut bacteria and CNS interact in a variety of ways, according to numerous researches (Sampson et al., 2015). These bidirectional interactions make up gut microbiota–brain axis (Bauer et al., 2016, Dinan, 2017). The first step in identifying whether and how the gut microbiota–brain axis influences human neurological illnesses is to conduct epidemiological investigations (Tremlett et al., 2017). Alzheimer's disease, multiple sclerosis, autism spectrum disorder, Parkinson's disease, and stroke have all been linked to the microbiome as a potential risk factor. Changed microbial composition contributes to the pathogenesis of such disorders, according to cross-sectional clinical research (Cryan et al., 2020).

Basic Microbiome Methodology: Until the 1990s, the majority of gut microbiology research was done using culture, staining, and microscopy. Many anaerobic microbes could not be cultivated or investigated because growth media and circumstances preferred fast-growing, aerobic microbes with DNA sequencing advent, this changed. The 16S bacterial ribosomal RNA (rRNA) gene sequencing method (hereinafter 16S) gained a lot of traction quickly (Matsuki et al., 2002). Conserved sections of this gene are utilized to make broad-spectrum polymerase chain reaction (PCR) primers that can amplify hypervariable areas that are rapidly developing across a wide range of bacteria. By comparing the amplified hypervariable area sequences to a curated library of fully sequenced bacterial 16S genes, the sequences can be taxonomically identified (Louis et al., 2007; Hiergeist et al., 2015).

Although 16S is still the most extensively used approach for describing bacterial communities in research, it has a number of drawbacks. For starters, taxonomic classifications are widely employed to classify microorganisms. Second, because many species within the hypervariable region under study have the same sequence, sequence classification is frequently confined to genus value. Using data from Human Microbiome Project, tools like PICRUSt (Phylogenetic Investigation of Communities by Reconstruction of Unobserved States) can infer potential functional pathways from 16S results, but 16S analysis is susceptible to primer bias and does not provide direct information about gut microbe function or potential interactions with host physiology (Langille et al., 2013; Srinivasan et al., 2015; Pollock et al., 2018).

Factors Infusing the Gut Microbiome: A variety of factors, beginning at birth, influence gut microbial makeup and metabolic capacities, as measured by various methods. The embryonic intestine has extremely few bacteria, if any, because the womb is normally sterile. Microbial colonisation begins at birth, and the method of delivery (vaginal, Cesarean, and newborn feeding) has a significant impact. Improved sanitation, immunisation, the eradication of enteropathogens, and exposure to antibiotics and nonantibiotic treatments are all factors that affect the commensal, or native, microbiota. Throughout one's life, one's diet has effect on microbial compositions of one's body (Penders et al., 2006; David et al., 2014; Perez-Muoz et al., 2017; Maier et al., 2018).

Parkinson's disease: Parkinson's disease (PD) is commonest neurological condition, second only to Alzheimer's disease in terms of prevalence. Clinically, it is distinguished by parkinsonism (rigidity, rest tremor, bradycinesia, and postural instability) and pathologically by

neuronal loss in the nigra and elsewhere, which is linked to ubiquinone protein deposits in neuronal cytoplasm (Lewy organisms) and protein-like threading inclusions within neuritis. Parkinson's disease strikes 0.1 percent of those aged 65 to 69, and 1-3 percent of those aged 80 and up. Other illnesses with significant parkinsonian symptoms and signs, such as postencephalitic, drug-induced, and arteriosclerotic Parkinsonism, may be mistaken for Parkinson's disease until an autopsy confirms the diagnosis. About six million people around world suffer from Parkinson's disease (Nussbaum et al., 2014, Armstrong et al., 2020).

Beyond the classic view of Parkinson's disease as a movement disorder, it has become obvious that non-motor symptoms such cognitive impairment, autonomic dysfunction, sleep issues, depression, and hyposmia are all part of the disease and contribute considerably to the total burden. Parkinson's disease strikes men twice as often as it does women in most regions. There was no gender split or perhaps a female excess in a few of villages, including one in Japan. The male majority could be explained by the protective effect of female sex hormones, a sex-related genetic mechanism, or sex-specific disparities in risk factor exposure in the environment, as well as health-care discrepancies (Van Den Eeden et al., 2003; Poewe et al., 2017).

Causes and Genetics of Parkinson's disease: People frequently question, "Why?" after receiving a Parkinson's diagnosis. Parkinson's disease has no recognized etiology for most people ("idiopathic"). Parkinson's disease triggered by a mix of causes, according to researchers. If there existed a continuum with hereditary causes on one end and environmental causes on the other, people with Parkinson's disease would tumble all over the place. Some cases may be genetically determined, while others may be more impacted by environmental factors. Aging is also a factor. Researchers may be able to develop medicines to slow or perhaps prevent the disease if they learn more about what's causing it. Genetics, according to researchers, accounts for roughly 30% of Parkinson's risk. Only around 10% of this risk can be explained by existing genetic linkages, implying that more Parkinson's genes have yet to be uncovered. Studies discovered a number of causal Parkinson's genes (GBA, LRRK2, PRKN, SNCA) in the last decade, where genetic abnormalities dramatically enhance one's risk of developing the disease. Other factors must play a role because not everyone with these genetic abnormalities develops Parkinson's disease,(Khan & Ali 2017, 2018, and Ali and Khan 2021).

Environment and Aging: Other factors linked to elevated risk of Parkinson's disease. Head injuries and pesticide exposure are two of them. After consuming drugs infected with a toxin called MPTP, a group of heroin addicts in California developed a form of Parkinson's disease in the early 1980s.Smoking and coffee usage have been related to lower incidence of Parkinson's disease in numerous studies. Parkinson's disease is most commonly caused by old age. Researchers predict that by 2040, the number of persons with Parkinson's disease will have doubled due to an ageing population. Scientists believe that as we age, our cells become more vulnerable to degeneration. Furthermore, the expression of our genes may alter with time, potentially triggering a cascade of biological processes that leads to Parkinson's disease (Ali and Khan 2021).

Microbiome and Parkinson's disease: Parkinson's disease is a neurodegenerative disease that causes both nonmotor and motor symptoms. Nonmotor symptoms of Parkinson's disease often appear years before motor symptoms. Pathophysiologic abnormalities in the gastrointestinal system, as well as the ENS and CNS, are hypothesized to be linked to dysbiosis of the typical gut microbiome. These alterations are thought to lead to the death of dopaminergic neurons by a variety of mechanisms, including the release of neurotoxins into the bloodstream, a decrease in the production of neuroprotective substances, and an increase in inflammatory and autoimmune responses (Shulman et al., 2011; Elfil et al., 2020).

Intracellular deposition of aggregated -synuclein, which leads to neuronal cell death and inflammation, has long been thought to constitute its pathogenic characteristic PD is now understood to be a multi-systemic disease that affects both the CNS and the PNS and results in a variety of non-motor symptoms like gastroparesis and constipation. Due to the early involvement of the gastrointestinal system, which commonly precedes motor symptoms by years, changes in gut microbiota composition were studied in relation to PD pathogenesis. The hypothesis that the gut microbiota has a role in Parkinson's disease and other neurodegenerative diseases is supported by animal research. According to Sampson and colleagues, the microbiota can affect synucleinopathy and neuroinflammation (2016). (Cersosimo et al., 2012; Pellegrini et al., 2018; Keshavarzian et al., 2020).

As a result, the microbiome could be exploited to provide diagnostic markers and as a therapeutic target. Increased gut permeability and inflammation have been linked to reduced gastrointestinal short-chain fatty acid (SCFA) concentrations in PD patients. SCFAs are the byproducts of bacterial fermentation of dietary components, and they are critical for colonic epithelium feeding and maintenance. Reduced SCFA-producing taxa in PD patients leads to low levels of SCFA. The composition of the PD gut microbiota has been studied in over 20 case–control studies. There were over 100 taxa that were found to be varied in abundance between PD patients and controls (Clairembault et al., 2015; Keshavarzian et al., 2015; Ungeret al.,2016; Hill-Burns et al., 2017; Schwiertz et al., 2018; Qian Yang et al., 2018; Pietrucci et al., 2019; Aho et al., 2019).

Several studies have suggested that persons with Parkinson's disease have a different gut microbiota than people without the condition, although the findings are often conflicting, and there is no consensus on which taxa are associated to the disease. Bacteria from the genus Akkermansia and the Verrucomicrobiaceae family were found to be enriched in patients with Parkinson's disease, but bacteria from the Lachnospiraceae family were found to be deficient. The

Lactobacillaceae family has been found to be high in PD in Western cohorts, although this has never been found in Chinese studies (Qianet al., 2018).

Bacteria belonging to the Prevotellaceae family have also shown inconsistent outcomes. Several studies revealed that the abundance of these taxa was dramatically reduced in PD patients when compared to controls, whereas others found no differences in abundance or found that these taxa were enriched in PD patients. Inherent variability of gut microbiota across cultures, lifestyles, and diets, as well as differences in study designs and methods for obtaining and evaluating 16S rRNA-gene amplicon data, could all lead to disparities between studies. To further understand the significance of changes in the intestinal microbiota composition in PD and assess its potential as a biomarker for PD risk, diagnosis, and prognosis, cross-study comparisons and identification of disease-specific modifications are required (Petrov et al., 2017; Heintz-Buschart et al., 2018; Aho et al., 2019; Savva et al., 2021).

The potential role of gut microbiota in PD pathogenesis: As a result of its critical role in human body functioning, the gut microbiota evolved and became an integral component of people's life. Gut flora influences the release of neurotransmitters such as serotonin, dopamine, norepinephrine, gamma-aminobutyric acid, and glutamate, which may have implications for intra-cerebral functions. As a result, gut dysbiosis could play a role in the disruption of brain signalling networks. Bacterial components such lipopolysaccharide and amyloid protein curli increase synuclein aggregation, suggesting gut microbiome role in synucleinopathies like Parkinson's disease. Additionally, in genetically sensitive animals, gram-negative bacteria in the intestines can cause PD-like symptoms.

Helicobacter pylori infection has been linked to more severe motor impairment, decreased brain dopamine levels, impaired levodopa absorption, as well as immunological and inflammatory reactions in Parkinson's disease patients. H. pylori eradication, on the other hand, had no effect on motor function, according to an RCT. Finally, the gut microbiome of people with Parkinson's disease differs from that of healthy people. Despite the fact that results vary widely due to a differences of confounding factors as geographic dispersion, diet, gender, age, BMI, and medication, the findings are encouraging (including catechol-O-methyl transferase inhibitors).

Two new meta-analyses reveal that people with PD have a pro-inflammatory gut dysbiosis, which is defined by low amounts of SCFA-producing bacteria. SCFAs are immunomodulatory and metabolic byproducts of bacterial fermentation. Another factor to consider when studying gut microbiota composition in Parkinson's disease is some bacteria's ability to metabolise levodopa, primarily via the tyrosine decarboxylase pathway, which causes premature conversion of levodopa to dopamine in the small intestine, resulting in decreased levodopa availability and increased levodopa dose required (Metta et al. 2021).

PD and Gastrointestinal Symptoms: Constipation had a positive probability ratio of 2.2 in a probabilistic approach for detecting prodromal PD in patients with non-motor symptomatic signs, according to the Movement Disorders Society. Some researchers hypothesized that early degenerative PD pathology is associated to constipation, or that early PD pathology begins in the intestinal plexus, based on these associations. However, the idea of multifocal disease, or at the very least the complicated interplay that happens years or decades before motor traits manifest as a result of centrally mediated non-motor prodromal traits like RBD and hyposmia, which have a high prodromal PD risk, should be mentioned (Abbott et al., 2001, Dickson et al., 2009, Hawkes et al., 2010; Berg et al., 2015).

Conflict of Interest: There is no conlfict of interest.

Data Availability Statement: The database generated and /or analysed during the current study are not publicly available due to privacy, but are available from the corresponding author on reasonable request.

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