Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com

General review

Oral and intestinal dysbiosis in Parkinson's disease

E. Berthouzoz [a], V. Lazarevic [a,b], A. Zekeridou [c], M. Castro [d], I. Debove [e], S. Aybek [f], J. Schrenzel [a,b], P.R. Burkhard [a,g], V. Fleury [a,g,*]

[a] Faculty of Medicine, University of Geneva, Centre Médical Universitaire, 1211 Geneva 4, Switzerland
[b] Genomic Research Laboratory, Department of Infectious Diseases, University Hospital of Geneva, 1211 Geneva 14, Switzerland
[c] Division of Regenerative Dentistry and Periodontology, University Clinic of Dental Medicine, University of Geneva, 1211 Geneva 4, Switzerland
[d] Movement disorders Unit, Department of Neurology, University Hospital of Lausanne, 1011 Lausanne, Switzerland
[e] Movement disorders Unit, Department of Neurology, Inselspital, 3010 Bern, Switzerland
[f] Psychosomatic Medicine Unit, Department of Neurology, Inselspital, 3010 Bern, Switzerland
[g] Movement disorders Unit, Division of Neurology, Department of Clinical Neurosciences, University Hospital of Geneva, 1211 Geneva 14, Switzerland

INFO ARTICLE

Article history:
Received 6 May 2022
Received in revised form
29 October 2022
Accepted 10 December 2022
Available online 16 March 2023

Keywords:
Parkinson's disease
Gut microbiota
Oral microbiome
Pathogenesis
Symptoms
Dopamine replacement therapy

ABSTRACT

The suspicion of an origin of Parkinson's disease (PD) at the periphery of the body and the involvement of environmental risk factors in the pathogenesis of PD have directed the attention of the scientific community towards the microbiota. The microbiota represents all the micro-organisms residing both in and on a host. It plays an essential role in the physiological functioning of the host. In this article, we review the dysbiosis repeatedly demonstrated in PD and how it influences PD symptoms. Dysbiosis is associated with both motor and non-motor PD symptoms. In animal models, dysbiosis only promotes symptoms in individuals genetically susceptible to Parkinson's disease, suggesting that dysbiosis is a risk factor but not a cause of Parkinson's disease. We also review how dysbiosis contributes to the pathophysiology of PD. Dysbiosis induces numerous and complex metabolic changes, resulting in increased intestinal permeability, local and systemic inflammation, production of bacterial amyloid proteins that promote α-synuclein aggregation, as well as a decrease in short-chain fatty acid-producing bacteria that have anti-inflammatory and neuroprotective potential. In addition, we review how dysbiosis decreases the efficacy of dopaminergic treatments. We then discuss the interest of dysbiosis analysis as a biomarker of Parkinson's disease. Finally, we give an overview of how interventions modulating the gut microbiota such as dietary interventions, pro-biotics, intestinal decontamination and fecal microbiota transplantation could influence the course of PD.

* *Corresponding author at*: Movement Disorders Unit, Division of Neurology, Department of Clinical Neurosciences, University Hospital of Geneva, Site Cluse-Roseraie, Rue Gabrielle-Perret-Gentil 4, 1211 Geneva 14, Switzerland.
E-mail address: Vanessa.FleuryNissen@hcuge.ch (V. Fleury).

Abbreviations: SCFA, short chain fatty acids; FMT, fecal microbiota transplantation; LPS, lipopolysaccharide; PD, Parkinson's disease; CNS, central nervous system; PNS, peripheral nervous system; SFA, saturated fatty acids.

https://doi.org/10.1016/j.neurol.2022.12.010

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease. It affects about 1% of people over 60 years of age with a male/female ratio of 3:2 [1]. Its pathogenesis has not yet been elucidated. Monogenic forms of PD are rare [2]. In the vast majority of cases, the cause of PD is unknown and is probably multifactorial involving a complex interaction between genetic predisposition (6–36% of cases with genetic variants, risk factors for the disease), environmental factors (pesticides, air pollution [3], oil and heavy metals as risk factors; tobacco, coffee and sport as protective factors [4]), epigenetic variations [5] and the interaction of these phenomena with age-related processes [6,7].

The hypothesis that PD originates in the gut has stimulated interest in environmental risk factors that may have a role in the pathogenesis of PD and has focused the attention of the scientific community on the microbiota. The microbiota is the set of microorganisms residing both in and on the human body. In recent years, a revolution has occurred as a result of the understanding that the microbiota plays an essential role in the course of human physiological functions. Numerous studies have shown that PD is associated with a disruption of the normal balance between microbiota and the host (i.e. dysbiosis) both orally and in the intestine [8–19].

In this paper, we first summarize how the scientific community has suspected a role for the microbiota in PD and we review how dysbiosis influences PD symptoms, contributes to PD pathophysiology, and dopaminergic treatment absorption. We also discuss the potential role of the microbiota as a biomarker of PD and how interventions modulating the gut microbiota could influence the course of PD.

2. The peripheral origin of non-genetic forms of PD

The common appearance of non-motor symptoms such as hyposmia (46% of newly diagnosed untreated patients), constipation (38.5%), postprandial fullness (23%) and loss of taste (14%), often several years before the onset of central nervous system (CNS) motor symptoms (akinesia, rigidity, tremor), suggests a peripheral onset of the disease process [21]. Furthermore, autopsy studies have found α-synuclein aggregates (i.e. a pathological hallmark of PD) in the periphery of the body, not only in the CNS (olfactory bulb) but also in the autonomic peripheral nervous system (PNS) in a rostro-caudal gradient with a higher density of synucleinopathy in the salivary glands and esophagus and less in the colon and rectum [22,23]. These pathological deposits can be found early, before the diagnosis of PD, in biopsies of the gastrointestinal tract [24]. Braak and colleagues developed this line of research and theorized the different stages of PD, which would begin at the periphery of the body, in the nose and the intestine (''dual-hit hypothesis''), and would then be transmitted to the brain in a second stage [25]. A recent study using multimodal scintigraphic imaging identified that PD begins either in the periphery of the body (''body-first'' PD subtype) and in particular in the digestive tract and myocardial muscle in about two thirds of patients, or centrally (''brain-first'' PD subtype) in about a third of patients with early involvement of the amygdala or olfactory bulb. Depending on the initial site of involvement, PD then spreads to the other side of the body by trans-synaptic transmission to neighboring neurons [26]. Alpha-synuclein has a ''prion-like'' propagation property, i.e. the aggregates trigger the misfolding (polymerization) of neighboring α-synuclein proteins, transforming them from previously healthy proteins into pathogenic ones [20].

3. Inflammation in Parkinson's disease

The pathophysiology of PD involves different mechanisms such as the accumulation and aggregation of abnormal α-synuclein, impairment of α-synuclein degradation, mitochondrial dysfunction favoring oxidative stress and neuroinflammation. A vicious circle established as the different phenomena described above aggravate each other and lead to neurodegeneration [7]. Neuroinflammation contributes to the onset and propagation of PD. In autopsies, microglial cells in the substantia nigra of PD patients are more activated than those in healthy brains [27,28]. Higher levels of inflammatory cytokines have been measured in the blood, cerebrospinal fluid, colon and saliva of PD patients compared to healthy controls [19,29,30]. Chronic inflammatory diseases of the gastrointestinal tract such as Crohn's disease and ulcerative colitis are recognized risk factors for PD [31]. In contrast, the chronic use of nonsteroidal anti-inflammatory drugs protects against PD [32]. Recent findings have shown that inflammation can influence α-synuclein levels and structure and conversely, α-synuclein can influence the immune response [33,34].

Finally, a higher level of intestinal inflammation [29,35] and an increased intestinal permeability have been demonstrated in PD [36]. These phenomena could promote the precipitation of abnormal α-synuclein, which then spread to the CNS via the vagus nerve [36].

4. The gut and oral microbiota

4.1. *The gut microbiota*

The gut microbiota is the set of microorganisms residing in the human digestive tract. It is mainly composed of bacteria ($\sim 3 \times 10^{13}$) but also includes viruses, fungi, protozoans and archaea [37]. It varies from one individual to another. Following a long co-evolution, it has reached a symbiotic relationship with the human being leading to physiological homeostasis [38]. Several human diseases are associated with reduced gut microbial diversity [39]. The gut microbiota is involved in many functions, including the development of the immune system and the maturation of the lymphoid tissue associated with the digestive tract. It strengthens the intestinal barrier by stimulating the immune response via the production of bactericides to inhibit colonization of foreign

and potentially pathogenic microorganisms. It also participates in the global functioning of the digestive tract, via the regulation of intestinal motility, cell differentiation, intestinal vascularization and the development of the enteric nervous system. In addition, the microbiota plays an essential role in digestion, notably by degrading dietary fibers otherwise not digested by the human body without the help of the microbiota, which results in the production of short-chain fatty acids (SCFAs) including butyrate. SCFAs play a key role for the host, for example, by providing energy to the colonocytes and thus ensuring the integrity of the intestinal wall [40].

4.2. *The brain-gut-microbiota axis*

The CNS and the gut microbiota influence each other through a two-way communication using neural, immune and endocrine signals. For example, the brain regulates the composition and functions of the microbiota by modulating intestinal transit, secretions and permeability. In turn, the gut microbiota influence the development and functions of the CNS via modulation of the immune response, an impact on metabolism (e.g. modulation of the level of some hormones, neuropeptides and neurotransmitters), and an effect on neuronal signaling [41].

4.3. *The oral microbiota*

The oral microbiota is composed of approximately 770 bacterial species and also includes archaea, microeukaryotes and viruses [42]. It is the second most complex microbiota after the gut microbiota and one of the microbiota with the lowest intrapersonal variability. There are different bacterial communities that depend on distinct microenvironments such as mucosal epithelial surfaces (gingival sulcus, tongue, cheek, palate and lips), non-adherent hard surfaces of teeth, and saliva. The proportion of the different species depends on multiple factors of our modern life (tobacco, type of diet, dental hygiene, antibiotic intake, etc.). The relationship between the oral microbiota and the host is dynamic and evolves throughout life, depending on age and hormonal changes (e.g. puberty, pregnancy). The symbiosis between the oral microbiota and its host provides many benefits. The commensal microbiota inhibits colonization by exogenous pathogens and prevent local infections, while contributing to the normal development of human tissues and the immune system. The oral microbiota can metabolize certain chemical compounds such as nitrates, which are important for vascular health. Oral diseases such as dental caries and periodontitis are associated with shifts in microbial community composition. As the entry point for almost all ingested material, and

Table 1 – Contribution of gut dysbiosis to the symptoms and pathophysiology of PD.

Normal gut microbiota	Gut dysbiosis in PD		
Functions	Impact on PD symptoms	Impact on PD pathophysiology	Impact on dopaminergic treatment
1. Development and modulation of the immune system 2. Development of the enteric nervous system 3. Promotion of intestinal wall integrity and strengthening of the mucous barrier 4. Inhibition of colonization by exogenous pathogens and prevention of local infections 5. Global functioning of the digestive tract. *Examples:* intestinal motility, cell differentiation, intestinal vascularization 6. Essential role in digestion *Example:* degrading of dietary fibers and production of short-chain fatty acids (SCFA)	1. Increased motor symptoms severity 2. Increased constipation *Mechanisms involved:* - increased proteolytic fermentation and some deleterious metabolites (p-cresol, phenylacetylglutamine); - decrease in SCFA-producing bacteria and carbohydrate-fermenting bacteria leading to disturbances in electrolytes and water absorption 3. Increased risk of polyneuropathy *Mechanisms involved:* bacterial contribution to folic acid deficit and hyperhomocysteinemia	1. Increased microbial capacity to degrade mucin and host glycans *Consequences:* alteration of the integrity of the intestinal mucus layer, leading to increased intestinal permeability, facilitation of the passage of bacterial toxins which promotes local and systemic inflammation and local and cerebral α-synuclein aggregation 2. Decrease in SCFA-producing bacteria and carbohydrate-fermenting bacteria *Consequences:* - altered colonic mucosa integrity; - decreased expression of anti-inflammatory cytokines and increased expression of pro-inflammatory cytokines leading to increased inflammation; - deleterious impact on brain microglia maturation and neurotrophic factors regulation 3. Increase in bacteria with pro-inflammatory potential and decrease in bacteria with anti-inflammatory potential *Consequences:* increased local and systemic inflammation and α-synuclein aggregation 4. Production of bacterial amyloid-like curli proteins *Consequences:* promotion of local and brain α-synuclein aggregation as well as inflammation	Conversion of levodopa to dopamine in the intestinal lumen by bacterial dopa-decarboxylase enzyme *Consequences:* - decreased efficacy of dopaminergic treatments by reducing the access of levodopa to the blood and then the brain; - reduction of gut motility induced by intestinal intraluminal dopamine increasing the risk of constipation and bacterial overgrowth syndrome

PD: Parkinson's disease.

due to its high vascularity, the oral cavity has ample opportunity to influence the activity of other sites in the body, such as the lungs and the digestive tract. It is therefore not surprising that, in addition to diseases of the oral cavity, oral dysbiosis is implicated in a number of systemic diseases such as infectious pathologies (e.g., infective endocarditis), rheumatological or intestinal inflammatory disorders, atherosclerosis, endocrine diseases (e.g., diabetes), and certain neoplasias, including oral, pancreatic, and colonic cancers [43].

5. Dysbiosis in Parkinson's disease

5.1. *Gut dysbiosis and PD*

A gut dysbiosis, with decreased or increased relative abundance of bacterial species, has been documented in PD [8–16]. Although differences in microbiota profiles varied across studies, three recent meta-analyses have shown consistent differences between PD patients and controls, which included: (1) an increase in the relative abundance of the genera Akkermansia, Catabacter, Lactobacillus, and Bifidobacterium, and the families Akkermansiaceae, Bifidobacteriaceae, Ruminococcaceae, Verrucomicrobiaceae, and Christensenellaceae; and (2) a decrease in the genera Roseburia, Faecalibacterium, and the families Lachnospiraceae and Prevotellaceae [16,44,45].

5.2. *Oral dysbiosis*

The link between the oral microbiota and PD has been less well studied. The role of the oral cavity in PD has long been overlooked. However, hyposialia and dysphagia, usually troublesome in advanced disease, may occur early in PD [46,47]. Poor oral health is more common in PD than the general population [48]. The link between oral microbiota and PD has recently been demonstrated with a different oral bacterial ecology between PD and healthy subjects [17–19]. While oral status was identical between early disease patients and controls, the relative amounts of Firmicutes, Negativicutes, Lactobacillaceae, Lactobacillus, Scardovia, Actinomyces, Veillonella, Streptococcus mutans, and Kingella oralis, were higher in patients, whereas Lachnospiraceae and Treponema were less abundant. The level of the proinflammatory cytokine interleukin-1β was increased in the gingival crevicular fluid of PD patients, suggesting a breeding ground for local inflammation [19].

6. Contribution of dysbiosis in PD

The contribution of dysbiosis in PD is summarized in Table 1 and Fig. 1.

6.1. *Methods in microbiome research*

To better understand how dysbiosis influences PD, various approaches can be utilized [49]. Metagenomics investigates taxonomic composition of tested material to identify bacterial species. This answers the question: ''What bacteria are in the sample?''. Secondly, the functional potential of microbiota members can be defined using functional metagenomics or metatranscriptomics. This answers the question: ''What do the bacteria potentially do?''. A third method called metabolomics allows to identify bacterial metabolites (e.g. sugars, amino acids, fatty acids, etc.). It addresses the question: ''What do the bacteria actually produce?''.

6.2. *Association of dysbiosis with PD symptoms*

The degree of PD severity and some of its motor and non-motor symptoms correlate with specific bacterial taxonomic differences [8,19]. Gut dysbiosis has been correlated with the severity of postural instability and gait difficulty [8]. In addition, salivary dysbiosis correlates with salivary flow rate [19] while gut dysbiosis varies with the degree of constipation [8]. Gut dysbiosis is not simply a consequence of constipation but it can itself modulate gut motility. A complex relationship exists between microbiota composition and gut function, probably involving bidirectional interconnection between the microbiota and colonic transit. In PD patients, the gut microbiota is characterized by increased proteolytic fermentation and production of deleterious metabolites such as p-cresol and phenylacetylglutamine. Increased levels of these proteolytic metabolites and taxonomic shifts in the gut bacterial community are strongly associated with constipation [50]. On the other hand, slower transit impacts on nutrient availability and modifies gut microbiota composition by favoring bacteria that have slower growth rates or that can use different energy sources [51]. In clinical practice, these data are of great interest because they corroborate a recent recommendation by the Movement Disorder Society that recognizes as ''effective'' and ''clinically useful'' a combination of probiotics and prebiotic fibers for the treatment of constipation in PD patients [52,53]. Finally, a link between gut dysbiosis and both anxiety and depression disorders has been suspected [54–62]. The role of dysbiosis on depressive and anxiety symptoms specifically in PD remains to be explored.

Conventional mice overexpressing α-synuclein (i.e., a genetic animal model of PD) show increased PD symptoms compared with mice of the same lineage that had not been exposed to microorganisms (''germ-free'' living conditions). Remarkably, the authors showed that colonization of these mice with microbiota from human PD patients (fecal microbiota transplantation) worsens the motor deficit compared to transplantation of microbiota from healthy human donors. No significant effect on motor function was triggered by the transplantation of microbiota from human PD donors to wild-type mice, suggesting that microbiota contribute to PD symptoms only in genetically susceptible hosts [63].

6.3. *Influence of dysbiosis in the pathophysiology of PD*

Through the use of functional metagenomics and serum metabolomics, an increased microbial capacity to degrade mucin and host glycans has been found in the gut microbiota of PD patients [64]. Mucin is important for the integrity of the intestinal mucus layer and for the maintenance of intestinal barrier function. A decrease in mucin could contribute to the

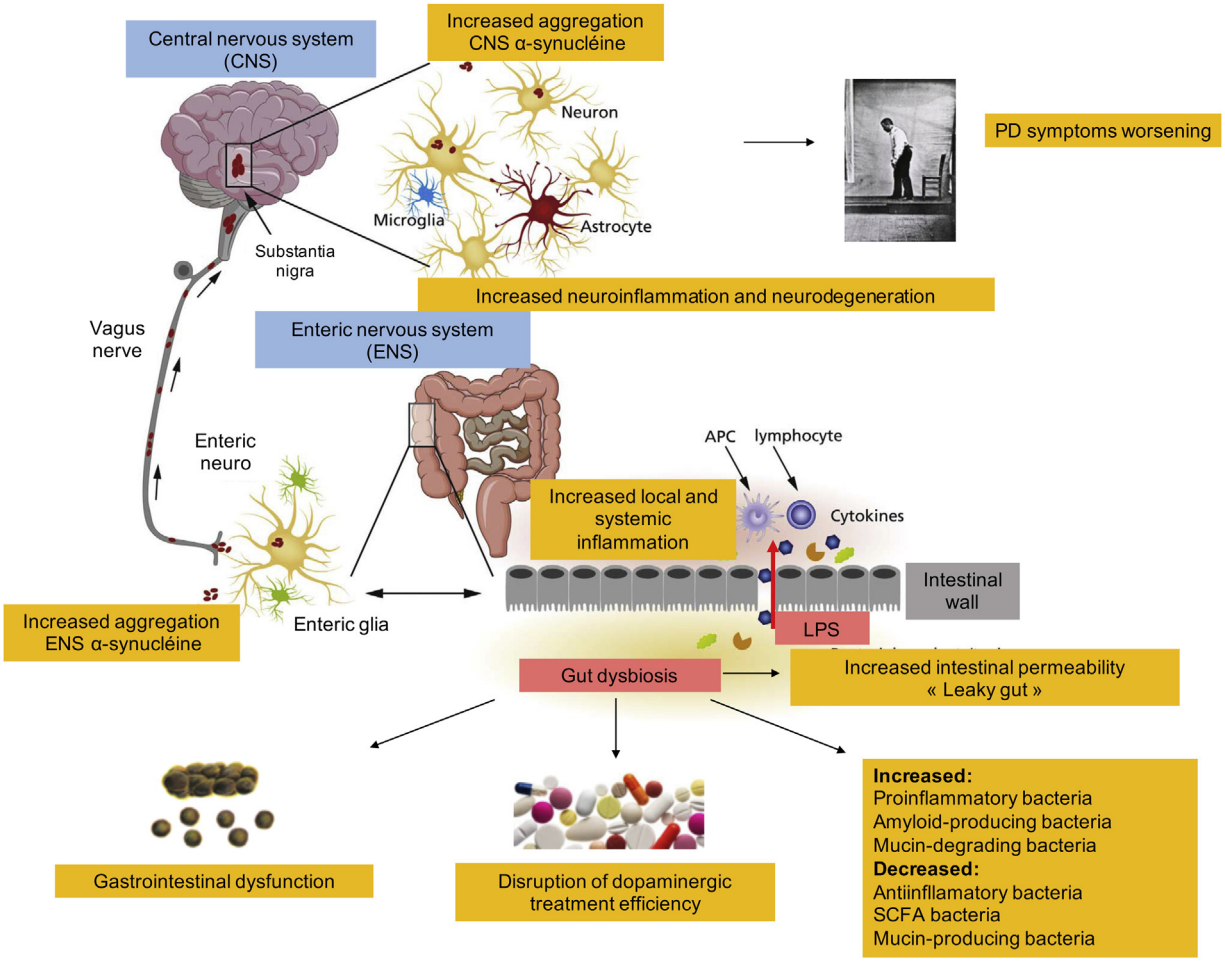

Fig. 1 – Schematic representation of the role of the gut microbiota in the pathogenesis of Parkinson's disease (PD). Gut dysbiosis alters metabolic capacity, disrupts intestinal permeability and promotes inflammation. These processes participate in the accumulation and propagation of alpha-synuclein from the enteric nervous system to the central nervous system via the vagus nerve. Gut dysbiosis also contributes to the motor and non-motor symptoms of the disease and to the reduced effectiveness of dopamine replacement therapy. SCFA: short chain fatty acids; LPS: lipopolysaccharides. Figure adapted from Perez-Pardo et al. with permission [99].

increase in intestinal permeability found in PD patients [65,66]. In particular, increased intestinal permeability facilitates the passage of bacterial toxins, such as lipopolysaccharides (LPS), from the intestinal lumen into the bloodstream, which promotes local and systemic inflammation and α-synuclein aggregation [36,67].

Integration of microbial data into metabolic modeling revealed the gut microbial contribution to the folic acid deficit and hyperhomocysteinemia observed in PD [64]. This is particularly interesting given the increased risk for PD patients to develop polyneuropathy [68,69].

Other studies have shown a decrease in SCFA-producing bacteria and carbohydrate-fermenting bacteria, while proteolytic fermentation and some deleterious metabolites were increased [10,50,70]. However, SCFAs are crucial for the maintenance of the gut homeostasis. Not only are they used as an energy source by the colonic mucosa, thus maintaining the integrity of the epithelial barrier, but they also play a role in the absorption of electrolytes and water, allowing normal transit [71]. The relative decrease in butyrate-producing bacteria is inversely associated with constipation [50]. In addition, they have both local and systemic anti-inflammatory functions. SCFAs, in particular butyrate and acetate, induce the expression of anti-inflammatory cytokines (e.g. IL-10) and inhibit the expression of pro-inflammatory cytokines (e.g. TNF-α, IL-6) [72]. These data are consistent with studies showing that dysbiosis in PD promotes bacteria with pro-inflammatory potential and to the detriment of bacteria with anti-inflammatory potential [9]. Finally, SCFAs are able to pass into the portal circulation and reach the brain where they have a neuroprotective role via modulation of microglia maturation and upregulation of neurotrophic factors [73].

Dysbiosis is also involved in α-synuclein aggregation and neuroinflammation. In genetic animal models of PD, microbiota is necessary not only to develop PD symptoms, but also for brain aggregations of α-synuclein and activation of

microglia (i.e. neuroinflammation) suggesting a combined effect of genetically mediated α-synuclein overexpression and gut microbiota composition on α-synuclein aggregation in the brain and neuroinflammation [63]. As mentioned above, LPS promotes cerebral α-synuclein aggregation [36,67]. Another way in which the microbiota could influence the pathophysiology of PD is through the production of bacterial amyloid-like curli proteins. These proteins allow the formation of bacterial biofilms, mediate adhesion to epithelial cells, and participate in defense against bacteriophages. In a mouse model of PD, colonization by curli-producing Escherichia coli promoted PD motor deficit, α-synuclein aggregation in the gut and brain, as well as inflammation [74].

6.4. *Influence of dysbiosis on dopaminergic therapy*

The microbiota influences the metabolism of dopamine replacement therapy. A portion of levodopa, normally absorbed at the jejunal level, is converted to dopamine in the intestinal lumen by the dopa-decarboxylase enzyme produced by gut bacteria, in particular Enterococcus faecalis. Consequently, the efficacy of dopaminergic treatments is decreased by reducing the access of levodopa to the blood and then the brain [75].

Moreover, the dopamine synthesized in the intestinal lumen reduces gut motility and thus increases the risk of bacterial overgrowth syndrome. As a consequence, an increase in the number of levodopa-metabolizing bacteria decreases the effectiveness of dopamine replacement therapy, creating a vicious circle which enhances bacterial overgrowth [76]. Variations in levodopa-metabolizing microbial activities may contribute to the heterogeneous responses to levodopa efficacy observed in some PD patients [75].

6.5. *Dysbiosis as a biomarker for PD*

Microbiota composition could serve as a biomarker for the diagnosis of PD with a sensitivity of 65–90% and a specificity of about 75% [77]. Similarly, the salivary microbiota was able to correctly assign ''PD'' or ''healthy control'' 75% of patients and 70% of healthy subjects, respectively [19].

In idiopathic rapid-eye movement (REM) sleep behavior disorder, a condition considered a prodromal stage of the α-synucleinopathies with a high conversion rate of about 73.5% at 12 years of follow-up [78], a dysbiosis pattern is closer to that observed in mild forms of PD (Hoehn and Yahr stage 1) [16,79]. Interestingly, the increased and decreased bacteria were similar as those found to be most frequently impaired in the 3 above-mentioned meta-analyses [16,44,45].

7. Modifying microbiota as a treatment for PD

Gut microbiota can be modulated by different strategies, including dietary interventions, microbiota decontamination by laxatives and antibiotics, fecal microbiota transplantation and exercise [80,81].

The type of diet influences the composition and balance of the intestinal microbiota and could have an influence on PD symptoms and pathophysiology [82]. Certain dietary patterns such as the Western diet, a diet rich in saturated fatty acids (SFA) and low in fiber, support dysbiosis and promote the growth of pro-inflammatory bacteria and intestinal inflammation. SFAs also promote the aggregation of α-synuclein and the destruction of dopaminergic neurons by increasing oxidative stress [83]. On the contrary, a diet rich in fiber and polyunsaturated fats, such as the Mediterranean diet, favors bacterial populations with anti-inflammatory potential and many protective biological processes, such as improvement of the intestinal epithelial barrier, reduction of NLRP3 inflammasome activation, production of interleukin IL-1beta cytokines, improvement of insulin sensitivity, increase in the production of brain-derived neurotrophic factor [40,84] and inhibition of the metabolic pathway of arachidonic acid generating prostaglandins and leukotrienes [85,86]. Recently, the Mediterranean-dietary approaches to stop hypertension-intervention for neurodegenerative delay (MIND) diet, a variation of the Mediterranean diet that favors green vegetables and berries, has been associated with a later age of onset of PD, particularly in women [87]. Emerging evidence suggests that a ketogenic diet may have beneficial effects in PD with significant improvement in both motor and nonmotor symptoms, probably via its bioenergetics benefits [88,89]. A study examining the combined role of ketogenic and Mediterranean diets is currently underway [90].

While in PD mouse models, the administration of probiotics resulted in improvements in motor function, systemic inflammation, and brain neuroinflammation [91,92], in PD patients the benefits of probiotics were limited to the treatment of constipation [93]. Effects on other aspects of PD in human subjects warrant further investigations.

Intestinal decontamination therapy could be of some interest in the treatment of dyskinesia and motor fluctuations in PD [94]. This therapy is based on the fact that dysbiosis reduces levodopa absorption leading to delayed ''ON'' or ''no-ON'' states. It consists of an enema followed by oral rifaximin and polyethylene glycol for 7 and 10 days, respectively. Further controlled randomized studies are needed to confirm these results and clarify the mechanism of improvement observed in this small open-label study.

Fecal microbiota transplantation (FMT) as an approach to restore gut microbiota in PD patients, significantly improved both motor (−7 to −13 points on the UPDRS-III scale) and non-motor (constipation, anxiety, depression, sleep) scores. The improvement was maintained to 3 months post-intervention. Side effects were mild and limited, consisting mainly of flatulence, abdominal pain, and diarrhea at the time of transplantation and sometimes abdominal pain and flatulence at follow-up [95–97]. These data obtained from a limited number of uncontrolled studies with small numbers of patients (6–15) need to be confirmed on larger cohorts, as well as in randomized, double-blind, placebo-controlled trials. Animal studies corroborate the above findings and show that FMT treatment restores the gut microbial community, attenuates gut inflammation and barrier destruction, reduces LPS levels in colon, serum and substantia nigra, and lowers systemic inflammation levels, neuroinflammation in substantia nigra and dopaminergic neurodegeneration [98].

8. Conclusion

Several gut microbiota members are differentially abundant between PD and healthy state. Dysbiosis in PD is associated with decreased abundance of SCFA-producing bacteria and changes in many bacterial pathways, resulting in increased mucin degradation, enhanced production of bacterial amyloid protein, folic acid deficiency and hyperhomocysteinemia. These changes promote intestinal permeability, serum passage of LPS, local and central α-synuclein aggregation, local and systemic inflammation, neuroinflammation, and neurodegeneration. Dysbiosis also leads to decreased efficacy of dopamine replacement therapy due to increased levodopa metabolization and gut dopamine levels, resulting in reduced levodopa absorption, increased constipation and enhanced risk of intestinal bacterial overgrowth syndrome. Dysbiosis is thus involved in both motor and non-motor parkinsonian symptoms. According to animal studies, dysbiosis would essentially affect individuals who are genetically vulnerable to PD. Dysbiosis would thus be a risk factor (and not a cause) of PD or a factor aggravating the disease. Since the composition of the microbiota can be modified, interventions aiming at correcting dysbiosis open a new avenue of therapeutic research. Moreover, microbial communities could represent a new biomarker of PD.

Disclosure of interest

The authors declare that they have no competing interest.

Funding source

This study was supported by a grant from the Association Swiss Parkinson.

Acknowledgements

We thank Dr. Michael Nissen for his assistance with proofreading.

REFERENCES

[1] de Lau LM, Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 2006;5(6):525–35.
[2] Blauwendraat C, Nalls MA, Singleton AB. The genetic architecture of Parkinson's disease. Lancet Neurol 2020;19(2):170–8.
[3] Fleury V, Himsl R, Joost S, Nicastro N, Bereau M, Guessous I, et al. Geospatial analysis of individual-based Parkinson's disease data supports a link with air pollution: a case-control study. Parkinsonism Relat Disord 2021;83:41–8.
[4] Belvisi D, Pellicciari R, Fabbrini G, Tinazzi M, Berardelli A, Defazio G. Modifiable risk and protective factors in disease development, progression and clinical subtypes of Parkinson's disease: what do prospective studies suggest? Neurobiol Dis 2020;134:104671.
[5] Sharma A, Osato N, Liu H, Asthana S, Dakal TC, Ambrosini G, et al. Common genetic variants associated with Parkinson's disease display widespread signature of epigenetic plasticity. Sci Rep 2019;9(1):18464.
[6] Wirdefeldt K, Adami HO, Cole P, Trichopoulos D, Mandel J. Epidemiology and etiology of Parkinson's disease: a review of the evidence. Eur J Epidemiol 2011;26 Suppl. 1:S1–58.
[7] Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. Nat Rev Dis Primers 2017;3:17013.
[8] Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 2015;30(3):350–8.
[9] Keshavarzian A, Green SJ, Engen PA, Voigt RM, Naqib A, Forsyth CB, et al. Colonic bacterial composition in Parkinson's disease. Mov Disord 2015;30(10):1351–60.
[10] Unger MM, Spiegel J, Dillmann KU, Grundmann D, Philippeit H, Burmann J, et al. Short chain fatty acids and gut microbiota differ between patients with Parkinson's disease and age-matched controls. Parkinsonism Relat Disord 2016;32:66–72.
[11] Petrov VA, Saltykova IV, Zhukova IA, Alifirova VM, Zhukova NG, Dorofeeva YB, et al. Analysis of gut microbiota in patients with Parkinson's disease. Bull Exp Biol Med 2017;162(6):734–7.
[12] Bedarf JR, Hildebrand F, Coelho LP, Sunagawa S, Bahram M, Goeser F, et al. Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naive Parkinson's disease patients. Genome Med 2017;9(1):39.
[13] Hopfner F, Kunstner A, Muller SH, Kunzel S, Zeuner KE, Margraf NG, et al. Gut microbiota in Parkinson disease in a northern German cohort. Brain Res 2017;1667:41–5.
[14] Gerhardt S, Mohajeri MH. Changes of colonic bacterial composition in Parkinson's disease and other neurodegenerative diseases. Nutrients 2018;10(6):1–23.
[15] Hasegawa S, Goto S, Tsuji H, Okuno T, Asahara T, Nomoto K, et al. Intestinal dysbiosis and lowered serum lipopolysaccharide-binding protein in Parkinson's disease. PLoS One 2015;10(11):e0142164.
[16] Nishiwaki H, Ito M, Ishida T, Hamaguchi T, Maeda T, Kashihara K, et al. Meta-analysis of gut dysbiosis in Parkinson's disease. Mov Disord 2020;35(9):1626–35.
[17] Pereira PAB, Aho VTE, Paulin L, Pekkonen E, Auvinen P, Scheperjans F. Oral and nasal microbiota in Parkinson's disease. Parkinsonism Relat Disord 2017;38:61–7.
[18] Mihaila D, Donegan J, Barns S, LaRocca D, Du Q, Zheng D, et al. The oral microbiome of early stage Parkinson's disease and its relationship with functional measures of motor and non-motor function. PLoS One 2019;14(6):e0218252.
[19] Fleury V, Zekeridou A, Lazarevic V, Gaia N, Giannopoulou C, Genton L, et al. Oral dysbiosis and inflammation in Parkinson's disease. J Parkinsons Dis 2021;11(2):619–31.
[20] Dunning CJR, JF R, Steiner JA, Brundin P. Can Parkinson's disease pathology be propagated from one neuron to another? Prog Neurobiol 2012;97:205–19.
[21] Pont-Sunyer C, Hotter A, Gaig C, Seppi K, Compta Y, Katzenschlager R, et al. The onset of nonmotor symptoms in Parkinson's disease (the ONSET PD study). Mov Disord 2015;30(2):229–37.
[22] Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White Iii CL, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. Acta Neuropathol 2010;119(6):689–702.

[23] Adler CH, Beach TG. Neuropathological basis of nonmotor manifestations of Parkinson's disease. Mov Disord 2016;31(8):1114–9.
[24] Hilton D, Stephens M, Kirk L, Edwards P, Potter R, Zajicek J, et al. Accumulation of alpha-synuclein in the bowel of patients in the pre-clinical phase of Parkinson's disease. Acta Neuropathol 2014;127(2):235–41.
[25] Hawkes CH, Del Tredici K, Braak H. Parkinson's disease: a dual-hit hypothesis. Neuropathol Appl Neurobiol 2007;33(6):599–614.
[26] Horsager J, Andersen KB, Knudsen K, Skjaerbaek C, Fedorova TD, Okkels N, et al. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 2020;143(10):3077–88.
[27] Stone DK, Reynolds AD, Mosley RL, Gendelman HE. Innate and adaptive immunity for the pathobiology of Parkinson's disease. Antioxid Redox Signal 2009;11(9):2151–66.
[28] McGeer PL, McGeer EG. Inflammation and neurodegeneration in Parkinson's disease. Parkinsonism Relat Disord 2004;10 Suppl. 1:S3–7.
[29] Devos D, Lebouvier T, Lardeux B, Biraud M, Rouaud T, Pouclet H, et al. Colonic inflammation in Parkinson's disease. Neurobiol Dis 2013;50:42–8.
[30] Qin XY, Zhang SP, Cao C, Loh YP, Cheng Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: a systematic review and meta-analysis. JAMA Neurol 2016;73(11):1316–24.
[31] Zhu F, Li C, Gong J, Zhu W, Gu L, Li N. The risk of Parkinson's disease in inflammatory bowel disease: a systematic review and meta-analysis. Dig Liver Dis 2019;51(1):38–42.
[32] Chen H, Zhang SM, Hernan MA, Schwarzschild MA, Willett WC, Colditz GA, et al. Nonsteroidal anti-inflammatory drugs and the risk of Parkinson disease. Arch Neurol 2003;60(8):1059–64.
[33] Kasen A, Houck C, Burmeister AR, Sha Q, Brundin L, Brundin P. Upregulation of alpha-synuclein following immune activation: possible trigger of Parkinson's disease. Neurobiol Dis 2022;166:105654.
[34] Pajares M, A IR, Manda G, Bosca L, Cuadrado A. Inflammation in Parkinson's disease: mechanisms and therapeutic implications. Cells 2020;9(7):1–32.
[35] Houser MC, Chang J, Factor SA, Molho ES, Zabetian CP, Hill-Burns EM, et al. Stool immune profiles evince gastrointestinal inflammation in Parkinson's disease. Mov Disord 2018;33(5):793–804.
[36] Forsyth CB, Shannon KM, Kordower JH, Voigt RM, Shaikh M, Jaglin JA, et al. Increased intestinal permeability correlates with sigmoid mucosa alpha-synuclein staining and endotoxin exposure markers in early Parkinson's disease. PLoS One 2011;6(12):e28032.
[37] Sender R, Fuchs S, Milo R. Revised estimates for the number of human and Bacteria cells in the body. PLoS Biol 2016;14(8):e1002533.
[38] Dethlefsen L, McFall-Ngai M, Relman DA. An ecological and evolutionary perspective on human-microbe mutualism and disease. Nature 2007;449(7164):811–8.
[39] Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012;488(7410):178–84.
[40] Maslowski KM, Mackay CR. Diet, gut microbiota and immune responses. Nat Immunol 2011;12(1):5–9.
[41] Morais LH, Schreiber HLt, Mazmanian SK. The gut microbiota-brain axis in behaviour and brain disorders. Nat Rev Microbiol 2021;19(4):241–55.
[42] Escapa IF, Chen T, Huang Y, Gajare P, Dewhirst FE, Lemon KP. New insights into human nostril microbiome from the expanded human oral microbiome database (eHOMD): a resource for the microbiome of the human aerodigestive tract. mSystems 2018;3(6):1–20.
[43] Radaic A, Kapila YL. The oralome and its dysbiosis: new insights into oral microbiome-host interactions. Comput Struct Biotechnol J 2021;19:1335–60.
[44] Romano S, Savva GM, Bedarf JR, Charles IG, Hildebrand F, Narbad A. Meta-analysis of the Parkinson's disease gut microbiome suggests alterations linked to intestinal inflammation. NPJ Parkinsons Dis 2021;7(27):1–13.
[45] Shen T, Yue Y, He T, Huang C, Qu B, Lv W, et al. The association between the gut microbiota and Parkinson's disease, a meta-analysis. Front Aging Neurosci 2021;13:636545.
[46] Cersosimo MG, Tumilasci OR, Raina GB, Benarroch EE, Cardoso EM, Micheli F, et al. Hyposialorrhea as an early manifestation of Parkinson disease. Auton Neurosci 2009;150(1–2):150–1.
[47] Noyce AJ, Silveira-Moriyama L, Gilpin P, Ling H, Howard R, Lees AJ. Severe dysphagia as a presentation of Parkinson's disease. Mov Disord 2012;27(3):457–8.
[48] Hanaoka A, Kashihara K. Increased frequencies of caries, periodontal disease and tooth loss in patients with Parkinson's disease. J Clin Neurosci 2009;16(10):1279–82.
[49] Cryan JF, O'Riordan KJ, Sandhu K, Peterson V, Dinan TG. The gut microbiome in neurological disorders. Lancet Neurol 2020;19(2):179–94.
[50] Cirstea MS, Yu AC, Golz E, Sundvick K, Kliger D, Radisavljevic N, et al. Microbiota composition and metabolism are associated with gut function in Parkinson's disease. Mov Disord 2020;35(7):1208–17.
[51] Vandeputte D, Falony G, Vieira-Silva S, Tito RY, Joossens M, Raes J. Stool consistency is strongly associated with gut microbiota richness and composition, enterotypes and bacterial growth rates. Gut 2016;65(1):57–62.
[52] Seppi K, Weintraub D, Coelho M, Perez-Lloret S, Fox SH, Katzenschlager R, et al. The movement disorder society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord 2011;26 Suppl. 3:S42–80.
[53] Barichella M, Pacchetti C, Bolliri C, Cassani E, Iorio L, Pusani C, et al. Probiotics and prebiotic fiber for constipation associated with Parkinson disease: an RCT. Neurology 2016;87(12):1274–80.
[54] Liu WH, Chuang HL, Huang YT, Wu CC, Chou GT, Wang S, et al. Alteration of behavior and monoamine levels attributable to Lactobacillus plantarum PS128 in germ-free mice. Behav Brain Res 2016;298(Pt B):202–9.
[55] Sulakhiya K, Keshavlal GP, Bezbaruah BB, Dwivedi S, Gurjar SS, Munde N, et al. Lipopolysaccharide induced anxiety- and depressive-like behaviour in mice are prevented by chronic pre-treatment of esculetin. Neurosci Lett 2016;611:106–11.
[56] Neufeld KA, Kang N, Bienenstock J, Foster JA. Effects of intestinal microbiota on anxiety-like behavior. Commun Integr Biol 2011;4(4):492–4.
[57] Felger JC. Imaging the role of inflammation in mood and anxiety-related disorders. Curr Neuropharmacol 2018;16(5):533–58.
[58] Goebel M, Stengel A, Wang L, Reeve Jr J, Tache Y. Lipopolysaccharide increases plasma levels of corticotropin-releasing hormone in rats. Neuroendocrinology 2011;93(3):165–73.
[59] Park AJ, Collins J, Blennerhassett PA, Ghia JE, Verdu EF, Bercik P, et al. Altered colonic function and microbiota profile in a mouse model of chronic depression. Neurogastroenterol Motil 2013;25(9) [733-e575].
[60] Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linlokken A, Wilson R, et al. Correlation between the

human fecal microbiota and depression. Neurogastroenterol Motil 2014;26(8):1155–62.
[61] Maes M, Kubera M, Leunis JC. The gut-brain barrier in major depression: intestinal mucosal dysfunction with an increased translocation of LPS from gram negative enterobacteria (leaky gut) plays a role in the inflammatory pathophysiology of depression. Neuro Endocrinol Lett 2008;29(1):117–24.
[62] Hata T, Asano Y, Yoshihara K, Kimura-Todani T, Miyata N, Zhang XT, et al. Regulation of gut luminal serotonin by commensal microbiota in mice. PLoS One 2017;12(7):e0180745.
[63] Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, et al. Gut microbiota regulate motor deficits and neuroinflammation in a model of Parkinson's disease. Cell 2016;167(6) [1469-80 e12].
[64] Rosario D, Bidkhori G, Lee S, Bedarf J, Hildebrand F, Le Chatelier E, et al. Systematic analysis of gut microbiome reveals the role of bacterial folate and homocysteine metabolism in Parkinson's disease. Cell Rep 2021;34(9):108807.
[65] Clairembault T, Leclair-Visonneau L, Coron E, Bourreille A, Le Dily S, Vavasseur F, et al. Structural alterations of the intestinal epithelial barrier in Parkinson's disease. Acta Neuropathol Commun 2015;3:12.
[66] Schwiertz A, Spiegel J, Dillmann U, Grundmann D, Burmann J, Fassbender K, et al. Fecal markers of intestinal inflammation and intestinal permeability are elevated in Parkinson's disease. Parkinsonism Relat Disord 2018;50:104–7.
[67] Kim C, Lv G, Lee JS, Jung BC, Masuda-Suzukake M, Hong CS, et al. Exposure to bacterial endotoxin generates a distinct strain of alpha-synuclein fibril. Sci Rep 2016;6:30891.
[68] Toth C, Breithaupt K, Ge S, Duan Y, Terris JM, Thiessen A, et al. Levodopa, methylmalonic acid, and neuropathy in idiopathic Parkinson disease. Ann Neurol 2010;68(1):28–36.
[69] Romagnolo A, Merola A, Artusi CA, Rizzone MG, Zibetti M, Lopiano L. Levodopa-induced neuropathy: a systematic review. Mov Disord Clin Pract 2019;6(2):96–103.
[70] Vascellari S, Palmas V, Melis M, Pisanu S, Cusano R, Uva P, et al. Gut microbiota and metabolome alterations associated with Parkinson's disease. mSystems 2020;5(5):1–15.
[71] van der Hee B, Wells JM. Microbial regulation of host physiology by short-chain fatty acids. Trends Microbiol 2021;29(8):700–12.
[72] Vinolo MA, Rodrigues HG, Nachbar RT, Curi R. Regulation of inflammation by short chain fatty acids. Nutrients 2011;3(10):858–76.
[73] Elfil M, Kamel S, Kandil M, Koo BB, Schaefer SM. Implications of the gut microbiome in Parkinson's disease. Mov Disord 2020;35(6):921–33.
[74] Sampson TR, Challis C, Jain N, Moiseyenko A, Ladinsky MS, Shastri GG, et al. A gut bacterial amyloid promotes alpha-synuclein aggregation and motor impairment in mice. Elife 2020;9:1–19.
[75] Maini Rekdal V, Bess EN, Bisanz JE, Turnbaugh PJ, Balskus EP. Discovery and inhibition of an interspecies gut bacterial pathway for Levodopa metabolism. Science 2019;364(6445):1.
[76] van Kessel SP, El Aidy S. Contributions of gut bacteria and diet to drug pharmacokinetics in the treatment of Parkinson's disease. Front Neurol 2019;10:1087.
[77] Qian Y, Yang X, Xu S, Huang P, Li B, Du J, et al. Gut metagenomics-derived genes as potential biomarkers of Parkinson's disease. Brain 2020;143(8):2474–89.
[78] Postuma RB, Iranzo A, Hu M, Hogl B, Boeve BF, Manni R, et al. Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain 2019;142(3):744–59.
[79] Nishiwaki H, Hamaguchi T, Ito M, Ishida T, Maeda T, Kashihara K, et al. Short-chain fatty acid-producing gut microbiota is decreased in Parkinson's disease but not in rapid-eye-movement sleep behavior disorder. mSystems 2020;5(6):1–10.
[80] Gubert C, Kong G, Renoir T, Hannan AJ. Exercise, diet and stress as modulators of gut microbiota: implications for neurodegenerative diseases. Neurobiol Dis 2020;134:104621.
[81] Tan AH, Lim SY, Lang AE. The microbiome-gut-brain axis in Parkinson disease – from basic research to the clinic. Nat Rev Neurol 2022;18(8):476–95.
[82] Bibbo S, Ianiro G, Giorgio V, Scaldaferri F, Masucci L, Gasbarrini A, et al. The role of diet on gut microbiota composition. Eur Rev Med Pharmacol Sci 2016;20(22):4742–9.
[83] Boulos C, Yaghi N, El Hayeck R, Heraoui GN, Fakhoury-Sayegh N. Nutritional risk factors, microbiota and Parkinson's disease: what is the current evidence? Nutrients 2019;11(8):1–24.
[84] Jackson A, Forsyth CB, Shaikh M, Voigt RM, Engen PA, Ramirez V, et al. Diet in Parkinson's disease: critical role for the microbiome. Front Neurol 2019;10:1245.
[85] de Lau LM, Bornebroek M, Witteman JC, Hofman A, Koudstaal PJ, Breteler MM. Dietary fatty acids and the risk of Parkinson disease: the Rotterdam study. Neurology 2005;64(12):2040–5.
[86] Marion-Letellier R, Savoye G, Beck PL, Panaccione R, Ghosh S. Polyunsaturated fatty acids in inflammatory bowel diseases: a reappraisal of effects and therapeutic approaches. Inflamm Bowel Dis 2013;19(3):650–61.
[87] Metcalfe-Roach A, Yu AC, Golz E, Cirstea M, Sundvick K, Kliger D, et al. Mind and Mediterranean diets associated with later onset of Parkinson's disease. Mov Disord 2021;36(4):977–84.
[88] Wlodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients 2019;11(1):1–11.
[89] Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP. Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. Mov Disord 2018;33(8):1306–14.
[90] Appel-Cresswell S. Ketogenic diet interventions in Parkinson's disease: safeguarding the gut microbiome; 2022 [Available from: https://www.clinicaltrials.gov/ct2/show/NCT05469997].
[91] Alfonsetti M, Castelli V, d'Angelo M. Are we what we eat? Impact of diet on the gut-brain axis in Parkinson's disease. Nutrients 2022;14(2):1–21.
[92] Ghyselinck J, Verstrepen L, Moens F, Van Den Abbeele P, Bruggeman A, Said J, et al. Influence of probiotic bacteria on gut microbiota composition and gut wall function in an in-vitro model in patients with Parkinson's disease. Int J Pharm X 2021;3:100087.
[93] Tan AH, Hor JW, Chong CW, Lim SY. Probiotics for Parkinson's disease: current evidence and future directions. JGH Open 2021;5(4):414–9.
[94] Baizabal-Carvallo JF, Alonso-Juarez M, Fekete R. Intestinal decontamination therapy for dyskinesia and motor fluctuations in Parkinson's disease. Front Neurol 2021;12:729961.
[95] Segal A, Zlotnik Y, Moyal-Atias K, Abuhasira R, Ifergane G. Fecal microbiota transplant as a potential treatment for Parkinson's disease – A case series. Clin Neurol Neurosurg 2021;207:106791.
[96] Xue LJ, Yang XZ, Tong Q, Shen P, Ma SJ, Wu SN, et al. Fecal microbiota transplantation therapy for Parkinson's disease:

a preliminary study. Medicine (Baltimore) 2020;99(35):e22035.
[97] Kuai XY, Yao XH, Xu LJ, Zhou YQ, Zhang LP, Liu Y, et al. Evaluation of fecal microbiota transplantation in Parkinson's disease patients with constipation. Microb Cell Fact 2021;20(1):98.
[98] Zhao Z, Ning J, Bao XQ, Shang M, Ma J, Li G, et al. Fecal microbiota transplantation protects rotenone-induced Parkinson's disease mice via suppressing inflammation mediated by the lipopolysaccharide-TLR4 signaling pathway through the microbiota-gut-brain axis. Microbiome 2021;9(1):226.
[99] Perez-Pardo P, Kliest T, Dodiya HB, Broersen LM, Garssen J, Keshavarzian A, et al. The gut-brain axis in Parkinson's disease: possibilities for food-based therapies. Eur J Pharmacol 2017;817:86–95.