Review

The Role of Ketogenic Diet in the Different Stages and Symptoms of Parkinson's Disease

The influence on (non)-motor symptoms and microbiota composition in the preclinical, prodromal, and clinical stage of Parkinson's disease

Author: H. T. Wouda
Supervisor: Prof. Dr. E.A. van der Zee

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Author: H. T. (Sterre) Wouda
Student number: S3229424
Study: MSc. Biomedical Sciences, Biology of Food and Nutrition
Institute: University of Groningen

Department of Molecular Neurobiology
Faculty of Science and Engineering, University of Groningen
Examiner: Prof. Dr. E.A. van der Zee

Abstract

Parkinson's disease (PD) is a slow progressive disease, and it is the second most common neurodegenerative disorder after Alzheimer's disease, characterized by a range of motor and non-motor symptoms that impair the quality of life. The concept of PD has shifted from a central nervous system disease to a multi-system disease, which includes impairments in the central, autonomic, and enteric nervous systems. This hypothesizes that the gut microbiome plays an important role in the pathogenesis of PD and increases potential therapeutic possibilities. There is still no proven diet suitable to reverse or slow down the progression of PD, however there are some studies using the ketogenic diet (KD) as one of these dietary approaches, characterized by a high fat, low carbohydrate, and normal protein intake. The aim of this review is to summarize the role of KD in the different stages and symptoms of PD, considering recent findings related to the microbiota-gut-brain axis. Several studies were discussed that have demonstrated the heterogeneity of PD stages before diagnosis, the interplay between the gut microbiota and PD, and the role of KD as a potential therapeutic intervention for PD. Both human and animal studies have found that KD positively affected energy metabolism, oxidative stress and neuroinflammation. Ketone bodies have neuroprotective properties and prevent mitochondria dysfunction. KD improves motor and non-motor symptoms, possibly enhancing levodopa efficacy. KD also influences the gut microbiota implicated in PD. By restoring microbial balance and reducing inflammation, KD may alleviate disease progression, emerging as a promising PD intervention. Further research is needed to evaluate efficacy, adherence, and adverse effects in PD and focus on understanding PD pathogenesis and its interaction with the microbiota-gut-brain axis. Implementing KD into PD treatment strategies holds promise for improving patient outcomes and quality of life worldwide.

Keywords: Parkinson’s disease; ketogenic diet; neurodegenerative disorder; gut microbiota; inflammation; ketone bodies

Abbreviations

Blood brain barrier	BBB
β-hydroxybutyrate	βHB
Central nervous system	CNS
Gastrointestinal	GI
Hydrogen sulfide	H_2S
Ketogenic diet	KD
Ketone body	KB
Lewy pathology	LP
Lipopolysaccharide	LPS
1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine	MPTP
Parkinson's disease	PD
Rapid eye movement	REM
Short chain fatty acid	SCFA
Substantia nigra	SN

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Introduction

The increase in frequency of neurological diseases, including neurodegenerative disorders, constitute a large burden on worldwide health. Neurological diseases are the most frequent cause of disability and the second most frequent cause of death worldwide [1]. Parkinson's disease (PD) is a slow progressive disease, and it is the second most common neurodegenerative disorder after Alzheimer's disease, characterized by a range of motor and non-motor symptoms that impair the quality of life [2, 3]. Motor symptoms include resting tremor, bradykinesia (slowness of movement), muscular rigidity, a shuffling gait, and postural instability. Next to that, patients also suffer from non-motor symptoms such as depression, pain, sleep disturbances (rapid eye movement (REM) sleep behavior disorder), hyposmia (reduced sense of smell), gastrointestinal (GI) dysfunction, cognitive impairment, and autonomic dysfunction [3, 4, 5, 6]. These non-motor symptoms have been considered valuable for early diagnosis of PD, because some of the symptoms can precede the classical motor symptoms by years [2, 4]. The motor symptoms are thought to be a result of the damage and death of the dopaminergic neurons within the substantia nigra (SN) [5, 7, 8]. Next to that, neurons in the SN and other regions of the brain develop Lewy bodies, which are abnormal intracellular deposits containing aggregated α-synuclein [4]. Studies show that PD has a worldwide prevalence of 200 per 100,000 individuals and the number of diagnoses is expected to double by 2040 [9]. The most dominant risk factor for PD is age because the prevalence and incidence increase almost exponentially with age and peak after the age of 80. Other risk factors include gender (the male-to-female ratio is roughly 2:1), environmental exposure (e.g., pesticide exposure, prior head injury, heavy metal exposure) and genetic risk factors (5-10% of the time PD is caused by autosomal dominant or recessive inheritance) [5, 8, 10, 11]. In addition to these risk factors, the last few years, the concept of PD has shifted from a disease of the central nervous system (CNS) to a multi-system disease, which includes impairments in the central, autonomic, and enteric nervous systems. This hypothesizes that the gut microbiome plays an important role in (the pathogenesis of) PD. Gut microbiota is the total number of micro-organisms living in the GI tract. This includes bacteria, viruses, protozoa, and fungi [12]. Several mechanisms intervening between the CNS and the intestine (or 'the microbiota-gut-brain axis') have been illustrated. It has been suggested that GI dysfunction, such as constipation and impaired gastric emptying, can result in numerous reactions, including an imbalance in the gut. This can result in the production of neuroinflammatory signals and α-synuclein accumulation and aggregation, disturbing the blood-brain barrier. This gut dysbiosis can even precede the (motor) onset of PD by decades [10, 12, 13]. Early diagnosis of PD is difficult, because patients diagnosed with PD usually have gradual development of non-motor symptoms for years before motor symptoms begin. A lot of these non-motor symptoms are not specific to PD, which makes it more difficult to directly link them to PD. However, when these symptoms co-occur, the risk of a PD diagnosis later in life is higher [11]. Next to that, PD consists of multiple subtypes with different implications for diagnosis, prognosis and expected treatment response. Currently, treatments for PD cannot cure the disease, they can only prevent or alleviate the clinical symptoms. The treatment of PD includes drug therapy and non-pharmacological treatment [14]. Drug therapy includes drugs that enhance intracerebral dopamine concentrations or stimulate dopamine receptors. The most commonly used drug in this category is levodopa. However, levodopa and other treatment drugs have proven not to be neuroprotective or disease-modifying in the treatment of PD, it only suppresses some of the motor symptoms when the patient experiences disability or discomfort [2, 8]. Next to that, they have no effect on non-motor symptoms, plus long-term use can lead to resistance and complications like levodopa induced dyskinesia. Also,

PD-associated dysfunction of the GI contributes to levodopa response fluctuations [2, 4, 14]. Non-pharmacological therapy includes exercise or dietary treatment. Since recent new insights have shown that the pathophysiology of PD resides in the microbiota-gut-brain axis, this has unveiled potential therapeutic possibilities in which various dietary approaches might influence the course of PD [15]. There is still no proven diet suitable to reverse or slow down the progression of PD, however there are some studies using certain dietary approaches with beneficial results. The ketogenic diet (KD) is one of these dietary approaches, characterized by a high fat, low carbohydrate, and normal protein intake. This diet has been effective for a wide range of neurological conditions, including epilepsy, PD, and autism [16]. However, more research is needed to clarify the possibility for ketogenic interventions to cure, prevent or relieve symptoms of PD [17]. Therefore, the aim of this review is to summarize the role of KD in the different stages and symptoms of PD, considering recent findings related to the microbiota-gut-brain axis. It invites an exploration of the diet's impact on the progression of PD and its symptomatic management, offering a clear direction for investigating the efficacy and potential benefits of dietary interventions in PD treatment.

Parkinson's Disease

PD is currently perceived as a slowly progressive neurodegenerative disease that initiates years prior to diagnosis, it involves various neuroanatomical regions, it arises from a combination of genetic and environmental influences and presents with a diverse range of symptoms [8]. The diagnosis of PD is clinical, and key characteristics include bradykinesia, rigidity, and tremor. The primary indicators for diagnosing PD are motor symptoms, although nonmotor symptoms are also prevalent and debilitating. Early nonmotor symptoms include REM sleep disorder, depression, constipation, fatigue, and impaired sense of smell, often preceding motor symptoms [18]. Nearly all individuals with PD reported experiencing nonmotor symptoms, with psychiatric symptoms being the most frequent [19]. As the disease progresses, additional nonmotor symptoms may emerge, including autonomic dysfunction like orthostatic hypotension and urinary dysfunction, significantly affecting patients' quality of life and care needs. Advanced stages of PD may involve severe nonmotor symptoms such as dementia and psychosis, leading to considerable debilitation [18]. Understanding the neuropathological progression of PD, highlights the importance of early detection and intervention to alleviate disease progression.

The Stages of Parkinson's Disease

The most widely cited model for the neuropathologic progression of PD is the Braak hypothesis. This hypothesis states that PD progresses in six neuropathological stages and subdivides the course of the disease into a presymptomatic and symptomatic phases [20]. Each neuropathological phase is marked by the continual development of inclusion bodies (abnormal aggregations of protein), including Lewy neurites, pale bodies, and Lewy bodies. These inclusion bodies consist mostly of aggregated misfolded α-synuclein. Not all neurons are susceptible to develop abnormal aggregation of inclusion bodies. As a result, PD exhibits a pronounced affinity for specific areas in the brain, resulting in a distinct pattern of lesion distribution [21]. In presymptomatic stages 1-2, inclusion body pathology is limited to the medulla oblongata and olfactory bulb. In stages 3-4, the SN, and other nuclear gray regions of the mid- and forebrain undergo initial mild and later severe pathological alterations [11, 20, 21]. At this stage, most patients cross the threshold to the symptomatic phase of the disease. Stages 5-6 are the end-

stages, where the process enters the mature neocortex and the disease manifests in its full clinical dimensions (Fig. 1) [20].

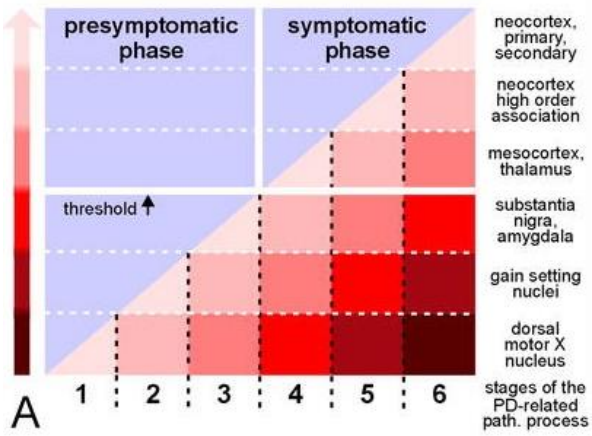

Figure 1. During the presymptomatic phase, Lewy neurites/bodies emerge in the brains of asymptomatic persons. In the symptomatic phase, the neuropathological threshold is surpassed (black arrow). The increasing slope and intensity of the colored areas below the diagonal signify the increasing severity of the pathology in vulnerable brain regions (right). Darker shading along the colored arrow indicates the severity of the pathology (left) [20].

There has been collaborative effort to connect Lewy pathology (LP), neuronal dysfunction and neuronal death in PD. Confirming the temporal sequence of LP as proposed by Braak and colleagues has been difficult since only about half of clinically diagnosed PD patients exhibit a pattern of LP consistent with the model. A significant limitation in this effort is the inability to observe LP in living patients, especially during the early phases of the disease [22].

Despite the growing recognition of the diverse clinical presentations of PD, there is still a lack of understanding regarding the heterogeneity of the phases before diagnosis. The International Parkinson and Movement Disorder Society has recommended to divide early PD into three stages: preclinical, prodromal, and clinical. Next to these three stages, even an earlier risk stage can be renowned. The risk, preclinical and prodromal stage together are considered pre-diagnostic PD (Fig. 2) [23, 24].

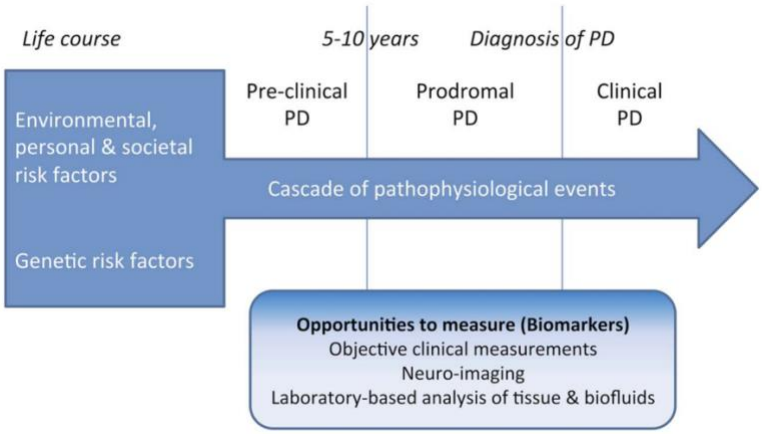

Figure 2. An illustration showing determinants of risk, the prediagnostic stage (preclinical and prodromal stages) and clinical stage of PD, along with the utilization of risk and disease progression markers to assess disease activity throughout these stages [24].

Risk Stage
In this stage, individuals can be exposed to various risk factors, and certain pathophysiological processes may begin. However, no PD-related pathology is evident yet [23].

Preclinical Stage
During the second stage of pre-diagnostic PD, the pathology has initiated and biomarkers that are suggestive of PD can be found. However, no symptoms of disease are evident yet. Promising measurements include α-synuclein detection in the cerebrospinal fluid, blood, and peripheral tissue, or looking at dopamine transporter abnormalities [23, 24].

Prodromal Stage
This stage can last more than ten years and is primarily characterized by non-motor symptoms and subtle motor deficits occurring years prior to diagnosis. Symptoms in the prodromal stage are frequently not identified as associated with PD due to their low specificity [23]. Prodromal markers of PD include REM-sleep behavior disorder and idiopathic anosmia [24]. Also, constipation, depression and anxiety, erectile dysfunction, and drowsiness (somnolence) are prodromal markers of PD [25].

Clinical Stage
In this stage, diagnosis of PD has been made based on the presence of classical motor symptoms [24]. PD is clinically characterized by the presence of cardinal motor symptoms, specifically bradykinesia with at least one of either resting tremor or rigidity [25].

This classification provides a framework for better understanding of the heterogeneity of PD progression and could provide valuable insights into the optimal timing and composition of specific interventions. Considering recent findings of PD related to the microbiota-gut-brain axis. It invites an exploration of the impact of diet on the progression of PD and its different stages and symptoms, offering a clear direction for investigating the efficacy and potential benefits of dietary interventions in PD treatment [26]. Longitudinal studies are needed to elucidate the causal relationships between the microbiota-gut-brain axis, dietary interventions, and PD development.

The Gut and Parkinson's Disease
Over the last decade, studies have shown that people with certain diseases tend to share similar features of their microbiota. Dysbiosis of the gut is associated with many diseases, including PD [26]. Also, the gut has been suggested as the initiation site of PD pathology [24].

Gut Microbiota
The gut microbiota comprises the total number of microorganisms residing in the human body. These microorganisms include bacteria, archaea, fungi, and viruses. The most dominant phyla in the gut are *Firmicutes* and *Bacteroidetes*. There is a consistency in microbial composition maintained over time in healthy people, however small daily variations can be individually found [27]. The gut microbiota protects us from harmful microorganisms, they help us regulate immunity, and they produce vitamins, secondary bile acids and short chain fatty acids (SCFA). Next to beneficial microbiota, there are also pathogenic microbiota which can cause GI dysfunction [26]. Also, the microbial composition can be disrupted by antibiotics, colonization by other microbes, changes in diet or lifestyle, or by disease [27].

Gut Dysbiosis

An abnormally altered gut microbiota or gut dysbiosis, is associated with many human diseases, such as obesity, inflammatory bowel disease and PD [26]. Gut dysbiosis reduces the levels of neurotransmitters and SCFAs and elevates the level of lipopolysaccharide (LPS)-induced inflammation. This ultimately modulates the interaction between the CNS and the gut. Additionally, gut dysbiosis contributes to inflammation and dysfunction of the intestinal barrier, which leads to elevated levels of inflammatory cytokines and LPS in circulation [28, 29]. Intestinal microbial overgrowth and a two-fold increase of indicant (an indicator for gut dysbiosis) in the urine of PD patients suggest that gut microbiota dysbiosis may play a critical role in PD pathogenesis [30]. Several studies have reported the gut dysbiosis seen in PD patients. As detailed in Table 1, PD patients show significant changes in gut microbiota compared to healthy controls [31-35]. Patients with PD exhibit some overall trends in gut microbiota changes, including an increased relative abundance of genera *Akkermansia, Bifidobacterium,* and *Lactobacillus*. Also, decreased abundance of genera *Prevotella* and the family Lachnospiraceae. Not all PD patient's microbiota compositions in these studies are similar. However, this can be explained by intra- and inter-individual variability [26]. The most important finding is that PD patients show gut dysbiosis regardless of external factors, such as where they live.

Table 1. Alterations in microbiota composition in human PD clinical studies.

Author (Year)	**Discovery**	**Study Design**	**Notable Taxa Abundance Findings (↑ = increase, ↓ = decrease)**
Scheperjans et al. 2015	Altered gut microbial compositions. Reduced Prevotellaceae indicating increased gut permeability.	Case-Control study - PD (N=72) - Control (N=72)	↑Lactobacillaceae family ↓Prevotellaceae family
Keshavarzian et al. 2015	Altered GI microbial composition. Positive correlations with certain phyla and negative correlations with others.	Case-Control study - PD (N=38) - Control (N=34)	Mucosa: ↓Faecalibacterium genus Feces: ↑Bacteroidetes phylum ↑Akkermansia genus ↑Clostridiaceae family, ↓Lachnospiraceae family
Hill-Burns et al. 2017	Altered GI microbial community.	Case-Control study - PD (N=197) - Control (N=130)	↑Bifidobacteriaceae family ↑Prevotella OTU ↑Lactobacillaceae family ↓Lachnospiraceae family ↓Faecalibacterium OTU ↑Akkermansia genus

Li et al. 2017	Altered GI microbial composition.	Case-Control study - PD (N=24) - Control (N=14)	↓Lachnospiraceae family ↓Faecalibacterium genus ↑Enterobacteriaceae family ↓Prevotellaceae family
Li et al. 2019	Altered gut microbial compositions. A decrease in species richness and phylogenetic diversity in comparison to healthy controls.	Case-Control study - PD (N=51) - Controls (N= 48)	↑Akkermansia genus ↑Clostridia class, ↑Lachnospiraceae family ↓Lactobacillus genus ↓Lactobacillaceae family

Prevotella are generally seen as beneficial bacteria, known for its metabolization of plant polysaccharides and vitamins into beneficial compounds [30]. The decreased abundance of *Prevotella* and the increased abundance of *Lactobacillus* have also been linked with lower levels of ghrelin. This is a gut hormone suggested to be involved in the maintenance of normal nigrostriatal dopamine functioning, whereas impaired ghrelin secretion has been seen in PD patients [2]. A study conducted in germ-free mice showed that oral administration of PD-derived microbiota induced motor dysfunction, microglia activation and α-syn pathology. This could be explained by increased abundance of *Akkermansia* and decreased abundance of *Faecalibacterium*, suppressing the production of SCFAs, leading to a dysfunction of the gut barrier, systemic inflammation and abnormal α-syn aggregation [36].

However, the causal link between gut dysbiosis and the development of PD still needs to be established. It is unclear whether changes in gut microbiota are the trigger for PD development or a consequence of PD. Changes in lifestyle after PD diagnosis and PD medication may contribute to change the gut microbiota composition, however it cannot always explain gut dysbiosis seen in patients prior to diagnosis. Hence, the hypothesis that gut dysbiosis plays an important role in in both the pathogenesis and the development of PD [26, 30]. Further longitudinal studies are required to establish causality between gut dysbiosis and PD pathogenesis and development.

Microbiota-Gut-Brain Axis

The gut microbiota involves mechanisms in the nervous, immune, and endocrine systems. The CNS is influenced by various neurotransmitters in the gut produced by the gut microbiota. These neurotransmitters include norepinephrine, dopamine, and γ-aminobutyric acid [29]. The microbiota-gut-brain axis involves a bidirectional flow of information between the gut and the brain (. 3A) [16, 30]. Most of the effects mediated by the gut microbiota on the functionality of CNS are exerted through vagal neurotransmission modulation. Therefore, the microbiota-gut-brain axis plays a key role in the maintenance and protection of one's overall health [27]. Since PD patients show a dysbiosis in the gut, evidence is accumulating that gut microbiota dysbiosis can have an impact on PD pathogenesis via different mechanisms within the microbiota-gut-brain axis (Fig. 3B) [30]. Recent studies have found that enteroendocrine cells in the gut can produce misfolded α-synuclein protein, which might contribute to PD pathogenesis or development. It has been shown that in every major part of the GI-tract and enteric nervous system of PD patients, aggregated and phosphorylated forms of α-synuclein have been found. Increased α-synuclein has even been found in the gut of PD patients in the prodromal stage,

suggesting abnormal enteric aggregation of α-synuclein appears before neurodegeneration. Next to that, another mechanism within the microbiota-gut-brain axis is the response to bacterial components, including inflammatory products like LPS. In turn, LPS could activate microglia and trigger neuro-inflammation [26]. Also, gut dysbiosis results in the elevated production of proinflammatory cytokines, including TNF-α, IL-1β, IL-6 and IFN-γ [4]. Therefore, the microbiota-gut-brain axis is a key player in the two-way interaction between the gut and the brain [26]. Microbiota-targeted interventions, including change in diet, probiotics, antibiotics, and fecal microbiota transplantation, are considered promising approaches to prevent and/or treat PD [36].

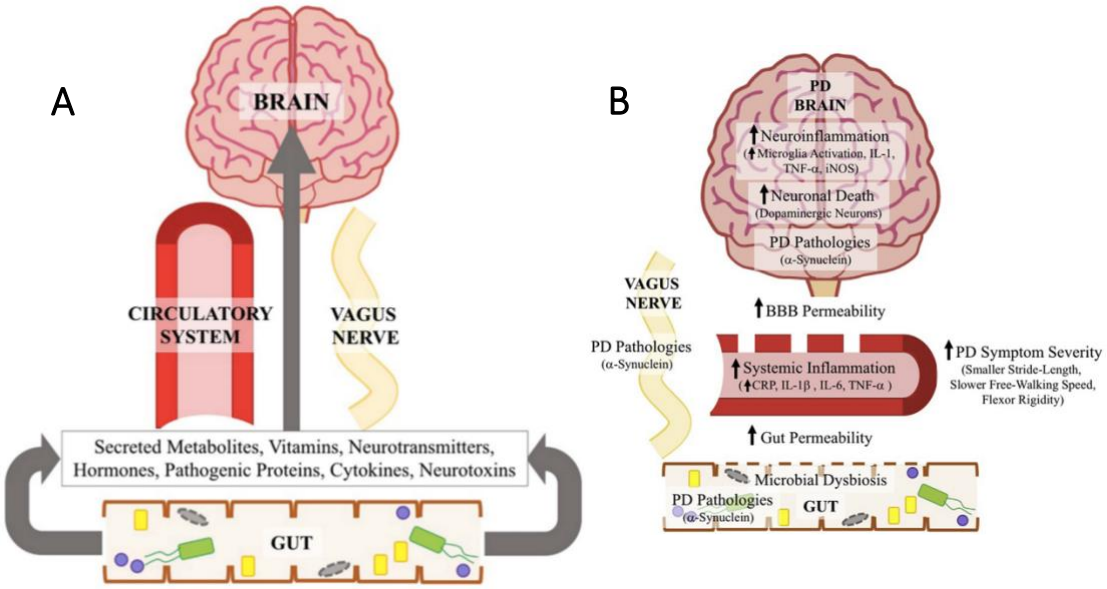

Figure 3. A. Communication between the gut microbiota and the brain. B. The role of the gut microbiota in the PD pathogenesis. CRP = C -reactive protein; IL = interleukin; iNOS = inducible nitric oxide synthase; TNF, tumor necrosis factor [30].

Diet and Parkinson's Disease

Diet can impact the body through direct effects on the body, but also through modulatory effects on the gut microbiota [26]. Diet plays a primary role in regulating the presence of specific microbiota in the gut. The composition of diet influences the extent, type, and composition of gut microbiota. Certain types of food can varyingly trigger inflammatory responses, particularly with advancing age, which is one of the most significant risk factors for PD. Also, some dietary components have been directly associated with an increased risk of PD [12]. Recently, diet has emerged as a risk factor for PD development and as a potential therapeutic approach to treat PD. The Western diet is one of the greatest risk factors for developing neurodegenerative diseases like PD. The Western diet consists of high caloric intake of energy dense foods, together with high intake of saturated and omega-6 fatty acids, and low intake of omega-3 fatty acids and fibers. Intake of high quantities of animal saturated fats has been associated with increased risk of developing PD. Next to that, a lot of foods are associated with faster advancement of PD, including soda, fried foods, beef, and dairy [26]. The Mediterranean diet, on the other side, has been associated with beneficial effects to cardiovascular diseases, cancer, but also CNS diseases like PD [37, 38]. This diet consists of a high intake of olive oil, fruits, vegetables, whole grains, legumes, fish, and nuts. The Mediterranean diet limits the intake of red meat, dairy products, and sweets [13, 15]. Fibers can promote the growth of SCFA-producing bacteria, and the diet can also target neuroinflammation and oxidative stress [38]. Therefore, this diet could be helpful in maintaining the normal microbial population in the gut and might be beneficial to tackle PD

pathogenesis or development [12, 38]. The KD is another diet with potential beneficial properties for PD. This diet depends on intermittent fasting and/or caloric restriction, which are both anti-inflammatory processes and has shown to ameliorate diseases like PD in several models [26]. The KD has also shown to increase the abundance beneficial gut microbes and decrease the abundance of harmful microbiota populations [12]. Considering these findings of the KD as a beneficial approach to tackle PD pathogenesis and/or development, this review will enlighten the effects of KD within the three stages of PD and its corresponding symptoms.

Ketogenic Diet

The KD was originally developed as a treatment for children with refractory epilepsy in the 1920s. In recent years, KD has been shown to be beneficial in several diseases, including neurodegenerative disorders like Alzheimer's disease, amyotrophic lateral sclerosis, and PD. The classic KD has an energy ratio (fat to nonfat) of 4:1 and is mostly based on the intake of long-chain triglycerides [28, 39]. The aim of a high-fat diet is to induce a state of ketosis, marked by increased lipolysis and ketogenesis. In the liver, fatty acids undergo extensive oxidation, resulting in the generation of ketone bodies (KBs), including β-hydroxybutyrate (βHB), acetoacetate, and acetone [28, 29]. The classical KD has been adapted to improve its versatility, resulting in many types of KD, varying in the proportions of macronutrients. This includes the Modified Atkins Diet, and lower ratio KDs (3:1, 2:1, and 1:1) (Fig. 4) [29]. Through the production of KBs and the inhibition of glycolysis, the KD plays a neuroprotective role in the CNS. First, as a crucial element of dietary restriction, inhibition of glycolysis controls insulin, boosts insulin sensitivity and refines glucose tolerance, delaying the onset of age-related conditions. Also, it has been known that the KD applies antioxidant effects on mitochondria because KBs protect the neurons and glial cells in the hippocampus against mitochondrial dysfunction mediated by oxidative stress. Long-term adherence to a KD promotes mitochondrial respiration and diminishes the production of reactive oxygen species (ROS), increases the expression of uncoupling proteins (UCPs), and promotes the production of adenosine triphosphate (ATP) [29, 39]. Next to that, KD can improve blood brain barrier (BBB) function and cerebral blood flow [28]. The KD also has anti-apoptotic effects, anti-inflammatory effects and it plays an indirect protective role through the microbiota-gut-brain axis (Fig. 5) [29, 39]. Recent research shows that KD can change the NAD^+/NADH ratio, which increases the availability of NAD^+ in the brain. NAD^+ is involved in several cellular pathways, including inflammatory response, DNA damage repair and regulation of the circadian rhythm [28].

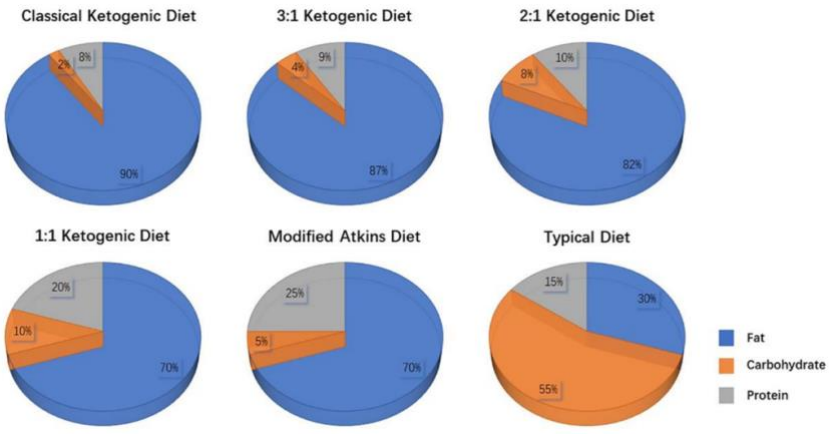

Figure 4. The classical ketogenic diet and its common modifications [29].

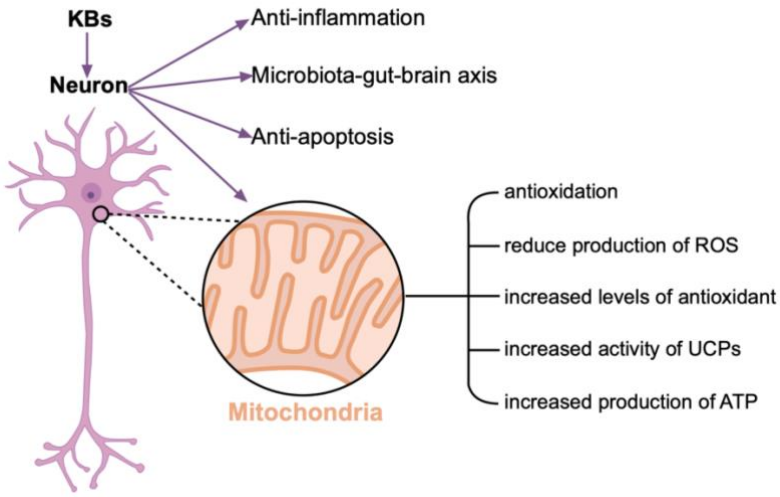

Figure 5. Neuroprotective mechanisms of the KBs [39].

Ketogenic Diet and Gut Microbiota Modulation

Diet can alternate the gut microbiota rapidly, and it has been suggested that KD can change gut microbiota in a way it mediates neuroinflammation. A study has shown that KD enriched beneficial microbiota like *Lactobacillus* and *Akkermansia* and it reduces pro-inflammatory microbes like *Turicibacter* and *Desulfovibrio* (Fig. 6) [39]. The mentioned beneficial microbes in turn produce SCFAs and control the production of γ-glutamyl amino acid [28]. SCFAs are neuroprotective and improve learning and memory. *Desulfovibrio* produces hydrogen sulfide (H_2S) and can destroy the mucosal barrier. The increase of these beneficial microbiota and the reduction of the pro-inflammatory microbiota induced by KD may improve the BBB and neurovascular function, cerebral blood flow and overall metabolic condition [39]. Another study showed that KBs can decrease growth of *Bifidobacterium*. Experiments in mice confirmed this depletion of *Bifidobacterium*. In result, KD-associated gut microbiota reduces the levels of intestinal pro-inflammatory Th17 cells, suggesting mediative effects on neuroinflammation [40].

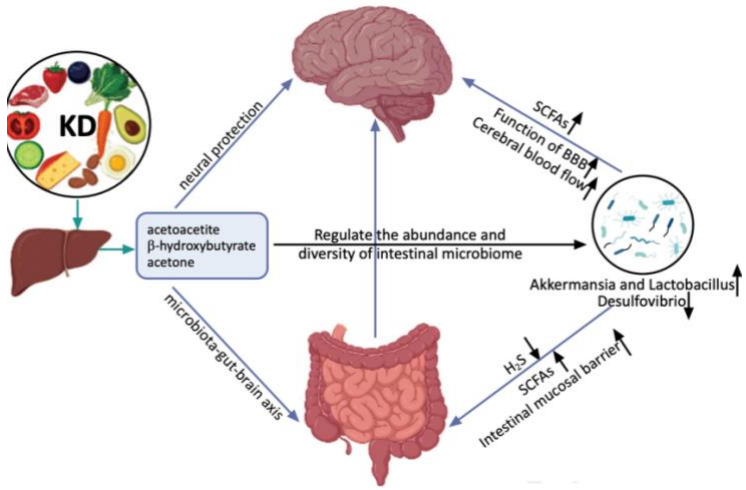

Figure 6. Direct and indirect (microbiota–gut-brain axis) effects of KD on the gut microbiota [39].

Ketogenic Diet and Parkinson's Disease

Combining the evidence that KD has shown beneficial effects on gut-microbiota composition and regulation, and the hypothesis that the microbiota-gut-brain axis plays an important role in

PD pathology and progression, this review aims to highlight the possible effects for the KD within the different stages of PD and its symptoms and on the PD-affected gut microbiota.

Effect of KD in the Preclinical Stage of PD

Nutrition holds potential importance in PD many reasons. Dietary factors can influence the preclinical stage by determining the risk of PD development, either negatively or positively (because of protective/harmful elements present in food). Several types of food have been linked to a decreased risk of future PD development, such as adherence to the Mediterranean diet, regular consumption of coffee or flavonoids, while others like a Western diet and high consumption of dairy products have been associated with an increased risk. Additionally, metabolic syndrome, another risk factor associated with a higher risk of PD development, is inherently connected to diet [41]. Oxidative stress plays a role in the development of PD, and it has been known that vitamin A, C, E, and β-carotene protect cells from oxidative stress damage. Therefore, the suggestion is that a higher intake of these nutrients might reduce the risk for PD. Also, macronutrients like dietary fats and its fatty acids might influence PD risk [42]. Many studies suggest the protective effects of different single nutrients, food groups and diets on the risk of PD, however there are no concrete studies found of KD effects on the preclinical stage. Precisely establishing the preclinical stage in PD patients is not easy. Therefore, there is a need for examining and clarifying this stage in PD, to increase the ability to conduct future studies in combination with potential (nutritional) therapies.

Effect of KD in the Prodromal Stage of PD

Before the clinical diagnosis of PD, there is a prodromal stage of ≥10 years during which individuals may experience a range of subtle nonmotor symptoms. In one study, they established the prodromal stage in patients based on seven features: constipation, REM-sleep behavior disorder, hyposmia, excessive daytime sleepiness, impaired color vision, depressive symptoms, and body pain [43]. Studies have shown that the Mediterranean diet is associated with a reduced risk of developing features of prodromal PD [44]. The studies showed that following this diet was inversely associated with the odds of ≥3 prodromal PD features and specifically with constipation, excessive daytime sleepiness, and depressive feelings. This suggests that a healthy dietary pattern may promote gut health in a way it protects against degeneration of the enteric nervous system or CNS. Again, suggesting an important role of the gut-brain axis in PD pathogenesis and development [43]. However, it remains unclear whether the Mediterranean diet delays the onset or lowers the incidence of PD [45]. KD is not comparable to the Mediterranean diet, because the KD restricts most of the protective foods included in the Mediterranean diet (vegetables, grains, legumes, and fruit) [46]. Evidence of the effects of KD in studies done in patients within the prodromal stage are limited. However, many studies investigating KD reported beneficial outcomes for different symptoms, including symptoms that can appear in the prodromal stage. This includes beneficial effects on cognition, speech, and voice disorders, both motor and non-motor symptoms, anxiety, and body composition [46, 47]. This emphasizes the need for further research done on the safety and effect of KD on the different symptoms of the prodromal stage.

Effect of KD in the Clinical Stage of PD

Diet can be important for patients clinically diagnosed with PD. In a first clinical pilot in five PD patients, improvements in motor score were noticed after 4 weeks of adherence to KD. A possible reason for improvement of these motor symptoms was suggested to be the low intake of proteins [48]. Dietary proteins normally split into amino acids after digestion, competing with

the absorption of levodopa in the gut and brain [41]. Therefore, low intake of protein increases the bioavailability of levodopa, enhancing its effectiveness on motor symptoms [48]. Also, a randomized controlled trial conducted for 8 weeks on 47 patients adhering to a low-fat diet or a KD showed that both diets positively affected their motor functions (hypokinesia, muscle tremors, or stiffness), and non-motor impairments (pain, fatigue, impaired memory, and cognitive function), but the KD exhibited greater improvements in non-motor functions [49, 50]. Another deficit observed in patients with PD is the conversion of tyrosine to dopamine. High-carbohydrate and low-fat diets, like a KD, may facilitate this conversion [49]. Another pathological mechanism in PD is the degeneration of the dopaminergic neurons in the SN of the midbrain. It is thought that decreased activity of mitochondrial complex I plays a key role in the death of dopaminergic neurons. KBs circumvent mitochondrial complex I by binding to mitochondrial complex II. They then provide an alternative fuel source for neurons and ketones, enhance mitochondrial function, and increase ATP production [28, 39, 49]. Next to that, in animal models of PD, the KD has shown to have protective effects in dopaminergic neurons by up-regulating glutathione in the striatum, reversing the decrease in dopamine [29]. KD also showed reduced microglial activation and downregulation of various inflammatory factors, such as IL-1β, IL-6 and TNF-α, and it can reduce the proliferation of astrocytes [28, 39]. In another study they administered 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a substance resulting in loss of dopaminergic neurons in striatum and SN, to create the common animal model of PD. They stated that KBs are beneficial in humans with PD and animal models of PD. They found protective effects of βHB against MPTP-induced damage to dopaminergic neurons in a rodent model of PD. They also found that injection of βHB in the brain of MPTP mice rescued mitochondrial function and ameliorates dopaminergic neurodegeneration and alleviates motor symptoms [26, 28]. To conclude, different studies have examined the effect of KD on animal models and humans. Most studies found suggestive evidence that KD has promising effects within the clinical stage of PD, but these effects were mostly to relieve symptoms. Therefore, more research aimed at unraveling the characteristic effect of KD on the pathophysiology of PD in the clinical stage and its symptoms needs to be done.

Effect of KD on Gut Microbiota in PD

In the study where they administered MPTP to create the common animal model of PD, they also evaluated the effect of a KD on the MPTP-model to clarify mechanisms within the microbiota-gut-brain axis. They found that an 8-week intervention with KD relieved motor dysfunction, dopaminergic neuron damage in the SN, and inflammation. Next to that, the KD restructured the gut microbiota, showing higher levels of *Akkermansia* and lower levels of *Desulfovibrio* and *Ruminococcus* (Fig. 7). *Desulfovibrio* generates LPS and H_2S, and can trigger inflammation, oxidative stress and α-syn aggregation. *Ruminococcus* could contribute to mucin degradation and increases intestinal permeability, which can lead to aggravated inflammation [36]. Research suggests that the microbiota composition in PD patients notably differs from that of healthy individuals. PD microbiota is characterized by reduced levels of *Prevotellaceae* and increased levels of *Enterobacteriaceae*. Gut dysbiosis can lead to impaired intestinal permeability, commonly referred to as "leaky gut," which, facilitated by bacterial-produced LPS triggers inflammatory responses and oxidative stress, promoting α-synuclein aggregation. KD has been shown to reverse this ratio, elevating *Prevotella* levels while reducing *Enterobacteriaceae* levels [28]. However, given that carbohydrates serve as the primary energy source for microbiota, a low-carbohydrate KD tends to diminish the overall diversity of gut microbiota. Next to that, the neuroprotective effect of KD manifested via the intestinal

microbiota is affected by individual factors, such as gender, age and race, and further research is needed to explore how KD affects the gut microbiota in PD [39].

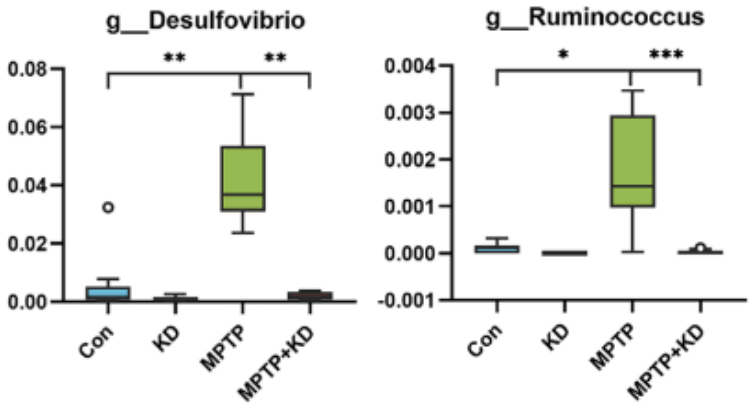

Figure 7. KD restructured gut microbiota in MPTP mice PD model. Significant change of relative abundance of Desulfovibrio and Ruminococcus [36].

Effect of KD in other Neurological Disorders

KD used to be initially established as an alternative therapy for refractive epilepsy. A high-fat and low-carbohydrate diet improved seizure control in patients with drug-resistant epilepsy [29]. Another study showed that the KD played an anti-seizure role by modifying the gut microbiota, systemic amino acid γ-glutamylation, and hippocampal γ-aminobutyric acid (GABA)/glutamate levels in mouse models of epilepsy [51].

Alzheimer's disease (AD) is the most common neurodegenerative disorder. A randomized pilot study indicated that a modified Mediterranean-ketogenic diet altered the gut microbiota and metabolites associated with AD biomarkers in cerebrospinal fluid [52]. Several other studies found that βHB inhibits neurotoxicity of the pathological AD hallmark amyloid-β, but that it also improves cognitive function and protects mitochondrial functionality in AD mouse models [29]. To conclude, the idea of KD being solely a treatment of epilepsy has shifted to the recognition that it plays a neuroprotective role in several neurodegenerative disorders. Therefore, KD offers a promising therapeutic approach for PD and other neurodegenerative disorders.

Limitations of KD

The relationship between gut dysbiosis, dietary interventions, and PD pathogenesis underscores the complex nature of this neurodegenerative disease. Understanding how dietary interventions, such as the KD, modulate gut microbiota to diminish disease progression could provide valuable insights into new therapeutic strategies for PD. While the KD is a promising potential therapeutic approach for PD, it is important to acknowledge several challenges. One of the main limitations include the fact there is a low number of available qualitative studies, since it is a relatively new research domain [1]. Hence there is a need for more comprehensive qualitative research to address this gap and provide deeper insights into the effects of KD on PD. Patients experiencing adherence difficulties is another one of the concerns. Most patients are initially motivated to comply, however the diet might induce poor tolerance to many fat-rich foods. Next to that, there is an uprise in adverse effects in KD intervention studies. These effects include abnormal lipid levels (dyslipidemia), digestive problems, weight loss and even dehydration, low blood sugar (hypoglycemia), low sodium levels (hyponatremia), atherosclerosis and impaired liver functions [29]. These adverse reactions are individual different, and the factors influencing this difference include gender, age, race, and underlying

diseases [39]. This suggest that modifications of the KD may be associated with better tolerance resulting in better adherence. Given these challenges, there is a need for more research to better understand the (adverse) effects of KD on pathogenesis and development of PD. This can be done by designing a standardized treatment protocol that monitors the dose and duration of the dietary intervention and prevents potential adverse effects.

Conclusions and perspectives

The prevalence of neurodegenerative disorders like PD is on the rise due to extended lifespans and unhealthy aging. With no cure presently accessible for PD, there is a need for identification of preventive measures and therapeutic approaches. This is crucial for delaying the onset, impeding its progression, and alleviating symptoms. Therefore, this review aims to strengthen our understanding of KD's promising effects across the different stages and symptoms of PD, while also providing insight on its role in modifying the gut microbiota composition in PD patients. Several studies have demonstrated the impact of KD on PD, affecting energy metabolism, oxidative stress, and neuroinflammation through diverse mechanisms. KBs like βHB can freely cross the BBB and prevent dysfunction of mitochondria and have neuroprotective properties, offering promising opportunities for PD treatment. While limited evidence exists regarding KD's impact on the preclinical and prodromal stages, clinical studies suggest improvements in motor and non-motor symptoms, possibly through enhanced levodopa efficacy, mitochondrial function, and neuroinflammation modulation. This effect of KD is exhibited through the regulation of the gut microbiota. Dysbiosis of the gut microbiota has been implicated in PD, affecting neurotransmitter levels, inflammation, and α-syn aggregation. KD's influence on gut microbiota presents a new path for therapeutic intervention in PD. By restoring microbial balance and reducing inflammation, KD may alleviate disease progression. The KD emerges as a promising intervention, modulating gut microbiota composition and exhibiting neuroprotective effects through mechanisms such as mitochondrial function enhancement and anti-inflammatory actions. Beyond PD, KD demonstrates promising results in other neurodegenerative diseases, highlighting its potential as a neuroprotective treatment for various conditions. However, some limitations of the KD express the need for further large-scale and long-term clinical research on PD, to evaluate the efficacy, adherence to and adverse effects of KD. Future research should focus on unraveling the precise pathogenesis and development of the different stages of PD and its symptoms, the interplay between PD, the microbiota-gut-brain axis, and the strengths and limitations of a KD as a treatment for PD. While there is still a long way to go, integrating nutritional approaches like KD into comprehensive PD treatment strategies holds great promise in improving the patient outcomes, quality of life and lifespan of millions of people worldwide.

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