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Preventing Progression: A Comprehensive Approach to Managing Parkinson's Disease

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Abstract

Parkinson's disease (PD) is the second-most common neurodegenerative disease and the most common synucleinopathy. It is a multi-system disease with both motor and non-motor disorders, cause of suffering for patients and a burden for healthcare system. Due to the constantly increasing number of patients and still unknown disease-modifying treatment, it is necessary to look for an effective way to slow down the progression. The article explores factors influencing PD progression, focusing on physical activity, nutrition, cognitive stimulation, and medical management. It underscores the need for a multidimensional approach to address the complex nature of PD and offers insights into potential strategies for slowing down Parkinson's disease progression.

Keywords: "Parkinson's Disease", "physical activity", "Mediterranean diet", "PD", "Ketogenic diet", "cognitive stimulation", "levodopa", "Parkinson's disease treatment", "PD treatment"

1. Introduction

Parkinson's disease (PD) is a progressive neurodegenerative disorder associated with the loss of dopaminergic neurons in the substantia nigra and the presence of Lewy bodies and Lewy neurites [1]. Lewy bodies occur in the midbrain and consist of many proteins including alpha-synuclein [2]. These pathological changes are responsible for the complexity of the symptoms that characterize Parkinson's disease. Clinical diagnosis focuses primarily on movement disorders such as asymmetric resting tremor, cogwheel rigidity, postural instability and bradykinesia. However, when diagnosing and treating PD, one must consider it as a complex multi-system disease and not forget about non-motor symptoms such as anosmia, gastrointestinal and sleep dysfunction, depression, autonomic dysfunction, pain and cognitive decline [1,3].

The prevalence of Parkinson disease has doubled over the last 25 years and it's expected to continuously grow reaching 12.9 million cases by 2040 [4,5]. The increase in the number of PD cases is related, among other things, to the aging of society and rising PD's incidence at the age 65 [6]. Studies have shown that Parkinson's disease is influenced by genetic, environmental and behavioral factors [7]. As there is currently no disease-modifying treatment for PD, it remains a chronic illness, the progression of which is not only suffering for patients but also a burden for the healthcare economy. The increasing number of PD patients forces us to look for different ways to change the course of the disease [8].

The purpose of this article is to summarize the most important known factors preventing progression of symptoms in Parkinson's disease.

2. Material and methods

The purpose of this study is to review the available data on treatment and known factors preventing progression of symptoms in Parkinson's disease. We reviewed the literature available in medical research databases PubMed, Google Scholar and Scopus. The keywords used in the title or in the body were: "Parkinson's Disease", "PD", "OFF time", "adenosine", "motor fluctuations", "treatment", "levodopa", "levodopa-resistance", "tremor", "Monoamine oxidase-B inhibitors", "rasagiline", safinamide", "selegiline", "COMT inhibitors", "dopamine

agonists", "dementia", "mild cognitive impairment", "neuropsychology", "neuromodulation", "neurorehabilitation".

We focused on full-text articles about the treatment of Parkinson's disease and the impact of lifestyle on the course of the disease.

3. The role of physical activity

Physical activity plays a crucial role in managing Parkinson's disease by improving both motion and non-motion aspects, with notable benefits in increasing confidence, preventing falls, and enhancing the overall quality of life. the type of physical exercise performed should be adapted to the patient's capabilities and the expected therapeutic effects.

Several studies have demonstrated that moderate-to-heavy exercise not only lowers the risk of developing PD but also slows down the onset and progression of PD. Large randomized controlled trials have consistently shown that exercise can improve cognitive decline and bradykinesia symptoms while effectively preventing falls in PD patients. Exercise intervention has also been associated with alleviating non-motor symptoms, reducing fear of falling, and enhancing the mental well-being of PD patients [9]. Studies showed that aerobic exercise in individuals with PD may contribute to stabilizing motor progression and enhancing cognitive performance by inducing functional and structural plasticity in corticostriatal sensorimotor and cognitive control networks [10]. Resistance training consistently demonstrates increased muscle force production and improved mobility in clinical studies. Balance training can reduce fall rates, especially in mild to moderate PD's stages. Treadmill training, Nordic walking, and external cueing [auditory and visual] are effective in improving various aspects of gait [11]. The study conducting virtual reality-based game exercise program showed significantly enhanced confidence in preventing falls and improved balance and stepping ability in older adults with mild-to-moderate PD [12]. The aquatic exercises have additional benefits of over land-based exercises such as greater balance capacity and lower fear of falling [13].

4. Nutrition and Diet

Diet and nutrition are representation of modifiable factors for either slow down or hast the progression of Parkinson's Disease. Different dietary strategies have been explored for their potential therapeutic effects.

Ketogenic diets, mimicking fasting by producing ketosis state, may have benefits in neurodegenerative diseases by influencing glucose utilization and mitochondrial function. Studies in animal models and limited human trials suggest that ketogenic diets might improve both motor and non-motor symptoms in PD. However best fat to carbohydrate ratio must be further investigated [14].

The mediterranean diet, characterized by a high intake of fresh vegetables, fruits, whole grains, legumes, nuts, olive oil, and moderate consumption of other food groups also is s associated with slower PD progression. It’s rich in antioxidants, anti-inflammatory agents, minerals, and vitamins, which are believed to contribute to its protective effects. Resveratrol and polyphenols derived from the olive tree may counteract oxidative stress and inflammation, which are recognized factors in PD. The Mediterranean Diet's fiber-rich content may promote the growth of beneficial bacteria, increase microbial richness, and enhance the production of short-chain fatty acids [SCFAs]. The increased production of SCFAs may fortify the intestinal barrier and inhibit inflammation, potentially influencing the gut-brain axis and contributing to the protective effects against PD [15].

Western diet, characterized by high caloric intake of energy-dense and processed foods such as beef, canned fruits and vegetables, fried foods and soda may accelerate PD progression.

Interestingly, diet soda showed a higher association with PD progression compared to regular soda, potentially related to the metabolism of aspartame leading to biochemical disruptions in the brain [16].

As studies showed, milk and dairy products may be associated with elevated risk of worsening the PD [17]. Potential reasons for that effect of dairy include the reduction in serum uric acid levels, exposure to neurotoxins due to pesticides contamination and causing insulin resistance [18, 19].

Additionally, substances like mannitol, known for its ability to open the blood-brain barrier, and palmitoylethanolamide, an endogenous lipid signaling molecule, have been investigated. Mannitol shows promise in reducing α-synuclein aggregates and improving behavioral deficits in animal models of PD [20]. Ultra-micronized palmitoylethanolamide, administered as an add-on, medical food treatment in individuals with PD, demonstrated a progressive reduction in symptoms, suggesting potential disease-modifying effects [21].

Foods linked to a slower progression of Parkinson's disease include fresh vegetables, fresh fruit, nuts, seeds, non-fried fish, olive oil, wine, coconut oil, fresh herbs, and spices. Quicker PD progression is associated with the consumption of canned fruits and vegetables, diet and non-diet soda, fried foods, beef, ice cream, yogurt, and cheese. Notably, nutritional supplements like

coenzyme Q10 and fish oil exhibited an association with reduced PD progression, while iron supplementation correlated with a faster rate of progression [16].

Another important factor being investigated that may influence the progression of Parkinson's disease is vitamin D. Vitamin D can be provided through supplementation or exposure to sunlight. Studies showed, insufficiency and deficiency of 25-hydroxyvitamin D and reduced exposure to sunlight can increase risk of Parkinson's disease [22#]. Conversely, vitamin D supplementation and sunlight exposure have shown preventive effects. High vitamin D doses may enhance balance and reduce falls, particularly in young PD patients. Elevated serum vitamin D level is linked to better cognition and potential impacts on mood and olfactory function in PD. Vitamin D may benefit PD by mitigating dopaminergic neurodegeneration, reducing neuroinflammation, restoring calcium homeostasis, inhibiting α-synuclein aggregation, preventing cell death, and upregulating factors crucial for dopamine neuron survival. These mechanisms highlight the potential neuroprotective role of vitamin D in PD. However, further, extensive research is necessary on the impact of vitamin D on the course of Parkinson's disease [23#]

5. Cognitive Stimulation

Mild cognitive impairment affects approximately 30% of PD patients and its frequency increases with age, disease duration and disease severity. A large proportion of patients with mild cognitive impairment develop dementia later on [24]. Five cognitive domains could be affected: memory, attention/working memory, language, visuospatial and executive functions [25]. The possible underlying mechanisms of cognitive impairment in PD include abnormal protein deposition, loss of dopaminergic neurons, neurotransmitter deficits, synaptic dysfunction, genetics, fatty acid oxidation, inflammation and oxidative stress, exosomal dysfunction, the gut microbiome and gut–brain axis involving the autonomic and enteric nervous systems, and prion-like aggregation of alpha-synuclein. As there are still no disease-modifying treatments known, the search for new methods to slow down the cognitive impairment process in ongoing [26].

Transcranial alternating current stimulation [tACS] can modulate brain oscillations based on mapping of cortical activity, that provides a personalized neurotherapeutic target. The combination of physical therapy with tACS has demonstrated its efficacy in enhancing both

motor and cognitive functions, particularly in individuals with mild to moderate impairment, and is often integrated as a complement to pharmacological and neurosurgical interventions. The synergy between physical therapy and transcranial alternating current stimulation serves a dual purpose: physical exercise activates cortical sensorimotor areas, preparing the neuronal population for stimulation, while tACS contributes to amplifying cortical plasticity during neurorehabilitation [27].

Neuropsychological rehabilitation plays a crucial role in managing cognitive impairment associated with Parkinson's disease. It involves psychological interventions aimed at optimizing cognitive, emotional, and psychosocial functions. The interventions include educational components, psychotherapy, cognitive exercises, and training in compensatory strategies. Physical exercise, good sleep hygiene, stress management, and social engagement form the foundation for improving cognitive function. Specific cognitive impairments are aimed through practices like challenging computer games. Compensatory strategies and devices, such as lists, calendars, and reminder alarms, offer practical solutions. Overall, neuropsychological rehabilitation is a valuable and cost-effective component of the comprehensive management of cognitive impairments in PD, providing patients with a sense of control and potential improvements in quality of life [28].

6. Medication and Medical Management

Levodopa has consistently stood out as the most effective medical treatment for addressing the motor symptoms of Parkinson's disease. However, the motor complications associated with levodopa such as levodopa-induced dyskinesia is a big disadvantage worsening the quality of life. In the last three decades, the range of medical therapies aimed at enhancing motor control in progressive PD has expanded [29].

Carbidopa and levodopa extended release is an oral medication designed to provide both immediate and extended release of levodopa, resulting in less frequent dosing and stable, longer-lasting plasma concentrations. Levodopa inhalation powder can be used for intermittent treatment of OFF episodes in PD. Administered through oral inhalation, it provides a rapid rise in plasma levodopa concentration, offering potential benefits for patients with motor fluctuations. However, it’s not recommended for patients with chronic respiratory diseases [29].

Dopamine agonists have been widely used in Parkinson's disease management, serving as both monotherapy in early stages and adjuncts to levodopa in advanced cases. Ropinirole, a selective nonergoline D2/D3 receptor agonist, has shown effectiveness in reducing daily OFF time and levodopa dose in PD patients with motor fluctuations. The 24-h prolonged release formulation demonstrated significant improvements in daily OFF time and ON time without troublesome dyskinesia. Pramipexole, a nonergoline D2/D3 receptor agonist is also available in the 24-h extended-release formulation [29,30].

Catechol-O-Methyltransferase Inhibitors [COMT Inhibitors] play a crucial role in the treatment of Parkinson's disease. Entacapone and opicapone both **i**ncrease ON and reduces OFF time and improve motor fluctuations when administered with levodopa. Tolcapone has greater improvements in ON time and OFF time and is preferred by patients due to better outcomes [29,31].

Monoamine oxidase inhibitors [MAOIs] reduce the degradation of dopamine, thus enhance its effects. Of the two MAO isoforms [A and B], selective inhibition of MAO-B is preferred to avoid dietary-related hypertensive crises. Selective MAO-B inhibitors approved for the treatment of Parkinson’s disease are: selegiline, rasagiline, and safinamide [29,32].

Istradefylline, an adenosine A2A receptor antagonist, was approved in Japan [2013] and the USA [2019] as an adjunctive treatment for Parkinson's disease [PD] with OFF episodes. It counteracts dopamine deficiency by reducing striatopallidal neuron overactivity. Common side effects include dyskinesia, dizziness, constipation, nausea, hallucination, and insomnia. [29,33].

Amantadine, a non-selective glutamatergic NMDA receptor antagonist, is effective against levodopa-induced dyskinesia. Studies showed its benefits in reducing dyskinesia scores and OFF time. Common side effects include hallucinations, dizziness, dry mouth, peripheral edema, constipation, falls, and orthostatic hypotension [29,34].

Clozapine, an atypical neuroleptic, has serotonin and weak dopamine receptor antagonism. Studies suggest its potential to reduce levodopa-induced dyskinesia. It’s rarely used due to severe agranulocytosis risk, requiring frequent monitoring. Other side effects of clozapine include sedation and sialorrhea. [29].

Summary

Parkinson’s disease is the second-most common neurodegenerative disease and the most common synucleinopathy. It’s a cause of suffering for patients and a burden for healthcare system. Due to the constantly increasing number of patients and still unknown disease-modifying treatment, it is necessary to look for an effective way to slow down the progression. According to studies, physical activity, especially aerobic and resistance training, has shown benefits in improving motion, cognitive function, and preventing falls in PD patients. Dietary strategies like ketogenic and Mediterranean diets have potential therapeutic effects, while a Western diet may accelerate PD progression. Specific foods and supplements are associated with either slower or quicker PD progression. Foods linked to a slower progression of Parkinson's disease include fresh vegetables, fresh fruit, nuts, seeds, non-fried fish, olive oil, wine, coconut oil, fresh herbs, and spices. Quicker PD progression is associated with the consumption of canned fruits and vegetables, diet and non-diet soda, fried foods, beef, ice cream, yogurt, and cheese. Cognitive impairment affects 30% of PD patients. Neuropsychological rehabilitation, transcranial alternating current stimulation [tACS] and physical exercise have shown efficacy in managing cognitive decline. Levodopa remains the most effective treatment, but other medications, including dopamine agonists, COMT inhibitors, MAOIs, istradefylline, and amantadine, are discussed for their role in PD management.

There is a great need for further research into the influence of lifestyle, environment and other modifiable factors that could prevent the progression of Parkinson's disease or stop it altogether.

Disclosure

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