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Cardiovascular Complications In Parkinson's Disease: Mechanisms, Prevalence, And Management

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Abstract
Parkinson's disease (PD) is a neurodegenerative disorder characterized by motor and non-motor symptoms. Cardiovascular complications in PD are increasingly recognized as significant contributors to morbidity and mortality. These complications are primarily caused by autonomic dysfunction, with mechanisms such as cardiac sympathetic denervation, vascular stiffness, and neurogenic orthostatic hypotension. Additionally, the deposition of alpha-synuclein, a hallmark of PD, plays a key role in disrupting cardiovascular function. Patients with PD are at an elevated risk for arrhythmias, ischemic heart disease, heart failure, and stroke, often exacerbated by traditional cardiovascular risk factors like hypertension and diabetes. Effective management of cardiovascular complications in PD requires a multifaceted approach, including both pharmacological interventions (e.g., midodrine, droxidopa) and non-pharmacological strategies (e.g., lifestyle modifications, physical activity, and multidisciplinary care). Regular monitoring and individualized treatment plans are critical to improving patient outcomes and reducing the risk of severe cardiovascular events. Future research into the molecular pathways linking PD to cardiovascular disease may yield novel therapeutic targets, enhancing the effectiveness of treatment approaches.

Keywords: Parkinson's Disease, Cardiovascular Complications, Autonomic Dysfunction, Orthostatic Hypotension, Cardiac Sympathetic Denervation, Alpha-Synuclein.

Introduction

Parkinson disease is a progressive neurodegenerative disease, which is mainly defined by the loss of dopaminergic neurons in the substantia nigra which causes motor symptoms of bradykinesia, rigidity and tremor [1]. In addition to these typical motor manifestations, Parkinson disease is also characterized by a range of non-motor symptoms, such as cognitive deficit, mood disorders, and severe autonomic dysfunction, which have a significant negative effect on the quality of life of a patient [2]. Cardiovascular complications are some of these non-motor features and they are highly prominent among the Parkinson patients in contributing to morbidity and mortality [3]. Parkinson disease

pathogenesis is not limited to the central nervous system as the accumulation of alpha-synuclein in the peripheral tissues can lead to dysfunction of the entire system, including cardiovascular pathology [4]. Such systemic involvement can be expressed in the form of cardiovascular dysautonomia, which includes the death of noradrenergic cells in the heart, one of the main facts that highlight the prevalence of the disease [5].

Autonomic dysfunction, a characteristic non-motor of Parkinson disease, often occurs in the form of orthostatic hypotension and cardiac arrhythmias and QT prolongation which all worsen the risk of falls and fatigue [6]. In addition, the presence of alpha-synuclein in the deposition of the sympathetic noradrenergic neurons is highly linked with myocardial noradrenergic loss resulting in neurogenic orthostatic hypotension [7]. The sudden cardiac death is another serious, but not very frequent event of patients with this disease, caused by this denervation [8]. This cardiac sympathetic neuroimaging-detectable noradrenergic denervation of the myocardium is an obvious clinical laboratory correlate of dysautonomia in PD [5]. In addition, a-synuclein deposition of sympathetic ganglia, especially in noradrenergic nerve fibres is substantially related to loss of cardiac noradrenaline and neuronal storage of a-synuclein, indicating a direct pathogenesis between a-synuclein deposition and retrogression of cardiac sympathetic nerve fibres. This complex interrelation between a-synuclein process and autonomic denervation to a larger cardiovascular dysregulation commonly includes orthostatic and postprandial arterial hypotension, which may be experienced by a significant number of patients [3]. The resultant cardiac autonomic dysfunction, which is usually measured in heart rate variability and measures of arterial stiffness, worsens cardiovascular risk still further by disrupting the body capacity to control heart rate and arterial rigidity [9]. Considering this, alterations in the mechanisms of heart rate variability and heightened arterial rigidity are commonly seen among people with Parkinson disease, which signifies dysfunction of the cardiac autonomic regulation and heightened cardiovascular pathology [9, 10]. An inactive lifestyle, which is common among patients with Parkinson since they have motor symptoms, can further increase this autonomic dysfunction and vascular deterioration, further increasing the risk of cardiovascular disease [9].

Definition, Epidemiology, and Neuropathological Characteristics

Parkinson disease is an idiopathic neurodegenerative condition that is associated with progressive destruction of dopaminergic neurons in the substantia nigra pars compacta, which is a key motor control area [10]. This loss of neurons causes a substantial loss of dopamine concentration in the striatum, which causes the typical motor symptoms of bradykinesia, rigidity, tremor, and postural instability [1]. Overview of Motor and Non-Motor Symptoms of PDBeyond these motor symptoms, PD is also linked to a broad range of non-motor symptoms, such as cognitive dysfunction, mood disorders, sleep disturbances, and autonomic dysregulation, which frequently occur before the onset of motor symptoms and have a great impact on the quality of life [11]. The progressive and chronic course of PD, as well as its rich symptomatic manifestation, explain the importance of the need to implement holistic management tools that cover non-motor and motor components of the disease [12]. Cardiovascular dysautonomia [such as orthostatic hypotension and decreased variability of the heart rate] is particularly prevalent among patients with Parkinson, which affects the overall health and the prognosis of patient outcomes [5,13].

Recent epidemiological data also suggests that PD patients are at risk of suffering stroke and subclinical ischemic insults more often than others, which underscores the larger cardiovascular frailty in the disease [14]. This increased risk is also increased due to the frequent comorbidities like hyperglycemia, insulin resistance, and dyslipidemia that is common among PD patient population and leads to the development of macrovascular complications. These metabolic abnormalities such as hyperinsulinemia, and hyperuricemia are other risk factors to the development of peripheral artery disease, and stroke, which in effect complicates the cardiovascular picture of patients with the disease Parkinson [15].

In addition, the high rate of Parkinson's disease worldwide with 8.5 million individuals with the condition in 2019 highlights the need to comprehend and implement the cardiovascular risks associated with the disease [16]. The motor symptoms of the severe type, which include bradykinesia, rigidity and tremors, are caused by the chronic and progressive nature of this neurodegenerative disorder, which is mainly marked by the loss of dopaminergic neurons within substantia nigra pars compacta [17,18].

Table 1: Mechanisms of Cardiovascular Complications in Parkinson's Disease [PD].

Mechanism	Description	References
Autonomic Dysfunction	PD leads to autonomic dysregulation, affecting heart rate, blood pressure, and vasomotor control.	[5,6,27]
Cardiac Sympathetic Denervation	Loss of sympathetic innervation in the heart, leading to orthostatic hypotension and arrhythmias.	[7, 32,33]
Alpha-Synuclein Deposition	Accumulation of alpha-synuclein in peripheral autonomic ganglia and myocardial cells causes dysfunction.	[3,5,34]
Neurogenic Orthostatic Hypotension [nOH]	Impaired baroreflex response, causing abnormal blood pressure fluctuations upon standing.	[6,27,56]
Vascular Dysfunction	Endothelial dysfunction and increased vascular stiffness contribute to cardiovascular pathology.	[15,24,25]

The Significance of Comorbidities in PD

Effects of Non-Motor Symptoms on Patient Quality of life and rate of Disease progressionThese non-motor symptoms, including cognitive impairments, mood disorders, and sleeping issues, can manifest themselves several years prior to the cardinal motor conditions, and they are associated with substantial disability and reduced life expectancy [6]. These non-motor symptoms, such as cardiovascular problems, have been recognized to be common and have led to the approach of interpreting the management of the Parkinson disease on a more holistic basis as to the critical interplay between the neurological degeneration and systemic well-being. Such an in-depth perspective is essential because about 80 percent-90 percent of patients with Parkinson will undergo modifications in the autonomic system, with an increased susceptibility to dying of the significant cardiac complications relative to the general population [19].

This cardiovascular susceptibility in people with PD is further supported by the emerging evidence that indicates the strong correlation between the history of cardiovascular disease and shallower types of idiopathic Parkinson disease development [20]. These results highlight the need to focus on early diagnosis and active management of cardiovascular risk factors in the PD population to reduce the development of the disease and overall patient outcomes. In its turn, this indicates that the molecular and systemic processes that connect PD with cardiovascular pathology should be examined in more depth to be able to devise specific interventions [6]. Further, the current worldwide trend of the increasing rates of neurodegenerative illnesses, such as Parkinson, requires an in-depth grasp of comorbidities, particularly cardiovascular complications, which play a crucial role in determining the prognoses and quality of life of patients [1,6].

Justification of Study of cardiovascular complications in PD

Cardiovascular disease is one of the most common causes of morbidity and mortality in PD patients and thus tends to complicate treatment interventions and reduce the effectiveness of interventions meant to address motor symptoms [21]. This demonstrates the urgency to explore the complex interaction between neurological degeneration and cardiovascular pathology as there are several neurodegenerative diseases such as PD, which share underlying pathogenic pathways cellular and subcellular in common with cardiovascular disorders. The finding of these common mechanistic pathways is promising directions of therapeutic development that would alleviate conditions of various diseases at the same time [22].

Mechanisms that mediate cardiovascular complications in Parkinson disease

A complex interplay among neurological, systemic, and pharmacological agents promoting cardiovascular dysfunction in PD will be clarified [not limited to autonomic dysregulation] but instead direct myocardial and vascular pathology. This will involve the investigation of the roles of

neuroinflammation, oxidative stress, and mitochondrial dysfunction that are involved in the neurodegenerative phenomenon of PD as well as pathogenesis of several cardiovascular diseases [23]. The two-way traffic between PD and cardiovascular health also harbors the need to explore the similarities in the common molecular pathways, including glucose and lipids metabolism, cellular stress, and inflammation, that may determine the disease progression and treatment efficacy [24]. As an example, cardiac b1-adrenergic and A1-adenosine receptors are important factors that cause the severe arrhythmias in animal models of PD, which makes them directly linked to each other on a molecular level [25]. Moreover, common pathological characteristics of protein misfolding, including alpha-synuclein deposits in PD are gaining recognition to extend beyond the central nervous system, to peripheral organs, including the heart and the vasculature, causing direct cardiovascular injury [6].

Dysfunction of the Autonomic Nervous System.

Examining the dysregulation that is affecting cardiovascular control. This asymmetry results in disorders like orthostatic hypotension and supine hypertension which are typical of neurodegenerative synucleinopathies such as Parkinson disease [26]. Cardiac Autonomic Neuropathy: Exploring the processes of cardiac denervation and outcome. It has been shown that PD patients demonstrate evident evidence of the baroreflex failure and the absence of sympathetic innervation, especially in the heart, which is one of the reasons of orthostatic hypotension [27]. The role of studying the changes in the levels of both catecholamine and acetylcholine that disrupt the control of the cardiovascular system. This dysregulation of neurotransmitters, particularly, the decline in cardiac sympathetic innervation, has the direct capacity to disrupt the response of the heart to physiological needs, and therefore, reducing the variability in heart rate and increasing the risk of arrythmias [28]. One of the elements of this autonomic dysregulation is vagal denervation, which may cause heart rate regulation and decrease heart rate variability, which increases cardiovascular risk [29].

The dysregulation of stress proteins including HSP27 has also been implicated in the dysregulation of the cardiovascular functions of PD because such proteins mediate the aggregation of proteins and homeostasis of cells [30]. Besides, the weakened blood-brain barrier and neuroinflammation that are common in PD worsen cardiovascular pathologies through facilitating systemic inflammation and endothelial dysfunction [31]. Autonomic ganglia Lewy body pathology. The extensive deposition of alpha-synuclein in the peripheral autonomic ganglia and nerve fibre including cardiovascular systems is a direct contributor of the severe dysautonomia of PD [30,32]. Effects of norepinephrine and dopamine disbalances on cardiovascular functionality. This imbalance, specifically a drop in cardiac norepinephrine, is a great setback to the sympathetic nervous system to maintain heart rate and blood pressure, deteriorating such conditions as orthostatic hypotension [33]. Cardiac noradrenergic deficits that are usually involved in this denervation are typically preceding the motor symptoms of PD implying that it is involved early in the disease pathogenesis [5]. These deficiencies do not only resemble symptoms but are indicative of a significant cardiac sympathetic noradrenergic lesion which may be due to denervation or a defect of synthesis, storage, or release of norepinephrine [34]. It is a crucial aspect of cardiovascular dysfunction in PD that is associated with denervation of the cardiac sympathetic nervous system that is also supported by the finding that heart rate variability is also reduced even at an early stage of the disease especially when the body is in the sympathetic dominant state [35].

Table 2: Common Cardiovascular Complications in Parkinson's Disease [PD].

Cardiovascular Complication	Description	References
Orthostatic Hypotension	A sudden drop in blood pressure upon standing, leading to dizziness and fainting.	[7,9,54]
Arrhythmias	Irregular heartbeats, including bradycardia, tachycardia, and atrial fibrillation, worsened by PD and medications.	[5,60,62]

Ischemic Heart Disease	Increased risk of coronary artery disease due to both PD-specific factors and traditional cardiovascular risk factors.	[49,50,63]
Heart Failure	A common consequence of PD-related autonomic dysfunction and structural heart changes.	[34,37,39]
Stroke	Higher vulnerability to both ischemic and hemorrhagic strokes due to endothelial dysfunction and hypertension.	[14,66,67]

Pharmacological Effect of Anti-Parkinsonian Therapies.

Dopaminergic Drugs: Cardiovascular adverse effects of levodopa, dopamine agonists, and so on. They comprise orthostatic hypotension, cardiac arrhythmias, as well as peripheral edema, and patients with PD must be monitored and managed with great attention [36]. Non-Dopaminergic Therapies: MAO-B Inhibitors, COMT Inhibitors and other Adjunctive Treatments. Although the non-dopaminergic therapy is less associated with direct cardiovascular side effects than the dopaminergic therapy, clinicians should be aware of their possible interactions and indirect cardiovascular consequences especially in patients who already have cardiac conditions. The cardiovascular effects of the antidepressants, anxiolytics, and antipsychotics commonly used to treat PD patients with non-motor symptoms [37].

Effects of deep brain stimulation on cardiovascular parameters and stress system. This involves measuring the possible changes in the heart rate, blood pressure, and baroreflex sensitivity that could be caused by the changes on the neural circles that regulate the cardiovascular functions. Also, spinal anesthesia, a commonly used form of anesthesia in surgical procedures in PD patients, has cardiovascular side effects known to have arterial hypotension, which should be managed with great care to avoid additional hemodynamic instability [36]. The effects of anticholinergic drugs on the work of the heart, especially their tendency to cause cardiac acceleration and slow the progression of already existing heart diseases also deserves close attention in PD patients. Moreover, numerous patients with PD are at a high risk of progressing to structural and functional heart diseases, including left ventricular hypertrophy and systolic dysfunction, which may lead to heart failure, ischemic heart disease, and ventricular tachyarrhythmias all of which are usually enhanced by dysautonomia [3]. The aggregate impact of these cardiovascular morbidities poses a challenge to the mortality rate causing a decrease in the quality of life among persons with PD [38]. Furthermore, antiparkinsonian drugs, especially dopamine agonists, are also often associated with orthostatic hypotension, which makes cardiovascular control more complex and exposes patients to additional adverse outcomes such as falls [39,40].

Common Pathophysiological Pathways and Risk Factors.

Onset of endothelial dysfunction, atherosclerosis acceleration, and direct tissue damage of myocardium by these processes result in the connection between neuroinflammation in PD and extensive cardiovascular impairment. Damage of vascularity. The reduced bioavailability of nitric oxide and imbalance of vasoactive substances that result in a decrease in vasodilation and an increase in vascular stiffness define this dysfunction [15]. Interaction with PD Pathology. All these together increase the susceptibility of people with Parkinson disease to cardiovascular events and require a thorough understanding of the synergy between them. Other comorbidities like diabetes and hypertension are very common among PD patients and they place a high risk of cardiovascular disease and surgical complications [41]. There is the existence of diabetes, which worsens the situation by increasing microvascular and macrovascular complications, resulting in even more cardiovascular incidents against stroke in PD patients [15]. Moreover, recent studies indicate that aberrant interoception, or the detection of internal body conditions may also be a contributing factor to the cardiovascular load in PD, possibly through modifying patient perception and reaction to physiological signals [28].

Lifestyle and Behavioral Modifiers

Effects of physical inactivity, diet and other lifestyle interventions peculiar to PD patients. Such modifiers may be very powerful determinants of cardiovascular health, and inactive lifestyles and unhealthy eating habits contribute to the further development of autonomic dysfunction and vascular hardening among this group of people [9]. Instead, regular physical exercise has the ability to alleviate

some of these risks through the enhancement of endothelial function, autonomic balance, and systemic inflammation [42]. On the other hand, a relative inactivity, which is characteristic of the patients of PD because of the motor symptoms, is accompanied by increased cardiovascular morbidity and mortality [43]. Dietary interventions including those that are rich in antioxidants and anti-inflammatory compounds also have potential in reducing the risk of cardiovascular disease through the reduction of oxidative stress and systemic inflammation [15]. Determination of stable biomarkers and clarification of complex genetic-environmental interactions is also central to a deeper appreciation of these factors in PD [44]. Such an integrated treatment method makes it possible to create specific therapeutic options that will be aimed at both neurological and cardiovascular components of the disease [20].

As a matter of fact, the multi-omics metrics and longitudinal cohort studies are urgently needed to unravel the sophisticated interplay between genetics, epigenetics, and environmental factors that cause cardiovascular complications in PD [45]. Additionally, the implementation of joint pathophysiological pathways, including systemic inflammation and endothelial dysfunction, in the development of PD and cardiovascular disease will be helpful in the creation of combined interventions [6]. Even though this has been achieved to a great extent, an absolute cause-effect relationship that cardiovascular risk factor modification changes the progress of the Parkinson disease via clinical trials is yet to be concluded [46].

Table 3: Management Approaches for Cardiovascular Complications in Parkinson's Disease.

Management Approach	Description	References
Pharmacological Treatment	Use of drugs like midodrine and droxidopa for managing orthostatic hypotension and improving blood pressure regulation.	[36,73,75]
Non-Pharmacological Interventions	Lifestyle changes such as fluid and salt intake, physical activity, and compression stockings to alleviate symptoms.	[77,79,86]
Multidisciplinary Care	Collaboration between neurologists, cardiologists, and other healthcare providers to manage both motor and cardiovascular symptoms.	[85,87,91]
Exercise Rehabilitation	High-intensity aerobic exercise to improve autonomic function, reduce cardiovascular risk, and enhance overall health.	[86,89,91]
Dietary Modifications	Antioxidant-rich diets and small frequent meals to alleviate postprandial hypotension and reduce systemic inflammation.	[15,42,80]

Prevalence of Specific Cardiovascular Complications in Parkinson's Disease

Research shows that the cardiovascular complications generally are significantly high in people with Parkinson's Disease in relation to the general population, which is why the effects of this neurodegenerative condition are systemic [47]. This increased vulnerability requires a more thorough epidemiological examination of individual cardiovascular diseases in order to redefine particular diagnostic and treatment measures [20]. As the example of hypertension, a common cardiovascular risk factor, shows, the prevalence trends of this condition in PD patients are complex as the prevalence rate may decrease in the early stages but increase in later stages, accompanied by a higher proportion of complications [48,49]. Additionally, cardiovascular burden of PD patients in different regions can be also contributed by the geographical difference in prevalence of hypertension as it is observed among general populations [50]. In addition to hypertension, comorbidities such as dyslipidemia and obesity are very common, as independent risk factors that increase the rate of atherosclerosis and cardiac events among the PD population [43].

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Hypertension

Prevalence and Manifestations:

The study of HTN and blood pressure dysregulation in PD. This involves the evaluation of persistent hypertension as well as incidences of paroxysmal hypertension, which may be as a result of autonomic dysregulation that is inherent to the disease [51,52].

Nocturnal Blood Pressure and Hypertension:

Specific challenges in PD. Such fluctuations usually involve diurnal blood pressure changes that are unusual as compared to healthy people, which further complicates the cardiovascular risk stratification and management in this population [53]. The intricate inter-relationship between orthostatic hypotension and hypertension makes it essential to consider a careful approach to diagnosing and tailoring the therapeutic interventions to meet the best cardiovascular outcomes of the PD patients [54,55,56]. The neurogenic orthostatic hypotension [nOH] is a common and disabling issue in synucleinopathies, such as Parkinson's disease, which is a major cause of poor patient outcomes and quality of life [57]. On the other hand, Supine hypertension, which is a related illness where blood pressure rises upon lying down can also be accompanied by neurogenic orthostatic hypotension, and can predispose to the occurrence of cardiovascular and cerebrovascular events in the long-term [58]. Such a paradoxical coexistence implies that a fine balance between the therapeutic measures implemented must be done to avoid worsening either of the two conditions, as they have unique pathophysiological processes but have common autonomic foundations [54,59]**.**

Cardiac Arrhythmias

Bradycardia, tachycardia, and atrial fibrillation risk in the patients of PD. Such arrhythmias may be as a result of direct activity of the autonomic nervous system in cardiac electrical activity, side effects of medication, or underlying structural heart disease, and predisposes an individual to adverse cardiovascular outcomes such as stroke and sudden cardiac death [60]. One of the characteristics of Parkinson’s disease is autonomic dysfunction, and it helps to trigger such arrhythmic events that are not well controlled by current treatment methods [61]. In this population of patients, more sophisticated monitoring methods are frequently needed to precisely describe the burden and precipitants of arrhythmias. Moreover, the cardiac sympathetic denervation, which is a common symptom of PD, may result in an excessive response to sympathomimetic drugs, which may cause life-threatening blood pressure changes during medical procedures [62]. These denervation patterns, which can be made by using imaging procedures, including MIBG scintigraphy, provide important information about the pathophysiology of the cardiovascular complications in PD [32].

Ischemic Heart Disease and Heart Failure

Risk factors and incidence of these significant cardiovascular occurrences among patients with PD. Shared traditional cardiovascular risk factors such as hypertension and dyslipidemia and PD-specific factors such as chronic inflammation and autonomic dysfunction usually increase these risks [49,63]. Moreover, diabetes which is often underdiagnosed is commonly associated with cardiac autonomic neuropathy where resting tachycardia and intolerance to exercise are common symptoms contributing to the increase in cardiovascular risk of patients with PD [15]. These comorbidities need to be systematically diagnosed and treated in an attempt to reduce the cardiovascular load in the PD population. These cardiovascular complications interact with each other in a complex manner that requires a multidisciplinary approach to treatment that combines pharmacological, lifestyle, and supportive interventions with the aim of enhancing patient outcomes [32]. The complexity of this

autonomic nervous system has to be taken into consideration in this integrated approach which constitutes the key to the maintenance of the cardiovascular functionality and is severely dysregulated in PD [64,65].

Cerebrovascular Disease

The risk of stroke and its connection to the disease of Parkinson. This is coupled with a higher vulnerability to both ischemic and hemorrhagic stroke that can be complicated by changes in blood pressure and other cardiovascular comorbidities typical in PD patients [66]. The neurodegenerative phenomenon of PD is also capable of directly affecting cerebral vasculature, with which contributes to a high possibility of cognitive dysfunction and dementia in such patients [67]. The relevance of the given increased susceptibility implies an urgent necessity of a thorough knowledge of the processes that connect PD to cerebrovascular pathology, as well as the involvement of endothelial dysfunction and the disruption of cerebral autoregulation [68]. Hence, the clarification of the specific molecular and cellular mechanisms of cerebrovascular impairment in PD is necessary to design a specific preventive and therapeutic approach [15]. The complex interaction between PD and cardiovascular health demonstrates the relevance of detecting and controlling cardiovascular risk factors early in life to enhance the overall prognosis and patient outcomes [69]. It is also established that aging, diabetes mellitus, and male sex are also important risk factors of both cardiovascular diseases and PD, indicating that underlying pathophysiology is similar [3].

Management Strategies for Cardiovascular Complications in Parkinson's Disease

To develop effective management strategies of cardiovascular complications in the Parkinson Disease, a multi-faceted management approach that involves combining pharmacological interventions with lifestyle modifications and constant control is needed to reduce the risks and enhance patient outcomes [49]. This comprehensive approach is usually accompanied by a subtle and careful approach towards drug interactions particularly due to the fact that most of the anti-Parkinsonian drugs have the potential to alter cardiovascular parameters [6]. As an example, dopaminergic medications, though essential in improving motor symptoms, may worsen orthostatic hypotension and have to be carefully titrated and treated with other complementary methods [42]. Additionally, non-dopaminergic drugs, including renin-angiotensin system blockers, have been shown to be protective in the progression of the development of the Parkinson disease, specifically in conditions of comorbidity with ischemic heart disease by mechanisms that could be explained by the regulation of the vascular health status and neuroinflammation [70]. Furthermore, the treatment of autonomic dysfunction, especially orthostatic hypotension, is usually performed by non-pharmacological approaches as well as pharmacological modification, such as compression stockings, hydration and sodium supplements and counter-manitures to increase venous flow [71]. Pharmacological treatment of orthostatic hypotension with midodrine and fludrocortisone is commonly used though should be monitored closely to prevent supine hypertension which underscores the delicate nature in the balance of autonomic dysregulation in PD [72].

Pharmacological Interventions

Existing pharmacological agents [e.g., midodrine, droxidopa] and new ones. Drugs such as fludrocortisone, midodrine, and droxidopa are used, but one should take special precautions in order to avoid supine hypertension as a side effect [73]. Individualization of PD patients with regard to drug interactions and side effects. This usually means the choice of the agents that have the least effect in the functioning of the central nervous system or in the aggravation of orthostatic hypotension, which is one of the typical problems in PD patients [39]. Modification of the standard procedures to use on the PD population. This accommodation often takes the form of a reserved attitude towards rate-controlling agents and attentive evaluation of possible drug-drug interactions with anti-Parkinsonian medications. Special attention should be paid to the management of the Levodopa-induced orthostatic hypotension because it is one of the most frequent side effects of using Levodopa, as it is present in 38% of patients after administering this treatment and 22% before [74].

Nonspecific management measures like the fluid and salt intake, compression stockings, and physical counter-maneuvers are very important preliminary steps in the management of orthostatic hypotension in PD patients as they sometimes precede or accompany pharmacological approaches [75]. New

pharmacological treatment of autonomic dysfunction on PD like atomoxetine or pyridostigmine is under study since it is believed that can enhance orthostatic hypotension without worsening supine hypertension [61,76]. Neurogenic orthostatic hypotension [nOH] is especially complicated to manage in such a population, and a multifactorial approach, a combination of lifestyle changes and specific pharmacotherapy, might be required because of autonomic dysfunction that is the prevalent case in PD [56].

Non-Pharmacological.

The focus on water consumption, nutrition, and specific training plans. The alterations play a pivotal role in reducing cardiovascular risk factors and enhancing the cardiovascular health of PD patients that are frequently used in conjunction with pharmacological intervention [77]. Function of enhancing locomotion and decreasing heart work. This is augmented with gait training and balance training, which indirectly invests cardiovascular functionality by stimulating routine exercise and proclivating sedentary request [78]. Self-management empowerment of patients. This involves education about blood pressure management and the identification of the symptoms of orthostatic hypotension or cardiac events so that one can respond to these events promptly and lead better lives [79]. As an example, the recommendations on fluids and salt intake, usually 2-2.5 liters of fluids and 1-2 teaspoons of salt a day, also represent a substantial contribution to intravascular volume, thus reducing orthostatic symptoms [11]. Further dietary change practices such as small and frequent meals and the exclusion of large amounts of carbohydrates may further help to reduce postprandial hypotension by reducing splanchnic blood pooling [80]. Moreover, exercise schedules, such as strength training, have also proven to be effective in heart fitness training and lessening the intensity of orthostatic hypotension in the patients with PD through better muscle pump activity and autonomic control [81,82].

These are the non-pharmacological measures that are usually thought to provide the first line of defense against orthostatic hypotension prior to the introduction of the pharmaceutical interventions [83]. Prodromal symptoms of orthostatic intolerance can be patient-taught with instructions on physical counter-maneuvers such as leg crossing or squatting, which may enable the sufferers to manage the acute alterations of the blood pressure, which is a symptom of orthostatic intolerance [84,85]. In addition to the acute episode treatment, long-term commitment to aerobic exercise regimens, with an individual approach based on individual abilities and heart rate goals, has been proven to positively affect the general cardiovascular status and even retard the disease process in PD patients [86].

Integrated Care and Therapeutic Balancing

Unable to equate anti-Parkinsonian medications to anti-cardiovascular ones. Such a complex balance demands the close interaction of neurologists with cardiologists in order to provide efficient therapeutic effects on both motor and cardiovascular symptoms [85]. Advocating interdisciplinary model of care that implies collaboration of neurologists, cardiologists, and other professionals. This interprofessional approach is a surety of an inclusive management strategy which covers both neurological and cardiovascular sides of the Parkinson disease, thus maximizing patient outcomes and life quality [84]. Considering the comorbidities of cardiovascular dysregulation in PD especially the autonomic dysregulation, holistic approach beyond the use of medication is necessary to manage cardiovascular parameters well: regular monitoring of cardiovascular parameters including 24-hours ambulatory blood pressure monitoring [3,87]. This type of comprehensive monitoring with the application of the early warning scores and individualized monitoring plans, which take into consideration the complex health conditions, enables the discovery of early signs of the physiological deterioration and the timely intervention [88].

In addition, exercise interventions, especially high-intensity aerobic exercise, is important because it has been demonstrated to decrease sympathetic activity and cardiovascular conditions, and thus delay the development of the disease in PD patients [86,89]. Exercise intensity is a very important factor and the high intensity training may have more significant effects on autonomic nervous system performance, stiffening of the arteries, and cardiorespiratory fitness [9]. Nevertheless, these strict exercise regimens might be difficult to follow by patients with motor fluctuations and other symptoms associated with PD, which require adaptive methods of exercise rehabilitation [90]. Sometimes integrated with heart rate tracking, supervised exercise is also a way to make training safer and safer, as well as give important

information about training effectiveness and the possible existence of arrhythmias [15,91]. Since PD has a sizeable impact on cardiovascular health, the next wave of research must be aimed at creating individual-based exercise prescriptions that accounted for the severity of the disease, medication intake, and autonomic malfunction to achieve maximum cardiovascular outcomes and minimum risks [91]. The collaboration between neurologists and cardiologists in a multidisciplinary setting is essential to the process of treating patients, in particular, to treat such conditions as neurogenic orthostatic hypotension when the individual usually needs combined knowledge [60].

Conclusion

Cardiovascular complications are an often-underappreciated aspect of Parkinson's disease that significantly impact patient quality of life and survival. The interplay between neurodegeneration and cardiovascular dysfunction is complex, involving mechanisms such as autonomic dysregulation, cardiac denervation, and vascular alterations. These complications, including orthostatic hypotension, arrhythmias, ischemic heart disease, and stroke, require careful management to optimize patient outcomes. A holistic approach, combining pharmacological treatments with lifestyle interventions and regular physical activity, is essential to mitigate the cardiovascular burden in PD. Furthermore, a multidisciplinary care model involving neurologists, cardiologists, and other healthcare providers is crucial to addressing the dual challenges of motor and cardiovascular symptoms in PD patients. Ongoing research into the molecular underpinnings of cardiovascular disease in PD holds promise for developing more targeted treatments that may improve the prognosis for affected individuals.

Conflict of Interest

The authors declare they don't have any conflict of interest.

Author contributions

The original author and the supervisor of the cross-ponding author write the work's initial drafts. Each author contributed to the manuscript's writing, gathered information, edited it, made tables, and received approval to submit it to a journal for publication.

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References

1. Shen Q, Guo H, Yan Y. Photobiomodulation for Neurodegenerative Diseases: A Scoping Review. Int J Mol Sci. 2024 Jan 28;25(3):1625. https://doi.org/10.3390/ijms25031625.
2. Hu Y, Xu S. Association between Parkinson's disease and the risk of adverse cardiovascular events: a systematic review and meta-analysis. Front Cardiovasc Med. 2023 Dec 7;10. https://doi.org/10.3389/fcvm.2023.1284826.
3. Grosu L, Grosu A, Crișan D, Zlibut A, Perju-Dumbravă L. Parkinson's disease and cardiovascular involvement: Edifying insights (Review). Biol Med Rep. 2023 Feb 14;18(3). https://doi.org/10.3892/br.2023.1607.
4. M S, Rajashekhar CV. Understanding Of Kriyakala with examples.
5. Jain S, Goldstein DS. Cardiovascular dysautonomia in Parkinson disease: From pathophysiology to pathogenesis. Neurobiol Dis. 2011 Nov 6;46(3):572. https://doi.org/10.1016/j.nbd.2011.10.025.
6. Chaudhary S, Chaudhary S, Rawat S. Understanding Parkinson's disease: current trends and its multifaceted complications. Front Aging Neurosci. 2025 Sep 18;17. https://doi.org/10.3389/fnagi.2025.1617106.
7. Sharabi Y, Vatine GD, Ashkenazi A. Parkinson's disease outside the brain: targeting the autonomic nervous system. Lancet Neurol. 2021 Sep 15;20(10):868. https://doi.org/10.1016/s1474-4422(21)00219-2.

8. Sierra LF, Araújo NS, Scorza FA. Morte Súbita na Doença de Parkinson: Qual o envolvimento do coração? Rev Neurociências. 2021 Aug 20;29. https://doi.org/10.34024/rnc.2021.v29.12642.
9. Soltani M, Baluchi MJ, Boullosa D, Daraei A, Doyle-Baker PK, Saeidi A, et al. Effect of Intensity on Changes in Cardiac Autonomic Control of Heart Rate and Arterial Stiffness After Equated Continuous Running Training Programs. Front Physiol. 2021 Dec 9;12. https://doi.org/10.3389/fphys.2021.758299.
10. Rodrigues LD, Oliveira LF, Shinoda L, Scorza CA, Faber J, Ferraz HB, et al. Cardiovascular alterations in rats with Parkinsonism induced by 6-OHDA and treated with Domperidone. Sci Rep. 2019 Jun 20;9(1). https://doi.org/10.1038/s41598-019-45518-z.
11. Kwaśniak-Butowska M, Dulski J, Pierzchlińska A, Białecka M, Wieczorek D, Sławek J. Cardiovascular dysautonomia and cognition in Parkinson's Disease — a possible relationship. Neurol Neurochir Pol. 2021 May 26;55(6):525. https://doi.org/10.5603/pjnns.a2021.0040.
12. Nassar EJ et al. BIOMATERIALS SCIENCE AND ENGINEERING Edited by Rosario Pignatello. 2011.
13. Sian-Hülsmann J, Riederer P. The brain and heart-axis in neurodegeneration and cardiovascular disease. J Neural Transm. 2025 Oct 13; Available from: https://doi.org/10.1007/s00702-025-03023-w.
14. Elfil M, Bayoumi A, Sayed A, Aladawi M, Aboutaleb PE, Grieb L, et al. Stroke in Parkinson's disease: a review of epidemiological studies and potential pathophysiological mechanisms. Acta Neurol Belg. 2023 Jan 30;123(3):773. https://doi.org/10.1007/s13760-023-02202-4.
15. Cade WT. Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Phys Ther. 2008 Sep 19;88(11):1322. https://doi.org/10.2522/ptj.20080008.
16. Currie AD, Wong JK, Okun MS. A review of temporal interference, nanoparticles, ultrasound, gene therapy, and designer receptors for Parkinson disease. npj Parkinsons Dis. 2024 Oct 23;10(1):195. https://doi.org/10.1038/s41531-024-00804-0.
17. Adam H, Gopinath SCB, Arshad MKM, Adam T, Parmin NA, Irzaman I, et al. An update on pathogenesis and clinical scenario for Parkinson's disease: diagnosis and treatment. 3 Biotech. 2023 Apr 27;13(5). https://doi.org/10.1007/s13205-023-03553-8.
18. Radad K, Moldzio R, Krewenka C, Kranner B, Rausch W. Pathophysiology of non-motor signs in Parkinson's disease: some recent updating with brief presentation. Exploration Neuroprotective Ther. 2023 Feb 27;24. https://doi.org/10.37349/ent.2023.00036.
19. Gonçalves V, Fonsêca VS da, Faria D de P, Izidoro MA, Berretta AA, Almeida AG de, et al. Propolis induces cardiac metabolism changes in 6-hydroxydopamine animal model: A dietary intervention as a potential cardioprotective approach in Parkinson's disease. Front Pharmacol. 2022 Oct 13;13. https://doi.org/10.3389/fphar.2022.1013703.
20. Acharya S, Lumley AI, Devaux Y, Ali M, Ramia NE, Arena G, et al. Cardiovascular history and risk of idiopathic Parkinson's disease: a cross-sectional observational study. BMC Neurosci. 2024 Jul 8;25(1). https://doi.org/10.1186/s12868-024-00875-y.
21. Malik D. Exploring autonomic dysfunction: Investigating its comprehensive impact on cardiovascular and neurological disorders, revealing mechanisms, clinical significance, and treatment approaches in a comprehensive review article. J Phys Ther Clin Pract. 2024 May 20;953. https://doi.org/10.53555/jptcp.v31i5.6272.
22. Zhang X, Zhang J, Ren Y, Sun R, Zhai X. Unveiling the pathogenesis and therapeutic approaches for diabetic nephropathy: insights from panvascular diseases. Front Endocrinol. 2024 Feb 22;15:1368481. https://doi.org/10.3389/fendo.2024.1368481.
23. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. Mov Disord. 2019 Sep 4;35(1):55. https://doi.org/10.1002/mds.27836.
24. Rodrigues FSM, Oliveira MP de, Araújo EA de, Ferraz HB, Finsterer J, Olszewer E, et al. Role of cardiac β1-adrenergic and A1-adenosine receptors in severe arrhythmias related to Parkinson's disease. Clin. 2023 Jan 1;78:100243. https://doi.org/10.1016/j.clinsp.2023.100243.
25. Khemani P, Mehdirad A. Cardiovascular disorders mediated by autonomic nervous system dysfunction. Cardiol Rev. 2019 Nov 25;28(2):65. https://doi.org/10.1097/crd.0000000000000280.
26. Goldstein DS. Dysautonomia in Parkinson disease. Compr Physiol. 2014 Mar 19;805. https://doi.org/10.1002/cphy.c130026.

27. Longardner K, Mabry SA, Chen G, Freeman R, Khalsa SS, Beach PA. Interoception in Parkinson's disease: A narrative review and framework for translational research. Auton Neurosci. 2025 Mar 8;259:103258. https://doi.org/10.1016/j.autneu.2025.103258.
28. Kwon K, Pyo SJ, Lee HM, Seo W, Koh S. Cognition and visit-to-visit variability of blood pressure and heart rate in de novo patients with Parkinson's disease. J Mov Disord. 2016 Sep 21;9(3):144. https://doi.org/10.14802/jmd.16012.
29. Navarro-Zaragoza J, Cuenca-Bermejo L, Almela P, Laorden ML, Herrero MT. Could small heat shock protein HSP27 be a first-line target for preventing protein aggregation in Parkinson's disease? Int J Mol Sci. 2021 Mar 16;22(6):3038. https://doi.org/10.3390/ijms22063038.
30. Su MP, Nizamutdinov D, Liu H, Huang JH. Recent mechanisms of neurodegeneration and photobiomodulation in the context of Alzheimer's disease. Int J Mol Sci. 2023 May 25;24(11):9272. https://doi.org/10.3390/ijms24119272.
31. Mendoza-Velásquez JJ, Flores-Vázquez JF, Barrón-Velázquez E, Sosa AL, Illigens BMW, Siepmann T. Autonomic dysfunction in α-synucleinopathies. Front Neurol. 2019 Apr 12;10:363. https://doi.org/10.3389/fneur.2019.00363.
32. Kehnemouyi YM, Coleman TP, Tass PA. Emerging wearable technologies for multisystem monitoring and treatment of Parkinson's disease: a narrative review. Front Netw Physiol. 2024 Feb 13;4. https://doi.org/10.3389/fnetp.2024.1354211.
33. Isonaka R, Sullivan P, Goldstein DS. Pathophysiological significance of increased α-synuclein deposition in sympathetic nerves in Parkinson's disease: a post-mortem observational study. Transl Neurodegener. 2022 Mar 8;11(1):15. https://doi.org/10.1186/s40035-022-00289-y.
34. Suzuki M, Nakamura T, Ohba C, Hatanaka M, Tsuboi T, Hirayama M, et al. Decreased heart rate variability in sympathetic dominant states in Parkinson's disease and isolated REM sleep behavior disorder. Parkinsonism Relat Disord. 2024 May 27;124:107020. https://doi.org/10.1016/j.parkreldis.2024.107020.
35. Mark JB, Steele SM. Cardiovascular effects of spinal anesthesia. Int Anesthesiol Clin. 1989 Jan 1;27(1):31. https://doi.org/10.1097/00004311-198902710-00007.
36. Casey P, Kelly B. Fish's Clinical Psychopathology: Signs and Symptoms in Psychiatry. 2024.
37. Cucinotta F, Swinnen B, Makovac E, Hirschbichler ST, Pereira EAC, Little S, et al. Short term cardiovascular symptoms improvement after deep brain stimulation in patients with Parkinson's disease: a systematic review. J Neurol. 2024 May 29;271(7):3764. https://doi.org/10.1007/s00415-024-12459-1.
38. Nimmons D, Bhanu C, Orlu M, Schrag A, Walters K. Orthostatic hypotension and antiparkinsonian drugs: A systematic review and meta-analysis. J Geriatr Psychiatry Neurol. 2021 Dec 29;35(5):639. https://doi.org/10.1177/08919887211060017.
39. Borovac JA. Side effects of dopamine agonist therapy for Parkinson's disease: a mini-review of clinical pharmacology. PubMed. 2016 Mar 1;89(1):37. https://pubmed.ncbi.nlm.nih.gov/27505015.
40. Reg No D, PATIL S, MAHANTASHETTI NS. Transesophageal echocardiographic assessment of regional left ventricular function in patients undergoing elective surgical revascularization. 2025.
41. Lim L. Modifying Alzheimer's disease pathophysiology with photobiomodulation: model, evidence, and future with EEG-guided intervention. Front Neurol. 2024 Aug 23;15. https://doi.org/10.3389/fneur.2024.1407785.
42. Zhong X, Yu J, Jiang F, Chen H, Wang Z, Jing T, et al. A risk prediction model based on machine learning for early cognitive impairment in hypertension: Development and validation study. Front Public Health. 2023 Mar 9;11. https://doi.org/10.3389/fpubh.2023.1143019.
43. Beheshti I. Exploring risk and protective factors in Parkinson's disease. Cells. 2025 May 14;14(10):710. https://doi.org/10.3390/cells14100710.
44. Adewale Q, Khan AF, Lin S, Baumeister TR, Zeighami Y, Carbonell F, et al. Patient-centered brain transcriptomic and multimodal imaging determinants of clinical progression, physical activity, and treatment needs in Parkinson's disease. npj Parkinsons Dis. 2025 Feb 15;11(1):29. https://doi.org/10.1038/s41531-025-00878-4.
45. Kotagal V, Albin RL, Müller MLTM, Bohnen NI. Cardiovascular risk factor burden in veterans and non-veterans with Parkinson disease. J Parkinsons Dis. 2018 Feb 17;8(1):153. https://doi.org/10.3233/jpd-171271.

46. Isaacson S, Skettini J. Neurogenic orthostatic hypotension in Parkinson's disease: evaluation, management, and emerging role of droxidopa. Vasc Health Risk Manag. 2014 Apr 1;169. https://doi.org/10.2147/vhrm.s53983.
47. Lee W, Lee J, Lee H, Jun C, Park IS, Kang SH. Prediction of hypertension complications risk using classification techniques. Ind Eng Manag Syst. 2014 Dec 30;13(4):449. https://doi.org/10.7232/iems.2014.13.4.449.
48. Prabhakaran D, Jeemon P, Ghosh S, Shivashankar R, Ajay VS, Kondal D, et al. Prevalence and incidence of hypertension: Results from a representative cohort of over 16,000 adults in three cities of South Asia. 2017.
49. Rahut DB, Mishra R, Sonobe T, Timilsina RR. Prevalence of prehypertension and hypertension among the adults in South Asia: A multinomial logit model. Front Public Health. 2023 Jan 27;10. https://doi.org/10.3389/fpubh.2022.1006457.
50. Cutsforth-Gregory JK, Low PA. Neurogenic orthostatic hypotension in Parkinson disease: A primer. Neurol Ther. 2019 Aug 27;8(2):307. https://doi.org/10.1007/s40120-019-00152-9.
51. McCullough PA. Treatment of orthostatic hypotension due to autonomic dysfunction (neurogenic orthostatic hypotension) in a patient with cardiovascular disease and Parkinson's disease. Cardiol Ther. 2019 Jan 9;8(1):145. https://doi.org/10.1007/s40119-018-0124-z.
52. Lim KB, Lim S, Hor JW, Krishnan H, Mortadza F, Lim JL, et al. Orthostatic hypotension in Parkinson's disease: Sit-to-stand vs. supine-to-stand protocol and clinical correlates. Parkinsonism Relat Disord. 2024 Apr 22;123:106980. https://doi.org/10.1016/j.parkreldis.2024.106980.
53. Pfeiffer RF. Autonomic dysfunction in Parkinson's disease. Neurotherapeutics. 2020 Aug 13;17(4):1464. https://doi.org/10.1007/s13311-020-00897-4.
54. Chowdhury MAB, Uddin MJ, Haque MR, Ibrahimou B. Hypertension among adults in Bangladesh: evidence from a national cross-sectional survey. BMC Cardiovasc Disord. 2016 Jan 25;16(1). https://doi.org/10.1186/s12872-016-0197-3.
55. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017 Jan 3;264(8):1567. https://doi.org/10.1007/s00415-016-8375-x.
56. Palma J, Kaufmann H. Epidemiology, diagnosis, and management of neurogenic orthostatic hypotension. Mov Disord Clin Pract. 2017 Jan 30;4(3):298. https://doi.org/10.1002/mdc3.12478.
57. Isaacson S, Dashtipour K, Mehdirad A, Peltier A. Management strategies for comorbid supine hypertension in patients with neurogenic orthostatic hypotension. Curr Neurol Neurosci Rep. 2021 Mar 9;21(4). https://doi.org/10.1007/s11910-021-01104-3.
58. Palma J, Kaufmann H. Orthostatic hypotension in Parkinson disease. Clin Geriatr Med. 2019 Sep 6;36(1):53. https://doi.org/10.1016/j.cger.2019.09.002.
59. Amjad F, Beinart SC. Management of neurogenic orthostatic hypotension in neurodegenerative disorders: A collaboration between cardiology and neurology. Neurol Ther. 2021 Sep 7;10(2):427. https://doi.org/10.1007/s40120-021-00270-3.
60. Kulshreshtha D, Ganguly J, Jog M. Managing autonomic dysfunction in Parkinson's disease: a review of emerging drugs. Expert Opin Emerg Drugs. 2020 Jan 2;25(1):37. https://doi.org/10.1080/14728214.2020.1729120.
61. Shirai T, Kitaura A, Uehara K, Uchida T, Fuyuta M, Iwamoto T, et al. Unusually large ephedrine-induced blood pressure increases due to cardiac sympathetic denervation supersensitivity in a patient with Parkinson's disease. JA Clin Rep. 2018 Jun 6;4(1). https://doi.org/10.1186/s40981-018-0181-2.
62. Wu X, Yuan X, Zhou S, Song L. Machine learning–based risk stratification model for young patients with hypertension: A prospective cohort study. 2020.
63. DePace NL, Colombo J, Mandal K, Eisen HJ. Autonomic testing optimizes therapy for heart failure and related cardiovascular disorders. Curr Cardiol Rep. 2022 Sep 5;24(11):1699. https://doi.org/10.1007/s11886-022-01781-7.
64. Karim S, Chahal CAA, Khanji MY, Petersen SE, Somers VK. Autonomic cardiovascular control in health and disease. Compr Physiol. 2023 Mar 30;4493. https://doi.org/10.1002/cphy.c210037.
65. Sharabi Y, Goldstein DS. Mechanisms of orthostatic hypotension and supine hypertension in Parkinson disease. J Neurol Sci. 2011 Jul 23;310:123. https://doi.org/10.1016/j.jns.2011.06.047.

66. Claassen DO, Adler CH, Hewitt LA, Gibbons CH. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. BMC Neurol. 2018 Aug 25;18(1). https://doi.org/10.1186/s12883-018-1129-x.
67. Suri JS, Paul S, Maindarkar M, Puvvula A, Saxena S, Saba L, et al. Cardiovascular/stroke risk stratification in Parkinson's disease patients using atherosclerosis pathway and artificial intelligence paradigm: A systematic review. Metabolites. 2022 Mar 31;12(4):312. https://doi.org/10.3390/metabo12040312.
68. Karabayir İ, Gunturkun F, Butler L, Goldman SM, Kamaleswaran R, Davis RL, et al. Externally validated deep learning model to identify prodromal Parkinson's disease from electrocardiogram. Sci Rep. 2023 Jul 29;13(1). https://doi.org/10.1038/s41598-023-38782-7.
69. Jo Y, Kim S, Ye BS, Lee E, Yu YM. Protective effect of renin-angiotensin system inhibitors on Parkinson's disease: A nationwide cohort study. Front Pharmacol. 2022 Mar 3;13. https://doi.org/10.3389/fphar.2022.837890.
70. Quarracino C, Otero-Losada M, Capani F, Perez-Lloret S. State-of-the-art pharmacotherapy for autonomic dysfunction in Parkinson's disease. Expert Opin Pharmacother. 2020 Jan 20;21(4):445. https://doi.org/10.1080/14656566.2020.1713097.
71. Mohammadi R, Ng SY, Tan JY, Ng ASL, Deng X, Choi X, et al. Machine learning integration of serial blood biomarkers enhances cognitive decline prediction in early Parkinson's disease. Res Square. 2025 Jul 28. https://doi.org/10.21203/rs.3.rs-7107548/v1.
72. Kumar L, Malhotra M, Sharma A, Singh AP, Singh AP. A holistic approach to Parkinson's disease: Integrating advances in pathophysiology, diagnosis, and therapy. J Drug Deliv Ther. 2024 May 15;14(5):141. https://doi.org/10.22270/jddt.v14i5.6558.
73. Cani I, Guaraldi P, Giannini G, Sambati L, Barletta G, Cortelli P, et al. Levodopa-induced orthostatic hypotension in parkinsonism: A red flag of autonomic failure. Eur J Neurol. 2023 Sep 19;31(1). https://doi.org/10.1111/ene.16061.
74. Palma J, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. Mov Disord. 2018 Mar 1;33(3):372. https://doi.org/10.1002/mds.27344.
75. Pérez-Lloret S, Rey MV, Traon AP, Rascol O. Emerging drugs for autonomic dysfunction in Parkinson's disease. Expert Opin Emerg Drugs. 2013 Feb 1;18(1):39. https://doi.org/10.1517/14728214.2013.766168.
76. Hale GM, Valdes J, Brenner M. The treatment of primary orthostatic hypotension. Ann Pharmacother. 2017 Jan 16;51(5):417. https://doi.org/10.1177/1060028016689264.
77. Weise D, Claus I, Dresel C, Kalbe E, Liepelt-Scarfone I, Lorenzl S, et al. Multidisciplinary care in Parkinson's disease. J Neural Transm. 2024 Jul 23;131(10):1217. https://doi.org/10.1007/s00702-024-02807-w.
78. Low PA, Singer W. Management of neurogenic orthostatic hypotension: An update. Lancet Neurol. 2008 Apr 16;7(5):451. https://doi.org/10.1016/s1474-4422(08)70088-7.
79. Kulkarni S, Jenkins D, Dhar A, Mir F. Treating lows: Management of orthostatic hypotension. J Cardiovasc Pharmacol. 2024 Jun 26;84(3):303. https://doi.org/10.1097/fjc.0000000000001597.
80. Mills P, Fung CKY, Travlos A, Krassioukov AV. Nonpharmacologic management of orthostatic hypotension: A systematic review. Arch Phys Med Rehabil. 2014 Oct 14;96(2):366. https://doi.org/10.1016/j.apmr.2014.09.028.
81. Hüsch S, Schauermann J, Fimm B, Haubrich C, Reetz K, Schulz JB, et al. Effect of strength training on orthostatic hypotension in Parkinson's disease—a pilot study. Clin Auton Res. 2022;32:213. https://doi.org/10.1007/s10286-022-00870-5.
82. Asad A, Ali NS, Waqas N, Bhan C, Iftikhar W, Sapna F, et al. Management of orthostatic hypotension: A literature review. Cureus. 2018 Aug 20. https://doi.org/10.7759/cureus.3166.
83. Eschlböck S, Wenning GK, Fanciulli A. Evidence-based treatment of neurogenic orthostatic hypotension and related symptoms. J Neural Transm. 2017 Oct 22;124(12):1567. https://doi.org/10.1007/s00702-017-1791-y.
84. Kalra D, Raina A, Sohal S. Neurogenic orthostatic hypotension: State of the art and therapeutic strategies. Clin Med Insights Cardiol. 2020 Jan 1;14. https://doi.org/10.1177/1179546820953415.
85. McKee K, Rafferty M, Sakata T, Hedges DM, Griffith G, Bingham MMK, et al. Parkinson's Elevated: Improving healthspan. Front Sports Active Living. 2025 Jun 2;7:1529075. https://doi.org/10.3389/fspor.2025.1529075.

86. Stuebner E, Vichayanrat E, Low DA, Mathias CJ, Isenmann S, Haensch C. Twenty-four hour non-invasive ambulatory blood pressure and heart rate monitoring in Parkinson's disease. Front Neurol. 2013 Jan 1;4. https://doi.org/10.3389/fneur.2013.00049.
87. National Safety and Quality Health Service Standards User Guide for the Health Care of People with Intellectual Disability. 2024.
88. Zanesco A, Antunes E. Effects of exercise training on the cardiovascular system: Pharmacological approaches. Pharmacol Ther. 2007 Apr 22;114(3):307. https://doi.org/10.1016/j.pharmthera.2007.03.010.
89. Ziaks L, Johnson K, Schiltz K, Pelo R, Lamotte G, Molin CD, et al. Adaptive approaches to exercise rehabilitation for postural tachycardia syndrome and related autonomic disorders. Arch Rehabil Res Clin Transl. 2024 Aug 19;6(4):100366. https://doi.org/10.1016/j.arrct.2024.100366.
90. Schootemeijer S, Kolk NM van der, Bloem BR, Vries NM de. Current perspectives on aerobic exercise in people with Parkinson's disease. Neurotherapeutics. 2020 Aug 17;17(4):1418. https://doi.org/10.1007/s13311-020-00904-8.
91. Barbosa ER, Limongi JCP, Chien HF, Barbosa P, Torres MRC. How I treat Parkinson's disease. Arq Neuro-Psiquiatr. 2022 May 1;80:94. https://doi.org/10.1590/0004-282x-anp-2022-s126.