Parkinson's disease and cardiovascular involvement: Edifying insights (Review)

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Abstract. Parkinson's disease (PD) is one of the most common neurodegenerative illnesses, and is a major healthcare burden with prodigious consequences on life-quality, morbidity, and survival. Cardiovascular diseases are the leading cause of mortality worldwide and growing evidence frequently reports their co-existence with PD. Cardiac dysautonomia due to autonomic nervous system malfunction is the most prevalent type of cardiovascular manifestation in these patients, comprising orthostatic and postprandial hypotension, along with supine and postural hypertension. Moreover, many studies have endorsed the risk of patients with PD to develop ischemic heart disease, heart failure and even arrhythmias, but the underlying mechanisms are not entirely clear. As importantly, the medication used in treating PD, such as levodopa, dopamine agonists or anticholinergic agents, is also responsible for cardiovascular adverse reactions, but further studies are required to elucidate the underlying mechanisms. The purpose of this review was to provide a comprehensive overview of current available data regarding the overlapping cardiovascular disease in patients with PD.

Contents

1. Background
2. Cardiovascular dysautonomia in patients with PD
3. Appraising the risk of heart disease in patients with PD
4. PD therapy related to cardiovascular disease
5. Conclusion

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1. Background

Parkinson's disease (PD) has a great negative impact on life quality and countless more comorbidities, significantly affecting both physical and psychological health. Overall, the most important unfavorable outcome of PD encompasses lack of dexterity and ambulation, along with disturbed cognition (1). Epidemiological studies have reported that, with the increasing life span, the prevalence of PD is facing a significant increase in most countries of the world, thus representing a healthcare burden not to be neglected (2). Advanced aging is also related with the increasing prevalence of cardiovascular diseases and, therefore, investigating possible associations between the two and PD is quite justified.

Furthermore, aging, diabetes mellitus and the male sex have been shown to be notable risk factors for both cardiovascular illnesses and PD (3). Studies have shown that various metabolic dysregulations which are found in cardiovascular diseases, are present in PD, as well. Increased glycemia values and insulin-resistance have been revealed to be associated with PD, while inflammatory markers, such as reactive oxygen species, lipid degradation products or C-reactive protein (CRP), have also been revealed to be associated with this disease (2). Consequently, these patients have significantly higher risk to develop cardiovascular disease, high blood pressure or diabetes mellitus. Additionally, another link between these two illnesses is represented by the molecular changes within the structures of cells, including storage of protein agglomerates, dysfunctional clearing process of proteins, mitochondrial involvement, inflammation within the nervous system and various gene mutations, all of which are responsible for the phenotype and severity of a disease (4,5).

By and large, the cardiovascular involvement in patients with PD is represented on the one hand by cardiovascular dysautonomia and, on the other hand, by structural cardiovascular illnesses. The most common cardiovascular abnormalities

found in patients with PD are related to dysautonomia, while structural cardiac diseases are more scarcely identified in this category of patients. Nevertheless, previous research has demonstrated a positive link between cardiovascular illnesses and PD (6). Autonomic nervous system dysregulation usually leads to the occurrence of orthostatic or postprandial hypotension, either nocturnal or supine hypertension (2). Moreover, either independent or in conjunction to dysautonomia, patients with PD have increased risk of developing structural and functional cardiovascular illnesses, such as left ventricular hypertrophy and diastolic dysfunction, in addition to, as the diseases progress, heart failure, ischemic heart disease and even ventricular tachyarrhythmias (2).

Furthermore, patients with PD are at risk of developing heart disease secondary to PD medication. While levodopa potentiates orthostatic hypotension, dopamine agonists are responsible for restrictive valvular heart disease (7,8). As for anticholinergic agents, donepezil has been reported to cause ventricular tachyarrhythmias, which were reversible after treatment cessation (9).

In the present state-of-the-art review, a unique and novel approach of presenting cardiovascular involvement in patients with PD is provided. To the best of our knowledge, to date, there is no research that has been published which covers the entire aspect of cardiovascular disease in patients with PD. For this purpose, the latest available articles were reviewed and reported, providing on the one hand a clear and comprehensive perspective on the matter and, on the other hand, starting from current findings, future research perspectives in terms of cardiovascular protection and risk assessment (2), along with specific possible future biomarkers. Another strength of the present review is its clinical viewpoint and the fact that it is addressed not only to experimental researchers, but also to clinical researchers and doctors as well (7,8). Thus, the present article is considered to be a comprehensive and useful review, which reveals several aspects in the field of PD and cardiovascular involvement.

2. Cardiovascular dysautonomia in patients with PD

Autonomic nervous system dysfunction represents a non-motor involvement in PD, which occurs early in disease progression and growing evidence suggests that it may predict the diagnosis long before the appearance of standard motor signs and symptoms (10,11). With regard to the mechanisms responsible for these manifestations, it has been considered that α-synuclein and autonomic nerve denervation were the keystones of cardiac dysautonomia, however recent research has shown that there is more than meets the eye in terms of pathogenesis (12). Amongst all, autonomic nervous system dysregulation is responsible for cardiovascular dysautonomia in >80% of cases, including orthostatic and postprandial arterial hypotension, supine arterial hypertension, as well as the presence of nocturnal nondipping profile in this category of subjects (Fig. 1) (13,14). In a meta-analysis conducted by Velseboer *et al*, it was concluded that orthostatic and postprandial hypotension usually occur in up to one third of patients with PD (15), with postprandial hypotension being more frequently observed in patients with orthostatic hypotension (16). Moreover, orthostatic hypotension has been shown to significantly impact the quality of life of sufferers and PD progression (12).

Orthostatic hypotension is one of the major cardiovascular illnesses, which occurs in patients with PD, requiring watchful and careful monitoring due to the patient's risk of falling and social isolation. Specific medications, comprising synthetic mineralocorticoids and pressor agents, along with general measurements, such as proper hydration, siting immediately after feeling lightheaded upon standing, external compression, physical counter-maneuvers that enhance venous return, are required (16,17). According to Jain *et al*, 30-40% of patients with PD have orthostatic hypotension, while others have suggested a percentage of >50% (18). In a study by Scorza *et al*, the incidence of various cardiovascular diseases was low, under 3-5% for myocardial infarction, with only one case of takotsubo cardiomyopathy reported. To date, there are no epidemiological studies that may clarify the true proportions of various cardiac diseases in patients with PD (6). Senard *et al* revealed that 58.2% of patients with PD have concomitant orthostatic hypotension and one third of them are asymptomatic at the moment of diagnosis (19). In a study by Blaho *et al* conducted in patients with PD, it was demonstrated that decreased baroreflex response was closely associated with supine hypertension and orthostatic hypotension (20). Similarly, the adaptability of systemic peripheral resistance was revealed to be severely dysregulated due to sympathetic nerve degeneration, thus promoting orthostatic hypotension (21). In addition, it was reported that parasympathetic nerve fibers are degenerated, thus contributing to orthostatic hypotension (22).

Another interesting aspect of orthostatic hypotension derives from the differences with Parkinson-like syndromes, such as multiple system atrophy (MSA) in terms of pathogenetic mechanisms. If in PD, the main mechanisms of orthostatic hypotension are neurological lesions of the brainstem, sympathetic denervation and postganglionic affliction, in MSA, central nervous system damages are exclusively responsible for this medical condition (23,24). Furthermore, in PD, the histological lesions are represented by the accumulation of Lewy bodies, while in MSA, α-synuclein aggregates are found in neurons and oligodendrogial cytoplasmatic inclusions (25,26). Moreover, in a recently published study by Cuoco *et al*, patients with MSA who also suffered from orthostatic hypotension had a significantly increased risk of cognitive degradation at 1-year follow-up (27).

As for the nocturnal nondipping profile of patients with PD, studies have shown that almost 90% were nondippers (12). In a study by Sommer *et al*, which comprehensively characterized the presence of a nondipping profile in a cohort of patients with PD, it was concluded that up to 95% of patients with orthostatic hypotension are nocturnal nondippers, however the underlying pathogenetic mechanism is quite independent of this because up to 80% of patients who did not present with orthostatic hypotension also had a nondipping profile at 24 h ambulatory blood pressure monitoring (14). This aspect represents a paramount link between cardiovascular risk and PD because, as demonstrated by de la Sierra *et al*, nondipping profiles are strongly related to cardiovascular illnesses (28).

Supine hypertension is considerably frequent in patients with PD, and it has been shown that this category of

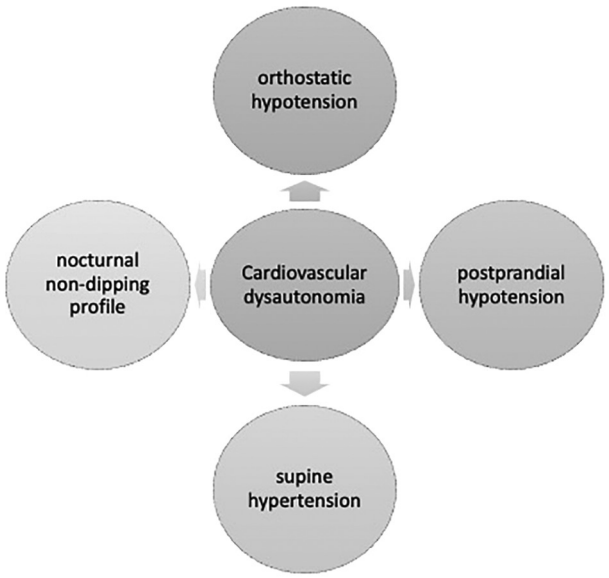

Figure 1. Subtypes of cardiac dysautonomia in patients with PD.

cardiovascular dysautonomia is associated with general cardiovascular risk, the occurrence of myocardial infarction and ischemic stroke (12). Likewise, supine hypertension has been strongly associated with left ventricular hypertrophy and, in the long term, diastolic dysfunction, and heart failure (29). Moreover, a recent study conducted by Shin *et al* sought to investigate the clinical risk factors of the dilated perivascular space-cognition-motor symptom axis. The study concluded that basal ganglia-dilated perivascular space secondary to supine hypertension is a major contributor to cognitive failure due to cerebral white matter hyperintensities and is responsible for more pronounced motor symptoms in patients with PD (30).

Another keystone component in PD is α-synuclein, the main constituent of Lewy bodies, which has significant roles in disease development. Recent technological advances in the field of molecular biochemistry and proteomics have led to a better understanding of the morphological and functional hallmarks of α-synuclein, thus providing even more enlightenment in PD (31). Furthermore, a recent study published by Javanshiri *et al* revealed that up to 82% of patients with α-synucleinopathies presented intracardiac α-synuclein at pathological examination, as compared to those without α-synucleinopathies for whom cardiac α-synuclein was completely absent (32). In addition, Isonaka *et al* demonstrated that in patients with neurogenic orthostatic hypotension, the accumulation of α-synuclein within the sympathetic ganglions, especially in the noradrenergic nerve fibers, is considerably correlated with the loss of cardiac noradrenaline, along with its neuronal storage. These findings may be in favor of a possible pathogenetic link between α-synuclein deposition, Lewy bodies and retrogression of cardiac sympathetic nerve fibers, although further research needs to be conducted (33). Furthermore, it has been shown that 6-hydroxydopamine, a neurotoxin with major implications in the pathogenesis of PD, plays significant roles in reducing cardiac sympathetic nerve fibers (12,34).

Notwithstanding, several specific gene mutations have been shown to be associated with autonomic nervous system dysfunction. Tijero *et al* revealed that E46K mutation within the α-synuclein gene was notably associated with significant degeneration of cardiac sympathetic nerves in both symptomatic and asymptomatic patients with PD (35). Moreover, another specific mutation, namely LRRK2, led to increased myocardial uptake of I-meta-iodobenzylguanidine (MIBG) at scintigraphy (36).

3. Appraising the risk of heart disease in patients with PD

In addition to cardiac dysautonomia, patients with PD commonly develop structural heart disease such as ischemic heart disease or heart failure, representing a paramount additive factor to their morbidity and mortality. As recently suggested by Park *et al*, patients with PD are at a significantly higher risk to develop cardiovascular disease, even though the exact pathogenetic mechanisms are not fully understood and further research is required in order to elucidate them (37).

In a recently published systematic review that sought to establish pathogenetic links between PD and heart disease, Suri *et al* emphasized the role of atherosclerosis in cardiovascular and cerebrovascular disease in this category of patients, endorsing the importance of constant evaluation for cardiovascular diseases (38). Notably, Driver *et al* conducted a prospective study on 330 patients who succumbed to PD and had similar comorbidities. They concluded that mortality was independent of aging and smoking in patients with PD (39).

Furthermore, Nam *et al* revealed that subjects with metabolic syndrome were at an increased risk of developing PD than healthy individuals. Moreover, the incidence of PD slightly increased with the number of metabolic syndrome components, especially in individuals who were ≥65 years old (40). In addition, a slight increase in arterial pressure in high-normal blood pressure individuals was revealed to significantly increase the risk of PD (41). Moreover, Liang *et al* conducted a case-control study on 3,211 patients with PD and a similar number of controls who underwent a 3-year follow-up. In the diseased group, a significantly increased risk of developing acute myocardial infarction, either fatal or not, was observed (42). Interestingly, a recently published study revealed that statins were significantly associated with increased risk of PD, while serum hypercholesterolemia slightly prevented the occurrence of the disease (43). Conversely, Vikdahl *et al* revealed that hypercholesterolemia, smoking, and obesity were slightly associated with increased risk of acquiring PD, while physical activity was a protective factor for this disease (44).

Similar to cardiovascular diseases, in PD there is a high grade of inflammation, insulin resistance, dyslipidemia and oxidative stress. Physical exertion and coffee consumption are inversely associated with the risk of both PD and cardiovascular diseases, along with optimal diabetes and hypertension therapy (43). Recently, Scorza *et al* revealed that in addition to ischemic heart disease, patients with PD may also develop cardiomyopathies, arrhythmias, or sudden cardiac death, although their real incidence is a topic of debate (6). Interestingly, Chohan *et al* performed a meta-analysis in which they sought to establish the link between diabetes mellitus and PD. The study revealed a strong relationship

between the presence of diabetes mellitus and the development of PD, showing a 21% increased risk to develop PD in diabetic patients (45). These findings may be elucidated by similar pathogenetic mechanisms, including mitochondrial malfunction, increased oxidative stress, insulin resistance and hyperglycemia. Moreover, reported data revealed a notable association even with the progression of PD and, conversely, the positive effects of anti-diabetic medication on halting PD were identified (46). In addition to diabetes, insulin resistance itself has been shown to be associated with PD. Insulin passes into the central nervous system and regulates neuronal development and apoptosis, dopaminergic transmission, and synapses functionality, while it may also promote α-synuclein synthesis (47).

Furthermore, previously reported data support the role of vitamin D in the progression of PD, specifically through its own receptor, and also through various molecules which are involved in different pathogenetic pathways. Therefore, several genes which are associated with vitamin D, including type II major histocompatibility complex, cytochrome P4502D6, chromosome 22, the renin-angiotensin system, heme oxygenase-1, poly-(ADP-ribose) polymerase-1 gene, neurotrophic factor, and Sp1 transcription factor, have been demonstrated to be strongly associated with PD. In addition, various inflammatory markers, such as L-type voltage-sensitive calcium channels, nerve growth factor, matrix metalloproteinases, prostaglandins and cyclooxygenase-2, have been revealed to be associated with PD via vitamin D (48-53). A possible pertinent explanation for these findings may be that vitamin D and its activating enzyme called alpha1-hydroxylase are considerably found in the substantia nigra. In a recently published review of the literature, Fullard *et al* concluded that sera vitamin D levels are closely related to the severity of motor signs, memory, psychological status, orthostatic hypotension, and loss of smell (54). It has recently been shown that decreased levels of vitamin D leads to apoptosis of dopaminergic neurons, while its systemic administration counterbalances the process (55). In addition, growing evidence suggests that vitamin D may become a feasible biomarker for PD, but larger cohort studies are required (56).

Moreover, low serum levels of vitamin D have been strongly associated with increased risk of numerous cardiovascular illnesses. Patients who experienced stable coronary artery disease and acute myocardial infarction were demonstrated to have decreased levels of vitamin D (57). Likewise, a meta-analysis which evaluated the relationship between this molecule and the risk of atrial fibrillation concluded that vitamin D deficiency significantly increases the risk of atrial fibrillation (58). Conversely, in a meta-analysis which included ~83,000 patients, exogenic supplementation with vitamin D did not reduce the risk of cardiovascular disease of any kind (59). Thus, based on these findings, vitamin D may become a useful marker of cardiovascular dysfunction in patients with PD.

As for biomarkers of inflammation, it has been proposed that CRP may become a valuable marker of disease progression in chronic inflammatory and neurodegenerative diseases, such as PD (60). Qiu *et al* conducted an interesting meta-analysis which compared patients with PD and healthy individuals and revealed that increased levels of CRP were identified in the diseased group, thus suggesting that this biomarker may become a risk factor for PD (61). Moreover, Sawada *et al* revealed that initial CRP levels were associated with mortality and prognosis prediction of patients with PD, independent of disease duration, severity, age or other confounders (62). Furthermore, urate is another important serum biomarker in patients with PD, having a multitude of anti-inflammatory effects within human cells and promoting reactive oxygen species within neurons (63,64). Clinical studies have shown that increased serum levels of urate were associated with a considerable decrease in the progression of PD and a lower unified PD rating scale score, promoting its protective effects in this category of patients (65,66). In addition to the potential role of urate as a biomarker of disease progression, its therapeutic ability to halt the development of PD has been recently assessed. In a recent clinical trial, it was determined whether high plasmatic levels of urate induced by inosine produced protective effects in patients with early PD. The results revealed that compared with placebo, patients with PD who were treated with inosine did not benefit in terms of clinical disease progression (67). Moreover, urate was also revealed to be associated with increased risk of cardiovascular diseases. In a recently published review, high levels of urate were closely associated with various cardiovascular diseases, increasing the risk of arterial hypertension, metabolic syndrome and intrinsic cardiac diseases, mainly by promoting vascular endothelial dysfunction, atherogenesis and lipid oxidation. Additionally, increased levels of urate have also been revealed to be associated with cardiovascular outcome and heart failure (68). These findings suggest an indirect, but strong association between PD and cardiovascular disease. Thus, although increased serum levels of urate are associated with a decreased progression of PD, they conversely, significantly increase the risk of cardiovascular diseases.

Another important serum marker in patients with PD is protein DJ-1, which is also a neuroprotector with significant impact in neurodegenerative diseases (69). Initially, Waragai *et al* revealed that this protein is increased in blood and cerebrospinal fluid in patients with PD (70). Furthermore, various mutations in genes of the DJ-1 protein have been associated with significantly increased risk of PD (71), and in a recently published review, its possible role as a biomarker of PD progression and even its ability to serve as a therapeutic target were suggested, however further studies still need to be conducted (72). Moreover, it has been shown that protein DJ-1 is an endogenous protective molecule that halts glycative stress, thus preventing heart failure induced by myocardial ischemia (73). In addition, protein DJ-1 may exert protective effects on the cardiovascular system, especially in patients with heart failure, pulmonary hypertension or those who have undergone coronary artery by-pass, by promoting antioxidant gene expression (74). These findings suggest that protein DJ-1 may become another pivotal biomarker which could mediate the association between PD and cardiovascular illnesses.

Furthermore, other serum biomarkers which are closely related with both PD and cardiovascular disease include coenzyme Q10, homocysteine and advanced oxidized protein products. These molecules are involved in the pathogenesis of cardiac diseases by promoting inflammation, myocyte disruption, atherogenesis, and heart failure, and thus may become biomarkers of PD progression (Fig. 2) in the near future and are presented in Table I (75).

Table I. Potential future biomarkers in PD.

Biomarker	Neurodegenerative effects
Urate	• Antioxidant effects • May prevent neurodegeneration of substantia nigra • Reduces mitochondrial oxidation
Protein DJ-1	• Neuroprotective role in oxidative stress • Reduces neurodegeneration • Modulates chaperone proteins • Reduces mitochondrial oxidation
Coenzyme Q10	• Destabilizes the redox equilibrium • Neuronal toxicity • Mitochondrial defects
Homocysteine	• Substantia nigra toxicity • Neurotoxicity, especially in dopaminergic neurons • Increases sera levels of amyloid β
8-Hydroxydeoxyguanosine	• Promotes reactive oxygen species synthesis • Substantia nigra toxicity
Advanced oxidized protein products	• Protein halogenation • Increases phagocytosis

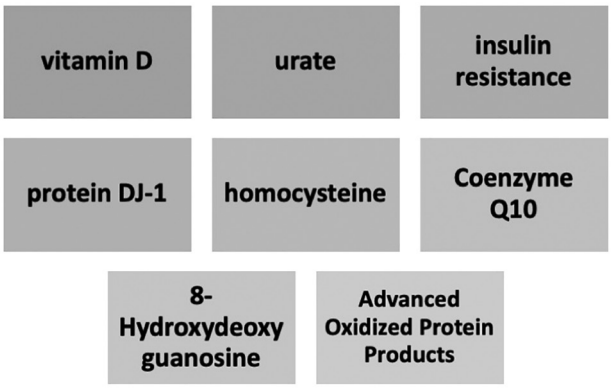

Figure 2. Biological factors that may aid cardiovascular risk stratification in patients with PD.

Despite the fact that there are only a handful of studies demonstrating significant associations between PD and structural heart disease, there is significant evidence to endorse further studies in this direction.

4. PD therapy related to cardiovascular disease

The most used medications in patients with PD include levodopa, dopamine agonists, inhibitors of monoaminoxidase B, inhibitors of catechol-O-methyltransferase (COMT), amantadine, and anticholinergic agents. Growing evidence has revealed the negative impact of PD therapy on the cardiovascular system, with research demonstrating a close association between this category of treatment and the development and progression of heart disease (76).

Levodopa. Considered to be the most efficient and extensively used for the treatment of PD, levodopa has major positive effects on survival, morbidity, quality of life, and significantly improving symptoms of PD (77). Previously reported data have indicated that levodopa is associated with increased stiffness within the aorta as well as hypertension, and that it promotes left ventricular diastolic dysfunction (7,78). It is also responsible for promoting orthostatic hypotension, however the pathogenetic mechanism for this, either vasodepressor or cardioinhibitory effect, is not fully elucidated, although certain data are in favor of a negative inotropic mechanism (7). In addition, levodopa is also responsible for increased sera levels of homocysteine due to its methylation through the COMT pathway (79). In a study by Kocer *et al*, which sought to evaluate the ability of a COMT inhibitor to prevent hyperhomocysteinemia secondary to levodopa therapy, the study failed to identify a protective effect of entacapone on preventing hyperhomocysteinemia (80). Furthermore, in a study by O'Suilleabhain *et al*, it was demonstrated that hyperhomocysteinemia in patients with PD was significantly associated with depression and poorer neuropsychometric activity, as compared to individuals with normal sera levels of homocysteine (81).

Ergot-derived agonists. Another pharmacological class of anti-PD drugs represented by ergot-derived dopamine agonists, such as bromocriptine and cabergoline, are even more incriminated in cardiovascular involvement. Initially, Van Camp *et al* reported two cases of PD with restrictive valvular heart disease and clinical signs of significant heart failure due to daily doses of pergolide (82). Subsequently, the same research team evaluated the incidence of restrictive mitral stenosis in a cohort of 78 patients with PD treated with pergolide. The results revealed that 33% of patients developed restrictive mitral stenosis, of whom 19% had a severe form of this illness, thus suggesting that this complication is not rare in patients treated with this medication (8). Similarly, Horvath *et al* also identified restrictive valvular heart disease and suggested a comprehensive echocardiographic evaluation at the beginning

and during treatment with pergolide and cabergoline (83). As for non-ergot-based dopamine agonists, pramipexole has scientific evidence for being responsible for heart failure. In a systematic review published by Tran *et al*, it was revealed that this drug was significantly associated with the risk of heart failure (84). However, further studies are required to elucidate the underlying mechanisms.

Anticholinergic agents. With regard to anticholinergic agents, donepezil has been found to prolong the QT interval in long-term administration. Additionally, a close monitoring strategy should be applied when this drug is used in combination with tricyclic antidepressants (85). Recently, Kho *et al* demonstrated that, due to increased sera levels of acetylcholine which blocks the potassium ion channel from the heart, donepezil may be responsible for adverse tachyarrhythmias, namely polymorphic ventricular tachycardia with oscillatory changes in amplitude of the QRS complexes around the isoelectric line (9).

Dexrazoxane, a potential cardioprotective agent in patients with PD. To date, there is no drug used in patients with PD that does not carry any cardiovascular risk. A noteworthy pharmacological agent which may benefit PD patients and also exert protective cardiovascular effects is dexrazoxane. Dexrazoxane was recently approved for the prevention of chemotherapy-induced cardiotoxicity in both adults and children who received anthracycline therapeutic regimens (86). A previous experimental study has suggested that dexrazoxane may act as protective agent against neurodegeneration, however further studies need to be conducted to reveal its potential clinical effects in patients with PD (87).

5. Conclusion

Compelling evidence supports a cause-effect relationship between PD and cardiovascular involvement. PD leads to cardiac dysautonomia and promotes ischemic heart, heart failure and arterial hypertension. Additionally, several drugs used to treat PD, such as levodopa, dopamine agonists and anticholinergic agents, are responsible for heart disease, as well. Nevertheless, there is not enough evidence available to identify the underlying mechanisms of these links. Further studies are required to provide appropriate data regarding the pathogenetic and clinical associations between PD and cardiovascular disease in order to deploy therapeutic options.

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Authors's contributions

LG, AIG, and AZ researched data for the article and wrote the manuscript. LG, DC and AIG discussed the content of the review, and LG and LPD reviewed and edited the manuscript before submission. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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