JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY 2023, 74, 4, 369-375
www.jpp.krakow.pl | DOI: 10.26402/jpp.2023.4.01

Review article

Q. XING[1], X. ZHAO[2], L. XIE[3], X. CHEN[4], Y. WANG[4], Y. XIE[4]

ADVANCES IN NON-PHARMACOLOGICAL MANAGEMENT OF PARKINSON'S DISEASE COMPLICATED WITH BLOOD PRESSURE ABNORMALITIES

[1]Department of Pain, Affiliated Hospital of North Sichuan Medical College, Nanchong, China;
[2]Department of Rehabilitation Medicine, The Second Clinical Medical School of North Sichuan Medical College, Nanchong Central Hospital, Nanchong, China; [3]School of Rehabilitation, Zigong Vocational and Technical College, Zigong, China;
[4]Department of Rehabilitation Medicine, Affiliated Hospital of North Sichuan Medical College, Nanchong, China

Parkinson's disease (PD) often presents with autonomic dysregulation, leading to blood pressure irregularities such as neurogenic orthostatic hypotension (nOH), neurogenic supine hypertension (nSH), and postprandial hypotension (PPH). Unfortunately, these conditions remain prevalent and receive insufficient attention in scientific discourse. They not only cause complications like syncope, falls, and fractures but also result in long-term damage to vital organs, diminishing patients' quality of life. Early implementation of appropriate non-pharmacologic management is crucial to prevent severe adverse events later on. This review focuses on the types, clinical characteristics, mechanisms, and common non-pharmacologic management measures for PD complicated by abnormal blood pressure. By promoting early diagnosis, recognizing symptoms of abnormal blood pressure, and employing non-pharmacologic interventions such as health education, dietary adjustments, exercise, and Chinese medicine techniques, we aim to improve patients' symptoms and quality of life while providing practical guidance for managing PD-related blood pressure abnormalities.

Key words: *Parkinson's disease, neurogenic orthostatic hypotension, neurogenic supine hypertension, postprandial hypotension, non-pharmacologic management, supine hypertension, autonomic dysfunction*

INTRODUCTION

Parkinson's disease (PD) is a prevalent neurodegenerative disorder with a rising global incidence (1). In China alone, it is projected that the number of PD patients will reach five million by 2030 (2). Autonomic dysregulation is an early symptom of PD (3), which typically appears prior to the onset of motor symptoms. Research indicates that approximately 70% of PD patients experience autonomic dysfunction before the onset of motor symptoms (4). The autonomic nervous system governs various automatic functions, including heart rate, blood pressure, digestion, and excretion. Notably, blood pressure abnormalities are prominent manifestations of autonomic dysregulation, resulting from impaired autonomic function and inadequate cardiovascular response to postural changes (5-7). Examples include neurogenic orthostatic hypotension (nOH), neurogenic supine hypertension (nSH), and postprandial hypotension (PPH). PD complicated by abnormal blood pressure can lead to syncope, falls, fractures (8), and long-term damage to vital organs such as the heart, brain, and kidney (9); significantly diminishing patients' quality of life and increasing mortality rates (10). Additionally, managing these conditions is challenging due to conflicting hemodynamics in nSH and nOH and drug interactions for blood pressure treatment (6, 11). Therefore, developing effective non-pharmacologic management strategies for PD patients with abnormal blood pressure is crucial. Currently, the diagnosis rate of PD complicated by abnormal blood pressure (*e.g.*, nOH, nSH, PPH) remains relatively low compared to chronic essential hypertension, indicating the need for increased awareness and attention (12).

Search strategies

In accordance with the objectives of our research, we employed the following keywords: Parkinson's disease, autonomic dysregulation, abnormal blood pressure, and management. We conducted searches in PubMed, Embase, and Web of Science databases from 2000 to 2022. The search strategy utilized for PubMed was as follows: Search: ((((Parkinson's disease) OR (Parkinson disease)) AND (abnormal blood pressure)) AND ((management) OR (intervention))) Filters: from 2000/1/1 – 2022/12/30. Similar search strategies were applied in the other databases. A total of 77 articles were retrieved from PubMed, 132 articles from Embase, and 58 articles from Web of Science. After eliminating duplicate publications, the full texts of these articles were meticulously examined and incorporated into the Endnote 20 reference management system. The inclusion criteria for final selection encompassed articles that explored non-pharmacologic approaches to managing autonomic dysregulation and abnormal blood pressure in PD. These articles provided insights into

recent advancements and innovative methodologies. Exclusion criteria involved articles solely focused on pharmacological treatment or conventional therapeutic methods, as well as those unrelated to PD autonomic dysregulation, or abnormal blood pressure. The reference lists of identified articles were scrutinized for additional potential studies.

PATHOGENESIS OF PARKINSON'S DISEASE COMPLICATED WITH ABNORMAL BLOOD PRESSURE

PD and the co-occurrence of nOH, nSH, and PPH are common, with two or three of these conditions often presenting simultaneously. This is attributed to a shared neurogenic pathogenesis that has been widely acknowledged by experts and scholars (13). Specifically, autonomic failure leads to insufficient release of norepinephrine, disruption in blood pressure regulation within the cardiovascular reflex arc, impaired vasoconstriction in peripheral and visceral regions, as well as compromised sympathetic and vagal stress reflexes. These factors collectively result in abnormal effects on the sympathetic nerves innervating the ventricular muscle, making cardiovascular reflex arc lesions the primary cause of early blood pressure abnormalities in PD patients.

Extensive evidence indicates that the mechanism underlying PD complicated by nOH involves the failure of pressure reflexes, severe deficiency in norepinephrine release, impaired peripheral and splanchnic vasoconstriction, and an inability to maintain blood pressure (14-16). When transitioning from a supine or sitting position to an upright posture, venous blood accumulates in the lower extremities and splanchnic circulation. Consequently, there is reduced ventricular filling and an inadequate increase in cardiac output, leading to a drop in blood pressure and the development of nOH (17, 18). The dysfunction of the baroreflex-mediated blood pressure control pathway and hypersensitivity response to residual norepinephrine release may also contribute to the occurrence of nSH (19). Additionally, Arnold *et al*. demonstrated that elevated plasma angiotensin II levels in autonomic failure and chronic activation of the renin-angiotensin system were associated with the development of nSH (20). Disruption of other pressure reflexes, including vasodilatory centers and effector organs such as the heart, small arteries, and veins, may also play a role in the mechanism of nSH (21).

The mechanism of PPH remains incompletely understood but may involve systemic sympathetic denervation, impaired pressure reflex-cardiac vagal increase, and inadequate compensatory sympathetic activation in PD patients. This includes the lack of a pressure reflex-sympathetic increase in postprandial visceral vascular pooling, all contributing to the development of PPH (22). Some theories propose that this could be attributed to insufficient compensation for the normal physiological drop in blood pressure after meals. Patients with PPH may experience increased visceral blood pool volume following food intake and a delayed sympathetic nervous system response to elevated heart rate, cardiac output, and systemic vascular resistance, which helps maintain blood pressure stability (23).

CLINICAL FEATURES OF PARKINSON'S DISEASE COMPLICATED WITH ABNORMAL BLOOD PRESSURE

Clinical features of neurogenic orthostatic hypotension

Orthostatic hypotension (nOH), a debilitating manifestation of autonomic dysfunction in PD, refers to a sustained decrease in blood pressure (BP) upon standing. According to expert consensus (11), the current definition of OH involves a systolic pressure drop of ≥20 mmHg and/or diastolic pressure drop of ≥10 mmHg within three minutes of assuming an upright position or tilting at 60 degrees. A heart rate (HR) increase of less than 0.5 beats per minute (*i.e*., DHR/DSBP ratio <0.5 bpm/mmHg) per 1 mmHg decrease in systolic pressure is highly sensitive and specific for diagnosing nOH (14). Patients with PD and nOH exhibit lower levels of plasma norepinephrine (14), which serves as a marker of sympathetic integrity, compared to those without nOH. Episodes of nOH typically occur during standing and resolve upon lying down. Symptomatology varies among individuals depending on the extent of BP decline during standing and individual adaptation to brain autoregulatory mechanisms (24). Common symptoms include dizziness, blurred vision, loss of consciousness, and syncope when there is a significant drop in BP. Some patients may also experience cognitive impairment, neck and shoulder pain, angina pectoris, and falls (25). Symptoms of nOH are often most pronounced in the early morning due to nocturnal intravascular volume loss (14). Ambulatory blood pressure monitoring can aid in the diagnosis and management of nOH. The severity of nOH symptoms tends to increase with longer PD duration, greater disease severity, older age, and levodopa usage (26).

Clinical features of neurogenic supine hypertension

Supine hypertension (nSH) is observed in 50% of PD patients with autonomic failure (26). The American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) jointly define nSH as follows (11, 21, 27): systolic pressure ≥140 mmHg and/or diastolic pressure ≥90 mmHg after resting in the supine position for ≥5 minutes. nSH can be further categorized into mild nSH (140–159/90–99 mmHg), moderate nSH (160–179/100–109 mmHg), and severe nSH (≥180/≥110 mmHg). In individuals with nSH, blood pressure is elevated while in the supine position, and symptoms are typically absent; however, some patients may experience non-specific manifestations such as dizziness, fatigue, headache, and blurred vision (28). Routine measurements and examinations often fail to detect nSH since patients exhibit normal seated blood pressure; nevertheless, nSH contributes to long-term cardiovascular and cerebrovascular risks (21). If necessary, 24-hour ambulatory blood pressure monitoring can be employed. Up to 70% of nOH patients develop nSH (21). nSH promotes nocturnal stress-induced natriuresis and volume depletion (28). Frequent nighttime voiding disrupts sleep, reduces nocturnal urine output, exacerbates morning nOH symptoms, increases the risk of falls, and raises the likelihood of hypertensive emergencies in individuals with nSH (24). Studies have demonstrated associations between nSH and left ventricular hypertrophy, renal impairment, and brain white matter injury (26).

Clinical features of postprandial hypotension

Postprandial hypotension (PPH) is defined as a systolic pressure drop of ≥20 mmHg within two hours after a meal, or to 90 mmHg when the pre-prandial blood pressure is ≥100 mmHg (29). The severity of PPH correlates with insulin release (14). Common symptoms include dizziness, visual disturbances, presyncope, and syncope. PPH increases the risk of falls, syncope, cardiovascular accidents, cerebrovascular accidents, and all-cause mortality (30, 31). A meta-analysis (32) revealed that the incidence of PPH in PD patients can reach up to 80%. It often coexists with nOH, typically occurs after breakfast, and predominantly affects the elderly.

NON-PHARMACOLOGIC MANAGEMENT OF PARKINSON'S DISEASE COMPLICATED WITH ABNORMAL BLOOD PRESSURE (*Fig. 1*)

Comprehensive patient assessment, documentation of daily activities, symptom screening, and understanding the patient's functional status are vital for managing abnormal blood pressure in PD patients. Early detection of fluctuations, evaluation of treatment tolerability and side effects, individual risk assessment, and consideration of hemodynamic concerns are crucial for diagnosis (26). Expert consensus (16, 33) emphasizes non-pharmacologic approaches as a priority, such as adjusting daily activities and implementing exercise therapy when necessary. Non-pharmacological interventions like dietary modifications, exercise programs, pressure garments, standing training, hydrotherapy, physical therapy, education, and psychological support can alleviate symptoms of nOH, nSH, and PPH. However, their effectiveness varies among individuals, and more severe cases may require pharmacological interventions (25). Additionally, recommendations include neuromodulation therapy, exercise therapy, psychological interventions, and comprehensive care.

Non-pharmacologic management of orthostatic hypotension, neurogenic supine hypertension, and postprandial hypotension

Non-pharmacological interventions aim to enhance the quality of life for individuals with nOH by alleviating symptoms, maintaining cerebral perfusion, optimizing autoregulation, enhancing orthostatic capacity, reducing symptom burden, prolonging standing time, and preventing falls (14, 16, 26).

The objectives include: 1) increasing cardiac output and blood pressure by augmenting venous return; 2) raising systemic vascular resistance through vasoconstriction; and 3) expanding blood volume (26). In cases where severe orthostatic intolerance is present in nOH patients, a combination of pharmacological treatment and non-pharmacological interventions may be employed (34, 35). Generally, when both nOH and nSH coexist, priority should be given to treating nOH, provided that nSH is mild to moderate (24).

For managing nSH, the goal of non-pharmacological interventions is to reduce nocturnal natriuresis (28) and maintain moderate orthostatic stress (26). Decreased sodium excretion improves morning orthostatic symptoms, reduces nocturia and sleep disruption, and lowers the risk of cardiovascular and renal diseases, as well as morbidity and mortality (8). However, there are no official guidelines or specific blood pressure targets for treating nSH (36). Antihypertensive medications are not approved for patients with nSH, and large-scale clinical trials and long-term efficacy studies are lacking (26). Non-pharmacologic management is preferred for individuals with mild nSH (26). When non-pharmacological measures prove insufficient for those with moderate to severe supine hypertension, pharmacological treatment becomes necessary, but caution should be exercised to avoid lowering systolic pressure below 130 mmHg during treatment (37).

In PPH management, individualized approaches and treatment plans should be developed based on each patient's overall condition, complications, and tolerance. Given the significant impact of diet on PPH severity (5), dietary modifications and exercise are recommended as the initial strategies for symptom improvement (25, 27).

Avoidance of inducing factors

A comprehensive medication review is essential to identify and eliminate exacerbating factors. In patients experiencing nOH worsening, adjustments and simplification of existing medications should be made based on individual risk-benefit assessment to avoid polypharmacy. This may involve reducing the current dose or changing the dosing regimen (25, 38). Additionally, it's worth noting that levodopa and dopamine agonists can also contribute to nOH through their side effects (39). Modifying PD medication regimens can help minimize blood pressure fluctuations in individuals with nOH. Drugs used to raise blood pressure for nOH treatment can also increase nSH.

Patients should avoid lying fully supine and taking evening doses of BP-raising drugs (the last daily dose should be taken at least 3–4 hours before bedtime) to prevent potential supine blood pressure elevation. Furthermore, avoiding long-acting BP-raising drugs like fludrocortisone can reduce the occurrence of sleep-related nSH (27, 28).

Polypharmacy (taking three or more drugs) is a risk factor for postprandial hypotension, and the severity of PPH is positively associated with the number of cardiovascular and

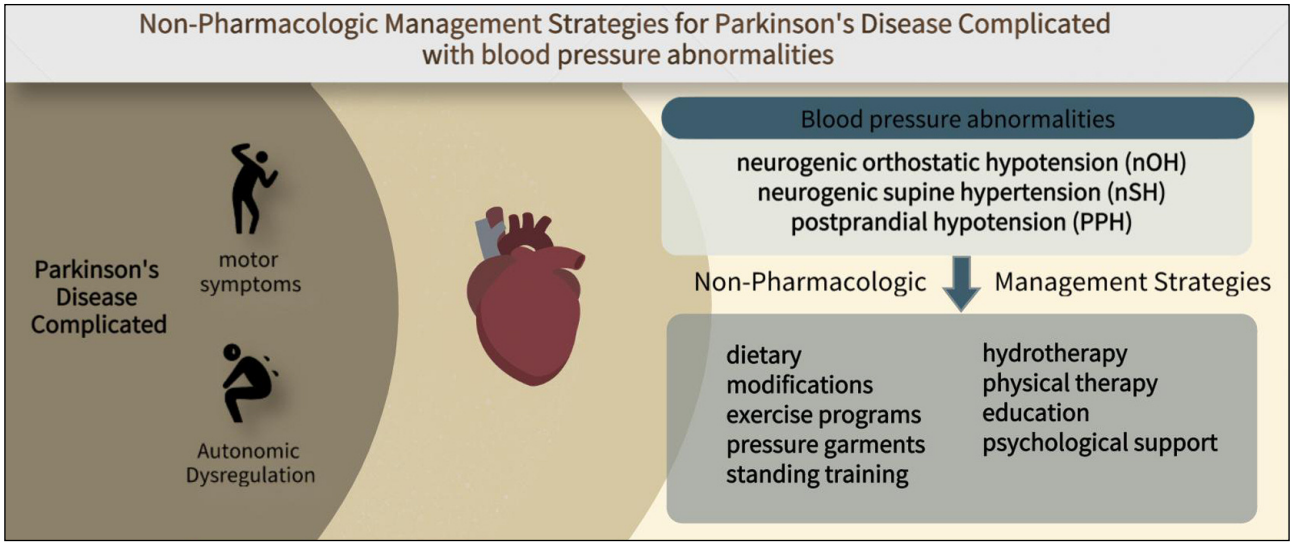

Fig. 1. Non-pharmacologic management strategies for Parkinson's disease complicated with blood pressure abnormalities.

psychotropic medications being taken (23). Therefore, it is recommended to avoid medications that may cause hypovolemia, particularly diuretics such as furosemide, which have been shown to worsen postprandial hypotension and potentially lead to PPH. Moreover, foods high in carbohydrates and consuming hot meals (drinking a 50°C glucose solution decreases blood pressure more than a 5°C glucose solution) should be avoided (23), as they further decrease PPH.

Health education

Education plays a vital role in managing abnormal blood pressure. The key objectives of patient education include: 1) helping patients recognize symptoms; 2) providing understanding of diurnal blood pressure variations and potential morning hypotension symptoms; and 3) instructing patients to transition positions gradually, avoid heat exposure, large meals, and Valsalva-like movements during urination or defecation (24, 39).

Dietary interventions

Increasing water and salt intake: adequate blood volume is crucial for managing nOH. Drinking 500 ml of water has a rapid and significant BP-raising effect in patients with nOH (peaking at approximately 30 minutes) (24, 39, 40), increasing water and salt intake: adequate blood volume is crucial for managing nOH.

Carbohydrate snacks: consuming small amounts of high-carbohydrate snacks before bedtime may slightly alleviate nSH symptoms (26). This is achieved by redirecting blood flow to the visceral circulation and triggering insulin release, which possesses direct vasodilatory properties (41).

Limiting water intake before bedtime: excessive water consumption close to bedtime can trigger a severe osmolarity response in nSH patients. Therefore, it is recommended that these individuals limit their water intake 60–90 minutes before going to bed.

Low-salt diet: when nSH symptoms outweigh those of nOH, reducing salt intake is an effective approach to manage supine hypertension, although it may exacerbate nOH symptoms (26).

Smaller and more frequent meals: the volume and caloric load of food significantly impact postprandial visceral hypotension. Replacing three large meals with six smaller ones per day, opting for low-carbohydrate foods, consuming cooler ingested foods, and avoiding alcohol can improve symptoms (25).

Pre-meal drinking: pre-meal drinking: it has been demonstrated that pre-meal drinking alleviates blood pressure drops in elderly patients and those with autonomic failure. This simple and relatively safe intervention promotes gastric dilation, stimulates the gastric vascular reflex, and activates sympathetic nerves. Additionally, consuming alcohol before bedtime can help reduce nocturnal nSH. However, it's important to note that while alcoholic beverages can dilate visceral vessels and lower blood pressure, alcohol consumption is not recommended as a treatment for nSH (16, 20, 27).

Postural and exercise interventions

To alleviate nOH symptoms, patients are advised to elevate the head of their bed by 10–20° during sleep. This helps reduce nocturnal sodium excretion and improves morning orthostatic symptoms (28). Simple physical movements, such as crossing legs, clenching fists, bending over, squatting, and engaging leg, abdominal, gluteal, or whole-body muscles, can be incorporated into daily activities to raise blood pressure (25). These movements effectively decrease venous pooling, increase return blood volume and cardiac filling, thereby enhancing cardiac output, blood pressure, and cerebral perfusion. Activating the leg muscles is particularly beneficial, as it boosts cardiac venous return and filling pressure, preventing presyncope and syncope symptoms through autoregulation even with a slight increase in blood pressure (39). However, patients should be aware that while these movements may temporarily improve symptoms, they can worsen when returning to an upright position (25).

Avoiding complete supine positioning is an effective non-pharmacologic strategy for managing nSH in most patients (14, 26). By inducing venous pooling below the level of the heart, this approach reduces the severity of nocturnal nSH. It minimizes pressure diuresis during nighttime supine positions while maintaining activation of the renal angiotensin system. As a result, it decreases the risk of falls when emptying the bladder, reduces nocturnal blood volume loss, and alleviates nSH symptoms (20). Simple postural changes, like sitting up, can lower blood pressure back to normal levels and prevent potential elevation associated with supine positions (26).

Physical exercise can improve symptoms and quality of life in PD patients (42, 43). Therefore, it is crucial to encourage individuals with this condition to engage in regular physical activity. The recommended duration is a minimum of 150 minutes per week, ideally with at least 30 minutes dedicated to exercise each day. It is important to maintain a moderate intensity level, which can be determined by monitoring heart rate, respiration, and perspiration. Evaluating exercise intensity using the Borg scale (ranging from 6 to 20) is advised. Optimal timing for exercise is within 30 minutes to an hour after taking medication, maximizing its therapeutic effects. Diversifying exercise routines is also beneficial, including aerobic activities like walking, cycling, and swimming, strength training involving weights and resistance bands, as well as balance exercises such as yoga and tai chi (44). A minimum of two strength training sessions and two balance training sessions per week are recommended. It is essential to recognize that each patient's circumstances are unique, requiring personalized exercise plans tailored to their individual needs. Prior consultation with a physician or professional exercise therapist is highly recommended before starting any exercise program.

Pressurized clothing

Long high-waisted compression stockings can increase blood pressure by enhancing venous return. However, patients with movement disorders often struggle to put them on, limiting their practicality (14). An elastic abdominal band is a viable alternative that significantly elevates blood pressure by pressurizing the abdomen (20–30 mmHg) or thighs (30–40 mmHg) (45). Okamoto *et al*. (46) have demonstrated the effectiveness of a new automatic abdominal inflatable pressurizer in preventing nOH, with selective pressures of 20 or 40 mmHg when the patient is standing. This device shows promising applications.

Appropriate traditional Chinese medicine techniques

Appropriate traditional Chinese medicine (TMC) techniques primarily include acupuncture and Chinese herbal medicine. Clinical evidence suggests that acupuncture or electroacupuncture has a therapeutic effect on specific types of hypotension (47). Acupuncture increases plasma norepinephrine and epinephrine concentrations, inhibits the reduction in cerebral blood flow rate, and improves symptoms of upright hypotension. This indicates that acupuncture enhances cardiac function, activates the peripheral sympathetic nervous system, and mitigates nOH symptoms by preventing the decrease in cerebral blood flow (48).

In a study conducted by Chiu *et al*., 169 untreated nSH patients were treated with acupuncture. Thirty minutes after treatment, there were significant decreases in systolic pressure, diastolic pressure, and plasma renin activity. However, no notable changes were observed in plasma pressor or cortisol concentrations. These findings suggest that acupuncture may reduce supine hypertension by decreasing renin secretion (49).

Previous studies have indicated that acupuncture's mechanisms for regulating blood pressure involve interactions between multiple systems and targets. It modulates endothelial function, affects the renin-angiotensin-aldosterone system, and inhibits oxidative stress. Additionally, acupuncture protects target organs by improving endothelial function and inflammatory responses (50). Nevertheless, meta-analyses have shown limited evidence supporting a sustained antihypertensive effect of acupuncture in treating chronic elevated blood pressure. The short-term effects of acupuncture remain uncertain. Future randomized controlled trials should employ sham acupuncture controls and assess whether acupuncture maintains an antihypertensive effect for at least seven days (51).

Herbal medicines also exhibit a modulating effect on blood pressure. Combining herbal medicines with antihypertensive drugs has demonstrated positive effects on blood pressure, blood pressure variability, postmenopausal symptoms, quality of life, and hormone levels compared to antihypertensive drugs alone. Notably, no serious adverse effects were observed (52). Many compounds derived from herbal medicines possess pharmacological activity comparable to drugs. These compounds often affect multiple targets and do not conform to the conventional one compound/one target model of drug discovery. Network pharmacology, a burgeoning field in drug development, explores the potential of using multiple compounds acting on multiple targets in combination (53).

However, existing randomized controlled trials evaluating herbal medicines have limitations such as small sample sizes and diverse outcomes, making it challenging to draw definitive conclusions regarding their benefits and harms. While herbal medicine may serve as a complementary and alternative approach to primary and secondary prevention of cardiovascular disease, further rigorously designed randomized controlled trials are necessary to assess their impact on long-term hard endpoints in patients with cardiovascular disease (54).

The incidence of abnormal blood pressure in PD is high, and its symptoms are hemodynamically conflicting. Pharmacological treatments for abnormal blood pressure in PD have unclear efficacy and numerous adverse reactions. Non-pharmacologic interventions offer safer and simpler alternatives with fewer adverse effects. This paper provides a summary of non-pharmacological management strategies.

For patients with neurogenic orthostatic hypotension (nOH), avoiding triggers, receiving health education, increasing circulating blood volume through salt and water intake, adopting appropriate body positions, using elastic lap bands, and employing TCM techniques such as medicinal dietary therapy, acupuncture, and auricular point pressing can be beneficial. Patients with supine hypertension (nSH) should avoid aggravating factors, adopt specific body positions, follow dietary recommendations, limit water intake before bedtime, and utilize TCM techniques like acupressure, auricular pressure, acupuncture, tea substitution, and Ba Duan Jin exercises. Local heating of the abdomen has also shown to reduce nSH (8). Polypharmacy should be avoided in patients with postprandial hypotension (PPH). Dietary modifications, including smaller and more frequent meals, pre-meal hydration, alcohol abstinence, and post-meal walks, play a crucial role in managing PPH. However, there is limited literature on the use of TCM techniques for PPH treatment.

It is important to note that research on PD complicated with abnormal blood pressure, such as nOH, nSH, and PPH, is scarce, with small sample sizes, short follow-up periods, and limited clinical trial data. More comprehensive data on the efficacy and safety of non-pharmacological interventions for abnormal blood pressure control in PD is needed. Additionally, while TCM techniques have shown effectiveness in lowering blood pressure, further studies with larger sample sizes are required, particularly in China. Future efforts should prioritize patient safety by exploring different non-pharmacological interventions and supporting evidence-based non-pharmacologic management measures for PD patients with abnormal blood pressure.

Authors' contribution: Qijia Xing and Xuesong Zhao contributed equally to this study.

Funding: Research Development Project of North Sichuan Medical College in 2022 (CBY22-QNA45); Research Development Project of Affiliated Hospital of North Sichuan Medical College in 2023 (2023JC011).

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Conflict of interests: None declared.

REFERENCES

1. GBD 2016 Parkinson's Disease Collaborators. Global, regional, and national burden of Parkinson's disease, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; 17: 939-953.
2. Li G, Ma J, Cui S, *et al*. Parkinson's disease in China: a forty-year growing track of bedside work. *Transl Neurodegener* 2019; 8: 22. doi: 10.1186/s40035-019-0162-z
3. Schrag A, Horsfall L, Walters K, Noyce A, Petersen I. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol* 2015; 14: 57-64.
4. Pfeiffer RF. Autonomic dysfunction in Parkinson's Disease. *Neurotherapeutics* 2020; 17: 1464-1479.
5. Pavelic A, Krbot Skoric M, Crnosija L, Habek M. Postprandial hypotension in neurological disorders: systematic review and meta-analysis. *Clin Auton Res* 2017; 27: 263-271.
6. Xu X, Fu Z, Le W. Exercise and Parkinson's disease. *Int Rev Neurobiol* 2019; 147: 45-74.
7. Elbaz A, Carcaillon L, Kab S, Moisan F. Epidemiology of Parkinson's disease. *Rev Neurol* 2016; 172: 14-26.
8. Palma JA, Kaufmann H. Treatment of autonomic dysfunction in Parkinson disease and other synucleinopathies. *Mov Dis* 2018; 33: 372-390.
9. Vetrano DL, Pisciotta MS, Brandi V, *et al*. Impact of disease duration and cardiovascular dysautonomia on hypertension in Parkinson's disease. *J Clin Hypertension* (*Greenwich*) 2017; 19: 418-423.
10. Goldstein DS, Holmes C, Sharabi Y, Wu T. Survival in synucleinopathies: a prospective cohort study. *Neurology* 2015; 85: 1554-1561.
11. Fanciulli A, Jordan J, Biaggioni I, *et al*. Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) : Endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH). *Clin Auton Res* 2018; 28: 355-362.

12. Claassen DO, Adler CH, Hewitt LA, Gibbons C. Characterization of the symptoms of neurogenic orthostatic hypotension and their impact from a survey of patients and caregivers. *BMC Neurol* 2018; 18: 125. doi: 10.1186/s12883-018-1129-x
13. Zhao Z, Xu H, Chi X. Blood pressure management in patients with Parkinson's disease. *Chin J Hypertens* 2017; 25: 733-736.
14. Palma JA, Kaufmann H. Orthostatic hypotension in Parkinson disease. *Clin Geriatr Med* 2020; 36: 53-67.
15. Cutsforth-Gregory JK, Low PA. Neurogenic orthostatic hypotension in Parkinson disease: a primer. *Neurol Ther* 2019; 8: 307-324.
16. Gibbons CH, Schmidt P, Biaggioni I, *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; 264: 1567-1582.
17. Loavenbruck A, Sandroni P. Neurogenic orthostatic hypotension: roles of norepinephrine deficiency in its causes, its treatment, and future research directions. *Curr Med Res Opin* 2015; 31: 2095-2104.
18. Mar PL, Shibao CA, Garland EM, *et al*. Neurogenic hyperadrenergic orthostatic hypotension: a newly recognized variant of orthostatic hypotension in older adults with elevated norepinephrine (noradrenaline). *Clin Sci* (*Lond*) 2015; 129: 107-116.
19. Ramirez CE, Okamoto LE, Arnold AC, *et al*. Efficacy of atomoxetine versus midodrine for the treatment of orthostatic hypotension in autonomic failure. *Hypertension* 2014; 64: 1235-1240.
20. Arnold AC, Okamoto LE, Gamboa A, *et al*. Mineralocorticoid receptor activation contributes to the supine hypertension of autonomic failure. *Hypertension* 2016; 67: 424-429.
21. Isaacson SH, Dashtipour K, Mehdirad AA, Peltier AC. Management strategies for comorbid supine hypertension in patients with neurogenic orthostatic hypotension. *Curr Neurol Neurosci Rep* 2021; 21: 18. doi: 10.1007/s11910-021-01104-3
22. Umehara T, Toyoda C, Oka H. Postprandial hypotension in de novo Parkinson's disease: a comparison with orthostatic hypotension. *Parkinsonism Relat Disord* 2014; 20: 573-577.
23. Luciano GL, Brennan MJ, Rothberg MB. Postprandial hypotension. *Am J Med* 2010; 123: 281.e1-e6. doi: 10.1016/j.amjmed.2009.06.026
24. Espay AJ, LeWitt PA, Hauser RA, Merola A, Masellis M, Lang AE. Neurogenic orthostatic hypotension and supine hypertension in Parkinson's disease and related synucleinopathies: prioritisation of treatment targets. *Lancet Neurol* 2016; 15: 954-966.
25. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension: JACC state-of-the-art review. *J Am Coll Cardiol* 2018; 72: 1294-1309.
26. Katsi V, Papakonstantinou I, Solomou E, Antonopoulos AS, Vlachopoulos C, Tsioufis K. Management of hypertension and blood pressure dysregulation in patients with Parkinson's disease-a systematic review. *Curr Hypertens Rep* 2021; 23: 26. doi: 10.1007/s11906-021-01146-5
27. Fanciulli A, Leys F, Falup-Pecurariu C, Thijs R, Wenning GK. Management of orthostatic hypotension in Parkinson's disease. *J Parkinsons Dis* 2020; 10 (s1): s57-s64.
28. Jordan J, Tank J, Heusser K, Reuter H, Biaggioni I. What do we really know about supine hypertension in patients with orthostatic hypotension. *Curr Opin Cardiol* 2019; 34: 384-389.
29. Jansen RW, Lipsitz LA. Postprandial hypotension: epidemiology, pathophysiology, and clinical management. *Ann Intern Med* 1995; 122: 286-295.
30. Zanasi A, Tincani E, Evandri V, Giovanardi P, Bertolotti M, Rioli G. Meal-induced blood pressure variation and cardiovascular mortality in ambulatory hypertensive elderly patients: preliminary results. *J Hypertens* 2012; 30: 2125-2132.
31. Jang A. Postprandial hypotension as a risk factor for the development of new cardiovascular disease: a prospective cohort study with 36 month follow-up in community-dwelling elderly people. *J Clin Med* 2020; 9: 345. doi: 10.3390/jcm9020345
32. Velseboer DC, de Haan RJ, Wieling W, Goldstein DS, de Bie RM. Prevalence of orthostatic hypotension in Parkinson's disease: a systematic review and meta-analysis. *Parkinsonism Relat Disord* 2011; 17: 724-729.
33. Jordan J, Fanciulli A, Tank J, *et al.* Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. *J Hypertens* 2019; 37: 1541-1546.
34. Cheshire WP. Chemical pharmacotherapy for the treatment of orthostatic hypotension. *Expert Opin Pharmacother* 2019; 20: 187-199.
35. Amin SN, Khashaba AS, Latif NS, El Gazzar WB, Hussein UK. Citicoline improved cardiovascular function in animal model of dysautonomia. *J Physiol Pharmacol* 2021; 72: 69-80.
36. Vallelonga F, Maule S. Diagnostic and therapeutical management of supine hypertension in autonomic failure: a review of the literature. *J Hypertens* 2019; 37: 1102-1111.
37. Williams B, Mancia G, Spiering W, *et al*. 2018 ESC/ESH Guidelines for the management of arterial hypertension. *Eur Heart J* 2018; 39: 3021-3104.
38. Brignole M, Moya A, de Lange FJ, *et al*. 2018 ESC Guidelines for the diagnosis and management of syncope. *Eur Heart J* 2018; 39: 1883-1948.
39. Darweesh SK, Raphael KG, Brundin P, *et al*. Parkinson matters. *J Parkinson's Dis* 2018; 8: 495-498.
40. Chelimsky G, Chelimsky T. Non-pharmacologic management of orthostatic hypotension. *Auton Neurosci* 2020; 229: 102732. doi: 10.1016/j.autneu.2020.102732
41. Palma JA, Redel-Traub G, Porciuncula A, *et al*. The impact of supine hypertension on target organ damage and survival in patients with synucleinopathies and neurogenic orthostatic hypotension. *Parkinsonism Relat Disord* 2020; 75: 97-104.
42. Wieling W, van Dijk N, Thijs RD, de Lange FJ, Krediet CT, Halliwill JR. Physical countermeasures to increase orthostatic tolerance. *J Intern Med* 2015; 277: 69-82.
43. Zoladz JA, Majerczak J, Zeligowska E, *et al*. Moderate-intensity interval training increases serum brain-derived neurotrophic factor level and decreases inflammation in Parkinson's disease patients. *J Physiol Pharmacol* 2014; 65: 441-448.
44. Su J, Huang P, Qin M, *et al*. Reduction of HIP2 expression causes motor function impairment and increased vulnerability to dopaminergic degeneration in Parkinson's disease models. *Cell Death Dis* 2018; 9: 1020. doi: 10.1038/s41419-018-1066-z
45. Figueroa JJ, Singer W, Sandroni P, *et al*. Effects of patient-controlled abdominal compression on standing systolic blood pressure in adults with orthostatic hypotension. *Arch Phys Med Rehab* 2015; 96: 505-510.
46. Okamoto LE, Diedrich A, Baudenbacher FJ, *et al*. Efficacy of servo-controlled splanchnic venous compression in the treatment of orthostatic hypotension: a randomized comparison with midodrine. *Hypertension* 2016; 68: 418-426.

47. Yin S, Cao Y, Zhang J. Treatment of primary hypotension by electroacupuncture at Neiguan and Gongsun - a report of 100 cases. *J Tradit Chin Med* 2004; 24: 193. PMID: 15510798
48. Sun J, Sang H, Yang C, *et al*. Electroacupuncture improves orthostatic tolerance in healthy individuals via improving cardiac function and activating the sympathetic system. *Europace* 2013; 15: 127-134.
49. Chiu YJ, Chi A, Reid IA. Cardiovascular and endocrine effects of acupuncture in hypertensive patients. *Clin Exp Hypertens* 1997; 19: 1047-1063.
50. Li J, Sun M, Ye J, *et al*. The mechanism of acupuncture in treating essential hypertension: a narrative review. *Int J Hypertens* 2019; 2019: 8676490. doi: 10.1155/2019/8676490
51. Yang J, Chen J, Yang M, *et al*. Acupuncture for hypertension. *Cochrane Database Syst Rev*. 2018; 11(11): CD008821.
52. Xiong X, Yang X, Li X, Yue G, Xing Y, Cho WC. Efficacy and safety of Chinese herbal medicine for patients with postmenopausal hypertension: A systematic review and meta-analysis. *Pharmacol Res* 2019; 141: 481-500.
53. Sucher NJ. The application of Chinese medicine to novel drug discovery. *Expert Opin Drug Discov* 2013; 8: 21-34.
54. Hao P, Jiang F, Cheng J, Ma L, Zhang Y, Zhao Y. Traditional Chinese medicine for cardiovascular disease: evidence and potential mechanisms. *J Am Coll Cardiol* 2017; 69: 2952-2966.

Received: July 7, 2023
Accepted: August 31, 2023

Authors'addresses: Yulei Xie, Department of Rehabilitation Medicine, Affiliated Hospital of North Sichuan Medical College, No.1 Maoyuan South Road, Nanchong, Sichuan Province, China. E-mail: xieyulei@foxmail.com

Yinxu Wang, Department of Rehabilitation Medicine, Affiliated Hospital of North Sichuan Medical College, No.1 Maoyuan South Road, Nanchong, Sichuan Province, China' E-mail: 34089681@qq.com