



## Prevalence and Associated Risk Factors of Symptomatic Orthostatic Hypotension in Patients with Parkinson's Disease

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### Declaration

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### ABSTRACT

**Background:** A major non-motor consequence of Parkinson's disease (PD) that greatly increases morbidity and lowers quality of life is symptomatic orthostatic hypotension (OH). Finding the prevalence and risk factors for symptomatic OH in PD patients was the goal of this investigation. **Objective:** In order to enhance early detection and management techniques, it is important to ascertain the prevalence of symptomatic orthostatic hypotension in patients with Parkinson's disease and identify risk factors that are linked to it, such as demographics, disease features, comorbidities, and drug use. **Methods:** The Neurology Department of a Liaquat National Hospital Karachi hosted a six-month qualitative study. Purposive sampling was used to enroll 130 PD patients in total. Semi-structured interviews and clinical evaluations were used to gather data, with an emphasis on comorbidities, medication use, illness features, and symptoms of OH. To find trends and risk variables, thematic content analysis was employed. **Findings:** Of the 130 participants, 46 (35.4%) had symptoms of OH. Levodopa use (87.0%), Hoehn & Yahr stage III-IV (76.1%), advanced age  $\geq 65$  years (60.9%), male gender (65.2%), disease duration  $>10$  years (43.5%), and combination therapy (54.3%) were the main risk variables. Dizziness (82.6%), weakness (69.6%), blurred vision (52.2%), and syncope (21.7%) were among the most common symptoms. **Conclusion:** Almost one-third of PD patients experienced symptomatic OH, which was linked to a number of risk factors that could be changed as well as those that couldn't. Improving patient outcomes and safety requires early detection and treatment.

### INTRODUCTION

PD affects from about 1 in 1000 in the general population and 1 in 100 over 65 years. It is estimated that there would be a doubling (1) in the prevalence of PD by 2030. Parkinson's disease has experienced a fascinating paradigm shift in the past few decades from being a "motor disease" to a "complex brain disease". Part of the reason for this is that the condition has well-researched non-motor symptoms such as autonomic impairment, including orthostatic hypotension, sweating, urinary symptoms, constipation, sexual dysfunction, blurred vision, and falls (2-8).

Orthostatic hypotension (OH), a symptom of cardiovascular autonomic dysfunction, is one of the most common non motor problems in PD patients [9]. There is a meta-analysis which reports that the prevalence of OH is 30.1% (95% CI: 22.9% to 38.4%) [10]. OH is defined by the joint statement of the American Academy of Neurology (AAN) and American Autonomic Society (AAS) as a slurred

blood pressure (BP) of at least 10 mmHg in the diastolic or  $> 20$  mmHg in the systolic within three minutes of active standing or head-up tilt of at least 60° [11].

Dizziness and lightheadedness (and even double vision in severe cases), whole-body weakness, fatigue, inability to concentrate, headaches or neck pain as well as syncope form OH clinical symptoms [12]. Postural tones are also non-neurogenic and the ones resulting from autoimmune are neurogenic and every one involves the ANS failure to regulate blood pressure in response to postural change as well as an insufficient release of norepinephrine (NE) by the postganglionic sympathetic neurons [13,14]. Neurogenic OH or efferent baroreflex failure is being mostly caused by the postganglionic sympathetic denervation in Parkinson's disease [15], [16]. It is essential to identify other non-neurogenic causes of OH in PD, including intravascular volume depletion, medications, or heart failure [13], [17] before speaking of neurogenic OH.

Several research has also defined predisposing factors for OH in PD patients. Among these are increased stage of disease, prolonged duration of PD [18], male gender [19], [20], [21], advanced age, poor posture and gait, low scores in mini-mental state test, and visual hallucinations [22]. In addition, it has been shown that anti-Parkinson drugs like monoamine oxidase-B (MAO-B) inhibitors, dopamine agonists, L-DOPA reduces blood pressure [23]. Combination therapy [25] and increased dosages of dopaminergic therapies [24] increase the risk of OH. Antiparkinsonian drugs may have this hypotensive effect at the beginning of therapy, usually it is well tolerated [26] or can be controlled by altering doses [27].

OH, is associated with significant morbidity and death in working-age adults and the elderly, with or without Parkinson's disease. OH, has been shown to be an IS outcome predictor across the middle-age population (53-57 years old) without a history of neurological conditions, and without heart disease and stroke at baseline [28]. Moreover, Ooi found that OH increased the elderly's probability of falling (RR = 2.1) [29]. It was found that, when standing, the PD patients with OH were more prone to observe postural sway compared to those without OH [30].

Depending on the blood pressure in terms of the diminution extent and the patient's ability to compensate the drop, OH in PD may be symptomatic or asymptomatic. Most OH patients have a greater decrement in blood pressure upon standing, and OH symptoms occur more frequently among patients with damage to the body's compensatory systems – the sympathetic nervous system, renin-angiotensin system, and/or aldosterone system [9]. It has been shown lately that symptomatic OH is also associated with the decreased performances of the Ambulatory Capacity Measure (ACM), instrumental activities of daily living (iADL), and activities of daily living (ADL) [31]. The goal of this research is to seek out the prevalence of symptomatic orthostatic hypotension and risk factors associated with it in Parkinson's disease patients.

## LITERATURE REVIEW

The orthostatic hypotension (OH) in Parkinson's disease (PD) and its growing recognition as an important non-motor complication with a significant impact and a high healthcare cost are the subject of our review. The present research has significantly improved our understanding of the underlying mechanisms for symptomatic OH and its impact on Parkinson's disease patients.

From different findings of various investigations, it has been apparent that the rates of OH symptoms in PD are highly variable depending on patient characteristics, pathogenesis of disease and standards of diagnosis. As observed by Malady et al. in a longitudinal study, approximately 20% of early PD patients within their first five years of being diagnosed had symptomatic OH, which showed progression of autonomic symptoms in the condition.

In the same line Norcliffe-Kaufmann et al. found that the frequency of autonomic failure is a hallmark of disease progression, reported in a ten year follow-up as up to 48% symptomatic OH [33].

Advances in the understanding of the mechanisms of OH in PD have been enabled by information provided by pathologic studies. Prevailing literature has shown that a high degree of autonomic symptoms including OH are related to Lewy body disease, which occurs in many autonomic centers such as sympathetic ganglia and dorsal motor nucleus of the vagus(34). Besides, cardioprotective research with iodine-123 MIBG scintigraphy (mild cardiac absorption in patients suffering from PD a symptomatic OH) confirmed detailed cardiac denervation as the specific feature of neurogenic OH in PD (35).

With accumulating evidence, it is now more accepted that comorbid metabolic disorders, such as diabetes and being overweight, play a huge role in OH occurrence in PD. In a large cross-sectional study, type 2 diabetes mellitus was found to increase the incidence of symptomatic orthostatic hypotension by a factor of two by Freeman et al. (36), further which diabetic autonomic neuropathy may complicate PD-related autonomic dysfunction. Obesity has also been found to up the risk of OH. A study by Camacho-Soto, et al. (37) indicates that greater body mass index might hamper baroreflex sensitivity in PD patients and thus cause more intense postural regression of blood pressure.

Established well is the fact that age as well as chronic nature of the disease have great roles in development of autonomic complications. Senard et al. illustrated the progressive effect of neurodegeneration because the presence of both advancing age and a longer disease duration increased the likelihood of developing symptomatic OH without dependency (38). Additionally, a correlation of increased OH symptoms levels and increased Hoehn and Yahr stages was found which suggests the progressive involvement of autonomic circuits in OH development.

Pharmacotherapy is an important and amenable contributor to the development of orthostatic hypotension (OH) in patients with Parkinson's disease (PD). Although dopaminergic drugs are important in controlling motor symptoms, they have been found to aggravate orthostatic hypotension. In controlled research, 33 percent of patients reported acute OH symptoms in their levodopa use (33 percent in the down titration and 39 percent in the up titration) (Oka et al., 33). Furthermore, patients using levodopa or dopamine agonists had longer and worse OH phenomena, which have the potential to illustrate the long-term effects of combined drug treatment.

Recent studies have focused on the ways in which OH impacts on PD other than on the typical physiological bases. To a 12-month follow-up, it was appreciated that patients experiencing symptomatic OH recorded twice the fall rate of those without OH, emphasizing a critical increase in fall risk (40). The correlation between OH and reduced postural control points to a straight cause for the negative outcomes, i.e. hospitalizations and fractures.

As medical studies show, OH symptoms are firmly related to measurable structural differences in the brain of Parkinson's disease patients. >>Ray Chaudhuri et al. used voxel-based morphometry to demonstrate that PD patients that exhibit OH symptoms have significant degeneration of central autonomic network shown by atrophy of brainstem and insular cortex (41).

## Research Objective

The main aim is to identify the frequency of symptomatic orthostatic hypotension (OH) in Parkinson's disease patients who report to the neurology outpatient's service. Moreover, the research will attempt to examine the main risk factors such as patient background, specifics of Parkinson's diseases, the presence of other diseases, and medical prescriptions that are contributing to the occurrence of symptomatic OH. This research is aimed at explaining the frequency with which symptomatic OH does occur in the patients with Parkinson & 2019; s and which factors contribute to it, so that eventually the management of OH can be improved and better quality of life supported for the affected individuals.

## METHODOLOGY

This qualitative study took place over an area of six months at Neurology Department at Liaquat National Hospital Karachi. One of the central themes of this research was to examine the occurrence and possible risk factors for symptomatic orthostatic hypotension in people with Parkinson's disease. The inclusion criterion included consent of the participants and a clinical diagnosis of Parkinson's disease; a purposive sampling method ultimately recruited a sample of 130 participants. The critical areas that were explored through in-depth, semi-structured interviews and clinical evaluation exercise during data collection include orthostatic hypotension symptoms, medical history of the patient, current medications on them as well as existing co-morbid conditions. Verbatim transcription and audio recording of the interviews as well as the thematic analysis were used to identify risk factors and thematic patterns of OH symptoms. Before proceeding with the study, permission was secured from the hospital's ethics review, and confidentiality of participants strictly maintained during the study.

## RESULTS

### Table 1

*Demographic Characteristics of Study Participants (n=130)*

Variable	Category	Frequency (n)	Percentage (%)
Age	40-49 years	18	13.8%
	50-59 years	35	26.9%
	60-69 years	47	36.2%
	70 years and above	30	23.1%
Gender	Male	82	63.1%
	Female	48	36.9%
Duration of Parkinson's	<5 years	40	30.8%
	5-10 years	58	44.6%
	>10 years	32	24.6%
Stage of Parkinson's	Hoehn & Yahr I-II	50	38.5%
	Hoehn & Yahr III-IV	80	61.5%

### Table 2

*Identified Risk Factors Associated with Symptomatic OH (n=46)*

Risk Factor	Frequency (n)	Percentage (%)
Advanced Age (≥65 years)	28	60.9%
Male Gender	30	65.2%

Disease Duration >10 years	20	43.5%
Hoehn & Yahr Stage III-IV	35	76.1%
Use of Levodopa	40	87.0%
Use of Combination Therapy	25	54.3%
Presence of Diabetes Mellitus	14	30.4%
History of Hypertension	10	21.7%

### Table 3

*Common Symptoms Reported by Participants with Symptomatic OH (n=46)*

Symptom	Frequency (n)	Percentage (%)
Dizziness/Lightheadedness	38	82.6%
Blurred Vision	24	52.2%
Weakness/Fatigue	32	69.6%
Syncope (Fainting)	10	21.7%
Difficulty Concentrating	15	32.6%
	12	26.1%

### Table 4

*Frequency of Comorbidities in Study Participants (n=130)*

Comorbidity	Frequency (n)	Percentage (%)
Hypertension	48	36.9%
Diabetes Mellitus	36	27.7%
Coronary Artery Disease	20	15.4%
Chronic Kidney Disease	10	7.7%
Depression/Anxiety	30	23.1%
No Comorbidities	40	30.8%

## DISCUSSION OF RESULTS

The research has focused on the prevalence of symptomatic orthostatic hypotension (OH) and its risk factors in the neurology outpatients suffering from Parkinson's disease (PD). It noted that 46 (35.4%) of the 130 subjects had symptomatic OH. What we observed is similar to earlier studies, such as the meta-analysis by Low et al. who reported that approximately 30% of PD patients reported OH. The data provides the grounds for OH receiving more attention from clinicians and treatment as it undoubtedly emerges as the primary non-motor symptom of PD, which should attract additional vigilance and care.

Deeper analysis of the risk factors enabled identification of more concrete clinical and demographic characteristics associated with OH symptoms. Old age (≥65 years) was identified as a significant risk factor for OH symptoms present in 60.9% of these patients. Like Senard et al., this result confirms that autonomic impairment usually becomes more pronounced as one's age advances. Age-associated reductions in vascular compliance and the sensitivity of baroreceptors would appear to exacerbate the pre-existing autonomic burdens in PD, raising vulnerability to OH symptoms.

There was a male predominance in the symptomatic group with OH at 65.2%. This is congruent with reports by Ha et al. and other investigators who demonstrated that male PD patients are more prone to develop autonomic problems such as orthostatic hypotension. Why exactly there is such a difference between genders is not definite, but hormones or variations in the progression of disease and autonomic function effects in men and women might play a role.

Longer engraving of the condition also was important to the emergence of symptoms; In the group of symptomatic OH, >4 in 10 of the population had PD for more than ten years. It shows that, as the contemporary consensus suggests, the length of the illness plays a major

role in aggravating autonomic failure. The trend towards increased OH in patients with longer disease durations most likely can be explained by a cumulative loss of neurons in autonomic centers (sympathetic ganglia and the dorsal motor nucleus of the vagus, to name a few) that may become more pronounced as time progresses.

Irfan et al. used Holzer's modified WHO definitions of OH symptoms in our study. Severely symptomatic patients (Hoehn and Yahr stage III-IV) experienced more obvious OH symptoms, relative to stages that were earlier. In particular, 76.1% of those affected were in stages III-IV, indicating the key nature of disease severity in causing OH. Newly formed evidence indicates that due to progression of Parkinson's disease there is increased intensity of both motor and non-motor symptoms, with autonomic dysfunction as a good example.

Medications were very effective in this context. Almost all individuals (87.0%) with symptoms of OH reported levodopa use and approximately 54.3% of those patients were on combination levodopa/anti-Parkinson treatment. The observations conform to former studies by Oka et al where they found that dopaminergic treatment can induce greater reductions in orthostatic blood pressure, notably at larger doses or during titration. Exacerbation of OH symptoms at the risk of treatment decisions with medications should be considered bearing in mind the evidence that these drugs mainly act on peripheral vasodilation and sympathetic tone.

Comorbidities were notably critical with 30.4% of symptomatic OH in diabetic patients with diabetes mellitus—an indication of diabetes-related autonomic neuropathy that might continue to interfere with autonomic function in Parkinson's. Similarly, 21.7% of patients who complained of symptoms were diagnosed with hypertension. In contrast with what one would take to be common sense, some antihypertensive drugs or perhaps baroreceptor desensitization could find itself pushing the rate of the orthostatic symptoms in hypertensive patients.

In symptomatic OH patients, the main symptom reported was weakness/fatigue in 69.6% of the cases, blurred vision in 52.2%, and dizziness/lightheadedness in 82.6%. Orthostatic intolerance, with these symptoms, is due to reduced cerebral perfusion while standing, and 21.7% of the participants reported syncope, highlighting the high risk and fall associated with symptomatic OH. As reported by Velseboer et al., the existence of symptomatic OH has been associated with not only poorer postural control and executive functioning, but symptoms such as inability to focus in our findings.

In the larger cohort, the biggest comorbidities reported were those of diabetes mellitus (27.7%), and hypertension (36.9%), the patterns of which are congruent with existing epidemiologic data in older adults and groups with PD. The fact that almost one in three subjects

(30.8%) had minimal comorbidities demonstrates that OH may occur less often even in healthy older adults, and in those with Parkinson disease.

Symptomatic OH in PD seems to be a result of several interrelated forms of causes, both intrinsic (age, gender and disease-related) and extrinsic (such as medication use and comorbidities). The data indicate that regular screening (including screening for OH) is crucial, particularly in older male patients with advanced PD who are on levodopa or combination therapy or have had the condition for many years. Symptomatic OH is frequently treatable by early interventions such as changing dopaminergic pharmacotherapy, combining non-drug procedures (e.g., physical maneuvers and compression devices), and curing accompanying medical conditions.

## CONCLUSION

It turned out that symptomatic orthostatic hypotension (OH) was present in 35.4% of the participants, which is a common and significant non-motor complication of Parkinson's disease (PD). The results of the study communicated the necessity of symptomatic OH identification as the principal cause of the affliction in those with Parkinson's disease. The association was further confounded by comorbid medical conditions associated with diabetes mellitus and hypertension indicating a complex relationship between PD and systemic diseases.

Apart from day-to-day living, such conditions as dizziness, weakness, blurred vision and syncope created significant safety dangers mainly because they were linked with falls. These symptoms significantly compromised patients' ability to do daily activities and life satisfaction. Through use of a qualitative approach focused on the psychological and physical impact of symptomatic OH and with the use of detailed interviews and clinical assessments, the study generated valuable insight regarding the phenomenological experience of symptomatic OH patients.

A range of modifiable and non-modifiable risk factors has been associated with symptomatic OH, illustrating that this is a common and clinically important issue in Parkinson's disease. The following steps were needed to address these concerns promptly and repeatedly identifying, changing medications, treating coexisting conditions, and educating patients. Successful management of symptomatic OH promised to improve the quality of life, reduce risk of falling, and strengthen patient safety. It became evident that there should be the wide approach to controlling OH and increased clinical awareness. Further investigation with the emphasis on longitudinal studies is encouraged to explain how OH develops in the case of PD, as well as to instruct more efficient ways of addressing and preventing it.

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