ORIGINAL RESEARCH

DOI: 10.4274/ejgg.galenos.2022.2022-3-2
Eur J Geriatr Gerontol 2022

Older Age is a Risk Factor for Diastolic Orthostatic Hypotension

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Abstract

Objective: This study aims to investigate the associations orthostatic hypotension (OH) and cognitive status of patients.

Materials and Methods: OH diagnosis was achieved by measuring the supine blood pressure (BP), which was taken twice after lying for 5 min and the standing BP, which was taken twice after standing for 3 min. Mini-Mental State Examination (MMSE) determined the cognitive status of patients. If the score of MMSE was below 24, then the patient was diagnosed with cognitive impairment (CI).

Results: The prevalence of OH, systolic OH (SysOH) and diastolic OH (DiOH) were 31.8% (n = 181), 16.7% (n = 95), and 24.1% (n = 137), respectively. 23.9% of participants had CI. Individuals with older age were at higher risk for OH and DiOH (odds ratio (OR) = 1.03, 95% confidence intervals (CI) = 1.01-1.05, p = 0.012 for OH and OR = 1.04, 95% CI = 1.01-1.06 p = 0.013 for DiOH). In multivariate analysis, OH, SysOH, and DiOH were not related to CI (all p>0.05).

Conclusion: The presence of OH increases with aging, so its evaluation should not be forgotten.

Keywords: cognition, diastolic hypotension, older adults, orthostatic hypotension, systolic hypotension

Introduction

A slight increase in systolic blood pressure (SBP) is expected when standing up from a lying or sitting position. This increase in SBP is due to the displacement of approximately 500-700 ml of blood from the central circulation to splanic or pulmonary circulation because of standing up. With the effect of gravity, some of the blood accumulates in the lower extremities, and this can cause some degree of cerebral hypo perfusion. The sympathetic nervous system is activated to increase the amount of blood in the central circulation. Factors such as baroreceptor activation, cardiac output, the release of neurotransmitters, and increased vascular tonus try to regulate blood pressure (BP). Neurotransmitters such as norepinephrine and dopamine are involved in the regulation of BP due to orthostatic change. The spectrum of the events occurring in the orthostatic response includes sympathetic system activation, parasympathetic system inhibition, and increased systole. With reduced parasympathetic activity, there is an increase in heart rate, sympathetic tone, and vasoconstriction, and then an increase in total peripheral resistance. As a result of all these events, SBP increases due to the change of position (1).

Orthostatic hypotension (OH) is identified as a decline in SBP of at least 20 mmHg and/or a decline of at least 10 mmHg in diastolic BP within 3 min of standing. OH is related to falls, cognitive impairment (CI), dementia, cardiovascular events, syncope, frailty, and mortality (2). OH prevalence in older adults varies from 9% to 50%. These variations in the OH rates are often because of the presence of multimorbidities (diabetes mellitus (DM), dementia, cerebrovascular accident (CVA), Parkinson disease, cardiovascular disease (CVD), hypertension (HT), etc.), older age, measurement technique (active standing test and head-up tilt table), and the status of the participants in the study (community-dwelling, outpatient, hospital, nursing home, etc.) (2, 3). The presence of OH, its severity, and chronicity of the decline in orthostatic BP, all affect perfusion of cerebrum and cognitive decline and may cause CI (2, 3). Some researchers found that cognition and OH were associated with each other (4, 5), while others found opposing views (6, 7). In

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Received: 10.03.2022 **Accepted:** 11.05.2022

Cite this article as: Şentürk Durmuş N, Akın S, Ertürk Zararsız G. Older Age is a Risk Factor for Diastolic Orthostatic Hypotension. Eur J Geriatr Gerontol

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some studies (6, 8-10), systolic OH (SysOH) and diastolic OH (DiOH) were considered separately. In these studies (6, 10), low SBP was found to be significantly with cognition, but in a few recent studies, it was seen that low DBP also affects cognitive functions as well as SBP and has a role in the development of dementia (8, 9). Although it is already known that the presence of SysOH and DiOH enhances the risk of dementia. Up to now, their relationship of OH with CI has not been clearly explained. There are many striking differences among the studies due to the use of different tests to evaluate cognitive functions, small sample sizes, and variable age range sof the samples (3-7).

In this study, we hypothesized that the presence of both DiOH and SysOH is a risk factor for CI. With this research, we aimed to show the relationship between OH, SysOH, DiOH and CI, and to define other states associated with OH.

Materials and Methods

Study design

This study was designed as cross-sectional and included 569 participants, who attended a geriatric outpatient clinic. All over 60 years old patients were included in the study. The patients diagnosed with mild cognitive impairment, dementia, eye/hearing impairment, depression, and delirium were excluded from the study.

All participants gave written informed consent. Written informed consent was obtained from patients or caregivers in case of cognitive impairment (dementia or delirium). The study was approved by the Local Ethics Committee of Erciyes University (Erciyes University Ethics Committee/Decision no: 2019/136).

Data collection

Sociodemographic data (age, gender, and educational level), number of medications, and history of chronic diseases (DM, CVD, HT, CVA, Parkinson's disease) were recorded. The patients were asked whether they had fallen in the last year, the number of falls and whether they were afraid of falling.

The blood pressure of the participants was measured on the brachial artery with an Omron brand oscillometric measurement device. OH diagnosis was achieved by measuring the SBP as taken twice after lying for 5 min and the standing BP taken twice after standing for 3 min. OH was defined as a decline in systolic BP (SBP) of at least 20 mmHg and/or a decline of at least 10 mmHg in diastolic BP (DBP) within 3 min of standing (11). Additionally, OH was evaluated as SysOH and DiOH. Furthermore, in examining OH using this description, SysOH (reduction in SBP > 20 mmHg) and DiOH (reduction in DBP > 10 mmHg) were investigated independently.

The cognitive status of patients was determined with the Mini-Mental State Examination (MMSE) (12). If the score of MMSE was below 24, then the patient was diagnosed with CI.

For each patient, basic and instrumental activities of daily living (ADL) (13, 14), (scores range from 0 to 18 points and from 0 to 24 points, respectively), SARC-F questionnaire (15), and FRAIL questionnaire (16) were also recorded. For FRAIL, a total of 0 points is categorized as non-frail, 1 as pre-frail, and 2 and above as frail.

Statistics

Histogram, q-q plots were examined and Shapiro-Wilk's test was applied to assess the data normality. The Levene test was used to test variance homogeneity. To compare the differences between groups, the Pearson chi-square test was applied for categorical variables, and the Mann-Whitney U test was applied for continuous variables. Binary logistic regression analysis models were built to investigate the effect of variables in estimating OH and SysOH and DiOH in geriatric patients. For this reason, each of these variables were dichotomized (OH, SysOH > 20 mg/dL and DiOH > 10 mg/dL) and separately evaluated. Moreover crude, age and gender-adjusted, and multiple models were fitted separately. Significant variables at $p < 0.25$ were included in multiple models and backward elimination was performed to identify independent risk factors. The Wald statistic was used as model selection criteria. Odds ratios (OR) were calculated with 95% confidence intervals. The linearity assumption between the log-odds and the independent variables was checked by visually inspecting the scatter plot between each predictor and the logit values. Multicollinearity assumption of the regression analysis were assessed by checking the Pearson correlation coefficients between the variables and calculating the variance inflation factors (VIF) for each variable. Hosmer-Lemeshow goodness of fit test statistic was calculated to assess the goodness of fit of the final models. All analyses were performed using TURCOSA (Turcosa Analytics Ltd. Co., www.turcosa.com.tr) statistical software. P values less than 5% were considered statistically significant.

Results

Five hundred and sixty-nine individuals over the age of 60 were included in the study. The mean age of the participants was 72.16 + 7.38 (range 60-96). Three hundred and ninety-eight (69.9%) of the participants were female. The prevalence of OH, SysOH, and DiOH were 31.8% (n = 181), 16.7% (n = 95), and 24.1% (n = 137), respectively. Table 1 shows the characteristics of the study population based on presence or absent OH, SysOH, and DiOH. Subjects with OH were more likely to be older (71.0 vs 72.0 p = 0.029), had more medications (p = 0.006), had a lower MMSE score (p = 0.003), and all BP measurements were significantly different from non-OH patients. Participants in

Table 1. Comparison of demographic and clinical variables between OH, systolic OH and diastolic OH groups

Variables	OH: Non-OH n=388, 68.2%	OH: OH n=181, 31.8%	p	Systolic OH: Non n=474, 83.3%	Systolic OH: Systolic OH n=95, 16.7%	p	Diastolic OH: Non n=432, 75.9%	Diastolic OH: Diastolic OH n=137, 24.1%	p
Gender **Male** **Female**	 109 (63.7) 279 (70.1)	 62 (36.3) 119 (29.9)	0.135	 143 (83.6) 331 (83.2)	 28 (16.4) 67 (16.8)	0.893	 119 (69.6) 313 (78.6)	 52 (30.4) 85 (21.4)	**0.021**
Age (years)	71.0 (66.0-76.0)	72.0 (67.0-79.0)	**0.029**	71.0 (66.0-77.0)	72.0 (72.0-78.0)	0.512	71.0 (66.0-76.0)	73.0 (68.0-80.0)	**0.001**
DM	164 (42.3)	86 (47.5)	0.240	202 (42.6)	48 (50.5)	0.156	185 (42.8)	65 (47.4)	0.342
HT	254 (65.5)	123 (68.0)	0.558	306 (64.6)	71 (74.7)	0.055	285 (66.0)	92 (67.2)	0.799
CVA	25 (6.4)	4 (2.2)	0.032	27 (5.7)	2 (2.1)	0.146	26 (6.0)	3 (2.2)	0.076
CVD	60 (15.5)	37 (20.4)	0.141	74 (15.6)	26 (24.2)	0.042	69 (16.0)	28 (20.4)	0.226
Parkinson disease	25 (6.4)	13 (7.2)	0.742	35 (7.4)	3 (3.2)	0.132	26 (6.0)	12 (8.8)	0.263
Number of comorbidites	3.0 (2.0-4.0)	2.0 (2.0-4.0)	0.855	3.0 (2.0-4.0)	4.5 (3.0-6.0)	0.170	3.0 (2.0-4.0)	2.0 (2.0-3.5)	0.825
Number of medications	4.0 (2.0-5.0)	5.0 (2.2-6.0)	**0.006**	4.5 (3.0-6.0)	4.5 (3.0-6.0)	0.081	3.0 (2.0-4.0)	5.0 (3.0-6.2)	**0.008**
History of falling	128 (33.0)	60 (33.1)	0.970	160 (33.8)	28 (29.5)	0.418	138 (31.9)	50 (36.5)	0.324
Fear of falling	163 (42.0)	90 (49.7)	0.566	208 (44.2)	45 (47.4)	0.566	182 (42.4)	71 (51.8)	0.054
Number of falling	1.0 (1.0-2.5)	2.0 (1.0-3.0)	0.177	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.186	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.492
SARC-F total score	3.0 (1.0-5.0)	3.0 (1.0-5.0)	0.328	3.0 (1.0-5.0)	3.0 (1.0-5.0)	0.899	3.0 (1.0-5.0)	3.0 (2.0-5.0)	0.078
FRAIL total score	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.920	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.788	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.283
KATZ ADL total score	18.0 (18.0-19.0)	18.0 (18.0-18.0)	0.368	18.0 (18.0-18.0)	18.0 (18.0-18.0)	0.734	18.0 (18.0-18.0)	18.0 (17.0-18.0)	0.081
KATZ ADL **Dependent** **Par. dependent** **Independent**	 3 (0.8) 54 (13.9) 331 (85.3)	 1 (0.6) 32 (17.7) 148 (81.8)	0.490	 4 (0.8) 69 (14.6) 401 (84.6)	 0 (0.0) 17 (17.9) 78 (82.1)	0.486	 3 (0.7) 59 (13.7) 370 (85.6)	 1 (0.7) 27 (19.7) 109 (79.6)	0.225
IADL total score	22.0 (18.0-22.0)	21.0 (16.5-22.0)	0.301	21.0 (17.0-22.0)	22.0 (19.0-22.0)	0.326	22.0 (18.0-22.0)	21.0 (16.0-22.0)	**0.021**
IADL **Dependent** **Par. dependent** **Independent**	 14 (3.6) 72 (18.6) 302 (77.8)	 9 (5.0) 36 (19.9) 136 (75.1)	0.670	 20 (4.2) 94 (19.8) 360 (75.9)	 3 (3.2) 14 (14.7) 78(82.1)	0.429	 15 (3.5) 75 (17.4) 342 (79.2)	 8 (5.8) 33 (24.1) 96 (70.1)	0.081
MMSE total score	27.0 (24.0-29.0)	26.0 (22.5-28.0)	**0.003**	27.0 (24.0-29.0)	26.0 (23.0-28.0)	0.246	27.0 (24.0-29.0)	26.0 (22.0-28.0)	**0.001**
MMSE **Low** **Normal**	 79 (51.8) 309 (71.4)	 57 (41.9) 124 (28.6)	**0.004**	 112 (82.4) 362 (83.6)	 24 (17.6) 71 (16.4)	0.733	 90 (66.2) 342 (79.0)	 46 (33.8) 91 (21.0)	**0.002**
Supine SBP	130 (120-140)	140 (120-150)	**0.001**	130 (120-140)	140 (130-155)	**<0.001**	130 (120-140)	140 (120-150)	**0.011**
Supine DBP	80.0 (70.0-80.0)	80.0 (70.0-90.0)	**<0.001**	80.0 (70.0-80.0)	80.0 (70.0-90.0)	**<0.001**	80.0 (70.0-80.0)	80.0 (70.0-90.0)	**<0.001**
Standing SBP	130 (120-140)	120 (110-130)	**<0.001**	130 (120-140)	120 (100-130)	**<0.001**	129 (115-140)	120 (110-132.5)	**0.025**
Standing DBP	80.0 (70.0-89.5)	70.0 (60.0-80.0)	**<0.001**	80.0 (70.0-85.0)	70.0 (60.0-80.0)	0.171	80.0 (70.0-88.0)	70.0 (60.0-80.0)	**<0.001**

ADL: Activities of daily living, CVA: Cerebrovascular accident, CVD: Cardiovascular disease, DBP: Diastolic blood pressure, DM: Diabetes mellitus, HT: Hypertension, IADL: Instrumental activities of daily living, MMSE: Mini mental state examination, OH: Orthostatic hypotension, SBP: Systolic blood pressure, data are summarized as n (%), median (1^{st}-3^{rd} quartiles). Significant p-values are shown in bold

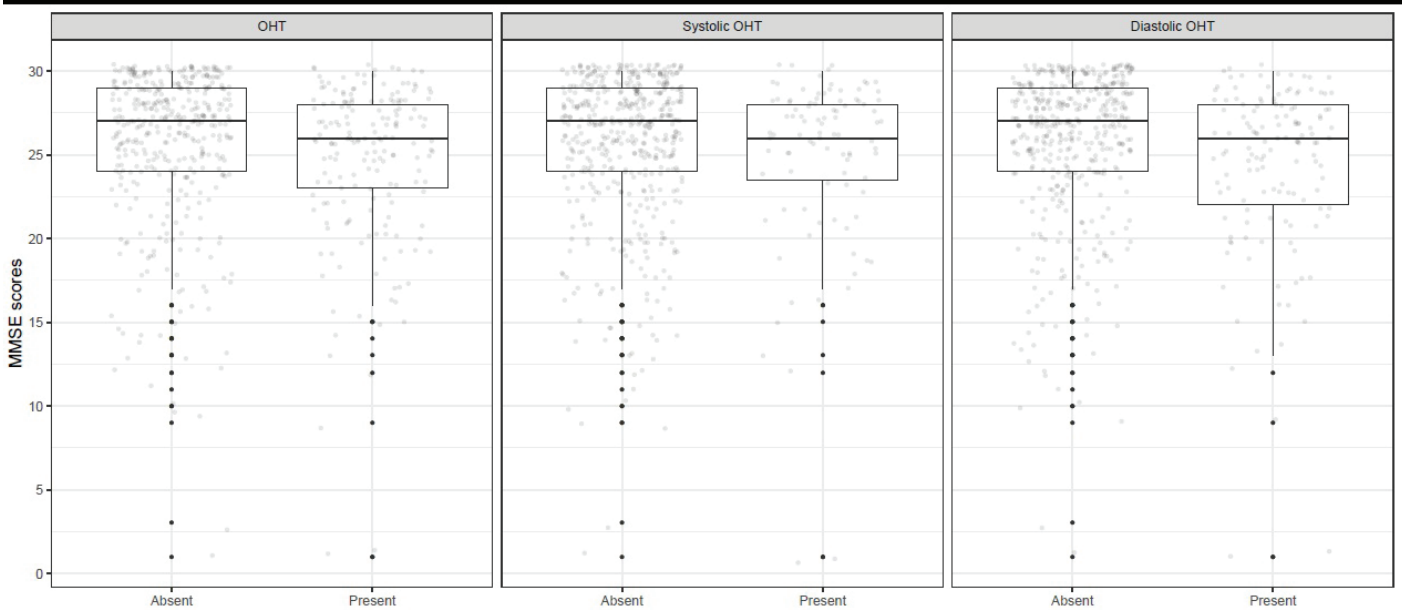

Figure 1. MMSE score distribution of OH, systolic OH and diastolic OH patients
The line in the middle is median, the bottom line is 25 percentiles, the upper line is 75 percentiles

the DiOH group were older (71.0 vs 73.0, p = 0.001), had more medications (p = 0.008), had lower instrumental activity of daily living (IADL) score (p = 0.021), had a higher supine SBP and DBP, had lower standing SBP and DBP (for BP p = 0.011, <0.001, 0.025 and <0.001 respectively). Individuals with SysOH had a higher supine SBP and DBP, and lower standing SBP (p<0.001 for all). The mean MMSE score was 25.30 + 4.72. One hundred and thirty-six (23.9%) participants were diagnosed with CI with less than 24 points in the MMSE test.

In the Chi-kare analysis, CI was significantly related to the presence of OH (p = 0.003). When we evaluated the SysOH and DiOH, only DiOH had a significant relationship with CI (p = 0.002). As seen in Figure 1, where the distribution of MMSE scores is shown, the mean of MMSE is lower in individuals with OH and DiOH.

After checking the scatter plots between the predictors and the logit values, we did not observe any non-linear relationship. In addition, all correlation coefficients were lower than 0.70 and VIF scores were lower than 5. Thus, we continued the analysis assuming that these assumptions were met. In the built multiple models, there were very few variables found to be significant. However, the p values of some variables (KATZ-ADL and MMSE score for SysOH, gender and MMSE score for DiOH) were very close to 0.05. These results show a trend toward statistical significance (17) and we left these variables in the model. The Hosmer–Lemeshow test resulted as X^2=9.179, p=0.327 for OH; X^2=4.745, p=0.784 for SysOH and X^2=14.315, p=0.074 for DiOH. These results revealed the appropriatness of the built multiple binary logistic regression model in order to predict OH, SysOH and DiOH in geriatric patients (Table 2). In the multiple analysis, the OR (95%CI) of age, IADL, MMSE score, gender were 1.03 (1.01-1.05), 1.05 (0.99-1.12), 0.95 (0.91-1.00), 0.66 (0.43-1.00), 1.03 (1.00-1.06) and 0.96 (0.92-1.00) respectively. Low MMSE scores was not associated with OH, SysOH and DiOH in older adults (p= 0.084, 0.248, and 0.062, respectively).

Discussion

In the present study, 31.8% of the participants had OH and 23.9% of the participants were diagnosed with CI. The prevalence of SysOH and DiOH was 16.7% and 23.7%, respectively. In this study, OH, SysOH and DiOH was associated with only older age not cognitive impairment.

The prevalence of OH reported in some studies was between 9% and 50%, and increased with older age (3, 6, 10, 18-23). In the present study prevalence of OH was 31.8%. The difference in the prevalence was because of the clinical conditions, ages, comorbidities, and community dwelling-outpatient-inpatient status of the participants. In our study, the prevalence of DiOH of the participants was higher than in the literature (6, 8, 10, 19, 23). None of these studies published the demographic data of the DiOH patients. Therefore, we could not compare them with our patients. In some of the studies (10, 19), the participants with OH were younger than those in present study. Additionally, one of the studies had more hypertensive individuals than in the present study (10). Assuming that those with DiOH present

Table 2. Univariate and multiple binary logistic regression analysis in estimating OH, systolic and diastolic OH in geriatric patients

Variables	Crude model		Adjusted model		Multiple model	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
OH						
Gender (male/female)	1.33 (0.91-1.95)	0.136	-	-	-	-
Age (years)	1.03 (1.01-1.05)	0.012	-	-	1.03 (1.01-1.05)	**0.012**
KATZ-ADL	0.98 (0.88-1.09)	0.693	1.01 (0.91-1.12)	0.887	-	-
IADL	0.99 (0.95-1.03)	0.570	1.01 (0.97-1.05)	0.699	-	-
SARC-F	1.03 (0.96-1.11)	0.382	1.03 (0.96-1.11)	0.439	-	-
Frail	0.98 (0.85-1.12)	0.805	0.97 (0.84-1.11)	0.627	-	-
Number of comorbidites	1.01 (0.88-1.15)	0.896	1.02 (0.89-1.16)	0.809	-	-
MMSE score	0.96 (0.92-0.99)	0.023	0.97 (0.93-1.01)	0.084	-	-
Systolic OH						
Gender (male/female)	0.97 (0.60-1.57)	0.893	-	-	-	-
Age	1.01 (0.98-1.04)	0.406	-	-	-	-
KATZ-ADL	1.05 (0.91-1.21)	0.539	1.06 (0.92-1.24)	0.423	-	-
IADL	1.03 (0.98-1.09)	0.198	1.05 (0.99-1.11)	0.080	1.05 (0.99-1.12)	**0.055**
SARC-F	1.01 (0.92-1.10)	0.818	1.00 (0.91-1.10)	0.989	-	-
Frail	0.95 (0.80-1.13)	0.599	0.94 (0.78-1.12)	0.467	-	-
Number of comorbidites	1.12 (0.95-1.31)	0.181	1.12 (0.95-1.32)	0.181	-	-
MMSE score	0.97 (0.93-1.02)	0.250	0.98 (0.93-1.03)	0.248	0.95 (0.91-1.00)	**0.056**
Diastolic OH						
Gender (male/female)	1.61 (1.07-2.41)	0.021	-	-	0.66 (0.43-1.00)	**0.053**
Age	1.05 (1.02-1.07)	<0.001	-	-	1.03 (1.00-1.06)	**0.017**
KATZ-ADL	0.93 (0.84-1.03)	0.176	0.97 (0.87-1.08)	0.569	-	-
IADL	0.96 (0.92-0.99)	0.041	0.98 (0.94-1.03)	0.451	-	-
SARC-F	1.06 (0.98-1.14)	0.126	1.06 (0.98-1.15)	0.149	-	-
Frail	1.06 (0.91-1.22)	0.456	1.04 (0.89-1.21)	0.645	-	-
Number of comorbidites	0.98 (0.84-1.13)	0.750	0.99 (0.85-1.15)	0.877	-	-
MMSE score	0.95 (0.91-0.99)	0.007	0.96 (0.92-1.00)	0.062	0.96 (0.92-1.00)	**0.062**

ADL: Activities of daily living, IADL: Instrumental activities of daily living, MMSE: Mini mental state examination, OH: Orthostatic hypotension, OR: Odds ratio, CI: Confidence interval, adjusted models are controlled for age and gender. Significant p-values are shown in bold

in these studies were younger and had more hypertensive participants, we can explain the difference between them and our study.

The relationship between OH and cognition was controversial (3-7, 22, 24). Some studies found a direct relationship between OH and CI, and OH related to cognitive decline and dementia in follow-up (3, 4, 19, 20, 22). Some of the researchers did not show any relationship between OH and CI, due to the retrospective design of the studies, the difference in method used in the diagnosis of OH, using different cognitive performance test, or characteristics (community-dwelling, low mean age) of participants (2, 3, 6). Until now, few articles have examined the relationship between the presence of OH- SysOH- DiOH, and CI (6, 10, 23). One of these studies found no relationship between these parameters (23). The others discovered that only SysOH was directly related to CI (6, 10). In studies to date, a relationship between SBP and cognition has been shown, but in a few studies in recent years, it has been seen that low DBP has an effect on cognitive functions as well as SBP and a role in dementia development (8, 9). Multiple mechanisms explain the relationship between OH and CI. In the presence of CI in an area where cardiovascular activities are regulated, OH be may seen together with CI (22). The relationship between OH and cognition is thought to be due to recurring cerebral hypo perfusion (25). In addition, Elmstahl et al. showed by EEG that in OH patients, the cerebral blood flow (CBF) decreases, so this may lead to cerebral damage and CI (26). A 50-60% reduction in CBF in healthy individuals is known to be associated with mild symptoms of cerebral hypo perfusion and the standing position, which is the biggest affect to the CBF, has most decreased CBF (27). Furthermore, CBF may decrease more when the compensatory response is not appropriate due to changes in vascular structures and impaired baroreceptor response in older individuals. Since the blood supply and oxygenation of the brain decreases, cognitive functions may be impaired. Cerebral hypo perfusion secondary to hypotension may induce cortical infarcts, which accelerate the degenerative process of Alzheimer's disease (28). Likewise, cerebral hypo perfusion may cause metabolic changes; this may increase oxidative stress and, cause neurodegeneration and atrophy due to neurotransmitter failure and amyloid deposition (29). In this study, when both SysOH and DiOH were investigated one by one, we did not observe any relationship between CI and both SysOH and DiOH.

Intensive blood pressure control with medications increases the risk of OH in older individuals. It is known in the results of the Systolic Blood Pressure Intervention Trial (SPRINT), that lower blood pressure is not protective from death and morbidities in frail and functionally limited older adults (30, 31). Therefore, older people who undergo intensive blood pressure control with medications should be carefully selected and questioned at every clinical visit for the presence and symptoms of OH, because OH may cause clinical situations that may result in morbidity and mortality in older patients.

Study Limitations

The present study has some limitations. One of them is the sample size. The sample size may not have been large enough to show the relationship between CI and SysOH and DiOH. Therefore, although the relationship between CI and OH, SysOH and DiOH was significant in the chi-square analysis, this significance was lost in the multivariate analysis. We hope that the relationship between OH and cognitive impairment can be better explained by increasing the sample size in future studies. In this study, MMSE was used to evaluate the cognitive performance of all participants. However, the use of MMSE may be limited for some reasons. The MMSE test is inadequate in evaluating verbal and visual memory, and MMSE is insufficient to detect cognition impairment in people with a high education level. People who have normal cognition with MMSE should be evaluated with other tests (such as Montreal Cognitive Assessment [MoCA]). However, the MMSE is easy to apply in an outpatient clinic and can be done quickly. It is also used in many clinical trials (3, 7). We believe that the MMSE is a good tool for cognition screening in outpatients.

Conclusion

Older age was associated with OH-DiOH and DiOH is more common. In older individuals, OH should be screened and treated appropriately. It should be kept in mind that blood pressure targets should be individualized according to frailty, dependency, and cognitive dysfunction in elderly individuals. Prospective studies are needed to reveal the causality between cognitive dysfunction and OH.

Ethics

Ethics Committee Approval: The study was approved by the Local Ethics Committee of Erciyes University (Erciyes University Ethics Committee/Decision no: 2019/136).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Authorship Contributions

Concept: N.Ş.D., S.A., Design: N.Ş.D., S.A., Data Collection or Processing: N.Ş.D., S.A., Analysis or Interpretation: N.Ş.D., G.E.Z., S.A., Literature Search: N.Ş.D., S.A., Writing: N.Ş.D., S.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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