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ORIGINAL RESEARCH

Association Between Cognitive Impairment and Blood Pressure Among Patients with Type II Diabetes Mellitus in Southern Iran

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Purpose: Both type 2 diabetes mellitus (T2DM) and hypertension are regarded as life-threatening diseases known to be risk factors for vascular diseases. They may be associated with the increased risk of cognitive impairment (CI), although there are conflicting data relating hypertension to the risk of CI. Therefore, this study aimed to explore the probable association between hypertension and CI in patients with T2DM.

Patients and Methods: This cross-sectional study assessed the degree of CI of a total of 350 patients with T2DM using the Mini–Mental State Examination (MMSE). In clinical examinations, the mean of the first, second, and third measurements of systolic and diastolic blood pressure (SBP and DBP) was recorded.

Results: The mean of subjects' MMSE scores was 25.48 ± 3.73. Additionally, the means of SBPSs and DBPs were found to be 118.50 ± 17.27 and 73.47 ± 10.25 mmHg, respectively. The Spearman correlation coefficient showed a mild, significant, negative correlation between MMSE scores and those of SBP ($r = -0.199$, $p < 0.001$) and DBP ($r = -0.233$, $p < 0.001$). Accordingly, a 1-unit increase in one's SBP would lead to a significant rise in mild CI (2.8%) in comparison with subjects who have normal CIs. However, it was shown that if one's DBP increased by 1 unit, the odds of mild CI occurring would increase significantly by 6.7% compared with those who have normal CIs.

Conclusion: The present findings revealed that hypertension might be related to the development of CI in people with a diabetic condition, thus emphasizing the fact that the prevention and treatment of these highly prevalent diseases assume the utmost significance.

Keywords: blood pressure, cognitive impairment, hypertension, type II diabetes mellitus

Introduction

Diabetes is considered to be a costly disease worldwide due to its many complications.[1,2] The chronic nature of the disease and its associated complications impose heavy economic burdens and reduce the quality of life for patients and their families.[3,4] According to the International Diabetes Federation (IDF), out of four diabetic people (352 million people), three are of working age (ie, between 20 and 64 years). It is expected that this figure will rise to 417 million and 486 million by 2030 and 2045, respectively. In 2019, an approximate 54.8 million adults aged 20–79 years, or 12.8% of the Middle East and North Africa regional population in the same age group, have diabetes, coupled with a total of 24.5 million adults whose diabetes are undiagnosed. Pakistan (19.4 million), Egypt (8.9 million), and Iran (5.4 million), respectively, account for the countries with the largest number of diabetic adults aged

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20–79 years old. Iran's national prevalence of diabetes in adults 20–79 years was 9.4 (7.4–12.3) in 2019.[5]

The effects of diabetes are not limited to early and late consequences, such as hyperglycemia and complications of small and large arteries.[6] It may also lead to primary and secondary disorders as well as complications in the central nervous system (CNS) and its higher levels, ie, cognitive functions and processes.[6] The primary effects of diabetes on CNS can be due to hyperglycemia, deficiency in insulin function, or both. Secondary effects, however, may be associated with diabetic vascular disorders, excessive insulin therapy, or brain damage caused by severe hypoglycemia.[7,8] One of the lesser known complications of T2DM is cognitive impairment (CI). CI caused by T2DM involves reductions in information processing speed, attention, memory, learning, problem-solving power, visual intelligence, and mental flexibility.[9] Biessels et al studied CI in patients with T2DM and concluded that this disease was associated with Alzheimer's disease. Indeed, the glucose metabolism process and metabolic disorders could be effective in reducing cognitive function.[10]

Cognitive disorder can, directly or indirectly, interfere with cognitive and nervous system functions, causing disturbances in individuals' awareness of themselves and the world around them. It can also create certain behavioral abnormalities that may greatly affect patients' individual and social lives. Therefore, identifying the risk factors for CI is of utmost importance.[11] The most predictable risk factor for CI is blood pressure (BP), because high BP and CI are quite common among elderly people.[12] Nonetheless, the mechanisms associated with CI are complex.[13] Recent evidence has suggested that hypertension might cause changes in brain structure and function by interfering with brain autoimmune regulation, therefore reducing brain perfusion and limiting the ability of the brain to eliminate potentially harmful proteins, such as β-amyloid.[10] Reduced cerebral blood flow after aging can disrupt the mechanisms regulating the brain, and this influence is enhanced by high BP.[14] In addition, it is likely that the severity of atherosclerosis of the arteries associates hypertension with CI.[11] The Framingham study conducted on 1702 patients showed that cognitive function is correlated with the baseline BP. In addition, the patients' CI worsened after 12–14 years.[12] Previous studies conducted to determine the relationship between BP and cognitive function have come to controversial results.[15] Some have reported that high BP (usually systolic blood pressure (SBP)) is associated with poor cognitive function,[16] while others have shown a positive relationship between CI and low BP.[17]

A major risk factor for cerebrovascular disease, hypertension has been reported to result in a weaker performance in neuropsychological tests. Furthermore, it has been revealed that one of the major complications of diabetes is CI.[18] However, the way in which diabetes, blood pressure, and cognitive performance are related to each other is not yet known unequivocally.[19] Traditionally, it has been believed that CI is a primary neurodegenerative disorder and that it is not of a vascular origin. Nevertheless, cumulative evidence has come to suggest that CI is not dissociated from vascular factors and disorders as once considered.[16,19,20] Whether hypertension is a risk factor for CI and decline or not has been the topic of much debate, such that some studies consider a positive association between these factors while others do not. Therefore, the present study aimed to evaluate the association between hypertension and CI in patients with T2DM.

Materials and Methods

This cross-sectional study was conducted on 350 patients with T2DM selected by random sampling in centers affiliated with Shiraz University of Medical Sciences, Shiraz, Iran (Imam Reza Clinic, Nader Kazemi Clinic, and Heart House). Inclusion criteria were age (30–60 years old), education, and diabetes for more than 1 year. The criteria for exclusion included a psychiatric or neurological disorder such as Alzheimer's disease, anxiety, depression, schizophrenia, multiple sclerosis, dementia, severe somatic disease unrelated to diabetes and capable of disrupting cognitive functioning, history of alcohol or drug abuse, cerebrovascular accidents, history of stroke, transient ischemic attack, cardiovascular disease, or liver and kidney diseases. All participants gave written informed consent to participate in the study. The present study was conducted in accordance with the principles of the revised Declaration of Helsinki, a statement of ethical principles which directs physicians and other participants in medical research involving human subjects. Moreover, the study was approved by the local Ethics Committee of Fasa University of Medical Sciences, Fasa, Iran (IR.FUMS.REC.1398.040).

The study data were gathered using a demographic information form and the Mini Mental Status Examination (MMSE). MMSE is a brief examination of CI first used by Folstein et al as a functional method for categorizing cognitive function.[21] The total score of this test is 30. Accordingly, scores 0–9, 10–20, 21–26, and 27–30 represent severe CI, moderate CI, mild CI, and normal CI, respectively. The

reliability of the test was approved by Cronbach's alpha which equaled 78%.

BP was measured on the basis of the criteria for the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure.[22] Briefly, three blood pressure measurements were recorded at 2-min intervals after the subject had been in a sitting position for approximately 1 h using a standard mercury sphygmomanometer (Exacta-Riester 1350, Rudolf Riester GmbH, Jungingen, Germany). Then, the mean of the three BP measurements was recorded. Hypertension was defined as SBP ≥120 mmHg, DBP ≥80 mmHg, or current use of antihypertensive medication. BP levels were then classified as follows:[22] SBP was graded as normal (90–119 mmHg), elevated (120–139 mmHg), stage I (140–159 mmHg), or stage II (>160 mmHg). DBP was classified as normal (60–79 mmHg), elevated (80–89 mmHg), stage I (90–99 mmHg), or stage II (>100 mmHg).

Statistical Analysis

All continuous variables were reported as mean ± standard deviation (M±SD), and categorical variables were presented as percentages. The Kolmogorov–Smirnov test was used to test for the normality assumption. The differences between subgroups of cognitive status were analyzed using Kruskal–Wallis with post hoc Mann–Whitney *U*-tests as well as Chi-square /Fisher's exact tests (applying the Bonferroni correction). Correlations between continuous variables were evaluated using the Spearman's rho correlation coefficient. The multinomial logistic regression model was also employed to assess the association between blood pressure and cognitive status. All statistical analyses were performed using SPSS statistical software version 24.0 for Windows (SPSS Inc.), and a p-value <0.05 was considered statistically significant.

Results

The descriptive characteristics of all subjects are summarized in Table 1. The study was conducted on a total of 350 patients suffering from T2DM (79 (22.6%) men and 271 (77.4%) women). The mean age of the patients was 52.156 ±8.11 years. The means of SBP and DBP were 118.50 ± 17.27 mmHg and 73.47±10.25 mmHg, respectively. The mean of the subjects' MMSE scores was 25.48 ± 3.73. Of all the patients, 141 (40.3%), 157 (44.9%), 52 (14.9%) reported normal, mild and moderate CI, respectively, and no one was shown to suffer from severe CI. In this study, hypertension was seen in 141 (40.3%) of the patients, of

Table 1 Demographic, Anthropometric and Social Factors Among the Sample Study

		Mean (SD) or N (%)	
Age (years)		52.16	8.11
MMSE scores		25.48	3.73
SBP (mmHg)		118.50	17.27
DBP (mmHg)		73.47	10.25
HbA1C (%)		8.16	1.96
T2DM duration (years)		7.37	6.30
Sex	Male	79	22.6%
	Female	271	77.4%
Menopause status	Postmenopausal	175	64.6%
	Premenopausal	96	35.4%
CI subgroups	Normal (27–30)	141	40.3%
	Mild (21–26)	157	44.9%
	Moderate (20–10)	52	14.9%
	Severe (0–9)	0	0.0%
Blood pressure	Yes	141	40.3%
	No	239	59.7%
SBP subgroups	Normal (90–119 mmHg)	210	60.0%
	Elevated (120–139 mmHg)	87	24.9%
	Stage I (140–159 mmHg)	47	13.4%
	Stage II (>160 mmHg)	6	1.7%
DBP subgroups	Normal (60–79 mmHg)	238	68.0%
	Elevated (80–89 mmHg)	88	25.1%
	Stage I (90–99 mmHg)	14	4.0%
	Stage II (>100 mmHg)	10	2.9%
Marital status	Single	22	6.3%
	Married	293	83.7%
	Divorced	6	1.7%
	Widow	29	8.3%
Household status	Urban	337	96.6%
	Rural	12	3.4%
Educational Level	Primary	202	57.7%
	Secondary to diploma	120	34.3%
	Academic	28	8%

(*Continued*)

Table 1 (Continued).

		Mean (SD) or N (%)	
Regular exercise	Yes	212	60.6%
	No	138	39.4%
Dependence on insulin	Yes	101	28.9%
	No	249	71.1%
Diabetes duration (years)	<5	168	48.0%
	5–9	93	26.6%
	10–15	46	13.1%
	>15	43	12.3%
Antihypertensive therapy	Yes	98	28.0%
	No	252	72.0%
Antidiabetic therapy	Yes	333	95.1%
	No	17	4.9%

Note: Statistical significance where p< 0.05.
Abbreviations: SD, standard deviation; MMSE, Mini–Mental State Examination; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1C, hemoglobin A1c; T2DM, type 2 diabetes mellitus; CI, cognitive impairment.

which 87 (24.9%) had elevated SBP, 47 (13.4%) had stage I SBP, and 6 (1.7%) had stage II SBP. Moreover, 88 patients (25.1%) had elevated DBP, 14 (4.0%) had stage I DBP, and 6 (1.7%) had stage II DBP. The means of SBP and DBP were 118.50 ± 17.27 mmHg and 73.47 ± 10.25 mmHg, respectively (Table 1).

Table 2 presents the comparison of the proportion of subjects with and without BP among the different CI subgroups. Hypertensive patients showed, respectively, 53.2% and 17.7% mild and moderate CI compared with 29.1% hypertensive patients without CI. Normotensive diabetic patients showed 47.8%, 38.2%, and 12.9% normal, mild, and moderate CI, respectively.

Table 2 Association of Blood Pressure with CI Subgroups

Blood Pressure	CI Subgroups	N	%	P-value
Yes	Normal (27–30)	41	29.1	**0.002**
	Mild (21–26)	75	53.2	
	Moderate (10–20)	25	17.7	
No	Normal (27–30)	100	47.8	
	Mild (21–26)	82	39.2	
	Moderate (10–20)	27	12.9	

Note: Boldface type indicates statistical significance where p< 0.05.
Abbreviation: CI, cognitive impairment.

Table 3 illustrates the comparison of SBP and DBP mean values with CI subgroups. The average of both SBP and DBP was significantly different within CI subgroups (p <0.001). Pairwise comparisons revealed that patients with mild and moderate CI had significantly higher SBP and DBP compared with patients without CI (Table 3).

The Spearman correlation coefficient showed that MMSE scores had a mild, significant, negative correlation with SBP (r = −0.199, p <0.001) and DBP (r = −0.233, p <0.001). Although a negative correlation was found between MMSE scores and age, it was not statistically significant (r = −0.068, p =0.207) (data not shown).

The association between SBP and DBP subgroups and those of CI is presented in Table 4. The results of the chi-square test showed that most patients with normal SBP (71.6%) and normal DBP (80.9%) levels had normal CI. Hypertensive patients showed a higher percentage of CI, moderate level (30.8% in SBP and 34.6% in SBP). Patients with stage I hypertension showed more cases of mild CI in both SBP (3.2%) and DBP (5.7%) groups. In addition, the majority of stage II hypertensive patients reported mild CI (Table 4).

Multinomial logistic regression was carried out in different models to determine the association of SBP and DBP with CI by adjusting the existing confounders. As shown in Table 5, in the model adjusted by all available confounders, the findings showed that if one's SBP increased by 1 mmHg, the odds of having mild CI were significantly increased (by 2.8%) compared with subjects with normal CIs. Moreover, if one's DBP increased by 1 mmHg, the odds of having mild CI were significantly increased (by 6.7%) compared with subjects with normal CIs. Although this trend between SBP, DBP, and moderated CI was the same, they did not show a significant association as shown by multinomial logistic regression. However, in the model adjusted by age and gender, both mild and moderate CIs showed a significant increase in the odds ratio compared with those with normal CIs (Table 5).

Discussion

Confirming the long-time prediction, a substantial increase in the occurrence of T2DM is currently prevailing, particularly in Iran. Despite the fact that the link between T2DM and CI is clinically relevant and obvious, on an individual level, whether there is an association between more mild to moderate CI and hypertension is not well known.[23] Because few diabetes healthcare professionals conduct analyses of their elderly patients for evidence of CI, the odds of an

Table 3 Comparison of SBP and DBP Mean Values with CI Subgroups

Blood Pressure	CI Subgroups	Mean	SD	P1	P2	P3	P4
SBP	Normal (27–30) Mild (21–26) Moderate (10–20)	114.04 121.86 120.48	16.08 17.41 17.62	**<0.001**	**<0.001**	**0.015**	0.621
DBP	Normal (27–30) Mild (21–26) Moderate (10–20)	70.16 76.01 74.81	9.80 9.90 10.16	**<0.001**	**<0.001**	**0.004**	0.344

Notes: Significant level = 0.017. Kruskal–Wallis Test for comparison of mean systolic/diastolic blood pressure in subgroups of Cognitive, Mann–Whitney test for pairwise comparison of subgroups. Boldface type indicates statistical significance where p< 0.05.
Abbreviations: SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cognitive impairment; P1, P-value for comparison of all three groups; P2, P-value for comparison of Normal and Mild groups; P3, P-value for comparison of Normal and Moderate groups; P4, P-value for comparison of Mild and Moderate groups.

Table 4 Association of SBP and DBP Subgroups with CI Subgroups

	Blood Pressure Subgroups	CI Subgroups						
		Normal (27–30)		Mild (21–26)		Moderate (10–20)		P-value
		N	%	N	%	N	%	
SBP	Normal (90–119 mmHg) Elevated (120–139 mmHg) Stage I (140–159 mmHg) Stage II (>160 mmHg)	101 27 12 1	71.6 19.1 8.5 0.7	82 44 26 5	52.2 28.0 16.6 3.2	27 16 9 0	51.9 30.8 17.3 0.0	**0.011**
DBP	Normal (60–79 mmHg) Elevated (80–89 mmHg) Stage I (90–99 mmHg) Stage II (>100 mmHg)	114 20 4 3	80.9 14.2 2.8 2.1	92 50 9 6	58.6 31.8 5.7 3.8	32 18 1 1	61.5 34.6 1.9 1.9	**0.002**

Note: Boldface type indicates statistical significance where p< 0.05.
Abbreviations: CI, cognitive impairment; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5 Crude and Adjusted Odds Ratios and 95% Confidence Intervals Derived from Multinomial Logistic Regression

		Model 1	Model 2	Model 3	Model 4	Model 5
SBP	Mild CI	**1.029 (1.014–1.043)**	**1.026 (1.011–1.041)**	**1.024 (1.009–1.040)**	**1.024 (1.008–1.039)**	**1.028 (1.012–1.045)**
	Moderate CI	**1.024 (1.005–1.044)**	**1.023 (1.003–1.043)**	1.020 (0.999–1.041)	1.017 (0.996–1.038)	1.018 (0.994–1.042)
DBP	Mild CI	**1.063 (1.037–1.092)**	**1.060 (1.034–1.088)**	**1.056 (1.030–1.084)**	**1.057 (1.029–1.085)**	**1.067 (1.037–1.097)**
	Moderate CI	**1.052 (1.018–1.087)**	**1.050 (1.015–1.086)**	**1.044 (1.007–1.081)**	**1.038 (1.001–1.076)**	1.036 (0.995–1.078)

Notes: Normal cognitive as the reference group. Model 1: Crude. Model 2: age and sex. Model 3: age, sex, marital and education. Model 4: age, sex, education and antihypertension drugs. Model 5: age, sex, marital, education, antihypertension drugs, household, insulin, HbA1C, T2DM Duration, T2DM Medication, and Exercise. Boldface type indicates statistical significance where p< 0.05.
Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; CI, cognitive impairment.

under-diagnosis is high. Hence, in the present study, the presence of CI in patients with T2DM suffering from hypertension was assessed in a population from southern Iran. The present findings revealed an association between hypertension and CI in this Iranian adult population, such that hypertensive diabetic patients showed a cognitive decline.

The current findings obtained from correlation analyses showed an association between CI scores and SBP, DBP, and age in T2DM patients, which is in line with the hypothesis that the increased risk of CI in older T2DM patients is related to underlying vascular disease. The findings were in agreement with those of previous studies.[24] Multinomial logistic regression results adjusted by existing confounders demonstrated that with a 1-unit increase in both SBP and DBP, the odds of having mild CI were significantly increased (by 2.8% and 6.7%, respectively) compared with subjects with normal CI. Although this trend occurred

in the same way between SBP, DBP, and moderated CI, no significant association was reported between them. The findings indicated the important role of hypertension in CI among patients with diabetes. The findings of Cacciatore et al showed that in subjects aged 75 years and older who had no neurological disorders, DBP rather than SBP predicted CI independent of gender, age, education, and antihypertensive treatment; their findings are not in line with the present findings.

High DBP leads to weakness in small vessels of the brain, thus extending these small areas of brain damage and CI.[16] In the current study, most patients with normal systolic and diastolic pressure levels had normal CI. However, previous studies have produced contradictory results regarding the relationship between BP and cognitive function. The potential link between T2DM, hypertension, and CI is intriguing. According to studies conducted by a specialist group under the supervision of the National Institutes of Health (NIH), the relationship between hypertension and CI is very weak due to heterogeneity in the definitions of mild CI and hypertension as well as differences in the hypertension detection methods (for example, measuring hypertension versus patients' self-reporting).[16] Alpérovitch et al examined changes in BP and the risk of dementia in the elderly and disclosed that changes in BP were associated with an increased risk of dementia, while the mean of BP was not associated with dementia.[25] On the other hand, Hassing et al[24] reported a statistically non-significant impact of hypertension on cognitive function despite the fact that the hypertensive patients in their study had a somewhat greater decline than the non-cases. Nevertheless, the present study showed that this trend was statistically significant. Moreover, according to Pandav et al,[26] low BP may be the result of, or a risk factor for, degenerative brain disease. The discrepancies between the results of these investigations and those of the present one might be attributed to differences in sample size, sampling methods, patients' cultures, patients' diets, definitions of hypertension, and BP measurement methods. For example, CI has been defined as a disorder with pathological features. Thus, if CI subtypes are defined differently, it would lead to varying outcomes.

T2DM has been shown to have various complications. Not only does T2DM influence the microvessels of the eyes, kidneys, and peripheral nerves, but it is also considered to be a crucial risk factor for macrovascular disease. Moreover, it results in significant degrees of morbidity and mortality through ischemic heart disease and stroke. It should also be noted that patients with T2DM, and especially those with the combination of diabetes mellitus and hypertension, are most vulnerable and prone to cerebrovascular and cardiovascular diseases.[27–30] Additionally, as dyslipidemia and obesity are conceived to be modifiable risk factors which, either directly or indirectly, make a contribution to the development of CIs in diabetes, it is strongly suggested that the risk of CI can be reduced by intensively managing the vascular risk factor. Thus, progression of vascular disease can be a factor upon which the relationship between cognitive changes and diabetes is based.[13,31,32]

Given that hypertension is clearly shown to be a risk factor for CI,[33] it was predicted that hypertensive patients would experience a greater cognitive decline, for many findings have confirmed such a result,[34–37] which is in keeping with the results of the present study in which high levels of cognitive decline were seen in hypertensive diabetic patients. According to previously conducted studies, if T2DM is accompanied by hypertension, the result would be a dramatic rise in the prevalence of CI.[24,35] Also, according to findings obtained by Elias et al, hypertensive patients with non-insulin-dependent diabetes mellitus (NIDDM) are the main group susceptible to risks for poor performance on tests which evaluate visual organization and memory.[35] On the other hand, the Frontal Assessment Battery (FAB) test has reportedly shown slight changes in normotensive diabetic patients.

Given that T2DM is a disorder with a metabolically complex nature, it can be suggested that the pathogenesis of diabetes-related CI is multifactorial.[1] However, to date, no study has been conducted particularly to assess the cognitive function of people with T2DM to produce a profound and comprehensive clinical characterization in order to make it possible to examine the effect of numerous cognitive risk factors. Even though macrovascular disease and hypertension per se are considered as major possible risk factors, the odds are that genetic susceptibility plays an important role as well. The need is great for further clinical trials and longitudinal studies encompassing a higher sample number with a focus on genetic susceptibility factors; better clarifying the potential mechanisms of these diseases would be much more fruitful.

Strengths and Limitations

Considering the limitations of this study, we must be cautious in interpreting the results. The first limitation

might be the relatively small sample size. In addition, a major limitation to this study was that the diagnosis of diabetes was based on self-report, HbA1C levels, or history of antidiabetic medication, and no objective measurements of fasting blood glucose were made. Moreover, another limitation of the present study was the comparatively higher number of women compared to men, which makes it difficult to easily generalize the current results. The main strength of the present study, however, is that unlike previous ones, patients with a history of stroke or transient ischemic attack were excluded. Therefore, the results indicated the effect of a vascular risk factor on cognitive changes in the absence of a potential clinical disease. Moreover, the present study addressed some methodological problems mentioned in recent studies, including dependence on self-reported BP or physicians' measurement of BP only once. The results of studies that are based solely on self-reported BP may be misleading. Another strength of this study was the diagnosis of CI using standard criteria and the completion of clinical evaluations related to BP.

Conclusion

The findings obtained from the present study demonstrate that hypertension might be associated with increased odds of CI, particularly mild CI, in diabetic conditions, suggesting that it should be taken into account at the time of managing T2DM combined with hypertension.

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Disclosure

The author reports no conflicts of interest in this work.

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