Original Article

Hypertension Coincident with Type 2 Diabetes Worsen Cognitive Function and Arterial Stiffness

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Background: The prevalence of concomitant of hypertension (HT) and type 2 diabetes (T2DM) mellitus have increased. However, the additional contribution of high blood pressure to T2DM on cognitive and vascular functions has not been published.

Objective: To compare the vascular functions and cognitive function among hypertensive with type 2 diabetic patients, hypertensive patients, and age-match healthy participants.

Materials and Methods: Twenty-three hypertensive-diabetic, 25 HT, and 23 sedentary individuals were included in this study. Using the cross-sectional design, the vascular functions were assessed with pulse wave velocity (PWV) and flow-mediated dilation (FMD) among the three groups. Global cognitive function tests were performed using Montreal Cognitive Assessment (MOCA).

Results: The hypertensive-diabetic group had higher brachial systolic blood pressure (SBP) ($p<0.05$), mean arterial pressure (MAP) ($p<0.05$), and pulse pressure (PP) ($p<0.05$) than the sedentary group. In addition, the hypertensive-diabetic patients had significantly higher PWV and worse cognitive performance than hypertensive and healthy participants ($p<0.05$) but did not significantly differ in FMD. Arterial stiffness, blood pressure, and fasting blood glucose were associated with level of cognitive performance ($p<0.05$).

Conclusion: Arterial stiffness and blood pressure are a determinant of cognitive functions in hypertensive diabetic subjects but not in individuals with hypertension without diabetes. These results suggested the additional effects of hyperglycemia on high blood pressure might worsen the cognitive functions through higher level of arterial stiffness and blood pressure.

Keywords: Cognitive function; Arterial stiffness; Type 2 diabetes; Hypertension

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The growth of aging population is the most substantial social and public health transformation in the twenty-first century. Thus, the prevalence of dementia, one of the major causes of disability and dependency among older people, is under consideration worldwide, because advanced age is the strongest risk factor and is not modifiable in nature[1]. However, mounting evidence indicates that the adaptable cardiovascular risk factors as well as subclinical atherosclerosis elevate the risk of dementia.

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Mild cognitive impairment (MCI) is a neuro-cognitive disorder defined as cognitive decline greater than that expected for an individual's age and education level but does not impact the ability to conduct everyday activities such as meal preparation. More than half of MCI individuals progress to dementia within five years[2]. Therefore, the detection of MCI is crucial for prevention of irreversible neuronal damage. Hypertension (HT)[3] and type 2 diabetes (T2DM)[4] are important predictors of MCI. The mechanism underpinning HT and T2DM with cognitive impairment has been the subject of long-standing debate but may include the subclinical atherosclerosis, which is vascular aging. It has been reported that individuals with either HT[5] or diabetes[6] have impaired endothelial function and increased stiffness of arterial elastic arteries. Endothelial function has an important role in the control of vascular tone, barrier function, leukocyte adhesion, and inflammation[7]. Elevated arterial stiffness results in decreased their buffering ability and increased the velocity of the propagating pressure wave[8].

Both cardiovascular disease risks and vascular

dysfunction are modifiable through lifestyle modification. Therefore, determining the modifiable causes of disease provide an opportunity of disease's prevention especially at midlife before the onset of irreversible cognitive decline in the later life. Accordingly, the present study chose middle-aged and young-old adults as the target population.

HT is related with T2DM and its prevalence doubles in diabetes compared to the general population[9]. Although the association between diabetes, HT, and vascular aging have been explored in the previous studies, the degree to which HT mediated an association between diabetes and vascular aging have not been elucidated. In addition, the potential role of vascular aging in relation with cognitive dysfunction profile in the coexisting HT and T2DM has not yet been published. Therefore, the aim of the present study was to investigate whether the vascular functions and cognitive functions in hypertensive with diabetic patients differed from hypertensive and age-matched healthy participants.

Materials and Methods

Study design

The present study was a cross-sectional group comparison among hypertensive-diabetic, hypertensive, and age-matched healthy individuals approved by the Institutional Review Board, Mahidol University (COA. No. 2018/092.0205).

Subjects

People with the diagnoses of essential HT or T2DM aged between 40 to 65 years were recruited from Nakhon Pathom area. Exclusion criteria were body mass index (BMI) greater than 30 kg/m^2, smoking, cardiovascular disease, chronic kidney disease, cardiovascular medications interfering with vascular function, hormonal therapy, insulin, and steroids and non-steroids anti-inflammatory drugs used. Control subjects were healthy, non-smoking, non-obese condition, and free of overt cardiovascular disease or diabetes. All subjects had sedentary lifestyle for at least one year prior to the study. None of the subjects has been previously diagnosed with Alzheimer's disease or vascular dementia.

Measurements

Before they were assessed, subjects fasted for at least four hours, with overnight fast for blood chemistry. Premenopausal women were assessed during the early follicular phase of the menstrual cycle. A blood drawn was obtained after 12-hour fast to analyze metabolic risk factors for cardiovascular disease including glucose and lipids, and lipoprotein.

Heart rate, bilateral brachial, ankle blood pressures, and pulse waves were measured by an automatic vascular screening device (VP-1000 plus, Omron Healthcare; Ukyo-ku, Kyoto, Japan) after subject rested in the supine position for 15 minutes. Pressure tonometry were set on the brachial and posterior tibial arteries. Pulse wave velocity (PWV), the index of arterial stiffness, was automatically calculated as the distance between the two recording sites divided by wave transit time. Ankle systolic blood pressure (SBP) divided by brachial SBP is the formula used for calculating the ankle brachial index (ABI).

Brachial artery flow-mediated dilation (FMD) was measured for endothelial function. Sphygmomanometric cuff was placed below antecubital fossa to produce a flow stimulus in brachial artery. Brachial diameter and blood flow velocity was acquired from a Doppler ultrasound machine (CX-50, Philips Healthcare; Everett Hwy, Bothell, USA). After baseline images were measured, the cuff was inflated at least 100 mmHg above systolic pressure to create arterial occlusion for five minutes and then the cuff was deflated. FMD was calculated as (maximum diameter – baseline diameter)/baseline diameter × 100[10].

Cognitive function was measured by the Montreal Cognitive Assessment: Thai version (MOCA-Thai version). Trial making test (TMT) A and B, digit span test (DST), and reaction time (RT) were employed to assess attention, executive function, working memory, and processing speed domain consecutively.

Statistical analysis

Data was analyzed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, NY, USA). One-way analysis of variance was used for group comparison. Because the FMD did not have normal distribution, the Kruskal-Wallis tests were used for data analysis. Post hoc test was done with LSD test and Mann-Whitney U test if data were not normally distributed. The correlation and regression were used to determine factors that can contribute to cognitive functions. A p-value of less than 0.05 was considered as significant level.

Results

As presented in Table 1, there were no significant differences among the three groups in age, weight, height, high density lipoprotein (HDL), and triglyceride. The sedentary group had significant

Table 1. Selected subject characteristics

	Sedentary (n=23)	Hypertensive patient (n=25)	Hypertensive-diabetic patient (n=23)
Male/female; n	6/17	6/19	7/16
Age (years); mean±SD	55.2±7.2	58.6±5.2	60.1±6.9
Weight (kg); mean±SD	62.3±10.2	69.2±11.1	64.9±10.1
Height (cm); mean±SD	160.8±9.6	160.7±10.1	157.6±8.9
Body mass index (kg/m^2); mean±SD	23.6±2.9	27.2±2.4*	26.6±3.1*
Waist circumference (cm); mean±SD	76.6±10.2	92.4±7.9*	89.3±6.3*
Education level (years); mean±SD	12.4±5.1	8.8±5.9	6.2±4.1*
Fasting blood glucose (mg/dL); mean±SD	93.4±32.1	92.1±27.7	126.1±26.7*†
Total cholesterol (mg/dL); mean±SD	220.2±24.6	203.1±49.7	177.4±41.1*
High density lipoprotein (mg/dL); mean±SD	52.7±16.5	49.4±14.3	49.6±9.2
Low density lipoprotein (mg/dL); mean±SD	142.6±28.3	126.0±43.4	109.6±33.2*
Triglyceride (mg/dL); mean±SD	147.0±92.3	141.7±38.3	147.2±43.3

SD=standard deviation

* p<0.05 versus sedentary, † p<0.05 versus hypertension

Table 2. Hemodynamic measurements at rest

	Sedentary (n=23); mean±SD	Hypertensive patient (n=25); mean±SD	Hypertensive-diabetic patient (n=23); mean±SD
Brachial blood pressure (mmHg)			
Systolic blood pressure	122.9±17.3	130.6±14.3	136.7±14.2*
Mean arterial pressure	93.7±13.3	98.8±11.4	103.6±10.4*
Diastolic blood pressure	75.7±10.4	77.1±8.1	78.7±8.1
Pulse pressure	48.5±9.3	53.6±9.1	58.6±9.4*
Ankle blood pressure (mmHg)			
Systolic blood pressure	147.3±22.7	152.2±18.0	160.5±15.5
Mean arterial pressure	103.0±15.2	107.1±12.4	108.4±9.3
Diastolic blood pressure	80.1±11.7	81.7±9.0	81.7±8.5
Pulse pressure	66.8±14.1	72.6±10.2	78.7±12.5*†
Ankle-brachial index	1.23±0.14	1.17±0.15	1.26±0.18

SD=standard deviation

* p<0.05 versus sedentary, † p<0.05 versus hypertension

lower BMI and waist circumference than the hypertensive-diabetic (p<0.001) and the hypertensive group (p=0.003). Education level of the sedentary group was significantly higher than the hypertensive-diabetic group (p=0.034). The hypertensive-diabetic group had significant higher fasting blood glucose than the other groups (p<0.001).

Table 2 shows the hemodynamic data. The hypertensive-diabetic group had higher brachial SBP (p=0.002), mean arterial pressure (MAP) (p=0.002), and pulse pressure (PP) (p<0.001) than the sedentary group. Ankle PP of hypertensive-diabetic group was higher than the hypertensive and the sedentary group (p<0.001).

The arterial stiffness data is shown in Figure 1. The brachial-ankle PWV (baPWV) of the hypertensive-diabetic group were significantly greater than the hypertensive group (p=0.021) and the sedentary group (p=0.004). In contrast to arterial stiffness data, FMD was not significantly different among the three groups. Nevertheless, the hypertensive-diabetic group showed the trend of lower FMD than the sedentary group (p=0.07) (Figure 2).

As shown in Table 3, there were no significant differences in MOCA score and DST among the three groups. The hypertensive-diabetic patients spent longer time in TMT-B and RT than the other groups (p=0.008). Hypertensive-diabetic patients spent more time in TMT-A than sedentary participants (p=0.037).

MOCA was negatively related with brachial SBP (r=–0.28, p=0.030), MAP (r=–0.28, p=0.041), and PP (r=–0.33, p=0.005). TMT-A was related with

Table 3. Cognitive function tests

	Sedentary (n=23); mean±SD	Hypertensive patient (n=25); mean±SD	Hypertensive-diabetic patient (n=23); mean±SD
Montreal cognitive assessment	23.1±4.3	21.4±3.2	21.9±4.1
Trail making test (Part A) (seconds)	31.6±13.7	34.8±16.3	45.1±24.2*
Trail making test (Part B) (seconds)	48.1±33.8	44.1±26.4	108.3±91.2*†
Digit span test	3.9±1.3	3.7±1.1	3.8±1.4
Reaction time test	0.4±0.1	0.5±0.3	0.6±0.3*†

SD=standard deviation

* p<0.05 versus sedentary, † p<0.05 versus hypertension

Table 4. Correlation between arterial stiffness, hemodynamic, blood glucose and cognitive function tests

	MOCA	TMT-A	TMT-B	DST	RT
baPWV	–0.09	0.02	0.15	0.01	0.32*
Brachial-SBP	–0.28*	0.22	0.13	–0.23	0.28*
Brachial-MAP	–0.28*	0.20	0.15	–0.28*	–0.25*
Brachial-DBP	–0.14	0.15	0.23	–0.19	–0.11
Brachial-PP	–0.33*	0.21	0.00	–0.23	0.35*
Ankle-SBP	–0.13	0.20	0.12	–0.12	0.21
Ankle-MAP	–0.15	0.26*	0.13	–0.16	0.19
Ankle-DBP	–0.07	0.13	0.21	–0.13	–0.02
Ankle-PP	–0.11	–0.15	–0.01	–0.13	0.30*
FBS	0.04	0.25	0.27	–0.10	0.29*

MOCA=Montreal Cognitive Assessment; TMT-A=trial making test A; TMT-B=trial making test B; DST=digit span test; RT=reaction time; baPWV=brachial-ankle pulse wave velocity; SBP=systolic blood pressure; MAP=mean arterial pressure; DBP=diastolic blood pressure; PP=pulse pressure; FBS=fasting blood glucose

* p<0.05 was considered statistically significant

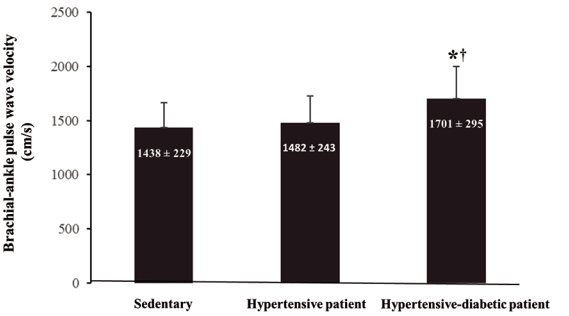

Figure 1. Brachial-ankle pulse wave velocity.

* p<0.05 versus sedentary, † p<0.05 versus hypertension

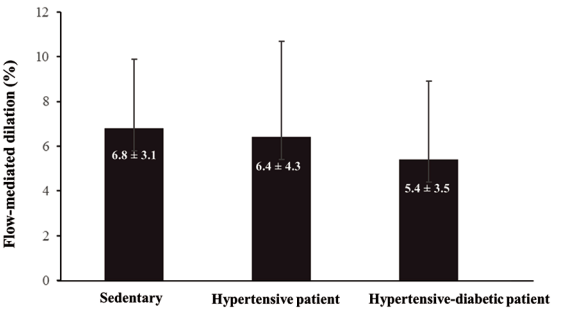

Figure 2. Flow-mediated dilation.

ankle MAP (r=0.26, p=0.036). DST was negatively related with brachial MAP (r=–0.28, p=0.020). RT was positively related with baPWV (r=0.32, p=0.009), brachial SBP (r=0.28, p=0.018), MAP (r=0.25, p=0.046), and PP (r=0.35, p=0.002). Level of fasting blood sugar was not significant related with any cognitive tests except reaction test (r=0.291, p=0.040). Brachial DBP, ankle SBP, and ankle DBP were not significantly related with any cognitive tests (Table 4).

Discussion

This is the first study, to the authors' knowledge, to investigate whether arterial stiffness and endothelial function could be a determinant of cognitive impairment in patients with HT, and whether the concomitant presence of T2DM might influence this relationship. The salient finding of the present study is that the coexisting of HT and T2DM worsens arterial stiffness more than in the hypertensive patients. Similar to the present study, Tedesco et al (2004) found coexisting HT and T2DM patients had higher arterial stiffness level than the healthy participants and those with one disease[11]. In addition, the hypertensive-diabetic patients had poor performance of cognitive functions particularly in executive function and information processing speed domains when compared with hypertensive patients.

The present study explored the role of arterial stiffness as a predictor of cognitive functions in hypertensive patients with T2DM but not in hypertensive patients without diabetes. Therefore, high blood sugar level might be more important affecting stiffening of arteries than high blood pressure. Reduction of insulin receptors in chronic

hyperglycemia is related to nitric oxide inactivation, stimulating inflammatory mediator, promoting vascular smooth muscle cell migration, decreasing arterial wall compliance, and developed arterial stiffness[12]. PWV, index of arterial stiffness in hypertensive patients were similar to sedentary healthy participants. The present study findings are in contrast with the previous review study showing the relationship between HT and arterial stiffness[13]. Blood pressure lowering drugs could be one factor that caused resembled PWV in hypertensive participants. Safar et al concluded that blood pressure lowering drugs can reduce both central and peripheral blood pressure, especially central PP that affected arterial stiffness reduction and wave reflection change[14]. In contrast, previous studies indicated that antihypertensive drugs reduced brachial SBP, brachial PP, and aortic PP after 10-weeks treatment but did not significant change in aortic arterial stiffness[15,16].

Although, the endothelial function was not different between the three groups, the hypertensive-diabetic group showed the trend of lower FMD than the sedentary group (p=0.07). The concomitance of two risk factors may cause a deleterious effect on nitric oxide dependent vasodilation of conduit arteries. Increasing insulin resistance and high blood pressure cause downregulation of insulin signaling, decreasing eNOS activation, promoting pro-atherogenic formation, and developing endothelial dysfunction. The hypertensive-diabetic patients tend to have impairment of endothelial function; however, this was not as worse as found in vascular dementia patients[17].

In term of cognitive function, the results of the present study demonstrated that hypertensive-diabetic patients had poor performance of cognitive functions particularly in attention, executive function, and information processing speed domains. The previous evidence showed the similarity as the present study. A review of longitudinal studies represented that increasing blood pressure was associated with a cognitive decline[18]. High blood pressure in middle aged is an important risk factor contributing to a cognitive decline and developing dementia that almost affected global cognition, executive function, and information processing speed, but was less related with worsening in memory[19]. Moheet et al concluded that type II diabetes was related to mild to moderate cognitive decline, particularly in memory, psychomotor speed, and executive function domains[20]. Although the HT-diabetic patients had poor performance in several domains of cognitive functions, theses were not as severe as MCI patients. Thus, the current study demonstrated early detection of cognitive impairment in the middle-aged HT-diabetic patients.

In addition, the correlation results represented that blood pressure variables, glucose level, and PWV were associated with cognitive function in middle aged HT or diabetes patients. The possible explanation is that high blood pressure level is associated with reducing total brain volume, especially in cortical, and hippocampal legions, decreased of cerebral blood flow, greater white matter hyper-intensity[19]. Moreover, hyperglycemia leads to neuronal damage, reduction of cerebral blood flow, and brain atrophy[21].

There are limitations in the present study. The cross-sectional design did not allow the authors to determine whether the association between arterial stiffness and cognitive functions shown in hypertensive diabetic patients reflected a cause-effect relationship. Further prospective and mechanistic studies are required to explain the present findings.

Lipid and lipoprotein profile are one of the risk factors of impaired vascular function and cognitive function[22]. Although lipid and lipoproteins in the sedentary group were high, the results showed better vascular functions and cognitive functions than the other groups according to setting hypothesis.

Conclusion

The present study results suggest that the hypertensive-diabetic patients had more risks to cognitive dysfunction than the middle-aged hypertensive patient and the sedentary participants. The mechanism that plays a key role in cognitive impairment in hypertensive patient with T2DM is arterial stiffness.

What is already known on this topic?

HT and T2DM are associated with arterial stiffness, endothelial dysfunction, and MCIs.

What this study adds?

A novelty of the study is the demonstration of an additive effect of HT on T2DM in arterial stiffness and cognitive dysfunction in middle-aged and young old adults.

Trial registration

Thai Clinical Trials Registry, TCTR 20190830001.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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