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Effects of hypertension on cerebral cortical thickness alterations in patients with type 2 diabetes

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ABSTRACT

Aims: Although hypertension (HTN) is the high comorbidity of Type 2 diabetes mellitus (T2DM) and known to be a vascular risk factor for brain damage, the effects of HTN on brain function in T2DM patients are not well understood. Present study was performed to investigate whether HTN might accelerate the Cerebral cortical thickness (CT) alterations in patients with T2DM.

Methods: We enrolled 35 participants with only T2DM, 25 T2DM patients with HTN (HT2DM) and 28 healthy controls (HCs). The cognitive function was assessed and brain image data was collected then the CT was calculated for each participant. Partial correlations between the CT of each brain region and standard laboratory testing data and neuropsychological scale scores were also analyzed. Multivariable regression analysis was performed to evaluate the vascular risk factors and brain regions with different CT in HT2DM patients.

Results: Cognitive impairment is associated with thinning of the cerebral cortical thickness reduction in T2DM patients. CT thinning in the left inferior parietal lobe, left posterior cingulate and right precuneus were observed in HT2DM group relative to only T2DM group. Furthermore, the CT decreasing in the right precuneus was negatively correlated with duration of HTN.

Conclusion: The current study revealed that coexistent HTN may accelerate the CT reduction in T2DM patients.

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1. Introduction

In 2013, a large cross-sectional survey based on 170, 287 people in China showed that the overall prevalence of total

diabetes was up to 10.9% [1]. Previous study showed that type 2 diabetes mellitus (T2DM) increased the risk of various complications in multiple organs, including the brain [2]. T2DM related complications in the brain may accelerate cognitive

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dysfunction and even increase the risk of dementia [3,4]. We have recently shown that T2DM is associated with cerebral cortical thickness (CT) reduction and that CT reduction may explain the association between T2DM and cognitive dysfunction [5]. Although the pathways leading to of CT reduction in T2DM are unknown, however, HTN is likely to play a contributory role.

People with T2DM and hypertension (HTN) are well-known highly prevalent risk factors for vascular disease in adults and have an increased risk of vascular mortality compared with those with either condition alone [6]. T2DM is often accompanied by HTN and about 60% of patients with T2DM have HTN [7]. In addition, previous study has shown worse cognitive function when combined HTN and T2DM is present, as compared to their separate effects [8]. There could be a direct effect of the vascular factors resulting in microvascular, metabolic-toxic or other changes in the brain, which ultimately could result in cognition impairment. Furthermore, Blood Pressure is associated with cerebral blood flow decrease in Patients With T2DM [9].

Individuals with HTN and T2DM have been shown to have thinner CT than controls [10,11]. However, the effects of high blood pressure or diabetes on the cerebral cortex are different. A previous study of the brain found that in T2DM patients, the atrophic cortical areas were mainly distributed in the frontal lobe, including the right superior frontal gyrus and left paracentral lobule [12], whereas HTN was found to associate independently with diffuse cortical thinning of the frontal, temporal, and occipital lobes [13,14]. In addition, A recent finding that T2DM and HTN show the most consistent association among all types of brain tissue types [15]. The precise mechanism of blood pressure or diabetes on the brain atrophy has not been elucidated.

At present, only a study has been conducted to investigate the effect of HTN in CT alterations in patients with T2DM, which has no healthy control and reported reduced CT in the elderly T2DM patients with HTN, in relative to HTN [16]. However, little is known about how the concurrent presence of HTN and T2DM may affect the structure and function of the brain. Therefore, this study was conducted to examine whether HTN affects T2DM-related structural changes in the brain and cognitive dysfunction.

2. Experimental procedures

This study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Medical Ethics Committee of Kunming Medical University. All subjects provided written informed consent to participate in the study. The study was registered with ClinicalTrials.gov (NCT03564431).

2.1. Participants

Thirty-five patients with T2DM alone and 25 with HT2DM were recruited from among inpatients admitted to the Department of Endocrinology at the First Affiliated Hospital of Kunming Medical University between November 2017 and July 2018 (Table 1). T2DM was diagnosed according to the

1999 criteria proposed by the World Health Organization. A diagnosis of HTN was based on a SBP of ≥ 140 mmHg and/or DBP of ≥ 90 mmHg or the use of antihypertensive medications. Currently, the arterial blood pressure monitoring (ABPM) criteria for a diagnosis of HTN include mean SBP/DBP values of $\geq 130/80$ mmHg over 24 h, $\geq 135/85$ mmHg over a day and $\geq 120/70$ mmHg overnight. Blood pressure was recorded as the average of all measurements collected using a 24-hour ambulatory blood pressure monitor. Subjects with Secondary HTN were excluded. Individuals with T2DM who had developed chronic diabetic complications, including clinical diabetic nephropathy, proliferative diabetic retinopathy, painful or symptomatic diabetic neuropathy or major cerebrovascular or cardiovascular events, were excluded. Individuals were also excluded if they had a history of brain injury, alcoholism, epilepsy, Parkinson's disease, major depression or another psychiatric or neurological disorder. Those with severe depression (Hamilton Depression Rating Scale score ≥ 18), severe claustrophobia or contraindications to magnetic resonance imaging (MRI) were also excluded. Twenty-eight volunteers without T2DM, cardiovascular diseases including HTN, nervous system diseases, cognitive complaints or psychiatric illnesses were also recruited as healthy controls (HCs). The height, weight, and BMI were measured for each participant. All participants underwent neurological and neuropsychological testing and structural MRI examinations. All participants were right-handed and provided signed informed consent prior to the start of the study.

2.2. Measurements and assessments

The Mini-Mental State Examination (MMSE) [17], Digital Symbol Substitution Test (DSST) [18], Hamilton Depression Scale (HAMD) [19], and Hamilton Anxiety Scale (HAMA) [20] were administered to all participants by the same psychiatric professional. Standard laboratory tests were performed following an overnight fast of ≥ 10 h. Venous blood samples were collected from all participants at 8 AM. The standard laboratory tests included evaluations of the levels of Hemoglobin A1c (HbA1c), Fasting Plasma Glucose (FPG), fasting C-peptide, fasting insulin, triglycerides (TGs), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and C-reactive protein (CRP).

2.3. MR image acquisition

All imaging data were obtained on a 3-T Trio MRI system (GE DISCOVERY 750W 3.0T) equipped with a 64-channel phase-array head coil. The subjects were requested to remain calm, keep their eyes closed and avoid any movement during the image acquisition period. Plain T1- and T2-weighted scans were performed to eliminate significant structural abnormalities. Subsequently, a 3-dimensional volumetric structural MRI scan sequence was acquired using a fast-spoiled gradient recalled acquisition (FSPGR). The following parameters were set: rotation time (TR)/echo time (TE): 8.7/3.2 ms, slice thickness: 1.0 mm, field of view (FOV): 256 mm \times 256 mm, matrix size: 256 \times 256, flip angle: 12°, slice number: 160 with no gap and scan duration: 4 min, 23 s. All sections were acquired parallel to the anterior–posterior commissure line.

Table 1 – Characteristics of study participants.

Characteristic	HCs (n = 28)	T2DM (n = 60)	p value	T2DM		
				NTN (n = 35)	HTN (n = 25)	p value
Demographic characteristic						
Age, mean (SD), years	50.5 (6.4)	51.4(7.3)	0.570	49.1 (6.0)	54.5 (8.5)	0.004
Sex (Male/Female)	15/13	43/17	0.095	27/8	16/9	0.265
Smoking, year	11.14 (13.6)	16.35 (15.2)	0.126	14.17 (14.3)	19.40 (16.3)	0.192
Drinking, year	3.23 (7.2)	7.48 (11.6)	0.085	6.94 (10.4)	8.24 (13.4)	0.674
Education level, year	10.86 (3.9)	11.02 (4.0)	0.862	11.19 (3.8)	10.79 (4.3)	0.932
Diabetes-related clinical characteristics						
Time since diagnosis of T2DM, mean (SD), years	–	6.70 (6.1)	–	5.26 (5.3)	8.64 (6.8)	0.044
HbA _{1c} , mean (SD),% (mmol/mol)	–	8.8 (2.4)	–	9.1 (2.5)	8.4 (2.2)	0.282
Fasting plasma glucose, mean (SD), mmol/l	4.87 (0.37)	7.32 (3.23)	<0.001	7.46 (3.29)	7.13 (3.20)	0.702
Fasting insulin, mean (SD), pmol/l	–	63.6 (33.2)	–	52.7 (26.7)	80.8 (36.4)	0.001
Fasting C-peptide, mean (SD), nmol/l	–	0.79 (0.39)	–	0.71 (0.38)	0.90 (0.37)	0.039
HOMA-IR, mean (SD) ^a	–	3.19 (2.56)	–	2.58 (1.78)	4.17 (2.28)	0.046
HOMA-beta cell function ^a , mean (SD),%	–	59.9 (59.3)	–	57.0 (44.3)	64.4 (48.6)	0.650
Hs-CRP, mean (SD), mmol/l	1.19 (1.60)	3.12 (4.9)	0.042	3.03 (5.61)	3.28 (3.29)	0.895
Anthropometric characteristics						
BMI, mean (SD), kg/m ²	22.7 (1.8)	25.5 (3.4)	<0.001	24.2 (2.6)	25.5 (2.5)	0.053
Blood pressure						
Time since diagnosis of HTN, mean (SD), years	–	–	–	–	2.97 (4.86)	–
Systolic, mean (SD), mmHg	117.2 (12.5)	122.0 (16.5)	0.183	114.2 (13.4)	138.2 (14.3)	<0.001
Diastolic, mean (SD), mmHg	77.4 (9.7)	78.1 (9.1)	0.722	75.5 (8.0)	83.1 (8.2)	0.002
Lipid profiles						
Total cholesterol, mean (SD), mmol/l	4.82 (0.67)	4.47 (1.03)	0.060	4.63 (1.06)	4.22 (0.97)	0.138
LDL-cholesterol, mean (SD), mmol/l	3.41 (0.66)	2.81 (0.81)	0.001	2.93 (0.85)	2.63 (0.74)	0.178
HDL-cholesterol, mean (SD), mmol/l	1.20 (0.35)	1.03 (0.26)	0.011	1.04 (0.25)	1.01 (0.29)	0.745
Triacylglycerol, mean (SD), mmol/l	1.61 (0.77)	2.57 (1.99)	0.002	2.61 (1.84)	2.53 (2.22)	0.884
Cognitive assessments						
Mini-Mental State Examination, mean (SD)	27.11 (3.24)	28.63 (3.52)	0.071	29.00 (3.02)	28.06 (4.21)	0.398
Digit Symbol Substitution Test, mean (SD)	45.85 (21.8)	31.11 (13.04)	0.001	33.27 (12.3)	28.06 (13.8)	0.211
Hamilton depression scale	3.89 (3.93)	3.81 (3.37)	0.928	3.31 (3.11)	4.59 (3.69)	0.227
Hamilton Anxiety Scale	3.54 (4.33)	4.53 (3.46)	0.286	4.23 (3.58)	5.00 (3.32)	0.483

T2DM, type 2 diabetes mellitus; HCs, healthy controls; NTN, Normotension; HTN, Hypertension; BMI, Body Mass Index; CRP, C-reactive protein; SD, Standard Deviation.

^a HOMA-IR and HOMA-beta cell function were calculated using the formula previously reported [26].

2.4. MRI preprocessing

MRI preprocessing was mainly performed as described in our previous report [21]. Cortical reconstruction and volumetric segmentation were performed using the FreeSurfer software package (version 5.3.0; available from <https://surfer.nmr.mgh.harvard.edu/fswiki/DownloadAndInstall/Download>).

The technical details of these procedures have been described previously [22]. Briefly, the implanted processing stream included motion correction, skull stripping, registration to Talairach space, normalization of intensity, segmentation of the white matter (WM) and gray matter (GM), extension of the cortical surface to the average sphere to locate both sides and the GM–WM boundary and automatic topology correction [23,24]. The transition of the GM/WM and the edges was indicated by detecting the maximum offset of the surface deformation intensity. Next, the entire cortex of each subject was identified to determine the accuracy of the segmentation. Each hemispheric cortex was automatically parcellated into 34 regions based on the 2006 Desikan–Killiany atlas, which subdivides the human cerebral cortex into standard gyral neuroanatomical regions [25]. The CT was then calculated as the shortest distance between the cortical surface and the GM–WM boundary. A cortical map was generated by calculating the average thickness of each cortex. The subjects were mapped at each vertex and the right and left hemispheres, and the data were mapped to the surface of a mean brain template to visualize data from the entire cortical surface. The FreeSurfer QA Tools (available from <https://www.freesurfer.net/fswiki/QATools>) was used to qualify all cortical parcellations.

2.5. Statistical analyses

All data were analyzed using the Statistical Package for Social Sciences, version 20.0 (SPSS, Inc., Chicago, IL, USA). All tests were 2-sided, and a P value <0.05 was considered statistically significant. Continuous data are presented as means [standard deviations (SD)] for normally distributed variables and as medians [interquartile ranges (IQR)] for all other variables. The variables were compared between groups using the t-test (normally distributed continuous variables), Kruskal–Wallis H-test (non-normally distributed continuous variables) or chi-square test (categorical variables). We further compared the demographic and clinical characteristics between patients with HT2DM and T2DM alone.

The average CT of the 34 regions in each hemisphere was extracted and entered into a general linear model (GLM). Subsequently an analysis of covariance (ANCOVA) was conducted to assess differences in the CT between the total T2DM patient group (combined HT2DM and T2DM alone groups) and HCs. For the sake of completeness, we further compared the thicknesses of the brain regions obtained in the previous steps between the HT2DM and T2DM alone groups after controlling for age as a covariate.

A partial correlation analysis was performed to compare the alterations in CT and diabetes-related clinical characteristics in the total T2DM and HT2DM groups. Again, age was adjusted as a covariate. The partial correlations between the

alterations in CT and cognitive scores were analyzed in both the total T2DM and HT2DM group, using age as a covariate.

A forced-entry vascular risk factor linear regression (SPSS) was performed to identify factors contributing to the observed changes in CT. These factors were classified as (1) non-modifiable, including age and sex, or (2) modifiable, including body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), HTN duration, diabetes duration, Hemoglobin A1c (HbA1c), homeostatic model assessment-insulin resistance (HOMA-IR) [26], homeostatic model Beta-cell function index (HOMA-beta) [26], total cholesterol (TC), triglycerides (TGs), low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). This model was adjusted for the non-modifiable factors. The results are presented as point estimates and 95% confidence intervals (CIs), in units appropriate to the risk factor and brain CT value.

3. Results

3.1. Differences in demographic and standard laboratory test parameters

The demographic and baseline characteristics of the study participants are shown in Table 1. The mean ages of the HCs and all T2DM patients were 50.5 and 51.4 years, respectively ($P = 0.57$). The mean ages of patients with T2DM alone and those with comorbid T2DM and HTN (HT2DM) were 49.1 and 54.5 years, respectively ($P = 0.004$). Compared with HCs, all patients with T2DM had higher levels of fasting plasma glucose (FPG; $P < 0.001$), triglycerides (TG; $P = 0.002$) and C-reactive protein (CRP; $P = 0.042$) and a higher body mass index (BMI; $P < 0.001$), as well as lower levels of low-density lipoprotein cholesterol (LDL-C; $P = 0.001$) and high-density lipoprotein cholesterol (HDL-C; $P = 0.011$). Compared to patients with T2DM alone, those with HT2DM had a longer duration of diabetes ($P = 0.044$), a higher homeostatic model assessment-insulin resistance (HOMA-IR) score ($P = 0.046$), higher systolic blood pressure (SBP; $P < 0.001$) and diastolic blood pressure (DBP; $P = 0.002$) values and higher fasting insulin ($P = 0.001$) and C-peptide levels ($P = 0.039$). No significant differences were found in Hemoglobin A1c (HbA1c) ($P = 0.282$) and HOMA-beta cell function ($P = 0.650$) between patients with T2DM alone and HT2DM patients. No significant inter-group differences were observed in the sex distribution, education levels, smoking habits, and drinking scores ($P > 0.05$).

3.2. Cognitive dysfunction in patients with T2DM

Compared with HCs, the total T2DM group had a lower Digital Symbol Substitution Test (DSST) score (45.8 vs 31.1, $P = 0.001$). By contrast, but the Mini-Mental State Examination (MMSE) scores did not differ significantly between the groups (27.1 vs 28.1, $P > 0.05$) (Fig. 1a, 1c). Compared with the T2DM alone group, the HT2DM group did not differ significantly in terms of DSST scores (33.3 vs 28.1, $P > 0.05$) or MMSE scores (29.0 vs 28.1, $P > 0.05$) (Fig. 1b, 1d). Similarly, there were no significant differences in the Hamilton Depression Scale (HAMD)

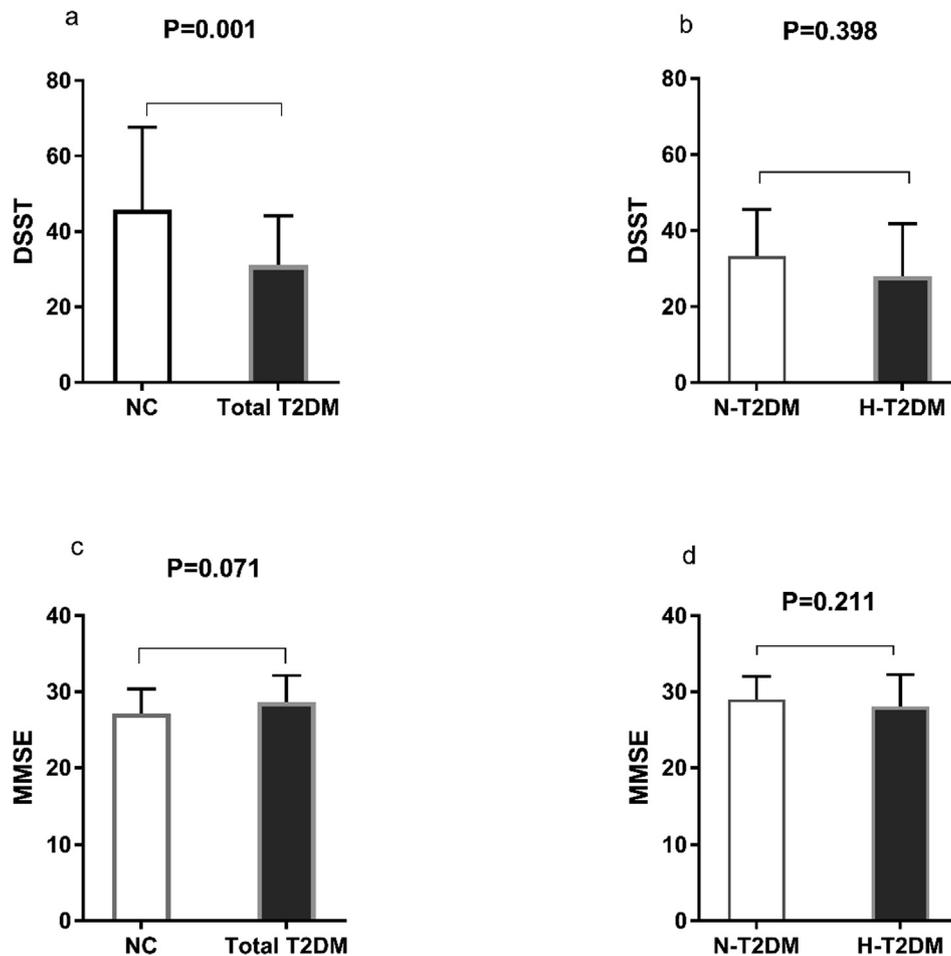


Fig. 1 – Neuropsychological scale scores among total T2DM patients, HC and N-T2DM, H-T2DM patients. (a and b) DSST among total T2DM patients, HC and N-T2DM, H-T2DM patients. (c and d) MMSE among total T2DM patients, HC and N-T2DM, H-T2DM patients. T2DM, type 2 diabetes mellitus; HCs, healthy controls; N-T2DM, Normotension-T2DM; H-T2DM, Hypertension-T2DM; DSST, Digit Symbol Substitution Test; MMSE, Mini-Mental State Examination.

and Hamilton Anxiety Scale (HAMA) scores ($P > 0.05$) between the groups (Table 1).

3.3. Abnormal cortical thickness in patients with T2DM

Compared with the HC group, patients in the total T2DM group exhibited alterations in CT. Specifically, reductions in CT were observed in the left paracentral (2.51 vs 2.43 mm, $P = 0.043$) and right paracentral lobule (2.54 vs 2.47 mm, $P = 0.01$), while an increase in CT was observed in the right pars triangularis gyrus (2.28 vs 2.35 mm, $P = 0.016$) (supplementary table, Fig. 2a). A negative relationship was identified between the CT of the right pars triangularis gyrus and the FPG score ($r = -0.315$, $P = 0.016$) in the total T2DM group (Fig. 3a).

Compared with the T2DM alone group, the HT2DM group exhibited statistically significant reductions in CT in the left inferior parietal lobe gyrus (2.38 vs 2.31 mm, $P = 0.028$), left posterior cingulate gyrus (2.59 vs 2.51 mm, $P = 0.036$) and right precuneus (2.40 vs 2.33 mm, $P = 0.010$) (supplementary table, Fig. 2b). Here, a negative correlation was identified between the CT of the right precuneus and the duration of HTN

($r = -0.453$, $P = 0.026$) in the HT2DM group (Fig. 3b). No significant differences were observed in CT of the left inferior parietal lobe, left posterior cingulate gyrus, right precuneus, and blood pressure levels including SBP and DBP ($P > 0.05$).

3.4. Vascular risk factors affecting the cortical thickness in the T2DM

Table 2 presents the associations of various vascular risk factors [body mass index (BMI), systolic blood pressure (SBP), HTN duration, total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), homeostatic model assessment-insulin resistance (HOMA-IR), homeostatic model Beta-cell function index (HOMA β), glycated hemoglobin (HbA $_{1c}$)] with changes in the brain CT in the HT2DM group relative to the T2DM alone group. In the multivariable models, the duration of HTN [-0.016 mm/year (95% confidence interval [CI], -0.028 to -0.005), $P = 0.012$], TC [-0.339 mm/mmol/L (95% CI, -0.51 to -0.169), $P = 0.002$], LDL-C [0.337 mm/mmol/L (95% CI, 0.15 to 0.525), $P = 0.003$] and HOMA-IR [-0.065 mm/HOMA-IR unit (95% CI, -0.1 to -0.03),

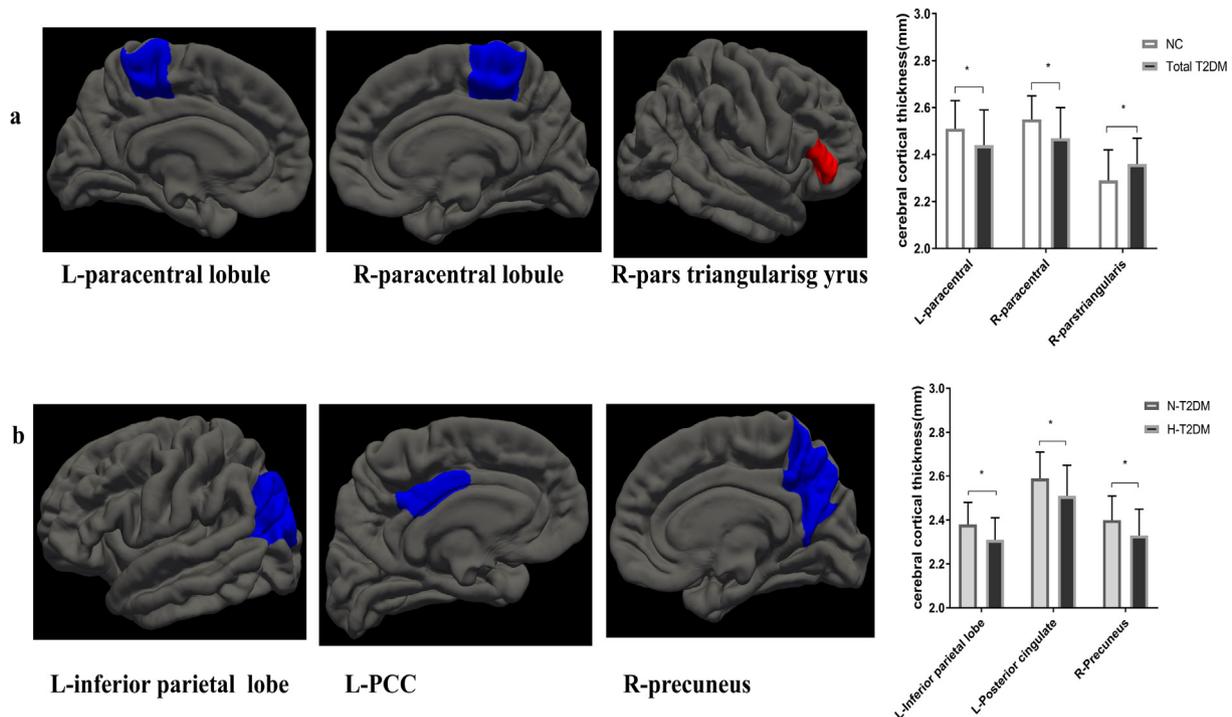


Fig. 2 – Cortical thickness abnormalities were identified using a general linear model (GLM) with age as covariate among groups. (a) Significant difference between total T2DM patients and HCs. The blue area shows the decreased left paracentral and right paracentral lobule. The red area shows the increased right pars triangularis gyrus. (b) Significant difference between HT2DM patients and NT2DM patients. The blue area shows the decreased left inferior parietal lobe, left posterior cingulate gyrus and right precuneus, * $P < 0.05$. HCs, healthy controls; T2DM, type 2 diabetes mellitus; NT2DM, Normotension-T2DM; HT2DM, Hypertension-T2DM; PCC, posterior cingulate cortex; L, left; R, right.

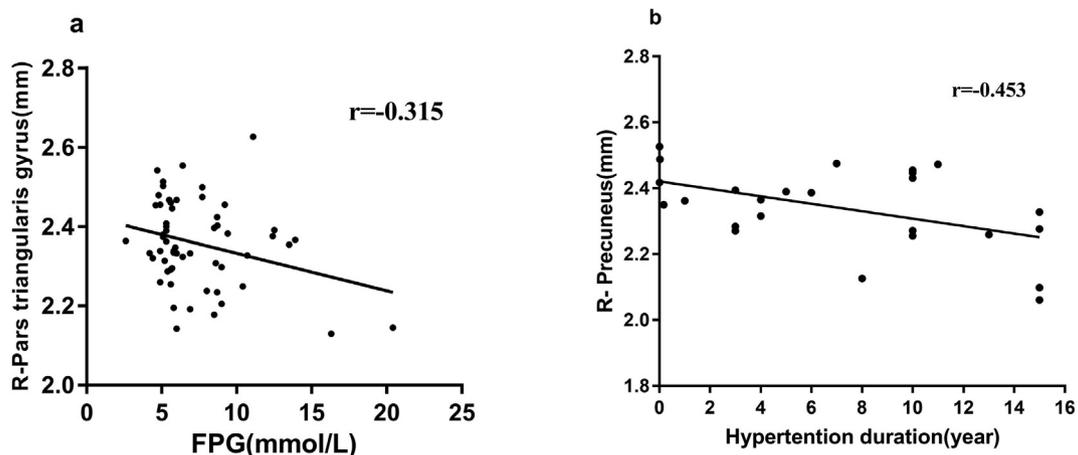


Fig. 3 – Partial correlations between abnormalities CT and standard laboratory testing data and neuropsychological scale scores. (a) Correlations between the right Pars triangularis CT and FPG data in the total T2DM patients. (b) Correlations between the right Precuneus CT and HTN duration data in the H-T2DM patients. The partial correlation coefficient (r) was corrected for age. * $P < 0.05$. cortical thickness, CT; T2DM, type 2 diabetes mellitus; HCs, healthy controls; N-T2DM, Normotension-T2DM patients; H-T2DM, Hypertension-T2DM patients; FPG, Fasting plasma glucose; L = left, R = right.

$P = 0.003$] were found to correlate significantly with a reduction in CT in the left posterior cingulate gyrus. A reduction in CT in the right precuneus was found to correlate with the duration of HTN duration [-0.014 mm/year (95% CI, -0.023 to -0.004), $P = 0.013$], total cholesterol [-0.235 mm/mmol/L

(95% CI, -0.379 to -0.091), $P = 0.006$], TG (0.032 mm/mmol/L (95% CI, 0.002 to 0.061), $P = 0.038$], LDL-C [0.246 mm/mmol/L (95% CI, 0.088 to 0.404), $P = 0.007$], HOMA-IR [-0.064 mm/HOMA-IR unit (95% CI, -0.093 to 0.034), $P = 0.001$] and HbA1c [0.057 mm/%HbA1c (95% CI, 0.018 to 0.097), $P = 0.01$] (Table 2).

Table.2 – Association between vascular risk factors and brain CT in HT2DM.

Coefficients	Multivariable-Adjusted Point Estimate (95% CI)		P Value
Brain CT	R2 = 0.848		0.029
L-Posterior cingulate gyrus/mm			
(Constant)	3.201	1.933 to 4.468	0
Hypertention duration, year	-0.016	-0.028 to -0.005	0.012
BMI	-0.017	-0.046 to 0.012	0.224
Systolic blood pressure, mmHg	-0.003	-0.008 to 0.001	0.128
Total cholesterol, mmol/L	-0.339	-0.51 to -0.169	0.002
Triglyceride, mmol/L	0.024	-0.011 to 0.059	0.155
LDL cholesterol, mmol/L	0.337	0.15 to 0.525	0.003
HOMA-IR	-0.065	-0.1 to -0.03	0.003
HOMAbeta	0	0 to -0.001	0.229
HbA1c (%)	0.071	0.024 to 0.117	0.008
Brain cortical thickness R-precuneus/mm	R2 = 0.843		0.032
(Constant)	2.383	1.311 to 3.455	0.001
Hypertention duration, year	-0.014	-0.023 to -0.004	0.013
BMI	-0.01	-0.034 to 0.015	0.386
Systolic blood pressure, mmHg	0.001	-0.003 to 0.005	0.441
Total cholesterol, mmol/L	-0.235	-0.379 to -0.091	0.006
Triglyceride, mmol/L	0.032	0.002 to 0.061	0.038
LDL cholesterol, mmol/L	0.246	0.088 to 0.404	0.007
HOMA-IR	-0.064	-0.093 to -0.034	0.001
HOMAbeta	0	0 to -0.001	0.135
HbA1c (%)	0.057	0.018 to 0.097	0.010

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; HOMAbeta, homeostatic model assessment of insulin Beta-cell function index. Model adjusted for nonmodifiable factors of age, sex and modifiable risk factors of hypertension duration, body mass index, systolic blood pressure, total cholesterol, triglyceride, LDL cholesterol, HOMA-IR, HOMAbeta and HbA1c. Exposure variables were available for HT2DM patients. The point estimate refers to the magnitude of change in the cortical thickness variable per unit change in the nonmodifiable and modifiable variables. HT2DM, Hypertension-T2DM.

3.5. Correlations between differences in CT and cognitive function in all T2DM patients and HT2DM patients

In the total T2DM group, a negative relationship was observed between the CT in the left paracentral lobule and the DSST score ($r = -0.375$, $P = 0.017$) (Fig. 4). No significant correlations were identified between any CT measures and cognitive scores ($P > 0.05$) in the HT2DM group.

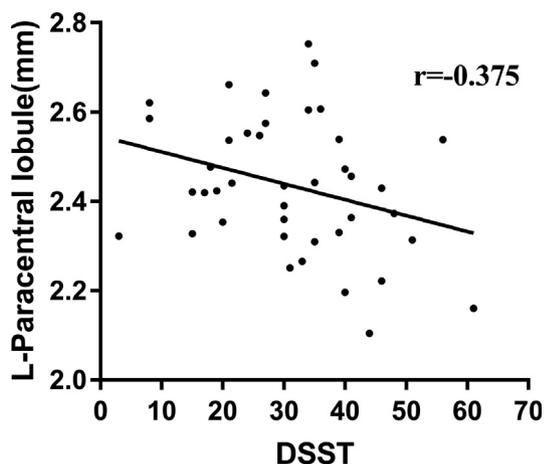


Fig. 4 – Correlations between the right Paracentral lobule CT and DSST scores in the total T2DM patients. The partial correlation coefficient (r) was corrected for age. DSST, Digit Symbol Substitution Test; CT, cortical thickness.

4. Discussion

In this study, we used FreeSurfer to investigate the potential association between changes in the CT and HT2DM. Our research disclosed several findings. Compared with HCs, the total T2DM patients exhibited a reduction in CT in the paracentral lobule, which was found to correlate negatively with cognitive performance. Most importantly, we found that hypertension exacerbated this reduction in CT in HT2DM patients and that a longer duration of HTN was associated with an increased reduction in the CT of the right precuneus. We also found that several vascular factors (duration of HTN, HOMA-IR and TC) were negatively associated with the CT in HT2DM.

Previous studies of the cortical gray matter (GM) thickness have emphasized the bidirectional nature of paracentral lobule decreases in patients with T2DM [6]. The paracentral lobule plays many important roles in the brain, particularly with regard to thought and planning. Indeed, we identified a negative correlation between the CT in the left paracentral lobule and the score on the DSST. Surprisingly, we observed an increased CT in the right pars triangularis in the total T2DM patient group. We hypothesized that the increased CT of right pars triangularis gyrus may represent a compensation for the cognitive decline. The pars triangularis has many important functions in the brain. It is involved in higher cognitive functions such as memory, emotion, and learning [5]. And, DSST score is a neuropsychological test that tests advanced cognitive functions such as memory and response rate. In current

study, DSST scores in total T2DM patients were significantly lower than in HCs. Our results suggest that CT increased of the right pars triangularis gyrus may be an intermediate compensatory phase associated with advanced cognitive function or a sign of functional reorganization as a compensatory response to early mild brain damage. Previous study also has found that the CT increased was observed in the T2DM with mild cognitive impairment (MCI) patients, Compared with the T2DM without MCI group [5]. In this study, significant negative correlation also was found between the CT of in the right parstriangularis and fasting plasma glucose (FPG). This result suggests that with increased severity of the illness, the CT of right pars triangularis gyrus may decrease due to decompensation or functional reorganization failure. Longitudinal studies are needed to confirm this hypothesis in the future.

HTN is known to contribute to the development of brain complication of T2DM. However, it is unclear whether the changes in CT can be attributed to T2DM alone, which is frequently comorbid with HTN, or the combined effect of these diseases. The results of the current study suggest that the comorbidity of T2DM and HTN contributes to a reduction in CT and that these changes exceed those that arise in patients with T2DM alone. Specifically, the combined effects of T2DM and HTN had deleterious effects on CT in the left inferior parietal lobe, left posterior cingulate gyrus and right precuneus. A previous study observed reductions in CT in the posterior cingulate, precuneus, superior and middle frontal and middle and inferior temporal regions of patients with comorbid T2DM and HTN, compared to patients with HTN alone [16]. Additionally, we found that the decrease in CT in the right precuneus correlated negatively with the duration of HTN in HT2DM patients. Our study suggests that changes in brain structure are associated with elevated long-term blood pressure. Recent research has been demonstrated that sustained HTN in midlife to late life were associated with increased risk for subsequent dementia [27]. In addition, Among adults with HTN, treating to a systolic blood pressure goal of less than 120 mmHg compared with a goal of less than 140 mmHg did not result in a significant reduction in the risk of probable dementia [28]. Furthermore, Power et al found HTN 15 to 24 years before neuroimaging to be most relevant to current brain volumes and the pattern of HTN followed by hypotension may be particularly detrimental [29]. Our study highlights the potential benefit on brain health of effective screening and subsequent treatment for HTN from the time of onset in T2DM patients. The precuneus is associated with high-level parameters of cognitive function, including episodic memory, self-related information processing and various aspects of consciousness. A previous study observed that patients with comorbid T2DM and HTN often exhibited more severe cognitive dysfunction [30].

Regarding cognitive function, we did not observe any significant difference in the MMSE scores between total T2DM patients and HCs. By contrast, we observed a significant intergroup difference in the DSST scores. Furthermore, the CT in the left paracentral lobule correlated negatively with the DSST scores in the total T2DM group. Although the MMSE scale can effectively screen for cognitive impairment, it is less sensitive to mild cognitive dysfunction. By contrast, the DSST,

a neuropsychological test of advanced cognitive functions such as the memory and response rate, was found to detect early cognitive impairment in the brain at a higher level of sensitivity. Our study thus suggests that impaired advanced cognitive function may initially manifest during early-stage T2DM. HTN is a risk factor for cognitive dysfunction. Our study found that the DSST score was lower in the HT2DM group than in the group with T2DM alone, although this difference was not statistically significant. Our findings also highlight the need for an early intervention that targets HT2DM individuals with the intent to preserve their brain structure and cognitive function by reducing their blood pressure.

HTN, diabetes, dyslipidemia and obesity have all been associated with preclinical changes in brain structure. However, these findings have often been derived from studies of comprehensive risk scores or single isolated factors. In our study, we identified negative correlations of the duration of HTN, HOMA-IR and total cholesterol with thinning of the left posterior cingulate and right precuneus cortex through a multiple linear regression model analysis of patients with HT2DM. Surprisingly, however, we found that the HbA1c and LDL-C levels correlated positively with a reduction in the CT. Indeed, this study have found that HT2DM group had significant insulin resistance compared with T2DM group. In early stages of the T2DM, HOMA-IR may be a more accurate marker than HbA1c levels for estimating brain cognitive alterations and insulin resistance (as measured by HOMA-IR) was negatively associated with global mean thickness [31]. Leritz et al also observed that increasing LDL-C levels were associated with the thicken of CT in older people [13]. T2DM may affect cortical morphology through several mechanisms, including chronic hyperglycemia, repeated hypoglycemic episodes, vascular disease, inflammation and even the direct effects of insulin on the brain [32–34]. In our study, we also found that patients in the total T2DM group had a higher level of CRP, compared to HCs. Consistent with our findings, significantly higher CRP levels were observed in patients with T2DM compared to the healthy population [12]. This result suggests that neuroinflammation may lead to thinning of the CT in T2DM patients.

Some limitations of our study should be noted. First, this was a cross-sectional clinical study with a relatively small sample size. Second, the current study did not recruit patients with HTN alone. Additionally, this study used the MMSE and DSST, which are simple screening scales used to identify cognition function. Further longitudinal studies based on a more elaborate framework to better describe the independent and combined (additive, synergistic or interactive) effects of T2DM and HTN on the brain.

5. Conclusion

In conclusion, this study revealed decreases in CT in the left inferior parietal lobe, left posterior cingulate gyrus and right precuneus of patients with HT2DM. Furthermore, the duration of HTN was found to correlate negatively with a decrease in CT in the right precuneus. In other words, HTN may further exacerbate the T2DM-associated reduction in CT. These

results indicate that blood pressure control may be important to delay a reduction in cerebral CT and prevent cognitive decline in patients with T2DM.

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Declaration of Competing Interest

The authors declare no conflicts of interest.

Author contributions

LS and XX designed the study and experiments. LS and YC contributed to the drafting of the manuscript. YC and ZS contributed to the data analysis. LS edited the manuscript. FZ and YL acquired the magnetic resonance images. LS, YC, CZ, LJ, and YZ contributed to the clinical studies and data acquisition. All authors approved the final draft of the manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2019.107872>.

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