

Gray matter alterations and correlation of nutritional intake with the gray matter volume in prediabetes

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Abstract

The neurophysiology of prediabetes plays an important role in preventive medicine. The dysregulation of glucose metabolism is likely linked to changes in neuron-related gray matter. Therefore, we designed this study to investigate gray matter alterations in medication-naïve prediabetic patients. We expected to find alterations in the gray matter of prediabetic patients.

A total of 64 prediabetic patients and 54 controls were enrolled. All subjects received T1 scans using a 3-T magnetic resonance imaging machine. Subjects also completed nutritional intake records at the 24-hour and 3-day time points to determine their carbohydrate, protein, fat, and total calorie intake. We utilized optimized voxel-based morphometry to estimate the gray matter differences between the patients and controls. In addition, the preprandial serum glucose level and the carbohydrate, protein, fat, and total calorie intake levels were tested to determine whether these parameters were correlated with the gray matter volume.

Prediabetic patients had lower gray matter volumes than controls in the right anterior cingulate gyrus, right posterior cingulate gyrus, left insula, left superior temporal gyrus, and left middle temporal gyrus (corrected $P < 0.05$; voxel threshold: 33). Gray matter volume in the right anterior cingulate was also negatively correlated with the preprandial serum glucose level gyrus in a voxel-dependent manner ($r = -0.501$; 2-tailed $P = 0.001$).

The cingulo-temporal and insula gray matter alterations may be associated with the glucose dysregulation in prediabetic patients.

Abbreviations: ACC = anterior cingulate cortex, GMV = gray matter volume, MTG = middle temporal gyrus, PCC = posterior cingulate cortex, STG = superior temporal gyrus, VBM = voxel-based morphometry.

Keywords: cingulate cortex, gray matter, insula, prediabetes, temporal gyrus

1. Introduction

Diabetes is a chronic and disable illness which consisted of the following criteria as HbA_{1c} $\geq 6.5\%$: fasting preprandial glucose level ≥ 7.0 mmol/L or 2 hours oral glucose tolerance test ≥ 11.1 mmol/L.^[1] The age-standardized prevalence of type 2 diabetes increased from 4.7% to 6.5% for men and from 5.3% to 6.6% for women in Taiwan.^[2] Prediabetes is defined by an HbA_{1c} level of 5.7% (39 mmol/mL) to $< 6.5\%$ (48 mmol/mL) or a fasting

glucose value of 100 to < 126 mg/dL.^[3] The relationship between nutritional intake and diabetes, such as higher intake of total carbohydrate is correlated with the higher incidence of diabetes, is also an interesting topic in these years.^[4] The prevalence of prediabetes in the United States increased from 27.4% in 1999–2002 to 34.1% in 2007–2010.^[5] The prevalence and incidence of prediabetes in Taiwan seemed not to be well studied. From the perspective of preventive medicine, the study of

Editor: Bernhard Schaller.

Authorship: C-HL collected and analyzed the data and wrote the manuscript. Y-TW reviewed and edited the manuscript. S-HY contributed to the discussion and reviewed and edited the manuscript. Y-CH collected the data and contributed to the discussion.

Funding: The authors would like to acknowledge the grant support provided by the Taipei Tzu-Chi General Hospital project (TCRD-TPE-103-04). This project was also supported by a grant from the Cheng Hsin General Hospital and National Yang Ming University cooperative project (104F003C03). The authors also acknowledge MRI support provided by National Yang-Ming University, Taiwan, which is partly supported by the MOE plan for top universities.

Ethical approval: all procedures involving human participants in this study were performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: informed consent was obtained from all the individual participants included in the study.

The authors have no conflicts of interest to disclose.

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Medicine (2016) 95:25(e3956)

Received: 11 February 2016 / Received in final form: 21 May 2016 / Accepted: 25 May 2016

<http://dx.doi.org/10.1097/MD.0000000000003956>

prediabetes provides additional information regarding the pathophysiology of the brain prior to diabetes, which is beneficial for the prevention and treatment of diabetes. The study of gray matter volume (GMV) alterations in prediabetes is very rare, but important due to the recent increase in the prevalence of prediabetes.

Diabetes mellitus is a type of illness resulting from the dysregulation of glucose metabolism. The dysregulation of glucose metabolism is likely linked to alterations in neuron-related gray matter. Several studies have investigated gray matter alterations in diabetes. Musen et al found a loss of gray matter density in the temporal, frontal, and parietal regions of patients with type I diabetes and that hemoglobin A1C is negatively correlated with the gray matter density in diabetic patients.^[6] However, another study of type I diabetes did not find any significant alterations in the gray matter volume (GMV) of patients.^[7] Studies of type 2 diabetes found a lower GMV in the superior temporal gyrus, middle temporal gyrus, frontal region, and hippocampus.^[8,9] These studies showed a consistent pattern of alterations in the temporal and frontal regions. The anterior cingulate cortex, another part of the frontal cortex, has also been shown to play a role in the cognitive pathophysiology of diabetes.^[10]

GMV deficits are also associated with impairments in cognitive function.^[10] The frontal and temporal regions are specifically involved in cognition, which explains impairments in diabetes-related cognitive function.^[6] The diabetes-related unstable glycemic status is also related to the lower GMV in the temporal regions.^[7] Based on the above-described findings, we hypothesized that GMV alterations in the frontal and temporal regions of diabetic patients may be related to glucose dysregulation.

We designed this study to investigate the GMV alterations in medication-naïve prediabetic patients. Examination of previous studies of the gray matter of diabetic patients led us to hypothesize that prediabetic patients would have a lower GMV in the frontal and temporal regions of the brain.

2. Participants

We recruited prediabetic patients (all Taiwanese people) between 20 and 65 years of age, who were diagnosed based on the following criteria as a fasting blood sugar value of 100 to 126 mg/dL because that is the easiest approach to screen prediabetes in clinical

practice.^[3] The diagnoses were made by the family physicians from the Outpatient Department of Family Medicine, Taipei Tzu Chi Hospital. The exclusion criteria was also the same as our previous report.^[11] In total, 86 prediabetic patients were screened and 19 were excluded due to the above selection criteria. The MRI (magnetic resonance imaging) scans were performed on the enrolled subjects. In addition, the 24-h nutritional intake records were obtained on the day of enrollment, and the 3-day nutritional intake records were collected from participants via fax. The details about the nutrition calculation from the intake records were mentioned in the previous report^[12] and our study.^[11] The study protocol was approved by the Institute Review Board of Taipei Tzu Chi Hospital. The approval number was 02-XD14-043.

The healthy controls were enrolled from the Taipei Tzu Chi Hospital and from the National Yang-Ming University with approval from the Institute Review Board of the National Yang-Ming University. The selection criteria were the same as our previous report.^[11] The age range of controls was also 20 to 65 years old.

A total of 67 prediabetic patients and 56 controls were originally enrolled in this study. Three prediabetic patients and 2 controls were excluded due to imaging motion artifacts. No participants were excluded due to MRI machine incompatibility, such as metal implants and claustrophobia. All eligible subjects were screened for vascular lesions using lesion filling and no one was excluded due to this reason. Sixty-four prediabetic patients and 54 controls were included in the final analysis (Table 1). The sample size was calculated according to the confidence level was set as 95%, confidence interval was set as 4 % and population was set as 80.

2.1. Data acquisition

Structural MRI brain scans were obtained using the 3 T Siemens scanner (TRIO 3-T MRI, Siemens MAGNETOM, Germany) housed in the MRI Center at the National Yang-Ming University. The scans from the patients and controls were obtained with 3-dimensional fast spoiled gradient-echo recovery (3D-FSPGR) T1W1 (TR 25.30 ms; TE 3.03 ms; slice thickness=1 mm [no gap]; 192 slices; matrix=224 × 256; field of view: 256 mm; number of excitations=1; total scanning time: 5 minutes and 23 seconds).

Table 1

Demographic data of the participating patients and controls.

	Patients (N=64)	Controls (N=54)	Sig P (2-tailed), Zdf=116
Age, mean (SD), years of age	52.83 (9.71)	53.50 (7.94)	0.897, -0.130
Gender (number)	F (28), M (36)	F (24), M (30)	0.197
Body height, mean (SD), cm	163.81 (9.05)	165.11 (8.19)	0.335, -0.963
Body weight, mean (SD), kg	66.85 (13.29)	69.92 (14.33)	0.322, -0.990
BMI	24.45 (3.03)	25.02 (3.18)	0.343, -0.948
Educated years, mean (SD)	16.18 (0.51)	16.13 (0.64)	0.405, -0.832
Handedness	R (63), L (1)	R (53), L (1)	0.601
Glucose-AC, mg/dL, mean (SD)	111.08 (8.31)	87.07 (5.07)	0.001, -9.340
Cholesterol, mg/dL, mean (SD)	166.57 (29.42)	170.19 (27.52)	0.762, -0.303
Calorie, kcal, mean (SD)	1564.07 (431.87)	N/A	N/A
Carbohydrate, g, mean (SD)	226.48 (82.57)	N/A	N/A
Protein, g, mean (SD)	59.74 (24.40)	N/A	N/A
Fat, g, mean (SD)	57.99 (19.82)	N/A	N/A

BMI = body mass index, df = degrees of freedom, F = female, M = male, N/A = not applicable, N = number, SD = standard deviation, Sig P (significance of P value) was obtained from the Mann-Whitney U test for nonparametric independent 2-sample t test.

Table 2**Areas of GMV alterations in patients with prediabetes compared with normal controls.**

Group comparison	Significant regions	MNI coordinate <i>x y z</i>	Cluster voxels	Statistical significance (corrected)
NC > PA	Right ACC	12, -16, 48	36	$P < 0.05$
	Right PCC	16, -14, 44	167	$P < 0.05$
	Left MTG	-50, 4, -24	128	$P < 0.05$
	Left STG	-40, 4, -16	136	$P < 0.05$
	Left insula	-38, 10, -14	33	$P < 0.05$
PA > NC	Negative findings			

ACC=anterior cingulate cortex, GMV=gray matter volume, MNI=Montreal Neurological Institute, MTG=middle temporal gyrus, NC=normal controls, PA=patients, PCC=posterior cingulate cortex, STG=superior temporal gyrus. All the statistical significance reach the level of corrected $P \leq 0.05$ after multiple comparisons.

2.2. VBM processing procedures

We used the FSLVBM (FSL voxel-based morphometry) (<http://www.fmrib.ox.ac.uk/fsl/fslvbm/>, version 1.1) function of FSL (FMRIB Software Library; version 4.1.1) to compare the differences in GMV between the patients and healthy controls. The FSLVBM was developed by Douaud^[13] and it implemented a motion correction algorithm using a hybrid global-local optimization method to correct the motion bias.^[14]

The theory consists of the following 3 major steps: stripping of the skull or other nonbrain tissue; tissue-specific segmentation produce partial-volume images of the gray matter^[15]; and the brain was nonlinearly registered to the self-template. All the Jacobian-modulated and segmented gray matter images were concatenated and smoothed by Gaussian kernels (sigma 3 mm).^[16,17] The more details of VBM processing can be referred to our previous report.^[17]

2.3. Statistical analysis

Permutation-based nonparametric inference by Threshold-Free Cluster Enhancement (TFCE) method was used to compare GMV between the 2 groups.^[18] An independent 2-group *t* test with group as the main random factor was performed. We included the global brain volume, age, gender, body mass index, and years of education as covariates to control for possible confounding factors for the permutations. This procedure produced test statistic images and sets of *P*-value images. We used family wise error (FWE) *P* value to obtain results after multiple comparisons and find regions of GMV deficits. The statistical threshold was set to a FWE *P* value < 0.05 .

A correlation was performed between the preprandial serum glucose level, nutritional intake data (from the combined evaluation of 24-hours record and 3-day record), and GMV with age and gender as covariates (FWE corrected $P < 0.05$). In addition, nonparametric Spearman's rho correlation between different nutritional intake compositions was calculated. The regression test for the different nutritional intake compositions to predict the preprandial serum sugar level was performed to confirm the impact of nutritional intake on serum sugar levels. The correlation analyses were only performed for the prediabetic patients.

3. Results

3.1. Demographic data

No significant differences in handedness, educational level, gender, age, BMI, body height, body weight, and cholesterol between the patients and controls were found. The only parameter with significance between patients and controls was the preprandial glucose (glucose-AC) (Table 1).

3.2. Correlations between different nutritional intake compositions (nonparametric Spearman's correlation) in prediabetic patients

Total calorie intake from the food record demonstrated a significant correlation with total carbohydrate intake (Spearman's rho correlation coefficient = 0.864; 2-tailed $P < 0.001$) and total protein intake (Spearman's rho correlation coefficient = 0.864; 2-tailed $P < 0.001$). Total carbohydrate intake was also positively correlated with total protein intake (Spearman's rho correlation coefficient = 0.427; 2-tailed $P = 0.015$). The regression model also showed that total calorie (standardized coefficient = 1.384; $P = 0.014$), carbohydrate (standardized coefficient = 1.484; $P = 0.005$), and protein intakes (standardized coefficient = 0.583; $P = 0.017$) predicted preprandial serum glucose levels.

3.3. GMV alterations in prediabetes

The prediabetic patients had lower GMVs in the right anterior cingulate cortex (ACC), the right posterior cingulate cortex (PCC), the left insula, the left super temporal gyrus (STG), and the left middle temporal gyrus (MTG) (Table 2, Fig. 1). The resulting *t* test images were 1-tailed. No significant increases in the GMV were observed in the prediabetic group compared with the controls. Total GMV was negatively correlated with the serum glucose level ($r = -0.501$; 2-tailed $P = 0.001$) and total carbohydrate intake ($r = -0.427$; 1-tailed $P = 0.037$), with a correction for the global brain volume, age, and gender of the prediabetic group. In addition, the voxelwise analysis showed that the serum glucose level and total carbohydrate intake were negatively correlated with GMV in the right ACC (corrected $P < 0.05$; multiple comparisons; cluster size = 40 and 43, respectively).

4. Discussion

Our study showed significant GMV reductions in the ACC, PCC, STG, MTG, and insula of prediabetic patients. We replicated previous findings reported in the literature, such as the ACC, STG, and MTG,^[8-10] from previous studies of diabetes. Our results were in line with the findings of functional and cognitive alterations in the frontal and cingulate regions of diabetic patients.^[19,20] The study in whole brain volume of diabetic patients also showed that the reductions probably play a role in cognitive decline.^[21] However, our study did not enroll the diabetic patients and collect the cognitive data from the prediabetic subjects, which were the weak points of the present study. A prior study of diabetes found no significant alterations in brain volume.^[22] Only 1 previous study found smaller brain volumes in prediabetic patients using the automated segmenta-

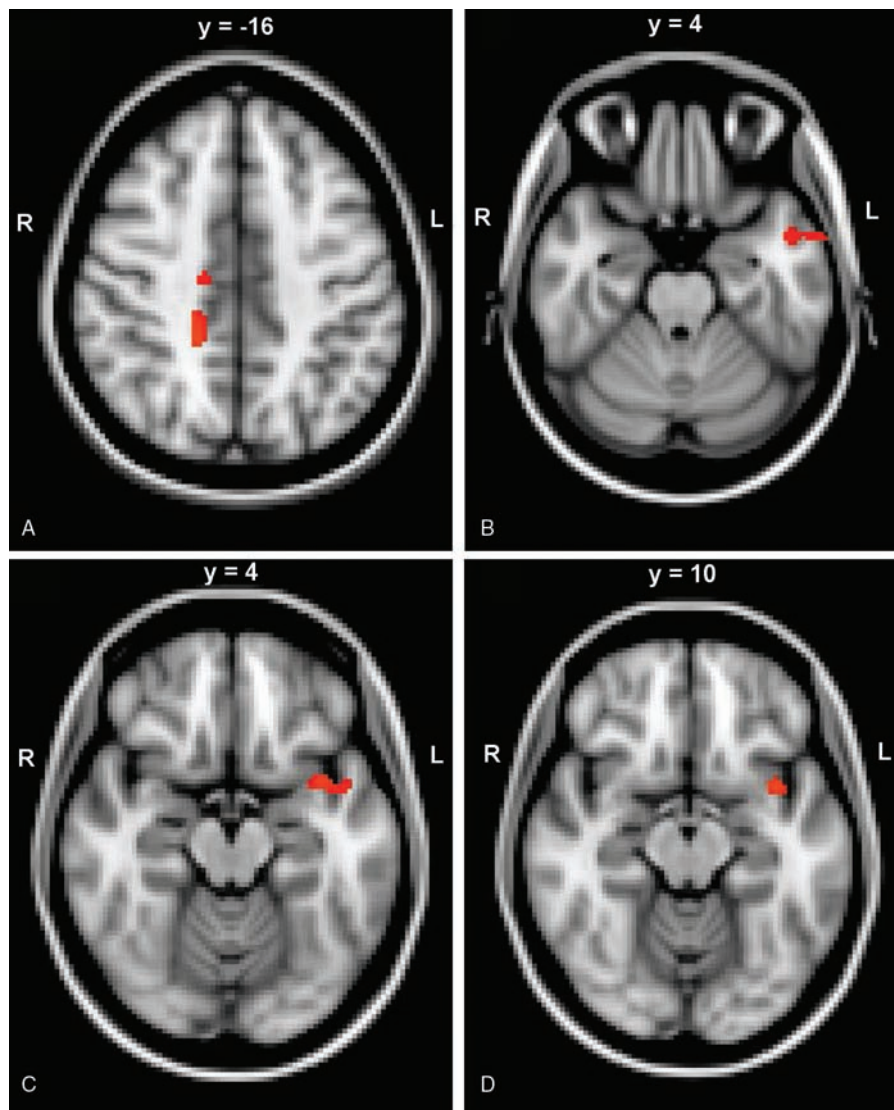


Figure 1. GMV alterations in the right ACC, right PCC (A), left MTG (B), left STG (C), and left insula (D) of prediabetic patients. ACC=anterior cingulate cortex, GMV=gray matter volume, MTG=middle temporal gyrus, PCC=posterior cingulate cortex, STG=superior temporal gyrus.

tion method.^[23] Our results provide the information for brain pathophysiology at the diabetes transition phase. We also found changes in 2 regions that have seldom been studied in previous diabetes research: the PCC and the insula. The study conducted by Hoogenboom et al suggested that the connectivity between the PCC and frontal regions would be impaired by diabetes, which may represent the different GMV alterations between prediabetes and diabetes.^[19]

GMV alterations in the ACC of diabetic patients have been mentioned in several reports.^[10,24,25] Kumar et al found that patients with type 2 diabetes presented significant GMV alterations in the prefrontal cortex, including the ACC.^[26] Another study also found that obese patients with type 2 diabetes exhibited significant GMV reductions in the frontal, temporal, and ACC regions.^[25] Alterations in the ACC, MTG, and frontal regions were also found in another study.^[10] These findings suggested the pattern underlying the neurodegeneration mechanism in type 2 diabetes.^[10] The ACC also works with the insula to result in sensory dysfunction in diabetes.^[27,28] The voxelwise analysis performed in our study also revealed a negative

correlation between the regional GMV of the right ACC, preprandial glucose levels, and total carbohydrate intake. This finding supports the hypothesis that the ACC plays a role in the brain pathophysiology of prediabetes.

Another region of the cingulate cortex, the PCC, was also found to present GMV alterations in the present study. This finding has not been mentioned in previous reports of diabetes. The decreased functional connectivity between the PCC and MTG was previously observed in diabetic patients.^[29] Another study also suggested dysfunction in the PCC and MTG, which are the core components of the default mode network.^[30] The cortical thickness of the PCC and MTG is also associated with the executive function of diabetic patients.^[31] The pattern of GMV alteration in the PCC may be more specific to prediabetes because no such results were found in previous studies of diabetes.

Many reports have indicated GMV alterations in the temporal lobe of diabetic patients.^[9,32–34] Several reports mentioned that GMV reductions observed in the temporal lobe may be associated with unstable glucose control.^[6,7] Insulin resistance is associated with reductions in brain size and a lower GMV in the temporal

lobe.^[35] The temporal lobe is likely influenced by the hyperglycemic effects of diabetes.^[6] Brundel et al also suggested that type 2 diabetes has significant effects on the GMV reductions in the temporal lobe.^[32] Other studies of diabetes also found significant reductions in the GMV of the STG and MTG.^[9,33] Another study showed that the GMV alterations in the MTG may predict mild cognitive impairment in type 2 diabetic patients.^[34] Our findings in the STG and MTG may be associated with glucose dysregulation in prediabetes.

The observed GMV alteration in the insula is likely associated with insulin resistance.^[36] These alterations also belong to the sensory matrix, which includes the cingulate cortex.^[27,37] The lower GMV in the insula may be associated with hyperglycemic effects, which are linked to the neuropathological process of gliosis.^[38] The insula connects the STG, ACC, MTG, PCC, and other brain regions to control sensory and cognitive functions.^[39] The findings in the insula may be the core issue for GMV alterations in prediabetes.

The correlations between GMV and carbohydrate intake or the preprandial serum glucose levels are another interesting finding of the present study. Our finding in ACC differs from the results of previous studies in obesity, which mostly found a correlation of carbohydrate intake with changes in the insula.^[40,41] A previous study of anorexia nervosa patients also revealed that GMV alterations in the ACC likely represent the pathophysiology underlying the dysregulation of food intake.^[42] The decelerated loss of GMV has been found to be associated with intensive glycemic treatment in diabetes. Intensive treatment decelerates the volume loss, particularly in regions adjacent to the frontal and temporal lobes.^[43] The severity of the frontal, temporal, and parietal gray matter alterations have also been associated with higher cumulative hyperglycemia.^[44] Glucose level and intake are also associated with GMV in the ACC.^[42] This concept supports the use of lifestyle interventions in the treatment of prediabetic or diabetic patients. An intensive lifestyle intervention is associated with a greater likelihood of achieving partial remission of type 2 diabetes compared with diabetes support and education.^[45] A randomized trial of medical nutrition therapy also supported the potential effects of decreasing the serum glucose level.^[46] Improvements in diet habits, regardless of the level of physical activity, have beneficial effects on insulin sensitivity and serum glucose levels.^[47] The correlation between nutritional intake or the serum glucose level and GMV in the ACC might be associated with this concept.

Resting-state functional MRI studies revealed that obesity is associated with alterations in the activities of the ACC, PCC, and insula.^[48] In addition, food intake has different impacts on functional connectivity between the insula and frontal cortex in obese and lean subjects.^[49] ACC-insula connectivity has also been correlated with carbohydrate intake.^[50] Task-related functional MRI reports also showed that fat intake is associated with changes in insula activity,^[51] protein intake is correlated with reward system changes,^[52,53] and glucose ingestion results in a decrease in hypothalamus signal.^[54] Our study results are also in line with previous functional MRI findings in the ACC and insula.

This study has several limitations:^[1] The relatively moderate sample size may limit the interpretation of our results. The lack of longitudinal study is also a concern. The results must therefore be interpreted with caution.^[2] The lack of a diabetes group limits a complete description and differentiation between prediabetes and diabetes. We did not enroll the group due to the concern of

medication-related bias, possible long-term hyperglycemic effects on brain and budget limits of present study. Another concern also arose from no comparison of food intake and impact of nutritional intake on gray matter volume between patients and controls due to lack of nutrition data in the control group.^[3] We focused on performing a brain structural analysis using MRI images, and thus, this is not a functional study, which may limit our ability to link the findings of the structural (GMV) results to the functional connectivity between the frontal regions and the insula, the regions found to present significant GMV alterations in the present study.^[4] The lack of an adjusted analysis (such as small volume correction in Statistical Parametric Mapping) due to the limitation of the FSLVBM analysis is a possible confounding factor.^[5] The lack of complete data for serum glucose-related parameters, such as the hemoglobin A1c and insulin glucose tolerance, would fail to exclude diabetes within this group of prediabetic patients. In addition, the lack of a biomarker for insulin resistance or sensitivity data, such as HOMA-IR, due to funding limitations limits the interpretation of the current results.

5. Conclusion

Cingulo-temporal and insula gray matter alterations may represent a possible indication of the brain structure of prediabetes. Further longitudinal studies comparing diabetes and prediabetes would help clarify the progression of GMV alterations in diabetic patients.

Acknowledgments

At last, we sincerely acknowledged the editing help from Heather S. Pixley, the managing editor of *Brain Imaging & Behavior*.

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