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Clinical Study

Cortical thinning in type 2 diabetes mellitus and recovering effects of insulin therapy

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ABSTRACT

The purpose of this study was to explore the brain structural changes in type 2 diabetes and the effect of insulin on the brain using a surface-based cortical thickness analysis. High-resolution three-dimensional T1-weighted fast spoiled gradient recalled echo MRI were obtained from 11 patients with type 2 diabetes before and after insulin therapy. The cortical thickness over the entire brain was calculated, and cross-sectional and longitudinal surface-based cortical thickness analyses were also performed. Regional cortical thinning was demonstrated in the middle temporal gyrus, posterior cingulate gyrus, precuneus, right lateral occipital gyrus and entorhinal cortex bilaterally for patients with type 2 diabetes mellitus compared with normal controls. Cortical thickening was seen in the middle temporal gyrus, entorhinal cortex and left inferior temporal gyrus bilaterally after patients underwent 1 year of insulin therapy. These findings suggest that insulin therapy may have recovering effects on the brain cortex in type 2 diabetes mellitus. The precise mechanism should be investigated further.

1. Introduction

Diabetes is a common metabolic disease with progressive end-organ damage in the cardiovascular system, kidneys, eyes, and the peripheral and central nervous systems (CNS). Previous studies demonstrated that patients with type 1 and type 2 diabetes can suffer from cognitive impairment [1–3], and our previous study also indicated that type 2 diabetes could lead to subtle brain structural changes (gray and white matter atrophy in the right temporal lobe) in patients who are free from dementia or macrovascular complications [4].

It has been demonstrated that insulin can prevent the pathogenic binding of Aβ oligomers to sites localized at the hippocampal nerve cell synapses, and this insulin protection is potentiated by rosiglitazone, an insulin-sensitizing drug used to treat type 2 diabetes [5]. Some studies have also indicated that insulin could have CNS-protective effects, presenting as the improvement of neural plasticity, learning and memory [6–8]. The current evidence for the brain protection mechanism of insulin has mainly been derived from basic and clinical research, and it is necessary to explore an *in vivo* quantitative evaluation method to investigate the protective effect of insulin on the brain.

Magnetic resonance (MR) imaging provides a good opportunity to explore structural changes within the diabetic brain. This can be achieved using rating scale methods [9,10] based on conventional MR images, voxel-based morphometry (VBM) [4] and cortical thickness measurement [11] based on the high resolution structural images. However, the detailed change of the regional cortical thickness over the whole brain after insulin therapy in type 2 diabetes mellitus is not clear.

The aim of this study is to evaluate both brain changes and the therapeutic effect of insulin therapy on the brain in patients with type 2 diabetes mellitus. We hypothesized that regional cortical thinning may occur in patients with type 2 diabetes mellitus, and insulin therapy could improve this cortical thinning. To address this hypothesis, we obtained MR images from patients with type 2 diabetes before and after 1 year of insulin therapy and measured the cortical thickness over the whole brain with a surface-based method. Then, we performed a cross-sectional analysis of the cortical thickness between patients with type 2 diabetes mellitus and normal controls as well as a longitudinal analysis covering the baseline (before insulin therapy) and follow-up (after 1 year of insulin therapy) of the patients.

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2. Methods

2.1. Subjects

Consecutive patients with type 2 diabetes were recruited from the diabetes outpatient clinic of the Department of Endocrinology at our hospital. Eleven patients with type 2 diabetes (aged 47–75 years, mean age 61.2 years) had to meet at least one of the following initial inclusion criteria [12]: a fasting plasma glucose (FPG) level > 7.0 mmol/l, a 2 hour plasma glucose level > 11.1 mmol/l during an oral glucose tolerance test, or a prior diagnosis of type 2 diabetes. The initial exclusion criteria included the following: any prior insulin therapy, a history of dementia, macrovascular complications (definite cerebral infarction or encephalomalacia), cranial trauma, CNS inflammatory disease, use of psychoactive drugs or hormones, dehydration, or overhydration. Of the 11 patients (three men, eight women), three had hypertension, with a duration between 2–30 years (mean 4.7 years); the diabetes duration ranged from 7 to 30 years (mean 13.9 years) at baseline. Brain atrophy was assessed through the use of a 10 level grading scale (grade 0 = normal, grade 9 = evident atrophy) according to ventricular size and sulcal width on conventional MR images [13], and the patients with grade 0 or grade 1 were included and other grades were excluded in this study. White matter lesions (WML) were also evaluated according to a 10 level scale from barely detectable white matter changes (grade 1) to extensive, confluent changes (grade 9) [13]; grade 0 (normal white matter) and grade 1 (barely detectable white matter changes) were included and the other grades were excluded in this study.

Eleven normal controls were recruited, and their ages ranged from 46 to 65 years (mean 56.2 years) with the sexes matched to the patient group (three men, eight women). The same exclusion criteria were applied to the normal controls, and none of the controls had a history of hypertension. All of the subjects were right-handed and underwent a Mini Mental State Examination (MMSE) [14] for the purpose of excluding dementia.

All patients received diabetes education and nutritional counseling at baseline and throughout the study in combination with insulin therapies (mixed protamine zinc recombinant human insulin lispro injection 25%, Protamine zinc recombinant insulin lispro 75%, made by Lilly France S.A.S, Fegersheim, France) for 1 year. The initial insulin doses were 0.4–0.6 international units (IU)/kg per day (50% before breakfast and 50% before dinner). The insulin doses were titrated following a planned schedule according to the preprandial glucose. The self-monitoring of blood glucose was performed twice a week in the first 4 weeks and once every 2 weeks in the following 8 weeks. The total insulin doses were decreased by 2 IU if the preprandial glucose was < 4.4 mmol/l and were maintained if the preprandial glucose was between 4.4–6.1 mmol/l. The total insulin was increased by 2 IU if the preprandial glucose was between 6.2–7.8 mmol/l, by 4 IU if the preprandial glucose was between 7.9–10 mmol/l, and by 6 IU if the preprandial glucose was > 10 mmol/l. During the following 9 months, the insulin doses were maintained, and a blood glucose test was performed when necessary. MR imaging was performed at baseline (before insulin therapy) and follow-up (after 1 year of insulin therapy). All of the subjects were right-handed and were also evaluated for body mass index (BMI), FPG, glycosylated hemoglobin (HbA1c, mmol/l), total cholesterol, triglyceride, urine protein (UP), creatinine clearance rate (Ccr), and mmSE score [14]. Written informed consent was obtained from all participants according to the approval of the ethics committee of the local Institutional Review Board.

2.2. MR imaging

All of the MR data were acquired on a 3.0 Tesla MR system (SIGNA EXCITE, GE Healthcare, Milwaukee, WI, USA), and a conventional eight-channel phased array head coil was also used. A high-resolution three-dimensional T1-weighted fast spoiled gradient recalled echo sequence generating 118 contiguous axial slices (repetition time [TR] = 6.3 ms, echo time [TE] = 2.8 ms, flip angle = 15, field of view [FOV] = 24 cm × 24 cm, matrix = 256 × 256, in-plane resolution of 0.9375 mm × 0.9375 mm, number of acquisitions [NEX] = 1) was used for VBM. Fast fluid-attenuated inversion recovery images (TR = 8802 ms, TE = 124.3 ms, inversion time = 2200 ms, slice thickness = 4 mm, gap = 1 mm, matrix = 256 × 256, FOV = 24 cm × 24 cm, NEX = 1) were obtained for general assessment purposes. The scan protocol was identical at baseline and follow-up for all subjects.

2.3. Data analysis

All of the MR imaging raw data were analyzed using the Freesurfer software (version 4.3.0) (http://surfer.nmr.mgh.harvard.edu/fswiki/FreeSurfer), which was run using the Linux 2.6.15-2.5 operating system (Red Hat, Inc., Raleigh, NC, USA).

The process of the whole brain cortical thickness mapping included the following procedures. (1) The raw structure images were reviewed to exclude images with artifacts, and the coordinate origin was set on the anterior commissure. (2) The segmentation of the white matter was performed [15,16] based on intensity information, then the volume was examined and regions containing more than one tissue type were marked for further processing. (3) The tessellation of the gray/white matter junction was performed [17]. (4) The inflation of the folded surface tessellation patterns was performed [17]. (5) The automatic correction of the topological defects in the resulting manifold was performed [18]. (6) The cortical thickness calculation was defined by the shortest distance between the gray/white matter surface and the pial surface based on coupled surface methods with submillimeter precision [19]. (7) The cortical thickness measurement was mapped to the inflated surface of the individual brain for a surface reconstruction. (8) The individual brain reconstruction was morphed and registered to an average spherical surface using a high-resolution surface-based averaging technique that aligned cortical folding patterns [20]. (9) All of the brain regions were labeled on the individual brain surface by the spherical transformation based on the Desikan–Killiany labeling system [21] and the Destrieux labeling system [22]. (10) The cortical thickness calculation was applied at each vertex, and the final volume and cortical thickness of each brain region was obtained [17,20].

The cross-sectional surface-based cortical thickness analysis was performed as follows. (1) The reconstructed brain surface was morphed and registered to an average spherical surface using a high-resolution surface-based averaging technique that aligned cortical folding patterns. (2) Smoothing was applied to the registered brain surface using a 10 mm Gaussian kernel. (3) An analysis of covariance (ANCOVA) was performed between the patients and the normal controls at each vertex of each hemisphere with age and BMI as covariants.

The longitudinal surface-based cortical thickness analysis was performed using the following steps. (1) Each individual's surface was mapped onto the average surface. (2) The difference between each of the pairs (baseline *versus* follow-up) was calculated for the average surface. (3) The differences were concatenated into one file. (4) The Gaussian smoothness was applied to the registered brain surface using a 10 mm Gaussian kernel. (5) One sample *t*-test was applied, and the null hypothesis was