Diffusion-weighted imaging of injuries to the visual centers of the brain in patients with type 2 diabetes and retinopathy

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Abstract. The present study aimed to investigate the ability of diffusion-weighted imaging (DWI) to identify injury to the visual centers of the brain in patients with type 2 diabetes with retinopathy. The study included 84 cases (63 patients with type 2 diabetic retinopathy and 21 healthy individuals) that were assessed using DWI. Diabetic patients were equally divided into three groups: Proliferative diabetic retinopathy (PDR), non-proliferative diabetic retinopathy (NPDR) and diabetic without retinopathy. The results demonstrated that individuals in the PDR group had significantly higher disease duration and glycated hemoglobin levels than the diabetic without retinopathy group ($P<0.05$). Apparent diffusion coefficient (ADC) values were significantly higher in functional brain areas of the PDR group compared with the NPDR group ($P<0.001$), whose values were significantly higher compared with the diabetic without retinopathy and control groups ($P<0.001$). In addition, glycated hemoglobin levels and disease duration were positively correlated with mean ADC values in the same functional areas of the brain. In conclusion, DWI-measured ADC values may be an effective indicator of brain dysfunction in individuals with type 2 diabetic retinopathy. DWI is able to assess brain injury in individuals with early diabetic retinopathy, which may make the diagnostic technique a useful predictor of early ocular disease.

Introduction

Diabetic retinopathy (DR), or damage to blood vessels of the retina, is a serious complication of diabetes. With the rising incidence of diabetes, DR is a common ocular fundus lesion and a leading cause of blindness and visual impairment (1-4). Worldwide prevalence of DR is 30-60% of individuals with diabetes and the prevalence in China is 35.6-63.5% (1-4).

Diffusion-weighted imaging (DWI) is a functional magnetic resonance imaging (MRI) technique that may be used in the central nervous system and is able to effectively provide information on pathological changes in the brain (5). DWI has become an important approach for radiographic diagnosis of brain lesions, including Parkinson's disease, tumors and cerebral apoplexy, as well as liver diseases (6-8). DWI may be used to calculate the apparent diffusion coefficient (ADC), a measure of brain injury, as it assesses diffusion of water molecules from blood vessels (9).

Early identification of DR is important to manage the disease and prevent progression to blindness. DR has been associated with injury to visual centers of the brain using DWI-measured ADC values (10). As the pathogenesis of brain injury is not fully understood, an effective approach to detect early injuries is required to improve the prognosis of individuals with DR.

The present study explored the correlation between DR and functional brain injury by comparing clinical data and weighted imaging from 63 individuals with type 2 diabetes and 21 healthy control individuals.

Subjects and methods

Subjects. The present study was approved by the Ethics Committee of Heilongjiang Provincial Hospital (Harbin, China) and informed consent was obtained from all subjects. The study cohort included 63 individuals with type 2 diabetes who were admitted to the Heilongjiang Provincial Hospital between April 2014 and April 2015. Of the 63 diabetic individuals, 31 were male (49.21%) and 32 were female (50.79%). Type 2 diabetes was diagnosed using the criteria established by the American Diabetes Association (11,12).

Based on funduscopy and fundus fluorescein angiography, diabetic individuals were divided into three groups. Group 1 included 21 proliferative diabetic retinopathy (PDR) cases, of which 11 were male (52.38%) and 10 were female (47.62%). Group 1 had a mean age of 54.95±10.86 years, a mean disease duration of 11.92±6.59 years and symptoms including vitreous hemorrhage and preretinal hemorrhage. Group 2 was composed of 21 non-proliferative diabetic retinopathy (NPDR) cases, of which 10 were male (47.62%) and 11 were

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female (52.38%). Group 2 had a mean age of 55.10±8.95 years, a mean disease duration of 8.12±3.71 years and symptoms including retinal hemorrhage and microangiomas. Group 3 included 21 diabetic without retinopathy cases, of which 10 were male (47.62%) and 11 were female (52.38%). Group 3 had a mean age of 54.73±6.05 years and a mean disease duration of 5.67±2.48 years.

The study also included 21 healthy volunteers who received examinations at Heilongjiang Provincial Hospital during the same period. Of the 21 healthy individuals, 11 were male (52.38%) and 10 were female (47.62%), with a mean age of 55.12±7.60 years. The diagnostic criteria for healthy volunteers were as follows: No type 2 diabetes; no cataracts, glaucoma or other eye lesions; no history of symptomatic cerebral apoplexy; and no other brain diseases. Regarding sex and age, there were no significant differences between the PDR, NPDR, diabetic without retinopathy and healthy control groups (P>0.05).

Data collection. Patients' blood glucose and glycated hemoglobin (HbAlc) levels were measured 10 h after fasting. Following this, fundus fluorescein angiography was performed. The immunoturbidimetry reagents for detection of HbAlc, matched quality control and calibration were manufactured by Randox Laboratories, Ltd. (Crumlin, UK). The tests were conducted on an automatic biochemistry analyzer (Hitachi 7600; Hitachi, Ltd., Tokyo, Japan) for quality control using fresh blood with anticoagulant ethylenediaminetetraacetic acid-K2 (Humica Weihai International Co., Ltd., Weihai, China).

MRI. A Philips Intera Master 3.0T superconducting MR scanner (Philips Medical Systems, Eindhoven, The Netherlands) was used for all MRI. Scan sequences included DWI, fluid-attenuated inversion recovery (FLAIR), T1-weighted imaging (T1WI) and T2-weighted imaging (T2WI). Scan parameters were as follows: DWI, echo time (TE)=60 msec and repetition time (TR)=1,924 msec; FLAIR, TE=136 msec and TR=8,700 msec; T1WI, TE=15 msec and TR=560 msec; and T2WI, TE=61 msec and TR=2,363 msec. Other parameters included: Field of view of 230 mm; matrix size of 128x128 mm; number of excitations of 2; slice thickness of 4 mm; number of slices of 25; scan time of 28 sec; slice gap of 1 mm; and diffusion sensitivity of 0 or 1,000 sec/mm^2.

ADC. ADC was used as an index of the magnitude of diffusion, and mean ADC values were calculated to analyze diffusion changes. As previously described, seven regions of interest (ROI) in the brain were selected, and their ADC values were measured (10). When selecting ROI, regions that contained cerebrospinal fluid and artifacts were avoided to preserve the accuracy of ADC values. The areas of measured regions included: Thalamus, 50-60 mm^2; visual cortex, 80-100 mm^2; corona radiate, 70-80 mm^2; dorsolateral frontal cortex; cingulate gyrus; dorsomedial frontal cortex; and orbitofrontal cortex, 30-40 mm^2 (Fig. 1).

Statistical analysis. Double data entry was performed using EpiData version 3.1 software (EpiData Association, Odense, Denmark) to create a data bank, and logic checks were performed with SAS version 9.2 software (SAS Institute, Inc., Cary, NC, USA). Statistical methods included analysis of variance (ANOVA) with Student-Newman-Keuls (SNK) method for comparison among multiple means and Spearman's rho correlation. MedCalc (version 16.2; MedCalc Software, Ostend, Belgium) was used to draw receiver operating characteristic (ROC) curves. Data are presented as the mean ± standard deviation. P<0.05 was considered to indicate a statistically significant difference.

Table I. Demographic and clinical features of patients.

Group	n	Disease duration, years	HbAlc, %
PDR	21	12.25±7.03[a]	9.71±2.73[a]
NPDR	21	8.24±3.59	7.92±1.68
Diabetic without retinopathy	21	5.57±2.73	7.13±0.84
F		8.47	6.95
P-value		<0.001	0.004

[a]P<0.05 vs. the diabetic without retinopathy group. Data are presented as the mean ± standard deviation. HbAlc, glycosylated hemoglobin; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy.

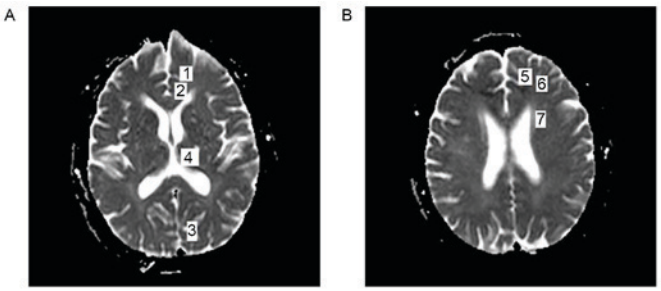

Figure 1. Measured areas of functional brain ROI. (A) ROI 1-4, including orbitofrontal cortex, cingulate gyrus, visual cortex and thalamus, respectively. (B) ROI 5-7, including dorsomedial frontal cortex, dorsolateral frontal cortex and corona radiate, respectively. ROI, regions of interest.

Results

Comparison of disease duration and HbAlc levels. ANOVA demonstrated that disease duration (P<0.001) and HbAlc levels (P=0.004) were significantly different among the PDR, NPDR and diabetic without retinopathy groups (Table I). However, SNK method comparison demonstrated that disease duration was only significantly different between the PDR and diabetic without retinopathy groups, with PDR having a longer disease duration than the diabetic without retinopathy group (P<0.05). HbAlc levels were also significantly higher in the PDR group than in the diabetic without retinopathy group (P<0.05); however, this did not differ significantly between the other groups.

Comparison of mean ADC values in functional areas of the brain. Mean ADC values in cingulate gyri, orbitofrontal

Table II. ADC in functional brain areas of patients.

Group	n	ADC						
		Cingulate gyrus	OFC	Visual cortex	Thalamus	Corona radiate	DMFC	DLFC
PDR	21	813.71±26.76	827.93±35.04	810.64±18.32	730.62±22.07	706.29±28.41	714.87±23.36	712.03±23.41
NPDR	21	786.91±26.10[a]	796.57±28.16[a]	791.98±28.42[a]	727.34±21.36	703.50±14.82	710.02±16.07	709.12±15.62
Diabetic without retinopathy	21	723.68±18.96[b]	723.50±24.76[b]	711.08±23.17[b]	727.12±18.67	706.11±11.70	709.50±25.67	703.87±16.60
Control	21	733.60±23.82[a,b]	713.07±23.14[a,b]	709.35±25.73[a,b]	721.06±19.30	702.93±20.65	708.71±20.62	701.36±21.75
F		70.69	71.25	67.53	0.86	0.17	0.45	0.89
P-value		<0.001	<0.001	<0.001	0.403	0.73	0.61	0.42

[a]P<0.05 vs. the PDR group; [b]P<0.05 vs. the NPDR group. Data are presented as the mean ± standard deviation. ADC, apparent diffusion coefficient; OFC, orbitofrontal cortex; DMFC, dorsomedial frontal cortex; DLFC, dorsolateral frontal cortex; PDR, proliferative diabetic retinopathy; NPDR, non-proliferative diabetic retinopathy.

Table III. Correlation of ADC with disease duration and HbAlc level.

Variable	ADC, R (P)		
	Cingulate gyrus	OFC	Visual cortex
HbAlc	0.287 (0.047)	0.328 (0.021)	0.361 (0.015)
Disease duration	0.517 (0.006)	0.583 (<0.001)	0.467 (0.001)

ADC, apparent diffusion coefficient; OFC, orbitofrontal cortex; HbAlc, glycosylated hemoglobin.

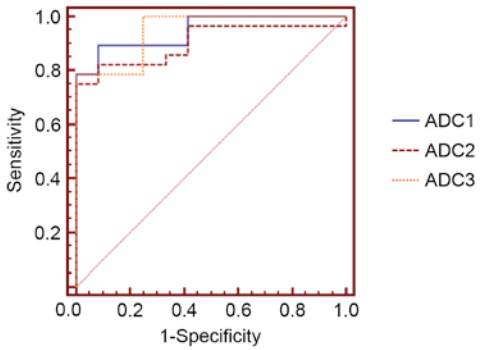

Figure 2. Receiver operating characteristic curves of ADC in regions of interest of the orbitofrontal cortex, cingulate gyrus and visual cortex in patients with type 2 diabetes with retinopathy. ADC1, ADC in the orbitofrontal cortex; ADC2, ADC in the cingulate gyrus; ADC3, ADC in the visual cortex; ADC, apparent diffusion coefficients.

cortices and visual cortices were significantly different among PDR, NPDR, diabetic without retinopathy and control groups (P<0.001; Table II). SNK method comparison demonstrated that mean ADC values in cingulate gyri, orbitofrontal cortices and visual cortices were significantly higher in the PDR group than NPDR group, and significantly higher in the NPDR group than diabetic without retinopathy or control groups (P<0.05). Mean ADC values in thalami, coronae radiatae, dorsolateral frontal cortices and dorsomedial frontal cortices did not significantly differ among the four groups (P>0.05).

Correlations of HbAlc levels and disease duration with mean ADC values in functional areas of the brain. Spearman's rho correlation was used to analyze correlations of HbAlc levels and disease duration with mean ADC values in the cingulate gyri, orbitofrontal cortices and visual cortices in PDR, NPDR and diabetic without retinopathy groups. HbAlc levels were positively correlated with mean ADC values in cingulate gyri (r=0.287; P=0.047), orbitofrontal cortices (r=0.328; P=0.021), and visual cortices (r=0.361; P=0.015; Table III). Disease duration was also positively correlated with mean ADC values in cingulate gyri (r=0.517; P=0.006), orbitofrontal cortices (r=0.583; P<0.001) and visual cortices (r=0.467; P=0.001).

ROC curve analysis of functional brain injuries in patients with type 2 diabetes with retinopathy. ROC curve analysis

of ADC values was used to judge injuries to visual centers of the brain in type 2 diabetic patients with retinopathy. In the cingulate gyrus, the area under the ROC curve was 0.902 [95% confidence interval (CI)=0.766-0.973], with a diagnostic cut-off value of 753.000, a sensitivity of 0.816 and a specificity of 0.851 (Fig. 2). In the orbitofrontal cortex, the area under the ROC curve was 0.946 (95% CI=0.826-0.993), with a diagnostic cut-off value of 749.600, a sensitivity of 0.855 and a specificity of 0.907. In the visual cortex, the area under the ROC curve was 0.952 (95% CI=0.826-0.993), with a diagnostic cut-off value of 739.800, a sensitivity of 0.862 and a specificity of 0.914.

Discussion

DR is a leading cause of blindness and visual impairment in patients with diabetes and is correlated with functional brain injuries (13). DWI is able to effectively provide information on pathological changes in the brain, including information on the diffusion rate of water molecules in tissues, transport of intracellular and extracellular water molecules, and microscopic and geometric structures of tissues, thus it offers an important basis for early diagnosis of diabetic encephalopathy (14). DWI may be used to calculate ADC, a measure of the diffusion capacity of water molecules in tissues, which can assess the degree of microstructural injuries in human tissues.

In the present study, mean ADC values were significantly higher in specific brain regions of individuals in the PDR group compared to the NPDR group. Mean ADC values were also significantly higher in the same brain regions of the NPDR group than in the diabetic without retinopathy or control groups. This result suggests that injuries to functional areas of the brain are correlated with DR. The results of the present study correlate with previous reports of increased ADC values in functional brain areas, which may be correlated with gliosis or nerve cell death (10,15). ADC values in visual cortices of PDR and NPDR groups may be higher than those in diabetic without retinopathy and control groups as DR may reduce stimulation of visual cortices and lead to fine structural changes. Similarly, previous studies have demonstrated that visual dysfunction may lead to structural changes in the occipital cortex of amblyopic patients (16).

HbAlc levels represent a patient's blood sugar level over the past 3 months and are an important indicator of DR (17). Effective control of blood sugar may reduce the incidence of DR. In the present study, HbAlc levels were positively correlated with mean ADC values in the cingulate gyri, orbitofrontal cortices and visual cortices. Disease duration was also positively correlated with mean ADC values in these areas of the brain. This may be because longer disease duration affords greater diffusion capacity of water molecules, which is caused by neuronal degeneration in functional areas of the brain (18).

In the present study, ROC curve analysis was used to determine ADC values to judge functional brain injuries. In the cingulate gyrus, orbitofrontal cortex and visual cortex, all areas under ROC curves were >0.9, with high sensitivities and specificities, indicating that ADC may be used to assess functional brain injuries caused by DR. In conclusion, the results from the present study demonstrate that retinopathy in individuals with type 2 diabetes is correlated with functional brain injuries. DWI is an effective tool to assess such injuries in early DR and therefore may be a powerful technique for the prevention and treatment of DR.

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