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Brain diffusion-weighted imaging in diabetic patients with retinopathy

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Abstract. – *Objective:* **Our aim was to detect whether there is any change in apparent diffusion coefficients (ADC) levels in different sites of the brain, particularly in areas associated with the vision, in diabetic patients with retinopathy by measuring diffusion-weighted imaging (DWI).**

Materials and Methods: **Conventional magnetic resonance imaging (MRI) and DWI of the brain were obtained from 45 diabetic patients (15 patients with proliferative diabetic retinopathy (group 1), 15 patients with nonproliferative diabetic retinopathy (group 2), 15 diabetic patients without retinopathy (group 3) and from 15 age-matched healthy volunteers (group 4). ADC values of visual cortex, cingulate gyrus, orbitofrontal, dorsomedial and dorsolateral frontal, corona radiate, and thalamus were obtained.**

Results: **The ADC values of visual cortex, cingulate gyrus and orbitofrontal cortex significantly increased in groups 1 and 2 compared to groups 3 and 4 ($p < 0.001$). The ADC values of visual cortex significantly increased in group 1 compared to group 2 ($p < 0.001$). The duration of disease and value of HbA1c positively correlated with ADC values of the visual and orbitofrontal cortexes, and cingulate gyrus.**

Conclusions: **We found an increase in ADC values supporting the neuronal loss in some regions, especially in visual center by DWI in the diabetic patients with retinopathy. This result supports the association between diabetic retinopathy and brain injury.**

Key Words:

Diabetic retinopathy, Diffusion-weighted imaging, Visual center, ADC.

Introduction

Diabetes mellitus (DM) is a multisystemic disease that causes damage in many organs and systems. While pathogenesis of diabetes until now has not been completely elucidated, brain is one of the target tissues of diabetic organ damage[1,2]. It is thought that several factors such as decreased blood flow, oxidative stress, metabolic disorders, irregular changes in blood glucose levels secondary to the use of exogenous insulin, and vascular disorders may cause functional and structural changes in the brain[3-5]. Decline of the cognitive efficiency which is developed in a long period in diabetic patients has been suggested that may occur as a result of increase in blood pressure or microvascular complications such as retinopathy[6]. In patients with diabetic retinopathy, detection of small punctate white matter lesions in the brain and cortical atrophy in some regions with functional magnetic resonance imaging (fMRI) suggest that there is an association between retinopathy and brain tissue damage[7].

Diffusion-weighted imaging (DWI) allows quantitative measurement of the water molecules in biologic tissues during the application of strong magnetic field gradients. Apparent diffusion coefficients (ADC) can be calculated quantitatively[8]. Diffusion of water molecules depends on tissue microstructure and microdynamics[9,10]. DWI is clinically used in a variety of intracranial diseases such as ischemia, tumors, infection and cysts[11,12]. DWI findings related to changes in the brain are limited in patients with diabetes.

In this study, our aim was to detect whether there is any change by measuring with DWI levels in patients with diabetic retinopathy in different sites of the brain, particularly in areas associated with the vision.

Materials and Methods

Patient Selection

The patients applied to our Retina Unit of Ophthalmology Department were enrolled in the

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study. 45 patients diagnosed with diabetes according to World Health Organization (WHO) criteria were divided into 3 groups according to the results of ophthalmologic examination. 15 patients with proliferative diabetic retinopathy had findings such as neovascularization, preretinal hemorrhage and vitreous hemorrhage in fundus examination were classified as group 1; 15 patients with non-proliferative diabetic retinopathy who findings such as retinal hemorrhages, microaneurysms, hard exudates and venous bleeding were classified as group 2; and the group without retinopathy and with normal ophthalmologic examination were classified as group 3. The patients with a posterior segment pathology other than diabetic retinopathy, the patients with active uveitis or uveitis sequelae, and the patients had cornea and/or lens pathology, therefore, could not have a ocular fundus examination, and patients with glaucoma were excluded from the study. Duration of disease and hemoglobin A1c (HbA1c) levels were recorded in groups. Control group (Group 4) includes 15 patients without DM who applied to Ophthalmology Clinic with the complaints of far-sightedness, had a normal opthalmologic examination, and did not have any sign except for presbyopia. This study was approved by Clinical Research Ethics Committee. Signed informed consent forms were taken from the patients before the study.

Magnetic Resonance Imaging (MRI)

The MRI examination consisted of routine imaging and DWI. MRI was performed on 1.5-T system (Philips, Gyroscan Intera Master, Best, The Netherlands). T1-weighted images (TR=560 ms, TE=15 ms) were obtained in the sagittal and axial planes. Fast spin-echo T2-weighted images (TR=4530 ms, TE=100 ms) were obtained in the axial and coronal planes. Subjects with normal conventional MRI findings were included in the study and further evaluated with DWI. For DWI, a singleshot echoplanar pulse sequence (TR=4832 ms, TE=81 ms, field of view=230 mm, matrix size=128×128, number of acquisitions=2, slice thickness=5 mm, slice number=22, slice orientation=axial plane, scan time=28 s, interslice gap=1 mm) was used in all patients and controls with two different b values (0 and 1000 s/mm^2). The ADC maps were reconstructed with the commercially available software. In the patients and the controls, 7 distinct neuroanatomic locations: visual cortex, cingulate gyrus, orbitofrontal, dorsomedial and dorsolateral frontal, corona radiate, and thalamus) were selected for the analysis (Figure 1a, b). These areas were selected according to recent literatures that were thought to be especially affected in diabetic patients[7,13]. Regions of interest (ROIs) drawn by same experienced radiologist manually on the regions identified and ADC values were automatically calculated from the ADC map. For all of these processes, the method described by us was used[9,14]. We minimized partial volume effects by inspecting the slices above and below the region to avoid averaging with cerebrospinal fluid. The areas of ROIs were 80-100 mm^2 in visual cortex, 50-60 mm^2 in thalamus, 30-40 mm^2 in cingulate gyrus, and orbitofrontal, dorsomedial and dorsolateral frontal cortex (Figure 1). The similar ROI size was used for an individual selected region in all patients, and the controls were carefully evaluated by the same experienced radiologist. ROI analyses were blinded on the condition of the subjects.

Statistical Analysis

All statistical analyses were performed using a commercially available SPSS release 15.0 software package (SPSS Inc., Chicago, IL, USA). The results are presented as the mean±SD. The distribution of ADC values in the patient and control groups were evaluated with Shapiro Wilk test.

Pearson correlation analyses, one way ANOVA test were used for statistical analyses and Bonferroni analysis was performed for post hoc analysis. *p* value below 0.05 was considered to be statistically significant.

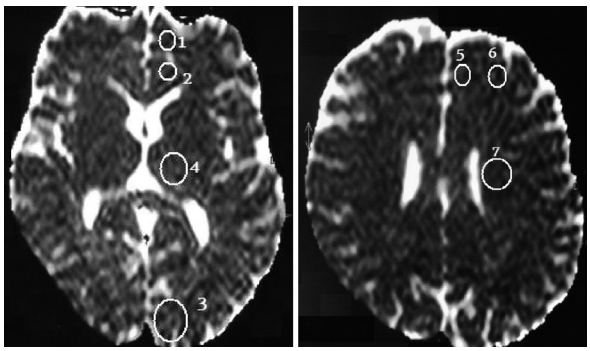

Figure 1. ADC maps show ROIs of diabetic subject in: orbitofrontaal cortex (1), Cingulate gyrus (2), Visual cortex (3), Thalamus (4), Dorsomedial frontal cortex (5), Dorsolateral frontal cortex (6), Corona radiate (7).

Table I. Demographic and clinical features of the groups.

	Groups				
	1	2	3	4	P
Age	55 ± 7	55 ± 8	50 ± 6	52 ± 7	0.11
Gender (F/M)	8/7	7/8	7/8	8/7	0.96
Duration of disease	14 ± 6	11 ± 4	7 ± 5		< 0.001
HbA1c (%)	8.9 ± 2.1	7.6 ± 1.4	7.1 ± 1.3		< 0.001

Results

Age, gender, disease duration, and HbA1c of all groups were shown on Table I. No statistically significant difference was found in age and gender between the groups ($p > 0.05$). HbA1c levels of group 1 were significantly higher than that of group 3.

Duration of disease was significantly different between groups 1 and 3 ($p < 0.001$), and between groups 2 and 3 ($p < 0.001$). Although the duration of disease was longer in group 1 than group 2, no significant difference was found between these groups. ADC values in visual cortex, thalamus, cingulate gyrus, orbitofrontal, dorsomedial, and dorsolateral frontal cortex were presented on Table II.

The ADC values of visual cortex, cingulate gyrus and orbitofrontal cortex significantly increased in groups 1 and 2 compared to groups 3 and 4 ($p < 0.001$). The ADC values of visual cortex significantly increased in group 1 compared to group 2 ($p < 0.001$).

ADC values of thalamus, dorsomedial and dorsolateral frontal cortexes showed no statistically significant differences between all groups ($p > 0.05$).

ADC values were similar in all regions in groups 3 and 4, and no statistically significant difference was detected.

ADC values of the visual and orbitofrontal cortexes, and cingulate gyrus increased with increasing duration of disease and increasing value of HbA1c (Table III).

Discussion

Advances in neuroimaging technology have given us the ability to evaluate the brain function *in vivo* and non-invasively[9]. DWI provides specific information about various pathological changes in the brain. DWI provides qualitative information, whereas ADC maps allow quantitative measurement of the diffusion of water molecules, which is altered in pathologic conditions in the brain tissue[14,15]. It has been shown that increased ADC values might suggest ultrastructural changes and, therefore, would reflect microstructural damage[9,16].

Table II. Comparison of ADC values of different brain locations in the groups.

	Groups				
ADC values (× 10^{-6} mm^2/s)	1 (n = 15) mean ± SD	2 (n = 15) mean ± SD	3 (n = 15) mean ± SD	4 (n = 15) mean ± SD	P
OFC	858 ± 39[a]	848 ± 38[a]	739 ± 31[b]	729 ± 27[b]	< 0.001
Cingulate gyrus	821 ± 36[a]	816 ± 26[a]	716 ± 18[b]	720 ±14[b]	< 0.001
Corpus striatum	689 ± 34	669 ± 16	671 ± 34	677 ± 23	0.23
Visual cortex	849 ± 32[a]	820 ± 28[c]	719 ± 16[b]	719 ± 13[b]	< 0.001
Corona radiate	737 ± 37	720 ± 31	713 ± 23	713 ± 25	0.12
DMFC	732 ± 13	731 ± 10	727 ± 10	726 ± 12	0.36
DLFC	739 ± 10	737 ± 13	738 ± 10	737 ± 13	0.94
Thalamus	718 ± 12	718 ± 19	716 ± 13	715 ± 13	0.90

OFC: indicates orbitofrontal cortex; DMFC: dorsomedial frontal cortex; DLFC: dorsolateral frontal cortex. [a,b,c]Are different from each other.

Table III. Correlation between ADC values and HbA1c and disease duration.

	Statistical value	OFC	CG	VC
HbA1c	*p*	< 0.001	0.003	< 0.001
	R	0.494	0.372	0.509
Duration of disease	*p*	0.018	0.005	0.006
	R	0.351	0.415	0.405

OFC: indicates orbitofrontal cortex; CG: cingulated gyrus; VC: visual cortex.

In this study, findings that may be compatible with the injury of some areas of the brain, especially the visual cortex, were detected in diffusion MRI of patients with diabetic retinopathy.

Nephropathy, retinopathy, and peripheral neuropathy are well-known microvascular complications of diabetes. Although the pathophysiology of DM has not been fully understood, it is known that the patients may also have brain changes since and brain injury may be multifocal evaluated by neuroradiologic, electrophysiologic, and cognitive tests[17,18].

There have been studies on a relationship between brain injury and retinopathy that has been very well-defined in diabetes. Wessel et al [7] performed fMRI examination of the brains of the patients with diabetic and non-diabetic retinopathy, and they showed that while patients with diabetic retinopathy had atrophic changes in some parts of their brain, these changes were not observed in patients with non-diabetic retinopathy.

In our study, ADC values in the visual cortex, cingulate gyrus, and orbital frontal cortex in patients with retinopathy (groups 1-2) were found to be higher than diabetic patients without retinopathy (group 3) and the control group (group 4). Authors have suggested that the increase in ADC values may be due to the rise of the amount of interstitial water caused by neuronal cell death and secondary gliosis[19]. In patients with diabetic retinopathy, atrophic changes in the occipital lobe and frontal gyrus were detected in brain functional(f) MRI (fMRI)[13]. In another study, activity reduction suggesting neuronal loss was also detected in anterior cingulate and orbitofrontal gyrus[7]. Similar findings supporting neuronal loss was detected in some regions of the brains of diabetic patients with brain magnetic resonance spectroscopy (MRS) examination[20,21]. Parallel to these studies, our results were considered to be suggesting neuronal cell death in the visual cortex, cingulate gyrus, and orbitofrontal cortex.

Various mediators released secondary to ischemia in diabetic retinopathies have been known to affect retinal neurons not only vascular structures. These neurodegenerative changes include apoptosis of neuronal cells, glial cell reactivity, and changes in glutamate metabolism[22,23]. Metabolic factors that cause neuronal cell death are insulin-dependent hexosamines, tumor necrosis factor-α, and the damage caused by the accumulation of glutamate[24,25]. In the studies using the test called electroretinogram in which electrophysiological activity of retinal neurons, the electroretinogram amplitudes were found to be decreased supporting that retinal neurons were affected[26]. In the light of these data, it can be said that diabetic retinopathy triggers neuronal apoptosis and causes the loss of vision. Our results support that these metabolic changes in diabetic retinopathy are not just limited to the retina, they may also result in the neuronal loss in cingulate gyrus and orbitofrontal cortex in visual cortex in the brain.

ADC values in all regions measured with DWI were similar in diabetic patients without retinopathy (group 3) and the control group (group 4) and no difference was found. Therefore, this result supports that there is a relationship between brain injury and retinopathy, as Wessel et al[13] claimed.

The duration of diabetes and poor glycemic control play an important role in the developement of diabetic retinopathy. HbA1c value is used for monitoring of glycemic control. HbA1c values increase in patients with poor diabetic control[20]. Sahin et al[21] showed a correlation between elevated HbA1c levels and neuronal loss in the frontal cortex in diabetic patients. In same study, there were findings supporting neuronal loss in white matter due to elevated fasting plasma glucose levels and increased insulin resistance. Our results are similar to that of Sahin et al[21] and there is a positive relationship between the duration of disease and HbA1c and ADC values in visual cortex, the orbitofrontal cortex, and

cingulate gyrus. According to these findings, it was thought that there may be a relationship between poor glycemic control and neuronal loss or neuronal dysfunction.

ADC values in visual cortex in diabetic patients with proliferative retinopathy (group 1) were observed to be higher than that of diabetic patients with non-proliferative retinopathy (group 2). This can be due to the poor controlled hypoglycemia in group 1 than group 2.

It is thought that the stimulation of the visual center decreased and cortical neurons accordingly degenerated owing to the retinal lesions caused by ophthalmic diseases such as age-related macular degeneration. Boucard et al[27] detected findings suggesting neuronal degeneration in visual center including a group of patients with retinal lesions by using fMRI. In the light of these results, we also think that changes in visual cortex may be due to the long-term decreases in the stimulation of cortical neurons.

It was detected by fMRI that there were changes in only orbitofrontal cortex and cingulat gyrus in the brains of a patient group with diabetic retinopathy. In our study, similar results supporting the neuronal loss in both these two regions as well as visual cortex were found in DWI examination. Hence, we can say that these regions are more affected in patients with diabetic retinopathy.

We found an increase in ADC values supporting the neuronal loss in some regions, especially in visual center by DWI in the patients with diabetic retinopathy. This result also supports that there is an association between diabetic retinopathy and brain injury. In addition, our findings are important for the clinicians in terms of strategies that will be applied in the treatment of visual impairment. Because, if the injury in the visual cortex is detected in DWI, only the approach focusing on the eye, may be missed during treatment. We conclude that DWI can be a guidance for follow-up and management of the patients with diabetic retinopathy.

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