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 cortices, 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. 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. 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. 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.

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. Diffusion of water molecules depends on tissue microstructure and microdynamics. DWI is clinically used in a variety of intracranial diseases such as ischemia, tumors, infection and cysts. 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
study. 45 patients diagnosed with diabetes ac-
cording 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, prereti-
nal hemorrhage and vitreous hemorrhage in fun-
dus examination were classified as group 1; 15 
patients with non-proliferative diabetic retinopa-
thy 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 oph-
thalmologic examination were classified as group 
3. The patients with a posterior segment patholo-
y other than diabetic retinopathy, the patients 
with active uveitis or uveitis sequelae, and the 
patients had cornea and/or lens pathology, there-
fore, 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=128x128, number of acquisi-
tions=2, slice thickness=5 mm, slice number=22, 
slice orientation=axial plane, scan time=28 s, in-
terslice gap=1 mm) was used in all patients and 
controls with two different b values (0 and 1000 
s/mm²). The ADC maps were reconstructed with 
the commercially available software. In the pa-
tients and the controls, 7 distinct neuroanatomic 
locations: visual cortex, cingulate gyrus, or-
bitofrontal, dorsomedial and dorsolateral frontal, 
corona radiate, and thalamus) were selected for 
the analysis (Figure 1a, b). These areas were se-
lected according to recent literatures that were 
thought to be especially affected in diabetic pa-
tients. Regions of interest (ROIs) drawn by 
same experienced radiologist manually on the re-
gions identified and ADC values were automati-
cally calculated from the ADC map. For all of 
these processes, the method described by us was 
used. 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 mm² in visual cortex, 
50-60 mm² in thalamus, 30-40 mm² in cingulate 
gyrus, and orbitofrontal, dorsomedial and dorso-
lateral frontal cortex (Figure 1). The similar ROI 
size was used for an individual selected region in 
all patients, and the controls were carefully eval-
uated 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 soft-
ware 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 Bonfer-
oni analysis was performed for post hoc analy-
sis. p value below 0.05 was considered to be sta-
tistically significant.

Figure 1. ADC maps show ROIs of diabetic subject in: or-
itofrontal cortex (1), Cingulate gyrus (2), Visual cortex 
(3), Thalamus (4), Dorsomedial frontal cortex (5), Dorso-
lateral frontal cortex (6), Corona radiate (7).
Table I. Demographic and clinical features of the groups.

|                | Groups
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<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>55 ± 7</td>
<td>55 ± 8</td>
<td>50 ± 6</td>
<td>52 ± 7</td>
<td>0.11</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Gender (F/M)</td>
<td>8/7</td>
<td>7/8</td>
<td>7/8</td>
<td>8/7</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Duration of disease</td>
<td>14 ± 6</td>
<td>11 ± 4</td>
<td>7 ± 5</td>
<td>&lt;0.001</td>
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<tr>
<td>HbA1c (%)</td>
<td>8.9 ± 2.1</td>
<td>7.6 ± 1.4</td>
<td>7.1 ± 1.3</td>
<td>&lt;0.001</td>
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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 cortices 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 cortices, 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. 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. It has been shown that increased ADC values might suggest ultrastructural changes and, therefore, would reflect microstructural damage.
Brain diffusion-weighted imaging in diabetic patients with retinopathy

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 tests17,18.

There have been studies on a relationship between brain injury and retinopathy that has been very well-defined in diabetes. Wessel et al7 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 gliosis19. 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 gyrus7. Similar findings supporting neuronal loss was detected in some regions of the brains of diabetic patients with brain magnetic resonance spectroscopy (MRS) examination20,21. 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 metabolism22,23. Metabolic factors that cause neuronal cell death are insulin-dependent hexosamines, tumor necrosis factor-α, and the damage caused by the accumulation of glutamate24,25. 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 affected26. 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 al13 claimed.

The duration of diabetes and poor glycemic control play an important role in the development of diabetic retinopathy. HbA1c value is used for monitoring of glycemic control. HbA1c values increase in patients with poor diabetic control20. Sahin et al21 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 al21 and there is a positive relationship between the duration of disease and HbA1c and ADC values in visual cortex, the orbitofrontal cortex, and

<table>
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<tr>
<th>Statistical value</th>
<th>OFC</th>
<th>CG</th>
<th>VC</th>
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<tr>
<td>HbA1c</td>
<td>$p &lt; 0.001$</td>
<td>0.003</td>
<td>$&lt; 0.001$</td>
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<tr>
<td></td>
<td>R 0.494</td>
<td>0.372</td>
<td>0.509</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>$p 0.018$</td>
<td>0.005</td>
<td>0.006</td>
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<tr>
<td></td>
<td>R 0.351</td>
<td>0.415</td>
<td>0.405</td>
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OFC: indicates orbitofrontal cortex; CG: cingulated gyrus; VC: visual cortex.
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. 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 IMRI 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.

References


