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Diffusion-weighted magnetic resonance imaging in diabetic retinopathy

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Abstract

Diabetic retinopathy (DR) is a complication of diabetes mellitus (DM) that may causes blindness. The vitreous is an extracellular matrix and it may have changes through liquefaction and syneresis in patients with DM, even in those without apparent DR. Diffusion-weighted imaging (DWI) is a new technique provide tissue contrast relying on difference with the diffusion of water molecules among tissues, which can be measured by the apparent diffusion coefficient (ADC) value. We aimed to investigate the vitreous of patients in different stages of DR using diffusion-weighted imaging technique. This prospective study included a group of 100 patients with DR and 100 members of an age- and gender-matched control group. All groups were tested using a head coil in conduction with a Achieva 1.5T magnetic resonans imaging (MRI) system (Philips Medical Systems, Best, The Netherlands). The mean ADC values were calculated and used for statistical comparisons. Mean duration of diabetes was 12.22±10.13 years in patients. Compared to controls, both eyes of the DR group had statistically and significantly lower values of ADC (p=0.025 and p=0.002, respectively). No significant correlations were found among the ADC values and central macular thickness, disease duration and stage of DR (all p>0.05) in patients. Mean ADC values revealed no significant differences among the subgroups of patients at different stages of DR (all p>0.05). Decreased ADCs in the vitreous of diabetes patients seem to be associated with the presence of diabetic retinopathy.

Keywords: Diffusion-weighted imaging, ADC, vitreous, diabetic retinopathy

Introduction

Diabetic retinopathy (DR) is the leading cause of blindness within the working-age population. Other reasons for loss of vision in diabetics are diabetic maculopathy and complications of proliferative diabetic retinopathy (PDR). Based on clinical features, DR has been subdivided into two main stages: non-proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR) [1].

Diffusion-weighted imaging (DWI) gathers information from the movement of water protons in tissues and creates an image that is not possible using conventional MRI [2-4]. A DWI image is created from the motion of water molecules in the extracellular space, intracellular space and intravascular space. [5] Using the DWI technique, ADC values in normal animal retinas were calculated and the restricted diffusion in a case of inflammatory optic neuropathy in a child with acute vision loss was reported. [6,7] Mono-exponential water diffusion in the animal retinal layers and vitreus were also quantitatively assessed by DWI. [8-10]

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One of the primary concerns with DR is that it cannot currently be diagnosed in its early stages. New studies have shown that the vitreous manifests changes in angiogenic and metabolic factors concordant with abnormalities in the retinal microvasculature that participate in the pathogenesis of DR. [11-14]

To our knowledge, there is no study evaluating DWI in the vitreous of patients with DR in the current literature. Therefore, in this study, we aimed to use a non-invasive DWI technique to investigate the vitreous of patients in early diagnosis of DR and different stages of DR.

Material and Methods

Patient Enrolment

This prospective study (December 2014 - June 2015) included a group of 100 patients with DR and 100 members of an age- and gender-matched control group. The medical history of each patient was taken and recorded, and patients were excluded from the study if their history included any of the following: uncontrolled hypertension, vitreoretinal pathology, uveitis, corneal and/or lenticular disease or glaucoma. Control group members (n=100) were selected from the patients from the Outpatient Unit who had a normal opthalmological examination.

The patient group included 100 patients, 36 (36%) males and 64 (64%) females, with a mean age of 63.29±10.11 years. The control group consisted of 100 patients, 38 (38%) males and 62 (62%) females, with a mean age of 61.07±13.21 years. There was no statistically significant difference between the groups in terms of age and gender (p=0.1, p=0.7, respectively).

Mean duration of diabetes was 12.22±10.13 years. Twenty-nine (29%) of the patients had apparent retinopathy (Group 1), 43 (43%) had non-proliferative retinopathy (Group 2) and 28 (28%) had proliferative retinopathy (Group 3). Table 1 shows the demographic parameters of the study groups.

Ethics Committe

The local ethics committee approved the research protocol (decision no. 26/04 on December 1, 2014) for the involvement of human subjects in this study and informed consent was obtained from all participants.

Diffusion-Weighted Images Technique

All MRI applications were performed by using a head coil via Achieva 1.5T MRI system (Philips Medical Systems, Best, The Netherlands). An echo planar imaging (EPI) sequence was used to achieve DWIs. The parameters were as follows: 25 slices were obtained in the axial plane (TR msn/TE msn; 2549/121, deflection angle 90°, FOV 150 x 162 mm, matrix 112 x 89 mm, 2.5 mm slice thickness, 1-mm intersection gap). Initially, T2- weighted images were acquired without the application of diffusion gradient (b=0 mm2/sn) and then, using the value of b=1000 mm2/sn, diffusion-sensitive gradients were applied in three directions (x; y; z). Trace images were acquired by averaging the three gradients. ADC mapping was reconstructed from these images.

A single radiologist independently determined that MR imaging findings of each orbit were normal in all participants, evaluated the quality of DWIs and selected the images for analysis that had a minimum of distortion from susceptibility artifacts. To avoid the artifacts, patients were told to close their eyes and to refrain from moving during MRI applications.

All measurements were calculated by the same blinded radiologist. ROIs were drawn on to the ADC mapping images by the software system supplied with the MR equipment. All ROI were elliptical, 25-30 mm2 in vitreous. In total, 3 ROIs were obtained from the right and left sides for the vitreous; one is center of the eye, second is the lateral peripheral portion and third is the medial peripheral portion (Figure 1). The mean values were calculated for statistical comparisons.

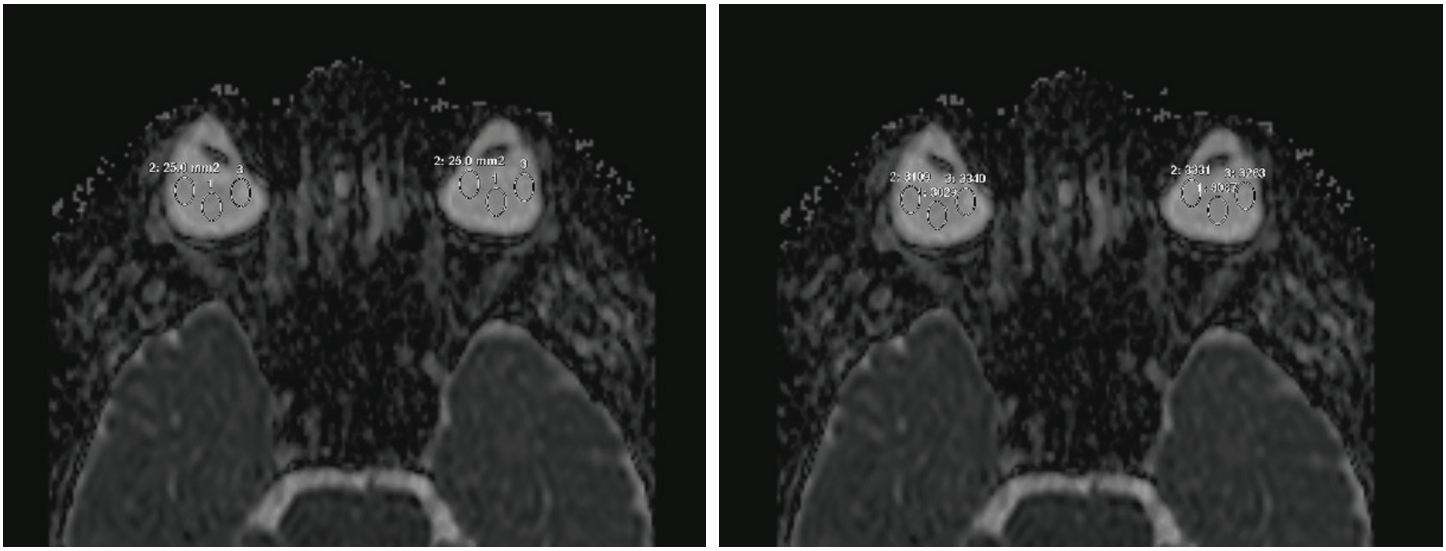

Figure 1. A) ROI (area: 25 mm2 one is center of the eye, second lateral peripheral portion and third medial peripheral portion) placement in the vitreous on to the ADC map images B) ADC values

Statistical Analysis

The statistical analyses were performed using SPSS for Windows 16.0 (SPSS Inc., an IBM Company, Chicago, Illinois). The data are presented as mean ± standard deviation (SD). ADC values obtained from the vitreous of each patient were analyzed using paired t tests and a post-hoc comparison Tukey test was used to compare subgroups. A p value less than 0.05 was considered to be significant.

Results

The mean ADC value obtained from the vitreous of the DR group was measured as 3145.24± 241.01 10-6 mm2/s in the right eye, while it was 3089.26±225.70 10-6 mm2/s in the left eye. In control eyes, ADC value was found to be 3224.09± 233.27 10-6 mm2/s on the right and 3177.53±205.06 10-6 mm2/s on the left side. Compared to controls, both eyes of the DR group had statistically significantly lower values of ADC (p=0.025 and p=0.002, respectively). Table 2 presents the mean ADC values obtained from the study groups.

No significant correlations were found between the ADC values of both eyes and central macular thickness, disease duration and stage of DR (all p>0.05). Table 3 and 4 present the mean ADC values obtained from the DR subgroups. Post-hoc analysis of the mean ADC values in the right and left eyes revealed no significant differences among the subgroups of patients at different stages of DR (all p>0.05).

Table 1. Demographic data in each study group

Parameters	Groups	
	Patients	Controls
Subjects (n)	100	100
Age		
Mean ± SD	63.29±10.11	61.07±13.21
Gender (n)		
Female	36	38
Male	64	62

Table 2. Mean ADC values in each study group

ADC Mean±SD (10-6 mm2/s)	Patients	Controls	P value
Right eyes	3145.24± 241.01	3224.09± 233.27	0.025
Left eyes	3089.26±225.70	3177.53±205.06	0.002

Table 3. Comparison of mean ADC values of right eyes in DR subgroups; Group 1 (apparent retinopathy), Group 2 (had non-proliferative retinopathy) , Group 3 (had proliferative retinopathy**)**

	ADC (Mean±SD) (10^{-6} mm^2/s)		P value
Group 1- Group 2	3133.86± 240.11	3160.70±251.86	0.9
Group 1- Group 3	3133.86± 240.11	3133.27±232.06	1
Group 2- Group 3	3160.70±251.86	3177.53±205.06	0.9

Table 4. Comparison of mean ADC values of left eyes in DR subgroups. Group 1 (apparent retinopathy), Group 2 (had non-proliferative retinopathy) , Group 3 (had proliferative retinopathy).

	ADC (Mean±SD) (10^{-6} mm^2/s)		P value
Group 1- Group 2	3112.98± 223.90	3110.93±238.71	1
Group 1- Group 3	3112.98± 223.90	3031.40±203.31	0,3
Group 2- Group 3	3110.93±238.71	3031.40±203.31	0.3

Discussion

We found in our study both eyes of the DR group had statistically significantly lower values of ADC compared to controls and no significant correlations between the ADC values of both eyes and central macular thickness, disease duration and stage of DR (all $p>0.05$).

Diabetic retinopathy is a potentially blinding complication of diabetes mellitus and the diagnosis is based on the documentation of structural or functional changes in the retina or its vasculature. Dilated fundus examination enables a proper stereoscopic evaluation of macula and peripheral retina [1]. Fluorescein angiography and optical coherence tomography (OCT) have made critical contributions to the diagnosis of structural changes. Diffusion-weighted imaging of the retina is a new technique relying on water diffusion in the tissues. It does not require any contrast medium and has a short imaging time [3-4]. In this study, we measured, for the first time, ADC values of the vitreus in the eyes of DR patients.

Previous studies in diabetic patients reported ADC levels in different tissues of the body. Doğan et al. [15] found increased ADC values in the visual cortex of the brain in patients with DR. They concluded that their results supported the association between DR and brain injury. Lu et al. [16] and Çakmak et al. [17] measured significantly lower ADC values in the kidneys of patients with diabetic nephropathy. Çakmak et al. found a significant negative correlation between the renal ADC values and clinical stages of diabetic nephropathy. They observed significantly lower renal ADC values in advanced-stage nephropathy patients compared to healthy control subjects. However, Lu et al. did not find any significant correlations between ADC values and renal function. In our study, we found significantly lower levels of ADC in the vitreus of DR patients compared to controls. We did not identify any significant correlations between the ADC values and central macular thickness, disease duration or stage of DR.

Diabetes mellitus affects the extracellular matrix and connective tissue throughout the body via non-enzymatic glycation and abnormal cross-linking of collagen. As the vitreous is also an extracellular matrix, of which collagen constitutes an important portion, it may show changes through liquefaction and syneresis in patients with DM, even in those without apparent DR. [18,19]. The vitreoretinal relationship is important in the development

and progression of proliferative changes in DR patients [20]. These relationships, such as the presence of posterior vitreous detachment, either complete or incomplete, have been extensively studied in hospital-based settings.

The pathophysiologic process underlying the observed decrease in ADC values in the vitreous of DR patients may occur due to various mechanisms, such as retinal microvascular abnormalities, tissue hypoxia, focal ischemia, vitreoretinal damage due to hyperglycaemia etc. Multiple mechanisms have been suggested to mediate ocular damage due to hyperglycaemia which may alter the structure and function of the collagen network of the vitreus via increased glycation and crosslinking of the collagen fibrils. The decrease in ADC values may be due to the effects of diabetes on vitreous collagen. Numerous studies have reported increased levels of pro-angiogenic factors and cytokines in the vitreous of DR patients, particularly those with severe diabetic macular edema and PDR [21-28].

The increased number of molecules in the vitreous could be the basis for DWI changes related to DR, although clearly, further clinical and preclinical studies are needed to better understand the relationship of these observations to the pathophysiologic changes in DR.

Conclusions

In summary, a decreased ADC in the vitreous of diabetes patients seems to be associated with the presence of diabetic retinopathy. This information may have a potential for diabetes patients in future and merits further studies to assess validity in staging and predicting patients at risk of retinopathy. Perhaps it could be used in future as a diagnostic tool in ophthalmology, particularly in patients with DR and also in the radiological evaluation of other anatomical structures in human body. It should be noted that the DWI is helpful to the clinician in the early diagnosis of DR.

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