Hypertension-Related Microstructural Changes in the Vitreous Humor Detected by Diffusion MRI

Davut Ünsal ÇAPKAN*

Abstract

Aim: Hypertension is known to affect several target organs through chronic microvascular injury. Although ocular involvement is usually assessed by retinal or choroidal vascular findings, possible changes in the vitreous humor have received limited attention. This study investigated whether diffusion-weighted magnetic resonance imaging (DW-MRI) could detect hypertension-related alterations in the vitreous humor by measuring apparent diffusion coefficient (ADC) values.

Method: This retrospective cross-sectional study included 100 patients with hypertension and 100 controls frequency matched to the hypertension group according to age and sex who had undergone orbital DW-MRI. Vitreous humor ADC values were measured on ADC maps using standardized regions of interest (ROI). Right, left, and mean ADC values were compared between groups. Multivariable linear regression was used to determine factors independently associated with mean ADC. Within-sample discriminative performance was explored using receiver operating characteristic (ROC) analysis. Intra-observer reliability was evaluated with intraclass correlation coefficients.

Results: Mean vitreous ADC was significantly lower in participants with hypertension than in controls (2.18±0.20 vs. 2.32±0.18 $\times 10^{-3}$ mm²/s; $p<0.001$), with a moderate-to-large effect size (Cohen's $d=0.72$). In multivariable analysis, hypertension remained independently associated with lower mean ADC after adjustment for age, sex, and diabetes mellitus ($B=-0.160$, 95% CI: −0.210 to −0.110; standardized $\beta=-0.42$; $p<0.001$). Mean ADC showed the highest within-sample discrimination among the evaluated measures (AUC=0.83, 95% CI: 0.77–0.89), with a data-derived cut-off of ≤2.25 $\times 10^{-3}$ mm²/s, 78.0% sensitivity, and 75.0% specificity. Age was inversely correlated with mean ADC ($r=-0.34$, $p<0.001$). Intra-observer reproducibility was excellent for mean ADC measurements (ICC=0.96, 95% CI: 0.94–0.97).

Conclusion: Patients with hypertension had lower vitreous ADC values than controls, which may reflect subtle differences in vitreous microstructure. Although mean ADC showed within-sample discrimination between hypertensive participants and controls, these exploratory findings do not establish vitreous ADC as a clinical diagnostic test. Prospective multicenter studies incorporating comprehensive ophthalmological assessments and external validation are required to clarify the clinical relevance of these findings.

Keywords: Hypertension, ocular microstructure, vitreous humor, imaging biomarker, apparent diffusion coefficient, diffusion-weighted MRI.

Özgün Araştırma Makalesi (Original Research Article)
Geliş / Received: 29.04.2026 **Kabul / Accepted:** 13.08.2026
DOI: https://doi.org/10.38079/igusabder.1939863
* Asst. Prof. Dr., Department of Radiology, Medical Point Hospital, Gaziantep, Türkiye.
E-mail: drdavutunsal11@gmail.com ORCID https://orcid.org/0009-0007-6937-8799

ETHICAL STATEMENT: The study protocol was approved by the Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee, Gaziantep, Türkiye (Number: 445/2026, Date: 06.03.2026).

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Hipertansiyon ile İlişkili Vitreus Humerusta Mikroyapısal Değişikliklerin Difüzyon MRG ile Değerlendirilmesi

Öz

Amaç: Hipertansiyonun kronik mikrovasküler hasar yoluyla çeşitli hedef organları etkilediği bilinmektedir. Göz tutulumu genellikle retina veya koroid vasküler bulguları ile değerlendirilse de, vitreus sıvısındaki olası değişikliklere sınırlı ilgi gösterilmiştir. Bu çalışma, difüzyon ağırlıklı manyetik rezonans görüntülemenin (DW-MRI), görünür difüzyon katsayısı (ADC) değerlerini ölçerek hipertansiyonla ilişkili vitreus sıvısındaki değişiklikleri tespit edip edemeyeceğini araştırmıştır.

Yöntem: Bu retrospektif kesitsel çalışmaya, orbital DW-MRG uygulanmış 100 hipertansiyon hastası ile hipertansiyon grubuyla yaş ve cinsiyet dağılımına göre frekans eşleştirmesi yapılmış 100 kontrol dahil edildi. Vitreus humor ADC değerleri, standartlaştırılmış ilgi bölgeleri (ROI) kullanılarak ADC haritaları üzerinden ölçüldü. Sağ, sol ve ortalama ADC değerleri gruplar arasında karşılaştırıldı. Ortalama ADC ile bağımsız olarak ilişkili faktörleri belirlemek amacıyla çok değişkenli doğrusal regresyon analizi kullanıldı. Örneklem içi ayırt edici performans, alıcı işletim karakteristiği (ROC) analizi kullanılarak araştırıldı. Gözlemci içi güvenilirlik, sınıf içi korelasyon katsayıları kullanılarak değerlendirildi.

Bulgular: Hipertansiyonu olan katılımcılarda ortalama vitreus ADC değeri kontrollere göre anlamlı derecede daha düşüktü (2,18±0,20'ye karşı 2,32±0,18 $\times 10^{-3}$ mm²/s; p<0,001) ve fark orta-büyük düzeyde bir etki büyüklüğüne sahipti (Cohen's d=0,72). Çok değişkenli analizde hipertansiyon; yaş, cinsiyet ve diabetes mellitus için düzeltme yapıldıktan sonra da daha düşük ortalama ADC değeriyle bağımsız olarak ilişkiliydi (B=−0,160, %95 GA: −0,210 ila −0,110; standartlaştırılmış β=−0,42; p<0,001). Ortalama ADC, değerlendirilen ölçütler arasında en yüksek örneklem içi ayırt edici performansı gösterdi (AUC=0,83, %95 GA: 0,77–0,89); veriden türetilen ≤2,25 $\times 10^{-3}$ mm²/s eşik değerinde duyarlılık %78,0 ve özgüllük %75,0 idi. Yaş ile ortalama ADC arasında ters yönlü korelasyon saptandı (r=−0,34; p<0,001). Ortalama ADC ölçümlerinin gözlemci içi tekrarlanabilirliği mükemmeldi (ICC=0,96, %95 GA: 0,94–0,97).

Sonuç: Hipertansiyonu olan hastalarda vitreus ADC değerleri kontrollere göre daha düşüktü; bu bulgu, vitreus mikroyapısındaki hafif farklılıkları yansıtıyor olabilir. Ortalama ADC, hipertansif katılımcılar ile kontroller arasında örneklem içi ayırt edici performans göstermiş olsa da bu keşifsel bulgular, vitreus ADC ölçümünün klinik bir tanı testi olduğunu ortaya koymamaktadır. Bu bulguların klinik önemini açıklığa kavuşturmak için kapsamlı oftalmolojik değerlendirmeleri ve dış doğrulamayı içeren prospektif, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Hipertansiyon, difüzyon ağırlıklı MRG, görünür difüzyon katsayısı, vitreus humor, oküler mikroyapı, biyobelirteçler.

Introduction

Hypertension remains one of the leading chronic disorders worldwide and continues to be a major contributor to cardiovascular morbidity and mortality. Long-standing elevation of blood pressure has been associated with progressive microvascular injury involving several organs, particularly the brain, kidneys, heart, and ocular tissues[1-4]. Ocular manifestations are considered especially important because the eye is highly vulnerable to disturbances in microcirculation. For this reason, hypertensive ocular involvement has mainly been investigated through retinal and choroidal vascular abnormalities, which are commonly described under the term hypertensive retinopathy[5-7].

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Although the vascular effects of hypertension on the eye have been widely investigated, considerably less attention has been paid to avascular structures, including the vitreous humor. The vitreous body consists largely of water, collagen fibers, and hyaluronic acid within a gel-like extracellular framework, contributing to both ocular integrity and biochemical balance[8-10]. Even in the absence of direct vascularization, the vitreous environment may still be affected by adjacent ocular tissues as well as systemic physiological alterations. Therefore, subtle systemic alterations—particularly those involving microvascular dysfunction and fluid homeostasis—may indirectly affect its microstructural properties[11,12].

Diffusion-weighted magnetic resonance imaging (DW-MRI) has emerged as a powerful, non-invasive imaging modality capable of evaluating tissue microstructure through quantitative measurement of the apparent diffusion coefficient (ADC). ADC values reflect the mobility of water molecules within tissues and are sensitive to changes in cellular integrity, extracellular space composition, and microvascular perfusion[13,14]. Over the past decade, diffusion MRI has gained increasing attention in the evaluation of orbital and ocular tissues because of its ability to provide quantitative information beyond that obtained with routine imaging methods[15-18]. By assessing water molecule mobility within tissues, this technique offers insight into subtle microstructural alterations that may not be visible on conventional examinations.

Several earlier studies have noted that vitreous ADC measurements may vary under both physiological circumstances and disease-related conditions, especially in elderly individuals and in patients with diabetic retinopathy[11,12,19]. These studies showed that the vitreous body undergoes measurable diffusion-related changes that may reflect systemic biological influences or underlying local tissue remodeling. In contrast, the relationship between hypertension and vitreous diffusion behavior has not been comprehensively studied, and the current evidence on this subject remains relatively limited.

Chronic hypertension has been associated with abnormalities in endothelial function, disruption of vascular autoregulatory mechanisms, and increased capillary permeability. These vascular and microenvironmental changes may alter extracellular fluid regulation and tissue organization, which could subsequently influence diffusion properties even within avascular structures such as the vitreous humor[20-22]. In this context, quantitative assessment of vitreous ADC values may offer an alternative approach for identifying subtle ocular involvement related to systemic hypertension.

Within this framework, diffusion MRI may provide additional insight into ocular microstructural alterations that cannot be readily identified by standard ophthalmological assessment. Detecting these subtle changes could improve understanding of the systemic effects of hypertension and may also contribute to the identification of early imaging markers of hypertensive target-organ involvement.

The present study retrospectively examined vitreous humor ADC values in patients with hypertension and compared them with those obtained from normotensive individuals using diffusion MRI. We proposed that hypertension would be associated with

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

measurable alterations in vitreous diffusion characteristics. Through quantitative evaluation of vitreous ADC measurements, this study aimed to further investigate whether systemic hypertension influences avascular ocular tissues and to broaden current knowledge regarding hypertensive end-organ injury.

Material and Methods

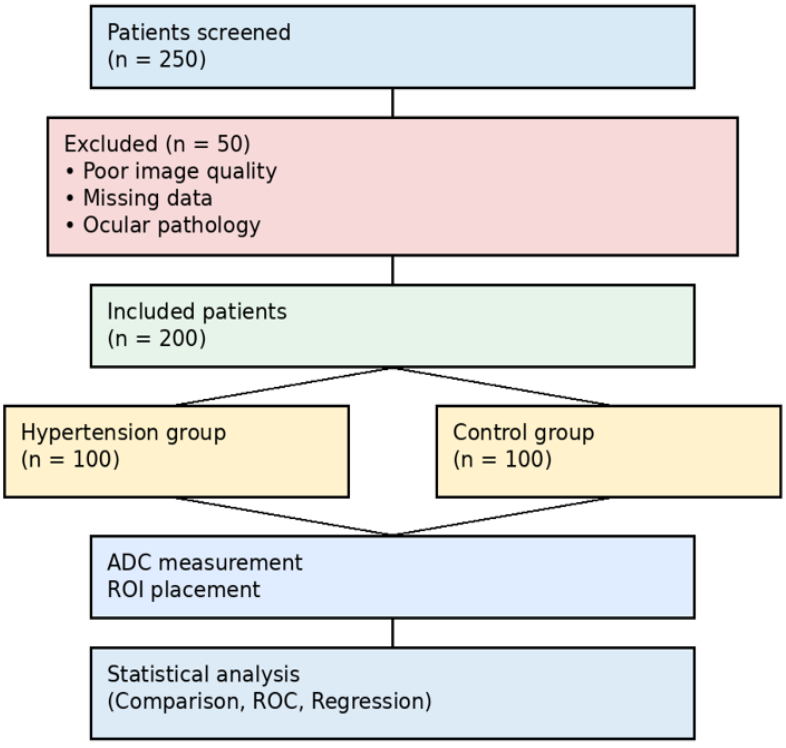
Study Design and Population

This retrospective cross-sectional study was designed to investigate whether hypertension is associated with alterations in vitreous humor diffusion properties assessed by DW-MRI.

Patients who underwent brain and orbital magnetic resonance imaging, including diffusion-weighted imaging, for clinical indications between January 2020 and April 2026 were retrospectively identified from the hospital Picture Archiving and Communication System (PACS) and electronic medical records. Hypertension status was determined from a physician-documented diagnosis recorded in the electronic medical records before the index MRI examination. Controls were operationally defined as individuals without a documented history of hypertension in the available clinical records. Controls were frequency matched, rather than individually matched, to the hypertension group according to the overall age and sex distributions, with an intended group ratio of 1:1; therefore, no fixed patient-to-patient matching pairs were created. Because standardized repeated office or ambulatory blood pressure measurements were not available for all participants, hypertension status was not independently reclassified according to blood pressure measurements obtained at the time of MRI. Eligible participants were required to be 18 years of age or older, to have DW-MRI data including ADC maps, and to possess sufficient image quality to allow reliable vitreous ADC measurements. Participants were required to have complete demographic and clinical records as well as MRI examinations without structural abnormalities that could interfere with ocular assessment. Subjects were excluded in cases of inadequate image quality caused by motion or technical artifacts, previous ocular surgery or trauma, or the presence of ocular disorders such as vitreous hemorrhage, retinal detachment, or intraocular masses. Individuals with diabetic retinopathy, active inflammatory eye disorders, or concomitant neurological and systemic conditions that might influence orbital diffusion findings were not included in the study population. In addition, pregnant or lactating women and subjects with incomplete demographic or clinical records were excluded from further evaluation (Figure 1).

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Figure 1. Flowchart of the study.



MRI Acquisition, ADC Measurement, and Data Collection

MRI examinations were performed using a 1.5-T magnetic resonance system (MAGNETOM Aera, Siemens Healthineers, Erlangen, Germany) with a 20-channel head/neck coil. Axial diffusion-weighted images were acquired using a single-shot echo-planar imaging sequence with b-values of 0 and 1000 s/mm². The acquisition parameters were as follows: repetition time/echo time, 3469/92 ms; section thickness, 5 mm; interslice gap, 1 mm; field of view, 230 × 230 mm; acquisition matrix, 128 × 128; number of excitations, 1; and acquired voxel size, 1.8 × 1.8 × 5.0 mm³. ADC maps were automatically generated on the workstation using a monoexponential signal-decay model.

ADC evaluation of the vitreous humor was carried out through the PACS-based analysis platform. Circular regions of interest with similar dimensions were manually placed in the central vitreous cavity while excluding adjacent ocular structures, including the retina, lens, and optic nerve head. Separate measurements were obtained for each eye, after which a mean ADC value was derived for every subject. Image interpretation and measurements were completed by a radiologist with experience in orbital imaging (D.U.Ç.), who had no access to the clinical characteristics of the participants during the evaluation process.

To assess intra-observer reproducibility, the same radiologist repeated ROI placement and ADC measurements in a randomly selected subset of 100 participants (50 patients

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

with hypertension and 50 controls) after a 4-week interval. During the second assessment, the radiologist was blinded to the initial measurements. Intra-observer agreement was assessed using a two-way mixed-effects, absolute-agreement, single-measure intraclass correlation coefficient model [ICC(A,1)].

For each participant included in the analysis, information regarding demographic characteristics, clinical findings, and imaging measurements was collected. Age and gender were recorded as demographic variables. Clinical data included the presence of hypertension, documented duration of disease where available, and concomitant conditions, including diabetes mellitus. Imaging evaluation included ADC measurements obtained from the right and left vitreous bodies and calculated average vitreous ADC values ($\times 10^{-3}$ mm^2/s). Prior to the analysis phase, all records were anonymized to ensure patient privacy and confidentiality.

Ethical Statement

The study protocol was reviewed and approved by the Gaziantep City Hospital Non-Interventional Clinical Research Ethics Committee (Approval No: 445/2026; Date: March 6, 2026). The study was conducted in accordance with the principles of the Declaration of Helsinki. Due to the retrospective design and the use of anonymized patient data, the requirement for written informed consent was waived by the ethics committee.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria). The distribution of continuous variables was evaluated using the Shapiro–Wilk test together with histogram and Q–Q plot inspection. Normally distributed continuous variables were expressed as mean ± standard deviation and compared using Student's independent-samples t-test. Non-normally distributed variables were expressed as median and interquartile range and compared using the Mann–Whitney U test. Categorical variables were presented as frequencies and percentages and compared using the chi-square test or Fisher's exact test, as appropriate. Effect sizes for between-group differences in continuous variables were reported using Cohen's *d*.

Associations between age and vitreous ADC measurements were evaluated using Pearson's or Spearman's correlation analysis, depending on the distribution of the variables. Hypertension duration was summarized descriptively but was not included in the correlation analyses because sufficiently complete and standardized duration data were not available for all patients. Multivariable linear regression analysis was performed with mean vitreous ADC as the dependent variable and hypertension status, age, sex, and diabetes mellitus as the prespecified independent variables. Linearity was assessed using partial residual plots, normality of residuals using Q–Q plots, and homoscedasticity using plots of standardized residuals against predicted values. Independence of residuals was evaluated using the Durbin–Watson statistic.

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Multicollinearity was assessed using variance inflation factors, with a value >5 considered indicative of relevant multicollinearity. Standardized residuals, leverage values, and Cook's distance were examined to identify potentially influential observations.

Receiver operating characteristic (ROC) curves were constructed for the right, left, and mean vitreous ADC values, ADC asymmetry, and ADC/age ratio, using clinically documented hypertension status as the binary reference variable. ROC curves were generated by plotting sensitivity against 1–specificity across all possible thresholds. The area under the curve (AUC) and its 95% confidence interval were calculated for each parameter. The optimal cut-off value was selected by maximizing the Youden index (sensitivity + specificity − 1), and the corresponding sensitivity and specificity were reported. Pairwise comparisons between correlated AUCs were performed using the two-sided DeLong test.

The extent of missing data was assessed for each study variable. Primary group comparisons, ROC analyses, and multivariable regression analyses were performed using complete cases, and no imputation was applied. Because eligibility required complete demographic, hypertension-status, diabetes-status, and ADC data, no observations were missing for the variables included in the primary analyses. Hypertension duration was analyzed descriptively using the available records only. Intra-observer agreement was evaluated using a two-way mixed-effects, absolute-agreement, single-measure intraclass correlation coefficient model [ICC(A,1)]. All tests were two-sided, and $p<0.05$ was considered statistically significant.

Results

The study included 100 hypertensive patients and 100 control subjects. The mean age was 58.4±10.2 years in the hypertension group and 57.9±9.8 years in the control group (p=0.72). The distribution of sex was similar between the groups (male/female: 54/46 vs. 52/48, p=0.76). The prevalence of diabetes mellitus was significantly higher in the hypertension group compared to the control group (32.0% vs. 12.0%, $p < 0.001$). The mean duration of hypertension in the patient group was 8.6 ± 5.1 years (Table 1).

Table 1. Demographic and Clinical Characteristics of the Study Population.

Variable	**Hypertension (n = 100)**	**Control (n = 100)**	**p-value**
Age (years)	58.4 ± 10.2	57.9 ± 9.8	0.72
Gender (Male/Female)	54 / 46	52 / 48	0.76
Diabetes mellitus, n (%)	32 (32.0%)	12 (12.0%)	<0.001
Hypertension duration (years) (n=100)	8.6 ± 5.1	–	–

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Comparison of vitreous humor ADC values between groups are presented in table 2. The hypertensive group demonstrated significantly lower vitreous humor ADC values compared to the control group. Both right and left vitreous ADC measurements were significantly reduced in hypertensive patients ($p < 0.001$ for both). Mean ADC values were significantly lower in the hypertension group (2.18±0.20 vs. 2.32±0.18×10^{-3} mm^2/s, $p<0.001$). Right–left ADC differences and ADC asymmetry were significantly higher in hypertensive patients, indicating increased heterogeneity in vitreous diffusion properties. The ADC/age ratio was also significantly lower in the hypertensive group ($p = 0.018$). Mean ADC demonstrated a moderate-to-large effect size (Cohen's $d = 0.72$) (Table 2).

Table 2. Comparison of Vitreous Humor ADC Values Between Groups.

Parameter	**Hypertension (n = 100)**	**Control (n = 100)**	**Cohen's d**	**p-value**
Right Vitreous ADC (×10^{-3} mm^2/s)	2.18 ± 0.21	2.32 ± 0.19	0.69	<0.001
Left Vitreous ADC (×10^{-3} mm^2/s)	2.17 ± 0.22	2.31 ± 0.20	0.66	<0.001
Mean ADC (×10^{-3} mm^2/s)	2.18 ± 0.20	2.32 ± 0.18	0.72	<0.001
Right–Left ADC Difference	0.06 ± 0.04	0.04 ± 0.03	0.57	0.003
ADC Asymmetry (%)	2.7 ± 1.9	1.9 ± 1.4	0.48	0.002
ADC/Age Ratio	0.038 ± 0.011	0.041 ± 0.010	0.28	0.018

In the multivariable linear regression model, hypertension was independently associated with lower mean vitreous ADC values ($B = -0.160$, 95% CI: −0.210 to −0.110; standardized $\beta = -0.42$; $p<0.001$). Increasing age was also negatively associated with mean ADC ($B = -0.0035$ per year, 95% CI: −0.0050 to −0.0020; standardized $\beta = -0.28$; $p<0.001$). Diabetes mellitus was independently associated with lower mean ADC values ($B = -0.075$, 95% CI: −0.130 to −0.020; standardized $\beta = -0.19$; $p=0.008$). Sex was not significantly associated with mean ADC ($B = 0.019$, 95% CI: −0.011 to 0.049; standardized $\beta = 0.06$; $p=0.210$) (Table 3).

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Table 3. Multivariable Linear Regression Analysis for Predicting ADC Values.

Variable	**Unstandard. B**	**SE**	**Standardized β**	**95% CI for B**	**p-value**
Hypertension (yes vs. no)	−0.160	0.026	−0.42	−0.210 to −0.110	<0.001
Age (per year)	−0.0035	0.0008	−0.28	−0.0050 to −0.0020	<0.001
Sex (male vs. female)	0.019	0.015	0.06	−0.011 to 0.049	0.210
Diabetes mellitus (yes vs. no)	−0.075	0.028	−0.19	−0.130 to −0.020	0.008

The dependent variable was mean vitreous ADC, expressed in $\times 10^{-3}$ mm²/s. B represents the unstandardized regression coefficient, whereas β represents the standardized regression coefficient. The 95% confidence intervals refer to the unstandardized B coefficients. SE, standard error; CI, confidence interval. Reference categories were absence of hypertension, female sex, and absence of diabetes mellitus.

Exploratory ROC analysis demonstrated that vitreous ADC measures could discriminate between participants with hypertension and controls within the study sample. Mean ADC showed the highest AUC (0.83, 95% CI: 0.77–0.89; p<0.001), with a data-derived cut-off of ≤2.25 $\times 10^{-3}$ mm²/s, corresponding to a sensitivity of 78.0% and specificity of 75.0%. Pairwise comparison using the DeLong test showed that the AUC for mean ADC was significantly higher than those for ADC asymmetry (p=0.004) and the ADC/age ratio (p=0.009), but did not differ significantly from the AUCs for right or left vitreous ADC (p=0.312 and p=0.428, respectively). Because the cut-off and performance estimates were derived and evaluated in the same retrospective case–control sample, these findings should be considered exploratory and should not be interpreted as evidence of clinical diagnostic utility (Table 4, Figure 2).

Table 4. Exploratory ROC Analysis of ADC Measures for Discriminating Between Participants with Hypertension and Controls.

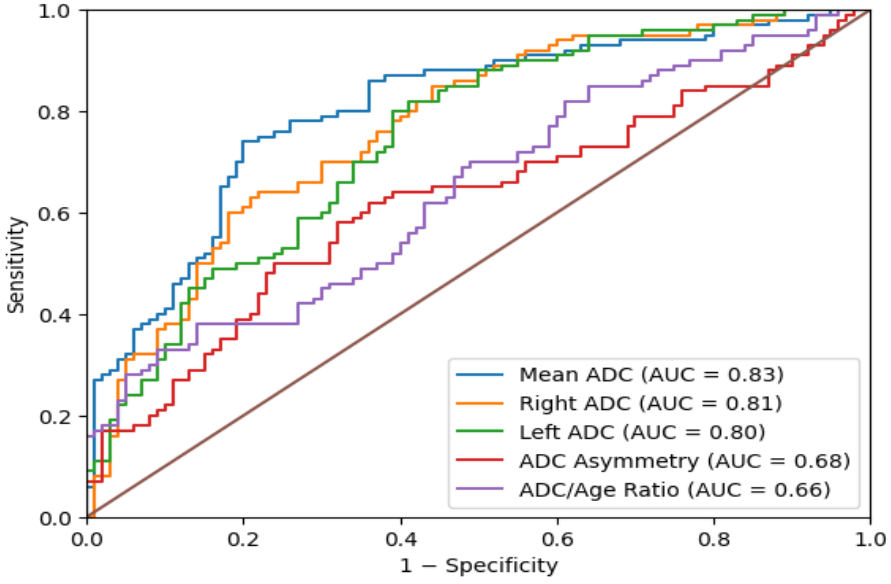
Parameter	**AUC**	**95% CI**	**Cut-off**	**Sensitivity (%)**	**Specificity (%)**	**p-value**
Mean ADC ($\times 10^{-3}$ mm²/s)	0.83	0.77–0.89	≤ 2.25	78.0	75.0	<0.001
Right Vitreous ADC	0.81	0.75–0.87	≤ 2.26	76.0	73.0	<0.001
Left Vitreous ADC	0.80	0.74–0.86	≤ 2.25	75.0	72.0	<0.001

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

ADC Asymmetry (%)	0.68	0.60–0.76	≥ 2.3	62.0	65.0	0.002
ADC/Age Ratio	0.66	0.58–0.74	≤ 0.039	60.0	63.0	0.005
Pairwise Comparison of AUCs (DeLong Test)						**p-value**
Mean ADC vs Right ADC						0.312
Mean ADC vs Left ADC						0.428
Mean ADC vs ADC Asymmetry						0.004
Mean ADC vs ADC/Age Ratio						0.009

Cut-off values were derived and evaluated in the same retrospective case–control sample and were not externally validated; therefore, they should not be interpreted as clinically validated diagnostic thresholds.

Figure 2. ROC curves comparing the diagnostic performance of vitreous humor ADC parameters for detecting hypertension.



Intra-observer reliability analysis based on repeat measurements obtained from 100 randomly selected participants after a 4-week interval demonstrated excellent agreement for vitreous ADC measurements. The intraclass correlation coefficients (ICC) were 0.94 (95% CI: 0.91–0.96) for right vitreous ADC, 0.93 (95% CI: 0.90–0.95) for left vitreous ADC, and 0.96 (95% CI: 0.94–0.97) for mean ADC values (Table 5).

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

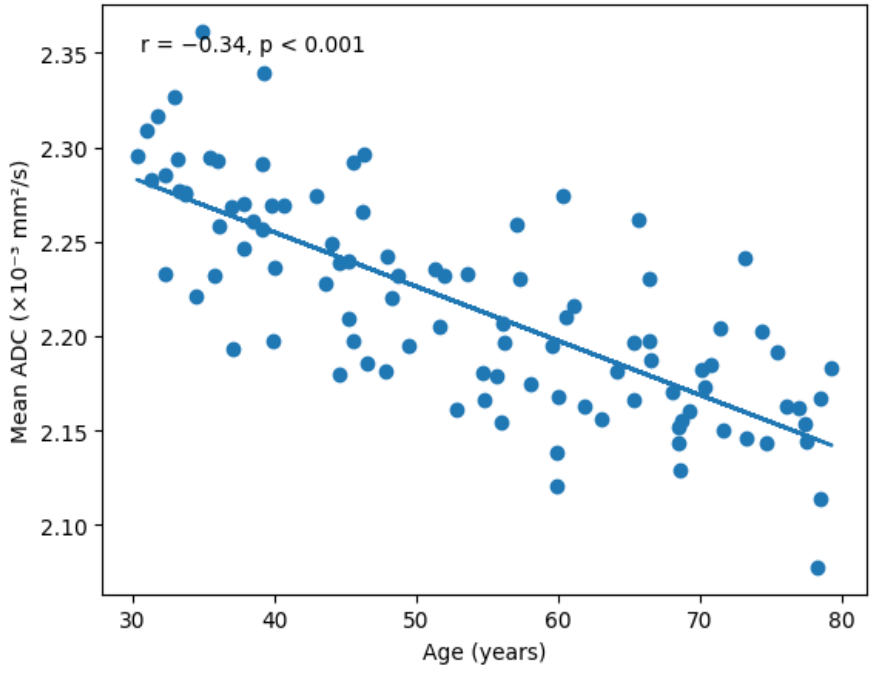
Table 5. Intra-observer reliability of ADC measurements.

Parameter	**ICC**	**95% CI**
Right Vitreous ADC	0.94	0.91–0.96
Left Vitreous ADC	0.93	0.90–0.95
Mean ADC	0.96	0.94–0.97

ICC estimates were calculated using a two-way mixed-effects, absolute-agreement, single-measure model [ICC(A,1)] based on repeat measurements obtained from 100 participants after a 4-week interval. ICC, intraclass correlation coefficient; CI, confidence interval.

Pearson correlation analysis demonstrated a significant inverse association between age and mean vitreous ADC ($r=-0.34$, $p<0.001$), indicating that vitreous ADC values decreased with increasing age. Similar inverse correlations were observed for right and left vitreous ADC values ($r=-0.31$ and $r=-0.29$, respectively; both $p<0.001$). In contrast, ADC asymmetry was weakly positively correlated with age ($r=0.18$, $p=0.021$), whereas the ADC/age ratio showed a strong inverse correlation with age ($r=-0.52$, $p<0.001$) (Figure 3).

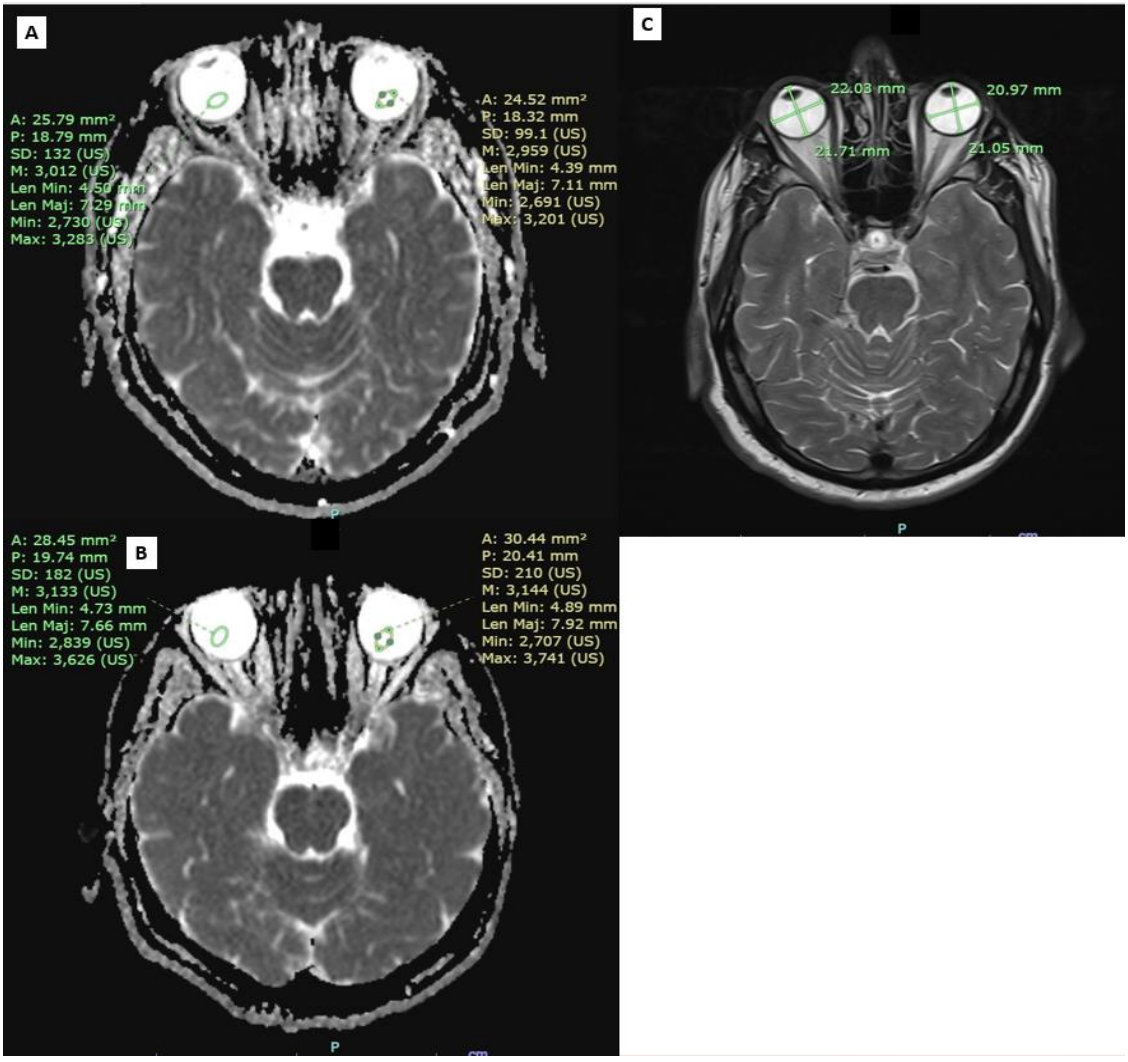
Figure 3. Correlation analysis between age and mean vitreous ADC values.



Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

ROI-based ADC assessments demonstrated consistent placement of the regions of interest within the central vitreous cavity. In the representative images, ROI areas ranged from 24.5 to 30.4 mm², and the within-ROI standard deviations ranged from 0.10 to 0.21 $\times 10^{-3}$ mm²/s. The representative ROI-derived ADC values were 2.17 $\times 10^{-3}$ mm²/s in a participant with hypertension and 2.33 $\times 10^{-3}$ mm²/s in a control participant, consistent with the corresponding group distributions (Figure 4).

Figure 4. Representative orbital diffusion MRI images illustrating vitreous ADC measurement. (A) ADC map from a participant with hypertension showing a manually placed circular ROI within the central vitreous cavity, with an ADC value of 2.17 $\times 10^{-3}$ mm²/s. (B) ADC map from a control participant showing central vitreous ROI placement, with an ADC value of 2.33 $\times 10^{-3}$ mm²/s. (C) Corresponding T2-weighted orbital image used as an anatomical reference for ROI placement. The retina, lens, optic disc, and ocular wall were excluded from the ROIs. ADC, apparent diffusion coefficient; ROI, region of interest.



Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Discussion

In this study, vitreous ADC values were lower in participants with hypertension than in controls, suggesting that systemic hypertension may be associated with measurable differences in the microstructural properties of avascular ocular tissues. Among the evaluated measures, mean vitreous ADC showed the largest between-group effect and the highest within-sample AUC. These observations suggest that hypertension-related alterations in microvascular regulation and tissue fluid homeostasis may influence the vitreous environment in addition to conventionally recognized vascular ocular structures. However, the present findings are exploratory and do not establish a causal relationship or clinical diagnostic utility.

Earlier investigations examining ocular involvement in hypertension have largely concentrated on vascular structures, particularly the retinal and choroidal circulation. Del Pinto et al. and Dziedziak et al. emphasized that hypertensive retinopathy mirrors systemic microvascular injury and may provide clinically relevant information regarding cardiovascular status[4,5]. Unlike those reports, which mainly addressed vascular alterations, our findings suggest that hypertension-related changes may also be detectable within avascular ocular compartments such as the vitreous humor, where measurable microstructural differences were observed.

Reduced vitreous ADC values observed in hypertensive individuals may be related to several mechanisms associated with chronic vascular injury, including endothelial impairment, disturbances in capillary permeability, and alterations in extracellular fluid regulation. Previous studies by Ambrosino et al. and Gallo et al. reported that hypertension can disrupt endothelial integrity and modify tissue fluid dynamics on a systemic level[20,21]. Even though the vitreous humor itself is avascular, its biochemical and structural environment remains closely connected to adjacent retinal and choroidal tissues. Consequently, hypertension-related microvascular abnormalities may indirectly influence diffusion behavior within the vitreous body.

Diffusion-weighted MRI is considered a sensitive imaging technique for identifying subtle alterations in tissue microstructure[23]. Fokkinga et al. demonstrated that diffusion MRI may function as an indirect indicator of tissue integrity across different organ systems[24]. Le Bihan et al. showed that ADC measurements are closely linked to water molecule motion and reflect characteristics of tissue organization and extracellular matrix composition[25]. Gupta et al. and Tanenbaum et al. reported the usefulness of diffusion MRI in the evaluation of orbital and ocular tissues, particularly for detecting changes that may not be apparent on routine imaging[26,27]. Taken together, these investigations support the rationale for using vitreous ADC measurements to investigate microstructural alterations in the eye.

Our findings are in line with earlier reports demonstrating that vitreous ADC measurements may change in different ocular and systemic conditions. Furthermore, Unlu et al. reported abnormal vitreous ADC values in diabetic retinopathy, suggesting that systemic metabolic disturbances may affect vitreous diffusion characteristics[11].

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

Ankamah et al. showed that aging-related vitreous degeneration, characterized by collagen aggregation and progressive liquefaction, can modify water diffusion within the vitreous body[28]. Meral et al. also reported that ADC values tend to decline with advancing age, reflecting gradual microstructural alterations in the vitreous matrix[12]. Consistent with these studies, our findings suggest that hypertension may also be associated with measurable differences in vitreous microstructure.

In the current study, increasing age was associated with lower vitreous ADC values, demonstrating a significant negative correlation. This observation is compatible with previous studies describing age-related degenerative changes within the vitreous body[12,27,28]. In addition, the marked inverse relationship identified for the ADC/age ratio suggests that both aging and systemic vascular alterations may jointly influence vitreous microstructure. Taken together, these results support the view that vitreous diffusion characteristics may be affected by a combination of physiological aging processes and hypertension-related pathological changes.

Multivariable regression analysis demonstrated that hypertension remained independently associated with lower vitreous ADC measurements after adjustment for potential confounders including age, sex, and diabetes mellitus. This finding is noteworthy because diabetes mellitus was more common among hypertensive participants and could potentially influence diffusion characteristics. Despite this imbalance, hypertension continued to show an independent relationship with vitreous ADC reduction, suggesting a possible direct effect of hypertensive vascular pathology on vitreous microstructure.

Previous studies have reported comparable microstructural alterations in other organs affected by chronic hypertension. Diffusion MRI studies involving the brain and kidneys have demonstrated that hypertension may produce measurable microstructural injury beyond the vascular system itself[3,15]. Furthermore, Liu et al. reported that hypertension-related cerebral small vessel disease is associated with detectable diffusion MRI abnormalities in brain tissue[29]. These observations further support the concept that hypertensive damage may have widespread systemic effects involving multiple tissue compartments.

From a diagnostic perspective, in exploratory within-sample ROC analysis, mean vitreous ADC showed discrimination between participants with hypertension and controls. DeLong comparisons indicated that mean ADC had a higher AUC than ADC asymmetry and the ADC/age ratio, whereas its performance was comparable to that of right and left ADC measurements. However, the cut-off value was selected and evaluated in the same retrospective case–control sample, which may result in optimistic estimates of discrimination. Therefore, these results do not establish vitreous ADC as a diagnostic test for hypertension, and the reported threshold should not be used for clinical decision-making without prospective external validation.

The high reproducibility of ADC measurements represents an important strength of this study. The excellent intra-observer agreement indicates that ROI-based vitreous ADC

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

assessment is a reliable and feasible method. Previous diffusion MRI studies in oncology and organ imaging have similarly demonstrated that ADC values can serve as reproducible quantitative biomarkers[16-18].

Compared with previously published studies, the present study provides a novel perspective by focusing on the microstructural properties of the vitreous humor in the context of systemic hypertension. Prior research has largely concentrated on vascular components of ocular involvement, particularly retinal and choroidal changes associated with hypertensive retinopathy[4,5]. In contrast, studies investigating diffusion characteristics of the vitreous humor have primarily been limited to aging and metabolic conditions such as diabetic retinopathy[11,12]. Unlike these studies, our work specifically evaluates the impact of hypertension on an avascular ocular structure using diffusion MRI. Furthermore, we extend previous findings by demonstrating not only significant group differences but also independent associations through multivariable regression analysis and clinically relevant diagnostic performance via ROC analysis. To the best of our knowledge, this is one of the first studies to systematically investigate vitreous ADC alterations in hypertension, thereby highlighting a previously underexplored pathway of hypertensive end-organ effects.

This study has some limitations. First, its retrospective design may introduce selection bias. Second, although major ocular pathologies were excluded, subclinical changes could not be entirely ruled out. Third, the imbalance in diabetes prevalence between groups may have influenced the findings, although this was addressed through multivariable adjustment. Finally, the single-center design may limit generalizability.

Conclusion and Recommendations

In conclusion, participants with hypertension had lower vitreous ADC values than controls, suggesting measurable differences in vitreous microstructure. Mean vitreous ADC showed the strongest association with hypertension and the highest within-sample discrimination among the evaluated imaging measures. However, because of the retrospective case–control design, these findings do not establish causality or support the use of vitreous ADC as a clinical diagnostic test. Prospective multicenter studies incorporating standardized blood pressure assessment, detailed antihypertensive treatment data, comprehensive ophthalmological evaluation, and external validation are needed to confirm these findings and clarify their clinical relevance.

REFERENCES

1. Durante A, Mazzapicchi A, Baiardo Redaelli M. Systemic and Cardiac Microvascular Dysfunction in Hypertension. *International Journal of Molecular Sciences*. 2024;25:13294-9. doi:10.3390/ijms252413294.

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

2. Kućmierz J, Frąk W, Młynarska E, Franczyk B, Rysz J. Molecular Interactions of Arterial Hypertension in Its Target Organs. *International Journal of Molecular Sciences*. 2021;22:9669-76. doi:10.3390/ijms22189669.

3. Sun D, Wang J, Shao W, et al. Pathogenesis and damage targets of hypertensive kidney injury. *Journal of Translational Internal Medicine*. 2020;8:205-9. doi:10.2478/jtim-2020-0033.

4. Del Pinto R, Mulè G, Vadalà M, et al. Arterial Hypertension and the Hidden Disease of the Eye: Diagnostic Tools and Therapeutic Strategies. *Nutrients*. 2022;14:2200-9. doi:10.3390/nu14112200.

5. Dziedziak J, Zaleska-Żmijewska A, Szaflik JP, Cudnoch-Jędrzejewska A. Impact of Arterial Hypertension on the Eye: A Review of the Pathogenesis, Diagnostic Methods, and Treatment of Hypertensive Retinopathy. *Medical Science Monitor*. 2022;28:935135. doi:10.12659/msm.935135.

6. Singh RB, Saini C, Shergill S, Agarwal A. Window to the circulatory system: Ocular manifestations of cardiovascular diseases. *European Journal of Ophthalmology*. 2020;30:1207-19. doi:10.1177/1120672120914232.

7. Sun C, Ladores C, Hong J, et al. Systemic hypertension associated retinal microvascular changes can be detected with optical coherence tomography angiography. *Scientific Reports*. 2020;10:1-10. doi:10.1038/s41598-020-66736-w.

8. Zhang R, Li B, Li H, Asiedu K. Extracellular-Matrix Mechanics Regulate the Ocular Physiological and Pathological Activities. *Journal of Ophthalmology*. 2023;2023:1-11. doi:10.1155/2023/7626920.

9. Mishra D, Gade S, Glover K, Sheshala R, Singh TRR. Vitreous Humor: Composition, Characteristics and Implication on Intravitreal Drug Delivery. *Current Eye Research*. 2022;48:208-18. doi:10.1080/02713683.2022.2119254.

10. Boneva S, Haritoglou C, Schultheiss M, Binder S, Sebag J. Die Rolle des Glaskörpers in der Pathogenese der exsudativen altersabhängigen Makuladegeneration. *Die Ophthalmologie*. 2023;120:992-8. doi:10.1007/s00347-023-01934-1.

11. Unlu S, Ilgar M. Diffusion MRI Evaluation of Vitreous Humor Changes in Diabetic Retinopathy Patients. *Medical Records*. 2022;4:187-90. doi:10.37990/medr.1054427.

12. Meral İ, Bilgili Y. Diffusion Changes in the Vitreous Humor of the Eye during Aging. *American Journal of Neuroradiology*. 2011;32:1563-6. doi:10.3174/ajnr.A2543.

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr

13. Pacinella G, Ciaccio AM, Tuttolomondo A. Endothelial Dysfunction and Chronic Inflammation: The Cornerstones of Vascular Alterations in Age-Related Diseases. *International Journal of Molecular Sciences*. 2022;23:15722. doi:10.3390/ijms232415722.

14. Sheikh AM, Yano S, Tabassum S, Nagai A. The Role of the Vascular System in Degenerative Diseases: Mechanisms and Implications. *International Journal of Molecular Sciences*. 2024;25:2169-77. doi:10.3390/ijms25042169.

15. Mohamed Osman NM, Abdel Kader M, Aziz Nasr TAEL, Sharawy MA, Keryakos HKH. The Role of Diffusion-Weighted MRI and Apparent Diffusion Coefficient in Assessment of Diabetic Kidney Disease: Preliminary Experience Study. *International Journal of Nephrology and Renovascular Disease*. 2021;Volume 14:1-10. doi:10.2147/ijnrd.S254022.

16. Fliedner FP, Engel TB, El-Ali HH, Hansen AE, Kjaer A. Diffusion weighted magnetic resonance imaging (DW-MRI) as a non-invasive, tissue cellularity marker to monitor cancer treatment response. *BMC Cancer*. 2020;20:1-9. doi:10.1186/s12885-020-6617-x.

17. Balaha HM, Ayyad SM, Alksas A, et al. Precise Prostate Cancer Assessment Using IVIM-Based Parametric Estimation of Blood Diffusion from DW-MRI. *Bioengineering*. 2024;11:629-36. doi:10.3390/bioengineering11060629.

18. Raju J, Shyna A, John A, Pillai MJ. Transforming Medical Imaging with IVIM MR Imaging: A Comprehensive Review of Advances and Challenges in Perfusion and Diffusion Analysis. *Applied Magnetic Resonance*. 2025;56:803-43. doi:10.1007/s00723-025-01758-z.

19. Hwang M, Shin SS, Thimm MA, et al. Apparent Diffusion Coefficient (ADC) of the vitreous humor and Susceptibility Weighted Imaging (SWI) of the retina in abused children with retinal hemorrhages. *Clinical Imaging*. 2017;44:38-41. doi:10.1016/j.clinimag.2017.03.017.

20. Gallo G, Volpe M, Savoia C. Endothelial Dysfunction in Hypertension: Current Concepts and Clinical Implications. *Frontiers in Medicine*. 2022;8:798958. doi:10.3389/fmed.2021.798958.

21. Ambrosino P, Bachetti T, D'Anna SE, et al. Mechanisms and Clinical Implications of Endothelial Dysfunction in Arterial Hypertension. *Journal of Cardiovascular Development and Disease*. 2022;9:136- 42. doi:10.3390/jcdd9050136.

22. Humphrey JD. Mechanisms of Vascular Remodeling in Hypertension. *American Journal of Hypertension*. 2021;34:432-41. doi:10.1093/ajh/hpaa195.

23. Le Bihan D, Iima M. Diffusion Magnetic Resonance Imaging: What Water Tells Us about Biological Tissues. *PLOS Biology*. 2015;13:e1002203. doi:10.1371/journal.pbio.1002203.

24. Fokkinga E, Hernandez-Tamames JA, Ianus A, et al. Advanced Diffusion-Weighted MRI for Cancer Microstructure Assessment in Body Imaging, and Its Relationship With Histology. *Journal of Magnetic Resonance Imaging*. 2023;60:1278-304. doi:10.1002/jmri.29144.

25. Bihan DL. Molecular diffusion, tissue microdynamics and microstructure. *NMR in Biomedicine*. 2005;8:375-86. doi:10.1002/nbm.1940080711.

26. Tanenbaum RE, Lobo R, Kahana A, Wester ST. Advances in magnetic resonance imaging of orbital disease. *Canadian Journal of Ophthalmology*. 2022;57:217-27. doi:10.1016/j.jcjo.2021.04.025.

27. Gupta L, Peterson EL, Williams C, et al. Diffusion-Weighted Imaging of the Orbit: A Case Series and Systematic Review. *Ophthalmic Plastic & Reconstructive Surgery*. 2023;39:407-18. doi:10.1097/iop.0000000000002325.

28. Ankamah E, Sebag J, Ng E, Nolan JM. Vitreous Antioxidants, Degeneration, and Vitreo-Retinopathy: Exploring the Links. *Antioxidants*. 2019;9:7-15. doi:10.3390/antiox9010007.

29. Liu N, Li N, Cao X, et al. More severe vascular remodeling in deep brain regions caused by hemodynamic differences is a potential mechanism of hypertensive cerebral small vessel disease. *Journal of Cerebral Blood Flow & Metabolism*. 2025;45:1593-605. doi:10.1177/0271678x251327919.

Istanbul Gelisim University Journal of Health Sciences (IGUSABDER) is indexed by TUBITAK ULAKBIM TR Index.
Web site: https://dergipark.org.tr/en/pub/igusabder
Contact: igusabder@gelisim.edu.tr