ORIGINAL ARTICLE

THE EVALUATION OF THE PARAMETERS AFFECTING ADC VALUES OF EXTRAOCULAR MUSCLES WITH ECHOPLANAR DIFFUSION-WEIGHTED IMAGING BY 3 TESLA MRI

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ABSTRACT

OBJECTIVE: The study aims to determine the parameters affecting Apparent diffusion coefficient (ADC) values of extraocular muscles (EOM). **METHODS:** This retrospective descriptive study was conducted with clinically normal 300 patients (150 females, 150 males; mean age, 42,93 – 19,19 - range 18-96 years-old). MRI had performed by applying 0-1000 s/mm^2 b value and EPI technique. ADC values were evaluated from medial and lateral rectus muscles and classified according to four main parameters [Age, side (right/Left), gender and muscle type]. **RESULTS:** Age: ADC values of EOM statistically increased with age (p:<0,05) at the rate of reaching a maximum of 0.413 10^{-3} mm^2/s. The difference in ADC values was approximately 40% from 18 years old to the maximum age. Side, gender, muscle type: Graphically and numerically, ADC values of males were higher than females in the right eye. This situation was statistically more significant in the 18-30 age group (p: 0,047 for right medial rectus, p: 0,01 for right lateral rectus). There was no significant difference between the right and left eyes in the total population. Although the presence a divergence in the ADC values between females and males in the right eye, the dominant and recessive eye s values were similar (p> 0,05). **CONCLUSION:** It is not possible to make mention an absolute normal ADC value for EOM. The ADC values vary according to age and gender. Age is the main parameter which affects ADC values. Gender is effective on values in the early age group and right eye (mainly dominant eye in the total population). The side of EOM and muscle type are not parameters that significantly affect the ADC values.

Keywords: orbit,extraocular muscles, diffusion weighted imaging, apparent diffusion coefficient, magnetic resonance imaging, echoplanar imaging

Introduction

Diffusion-weighted imaging (DWI) is a method ofmagnetic resonance imaging (MRI) based on the detection of water movements at the cellular level.[1,2] DWI is a noninvasive, non-contrast MRI method as well as can be obtained short time. It is mostly used for the diagnosis of brain ischemia and infarct. Nowadays, the usage of DWI comprises whole body. Benign and malignant thyroid nodules, cervical lymph nodes, parathyroid lesions and parotid masses are the most frequent fields using DWI in head and neck radiology.[3,4] It is an auxiliary technique in the radiological examination of orbits. Extra orbital muscles (EOM) are one of the major orbital anatomical structures evaluated with DWI. Although most of the studies focus on thyroid ophthalmopathy, it is known that DWI is more effective in detecting malignancy in orbital tumors, distinguishing orbital pseudotumor from orbital lymphoma, evaluating orbital cellulitis,

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abscess, detecting inflammatory lesions and infarction of the optic nerve.[3,5] Also, ADC evaluation of adjacent anatomic structures such as the lacrimal gland is among actual topics nowadays.[6] Apparent diffusion coefficient (ADC) is the main calculation method in the evaluation of DWI.[7] Therefore, it is crucial to know normal ADC values of EOM.[8,9] Although echoplanar imaging (EPI) is used more in DWI modalities, it is less researched than turbo spine echo (TSE) which is the alternative technique.[1,8,9,10] As far as we know, although there are studies comparing pathological values with normal values, there is no any study detailed and directly targeting on the parameters affecting ADC values of EOM, especially using EPI technique. In the study, extrinsic factors were fixed and major intrinsic factors that could affect the ADC value were evaluated. The study aims to determine the parameters in four different main groups as age, side of EOM, gender and muscle type that affect normal ADC values of EPI DWI technique.

Materials and Methods

Patient selection:

The ethic approval was taken from Human Research Ethics Committee before starting the study with the document number: 2021/200211. Power analysis was performed with a G-power test. The sample group was calculated between 290 and 310 for %90 power and with 0.05 alfa parameter. Totally, 349 patients were evaluated and 300 patients were included in the study. Patient sample was sufficient.

The images were selected among the cranial diffusion MRIs performed between April 2018 and November 2020. We excluded thirty-two patients from the study because of the following medical reasons: 24 patients had thyroid ophthalmopathy or known thyroid disease, 4 patients had lymphoma or leukemia, 2 patients had orbital pseudotumour, and 2 patients had trauma-related EOM oedema. Also, seventeen MRIs with artefacts were not proper for evaluation and were excluded from study.

MRI evaluation:

The MRI was performed on a 3 Tesla MRI device (Siemens Skyra 3 Tesla, 2016, Germany) using 12 canal head coils. The single-shot echoplanar (SS-SE-EPI) sequence technique was applied. The used MRI parameters were as follows: (TR / TE; 2500/140 ms, FOV; 230x 230 mm, matrix size; 128 x128 pixels, acquisition time; 2, the time interval between leading edges of diffusion gradients (Δ) / pulse gradient duration (δ): 39/32 ms; slice thickness / gap: 4 mm / 1 2 mm; flip angle (FA): 900, number of excitations (NEX) = 1. The data acquisition time for DWI was 1.33 min. b-values were 0 and 1000 s/mm^2.

ADC maps and DWI images evaluated together. The ADC values of the muscles were measured from three different points at the workstation. The Region-of-interest (ROI) were applied as 5.16 mm. The measurements were made separately from the right and left orbits for each patient. ADC values of two dominant EOM which proper for evaluation [lateral rectus (LatR) and medial rectus (MedR) muscles] were measured. (Fig.1).

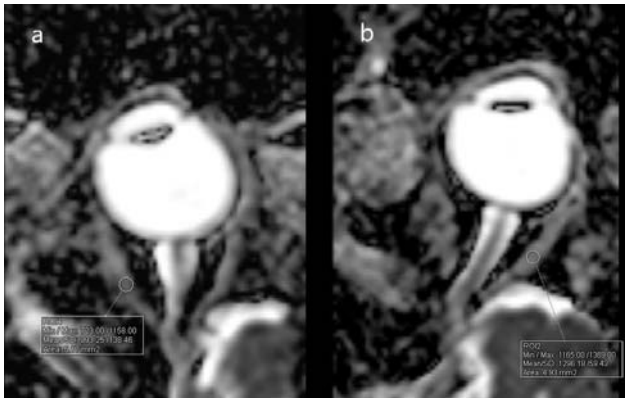


Figure 1: a. The measurement of ADC values for Lateral Rectus Muscles **b.** The measurement of ADC values for Medial Rectus Muscles

Statistical analysis:

The calculations were made separately by two radiologists who are long-term experienced. When results were discordant, the images were re-evaluated by both authors. The patients were classified according to age groups (as 18-30, 31-50, and >50 years old) after the ADC values were obtained for each bilateral muscles and both genders.

The data were enrolled on Microsoft office excel file (Excel 2010, Microsoft). Statistical software (SPSS, version 22.0, IBM) was used for analysis. Continuous variables were expressed as mean– SD (Standard deviation) values. Qualitative variables were expressed

as counts and percentages. Student's t-test was performed for the calculation of the means of normal distributed data and comparison age groups. Mann-Whitney Utest was used for parametric data that did not show normal distribution. Pearson chi-square ($\chi 2$) analysis was used to evaluate the relationship between variables. P <0.05 values were accepted statistically significant.

Results

This is a retrospective study performed on 300 clinically normal patients (150 females, 150 males; mean age: 42.93 – 19.19 years old, age range: 18-96). ADC values were calculated according to the age group, gender, side and separately for two muscles (MedR and LatR).

In the 18-30 age group, the lowest mean values were 1.0500 – 0.15275 $10^{-3}mm^2/s$ for the right MedR in the females, while the highest mean values were 1.1950 – 0.12964 $10^{-3}mm^2/s$ for the right LatR in males. In the 30-50 age group, the lowest mean values were 1.2100 – 0.08151 $10^{-3}mm^2/s$ for the right LatR in females, while the highest mean values were 1.3130 – 0.13801 $10^{-3}mm^2/s$ for the left MedR in females. In the > 50 age group, the lowest mean values were 1.3280 – 0.12506 $10^{-3}mm^2/s$ for the right MedR in females, while the highest mean values were 1.4980 – 0.24899 $10^{-3}mm^2/s$ in the right LatR in males. Totally, the lowest values were 1.0500 – 0.15275 $10^{-3}mm^2/s$ for the 18-30 age group in the females, while the highest values were 1.4980 – 0.24899 $10^{-3}mm^2/s$ for the right LatR in the age> 50 years (Fig.2) (Tab.1).

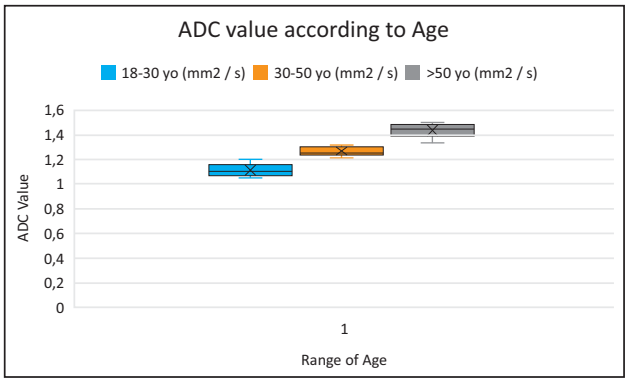


Figure 2: Box plot of the ADC value range according to age groups. It is clearly seen increasing of ADC with age in the graphic.

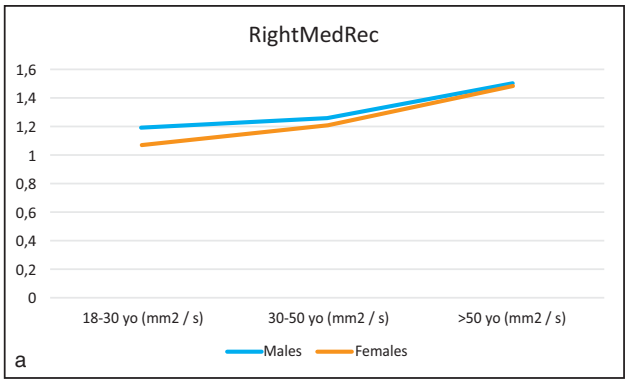
Distribution according to Muscle/ Gender/Age group/side	Gender	18-30 yo ($10^{-3}mm^2/s$)	30-50 yo ($10^{-3}mm^2/s$)	>50 yo ($10^{-3}mm^2/s$)
Right MR	Males	1,1080 ± 0,15831	1,2430 ± 0,21975	1,4570 ± 0,14855
	Females	1,0500 ± 0,15275	1,2380 ± 0,10528	1,3280 ± 0,12506
Right LR	Males	1,1950 ± 0,12964	1,2610 ± 0,15954	1,4980 ± 0,24899
	Females	1,0700 ± 0,14414	1,2100 ± 0,08151	1,4830 ± 0,18476
Left MR	Males	1,1260 ± 0,13713	1,2430 ± 0,16984	1,4390 ± 0,19017
	Females	1,0830 ± 0,12293	1,3130 ± 0,13801	1,3720 ± 0,19871
Left LR	Males	1,1650 ± 0,13352	1,2520 ± 0,09566	1,4360 ± 0,24305
	Females	1,1020 ± 0,12218	1,3120 ± 0,09705	1,4470 ± 0,22598
ADC value according to groups in total	**Total (mm^2/s)**	**18-30 yo ($10^{-3}mm^2/s$)**	**30-50 yo ($10^{-3}mm^2/s$)**	**>50 yo ($10^{-3}mm^2/s$)**
Total	1,2678 ± 0,15553	1,1121 ± 0,13763	1,2590 ± 0,13333	1,4325 ± 0,19565
Females	1,2506 ± 0,14153	1,0762 ± 0,13552	1,2682 ± 0,10546	1,4075 ± 0,18363
Males	1,2963 ± 0,16951	1,1493 ± 0,13965	1,2822 ± 0,16119	1,4575 ± 0,20769
Right	1,2617 ± 0,15484	1,1057 ± 0,14617	1,2380 ± 0,14152	1,4415 ± 0,17684
Left	1,2741 ± 0,15618	1,1190 ± 0,12894	1,2800 ± 0,12514	1,4235 ± 0,21447
MedRec	1,2500 ± 0,15554	1,0917 ± 0,14278	1,2592 ± 0,15822	1,3990 ± 0,16562
LatRec	1,2692 ± 0,15550	1,1330 ± 0,13237	1,2587 ± 0,10844	1,4160 ± 0,22569

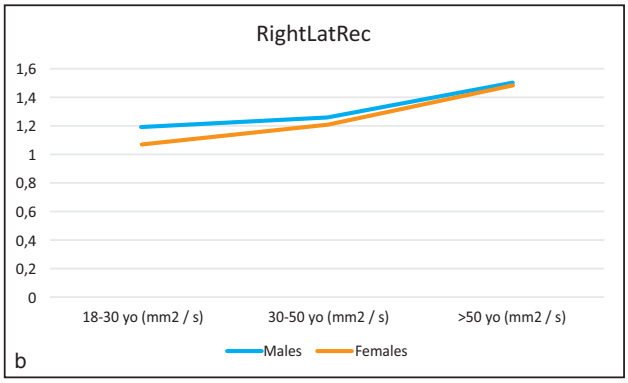
Table 1: Distribution of ADC values according to Muscle / Gender / Age group / Side Abbreviation: yo (years old).

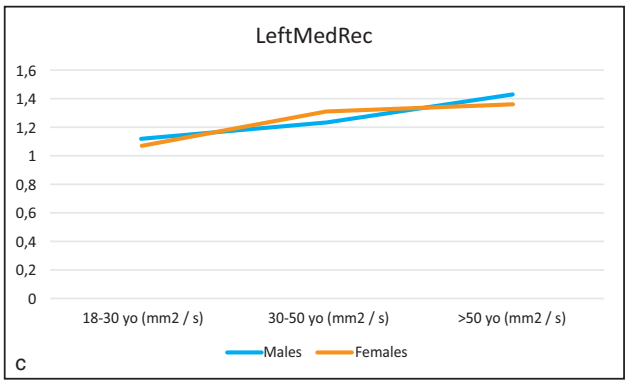
The ADC values were higher in males than females for the right eye numerically and graphically. There was a statistically significant difference in the 18-30 age group (p-value was 0,047a for right medial rectus between males and females; p-value was 0,001a for left medial rectus between males and females). We didn't detect a significant difference in the 30-50 and >50 age groups between genders (p>0,05 a). In addition, there was a relationship between age groups and ADC values similar to the box plot (p<0,05). ADC values increased with ageing (Fig.3A,B).

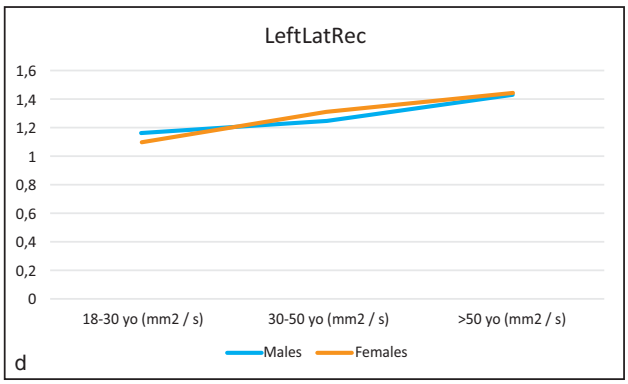
It was observed that there was no difference reflected in the graph between the genders in the left eye, unlike the right one. In both muscles, the female ADC values in the 30-50 age group were higher than the male values. The increase in ADC value with ageing is also clearly seen in these graphics (Fig.3C,D).

For eachage groups, both muscle s (lateral and medial rectus) ADC were compared in pairs using the student s t-test.









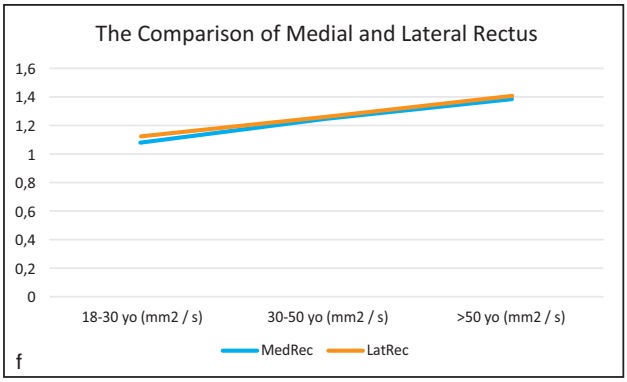


Figure 3: a. ADC distribution in Right Medial Rectus muscle according to age groups and gender **b.** ADC distribution in Right Lateral Rectus muscle according to age groups and gender **c.** ADC distribution in Left Medial Rectus muscle according to age groups and gender **d.** ADC distribution in Left Lateral Rectus muscle according to age groups and gender **e.** The comparison of right and left eyes according to ADC values and age groups **f.** The comparison of medial and lateral rectus muscles according to ADC values and age groups

The mean of both muscle s ADCfor the range age >50 years old is much stronger than the mean of both muscle s ADC for the range age 30-50 years old t (158) = 6,42; p<0,001. There was a significant difference between the means of the two groups.

The mean of both muscle s ADC for the range age > 50 years oldis much stronger than the mean of both muscle ADC for the range age 18-30 years old t (158) = 11,81; p<0,001. There was a significant difference between the means of the two groups.

The mean of both muscle s ADC for the range age 30-50 years old is much stronger than the mean of both muscle s ADC for the range age 18-30 years old t (158) = 6,67; p<0,001. There was a statistically significant difference between the means of the two groups.

The data confirmed with Mann-Whitney U test (p<0,05). ADC value increased with ageing to statistically

significant degree.
In the separated evaluation for every parameter; In the 18-30 age group, the lowest ADC valueswere 1.0762 – 0.1352 $10^{-3}mm^2/s$ in females and 1.0917 – 0.14278 $10^{-3}mm^2/s$ in MedR, while the highest values were 1.1493 – 0.13965 $10^{-3}mm^2/s$ in males and 1.1330 – 0.13237 $10^{-3}mm^2/s$ in the Lat R. In the 30-50 age group, the lowest values were 1.2380 – 0.14152 $10^{-3}mm^2/s$ in the right eye, the highest values were 1.2822 – 0.16119 $10^{-3}mm^2/s$ in the males, and 1.2800 – 0.12514 $10^{-3}mm^2/s$ in the left eye. In the > 50 groups, the lowest values were 1.3990 – 0.16562 $10^{-3}mm^2/s$ in the Med R, while the highest values were 1.4575 – 0.20769 $10^{-3}mm^2/s$ in males (Tab.2).

	Muscle	18-30 yo	30-50 yo	>50 yo
The comparison of Male / Female ADC values	RMR	0.047[a]	0.407	0.055
	RLR	0.001[a]	0.063	0.951
	LMR	0.171	0.346	0.355
	LLR	0.402	0.535	0.369
Females	RMR/LMR	0.865	0.275	0.161
	RLR/LLR	0.718	0.630	0.924
Males	RMR/LMR	0.855	0,316	0.811
	RLR/LLR	0.388	0,254	0.081

Table 2: Distribution of p values and statistical analysis according to Muscle / Gender / Age group / Side Abbreviation: yo (years old).

In the comparison, there was no statistically significant difference between right and left eyes or between medial and lateral rectus muscles in terms of ADC values. The increase in ADC value with ageing also reflected in these graphs (Fig.3 E,F).
Totally, the mean of ADC values of all age groups

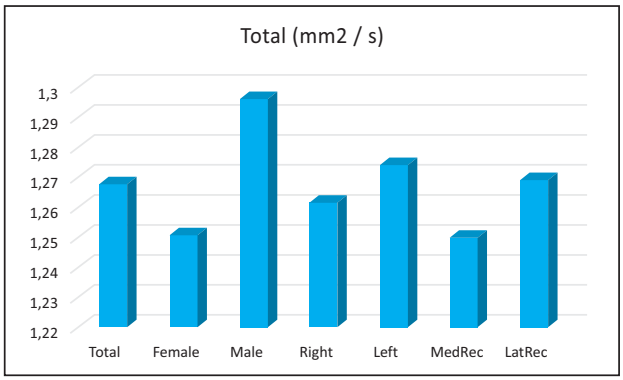


Figure 4: Comparison of the main groups totally

was 1.2678 – 0.15553 $10^{-3}mm^2/s$. The median age of the ADC map was 46,496 – 4,783 (Age – SD). The lowest ADC values were 1.2500 – 0.15554 $10^{-3}mm^2/s$ in the MedR and 1.2506 – 0.14153 $10^{-3}mm^2/s$ in the females, while the highest values were 1.2963 – 0.16951 $10^{-3}mm^2/s$ in males (Fig.4).

Discussion

MRI is a non-radioactive advanced radiological method, frequently used in the brain and head imaging, and showing the soft tissue anatomy in detail (11-13).DWI MRI is one of the advanced examination methods. In EOM evaluation, except for EPI, the TSE technique is also used.[10] Although it is the most performed technique, EPI is not preferred in previous scientific research due to technical difficulties.[1,10,14,15] In our study, measurements were made clearly in our 3 tesla device.

Extrinsic factors:
The subject of our study is intrinsic factors that affect ADC values. Apart from this, there are also extrinsic factors due to the technique. The '' b value '' is the most important one among these factors.[16] If the amplitude and duration of the gradient field increases or intervals of the gradients wide, the b value increases.[17] To detect slow-moving water molecules and smaller diffusion distances, b values should be higher.[18] In the studies of Kilin arslan[9] and Politi,[1] respectively, the b value was applied as 0-1000 s / mm^2 and 0-700 s/mm^2. Therefore, there was a significant difference between the ADC values in the proportion of b values. Respectively, the ADC values were 1765 $10^{-3}mm^2/s$ for Politi's study,[1] while 1299-1367 $10^{-3}mm^2/s$ for Kili arslan's study.[9] The last study on this subject belonged to Liu et al. (2021) and confirmed this difference.[19] If a correction is made according to the formula of "b ADC=1", respectively, normal values return to 1299-1367 10^{-3} mm^2/s and 1235 $10^{-3}mm^2/s$ in Politi's[1] and Kilin arslan's[9] studies. Ultimately, they reach our scale.[20] The b value used in our study was 0-1000 s/mm^2.
In addition, comparison problems resulting from the research method is another question. In Politi's study,[1] the ADC values of each patient were normalized

according to the anterior right thalamus. The main message tried to be given herein is that extrinsic factors are important for comparing different studies. However, since our study was performed on a single device and the scanning parameters were the same for every patient, the extrinsic factors were stable. Therefore, there was no expected effect on the study's result.

Intrinsic factors:
The main evaluated parameters as intrinsic factors were age group, gender, side and muscle group. Especially age was our main parameter.

Age groups:
In our study, the mean of the ADC values was ranged between 1.080-1.195 10^{-3} mm^2/s for 18 -30 years old, 1.210-1.313 10^{-3} mm^2/s for 30-50 years old and 1.328-1.483 10^{-3} mm^2/s for >50 years old. ADC values showed a statistically significant increase with age in our study ($p<0.001$). ADC values are affected by many factors such as oedema, fibrosis, glycosaminoglycan, fat content and cellularity. The value increase with ageing because of changing muscle molecular contents.[1,10,21] Theoretically, the ADC value decreases with cellularity, increases with fat deposition. The factors increasing ADC values will be dominant with ageing. The other key point that our study show here is the rate of this increase in ADC value. The maximum difference was 0,413 mm^2/s. In other words, the changes that occur as a result of ageing roughly increased the ADC value by 40%. Although this study is the first to evaluate intrinsic factors affecting ADC values in extraocular muscles, there are similar studies for other organs. Tang et al. have shown that kidney ADC values increase with ageing. In this study, the mean age was 40 years old for the kidney.[22] In our study, this mean age for EOM was 46.496 – 4.783. In addition, there is an interesting novel study showing the increase in ADC values of the brain in the fetus. This area is open to future research within EOM.[23]

Gender:
Male s ADC values in the right eye were higher than females numerically and graphically. It was statistically significant in the 18-30 age group. There was no gender difference for the left eye.Given that the right eye is dominant in most of the population, the gender difference was only in the dominant eye. In a Pancreas DWI study, gender was found as an important factor in changing ADC values. However, ageing did not influence organ ADC values according to this study.[24] In other words, the factors affecting the ADC value vary according to the anatomical region. According to our study, gender is a partially effective factor on the ADC value.

Dominance and side:
There were no significant difference in ADC values between genders and right /left eyes ($p >0,05$). In the general population, the right eye is overwhelmingly dominant.[25,26] Side or dominancy are not influenced factors on ADC.

Muscle Type:
The ADC value also varies according to the tissue. For example, considering the brain where the technique is used the most, the average ADC values are for white matter: 600-800 10^{-3} mm^2/s, for deep grey matter: 700-850 10^{-3} mm^2/s, for cortical grey matter: 800-1000 10^{-3} mm^2/s. As can be seen, ADC values are evaluated within a certain scale, not as a single number. This difference refers to the shifts within the scale caused by intrinsic and extrinsic factors.[27,28] Like the tissues given above, this shift is present for also the EOMs. The range in the study varies between 1,0500 and 1,4980 10^{-3} mm^2/s. The ADC values of EOMs have a different scale within themselves. However, there is no difference separately for every muscle groups. For EOM, muscle type is not a determining factor in ADC value ($p>0,05$).

Conclusion

It was observed that the total ADC value of all age groups was 1.2678 – 0.15553 $10^{-3}mm^2/s$. Median age of ADC map was (Age – SD) corresponding to this value was 46,496 – 4,783.
ADC values increasewith age ($p<0,05$). Age is the main factor affecting the ADC values of EOM. In the early and late age groups comparison, the maximum difference was 0,413 10^{-3} mm^2/s. In other words, the changes that occur as a result of ageing roughly increased the ADC value by 40%.

Graphically and numerically, male ADC values were higher in the right eye than females. This situation was statistically significant in the 18-30 age group (p: 0.047 for right medial rectus, p: 0.01 for right lateral rectus). Unlike, this situation wasn t valid for left eye.Gender is the partially effective factor on ADC values of EOM.

Although there was a divergence in the ADC values of the female and male gender in the right eye, there was no statistically significant difference between the right and left eyes in the total population. (p> 0.05).Side or dominancy are not influenced factors on ADC.

As a result, it is not possible to make mention an absolute normal ADC value for EOM. Age and partially gender are effective factors on ADC value, while side and muscle type are not.

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