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IMPACT OF DIFFERENTIAL PATTERN OF APPARENT DIFFUSION COEFFICIENT (ADC) OF ORBITAL TISSUES IN THYROID ASSOCIATED ORBITOPATHY (TAO)

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ABSTRACT

AIM-To study the Apparent diffusion coefficient (ADC) values in orbital tissues in patients with thyroid associated orbitopathy (TAO). METHODS- 65 TAO patients and data of 65 controls were included. ADC values of extraocular muscles (EOMs) and orbital fat were calculated. The ADC values of mild, moderate-severe and sight threatening stages were compared. RESULTS- A significant statistically difference was present between the ADC values of cases and controls ($p<0.001$). The mild cases having normal muscle thickness on conventional MRI also showed higher ADC values. CONCLUSION- A differential pattern exists between the various severity stages and activity phases of TAO.

KEYWORDS: Thyroid associated ophthalmopathy, Apparent diffusion coefficient, extraocular muscles, orbital fat, Magnetic resonance imaging.

INTRODUCTION

Thyroid associated orbitopathy (TAO) is an autoimmune inflammatory orbital disorder, known to occur in hyperthyroid, euthyroid or hypothyroid disease states. The disease follows the Rundel's curve.[1] The inflammation involves various orbital tissues including extraocular muscles (EOMs) and orbital fat. The orbitopathy is assessed in terms of activity and severity.[2]

The presence of inflammation in the orbital tissues and its quantification can be assessed by using Apparent diffusion coefficient (ADC) values obtained by diffusion weighted imaging (DWI). It analyses the movement of water at the cellular level. Thus, providing a non-invasive characterization of micro-structural changes.[3]

The authors hypothesized that ADC provides evidence of orbital tissue inflammation in all stages of thyroid associated orbitopathy. With this background, the authors proposed to study the ADC values in all orbital tissues in TAO patients and establish its differential pattern in various stages.

MATERIALS AND METHODS

The authors confirm adherence to the tenets of the Declaration of Helsinki. A case control analysis was conducted at King George's Medical University, Lucknow, after institutional review board clearance. 65 patients of TAO were included in the study (45 females, 20 males with mean age 39.2 ± 8.3 years). The orbital data of 65 age matched controls was retrieved from institutional patients undergoing MRI for diseases other than TAO. Patients with co-morbidities of the orbit (trauma, non-specific orbital inflammatory diseases, any orbital mass), having any contraindication to MRI, patients on radioactive iodine or having strabismus due to causes other than TAO, were excluded from the study. The activity of the disease was assessed using the clinical activity score (CAS). The disease was labelled as active when the CAS was more than 3. The severity of the

disease was classified as mild, moderate-severe and sight threatening stages according to EUGOGO guidelines.

Imaging techniques

MRI was performed in all the patients after evaluation of CAS and EUGOGO staging. To minimize the eye movements, the MRI was performed with the patient's eye closed in primary position. The study was performed on SIGNA EXCITE 1.5T GEMSOW (GE) MR SCANNER installed in Department of Radiodiagnosis, King George's Medical University, Lucknow.

The imaging parameters included Time to repetition (TR)- 10000msecs, Time to echo (TE)- 124.2 milli sec, b-value 1000s/m2, field of view 24 cm, 2mm slice thickness and 1.5 mm interslice gap. The ADC values of the EOMs and orbital fat were calculated on axial sections. (Figure 1) DWI images were obtained before contrast administration in the same T1W plane. There was an automatic reconstruction of the ADC maps by the commercially available software and calculated in $x10^{-3}$ $mm^2 s^{-1}$. (Figure 1).

ADC values of superior and inferior oblique muscles were not calculated. The ADC value of superior rectus muscle was calculated along with levator palpebrae superioris muscle as part of the SR-LPS complex. For the purpose of data analysis, one radiologist blinded to the clinical history, measured the ADC values of each muscle and orbital fat of patients and control subjects on axial scan. The conventional MRI findings were evaluated by the same radiologist. Cases were compared with the controls.

Statistical analysis

Mean and standard deviations were used to summarize the numerical data. Student t-test and ANOVA tests were used to calculate the correlations between the ADC values. The mean difference in p value was considered as statistically significant at the <=0.05 level. All data analysis was performed using SPSS 17.0 for windows.

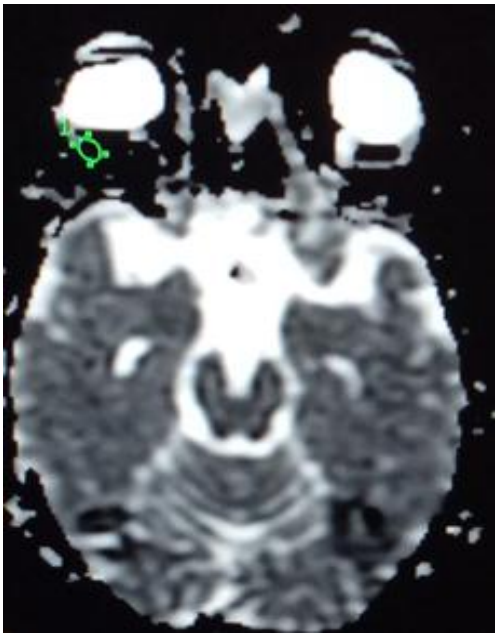
RESULTS

All orbital tissues (extraocular muscles and orbital fat) of cases showed higher ADC values as compared to the controls (highly statistically significant values $p<0.001$). (Table 1,2).

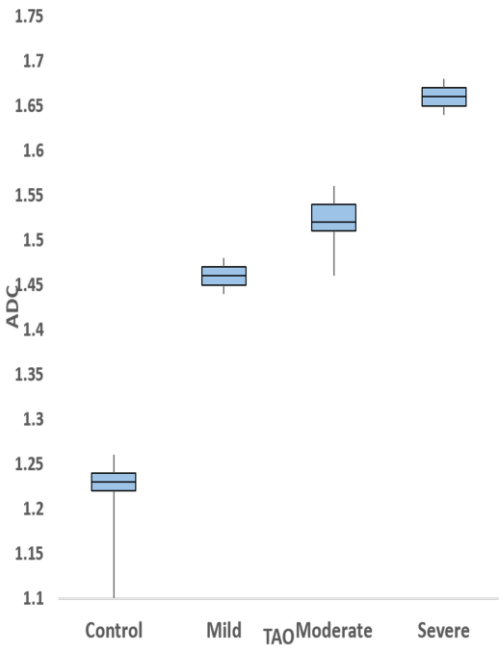
The mean ADC values for controls was 1.14 for Medial rectus (MR), 1.14 for inferior rectus (IR), 1.12 for lateral rectus (LR), 1.08 for SR-LPS complex, 1.06 for orbital fat. The ADC values among cases were highest for IR and followed the pattern IR>MR>SR-LPS complex > LR.

The EOMs and orbital fat showed a statistically significant difference between the ADC values in mild, moderate-severe and sight threatening stages. (Figure 2,3).

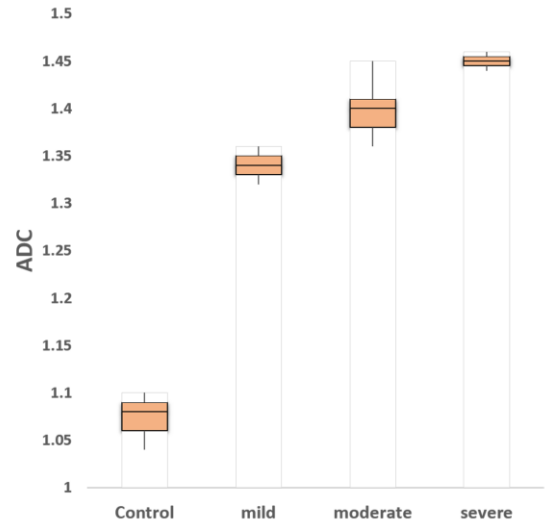
ADC values of EOMs of cases was significantly more in active disease in all the stages of thyroid associated orbitopathy ($p<0.05$). There was no significant difference between ADC values of orbital fat in active and inactive stages. (Figure 4,5).



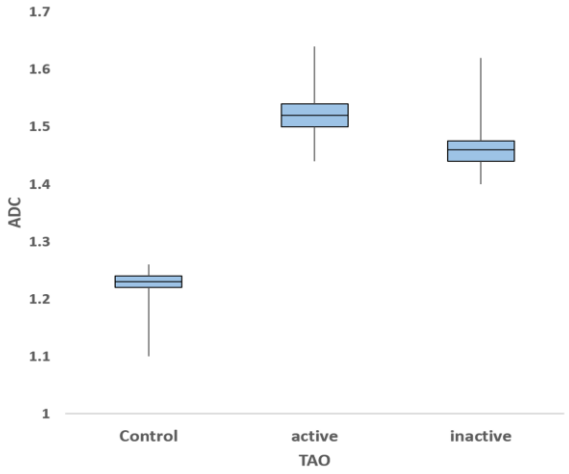
1. Axial view MRI Orbit showing enlargement of extraocular muscles in TAO



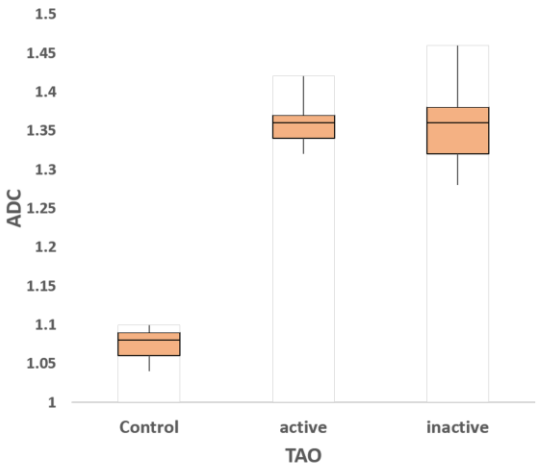
2. Box plot comparing the ADC values of extraocular muscles of controls with mild, moderate-severe and sight threatening stages of TAO cases.



3. Box plot comparing plot comparing the ADC values of orbital fat of controls with mild, moderate-severe and sight threatening stages of TAO cases.



4. Box plot comparing ADC values of extraocular muscles of patient with active and inactive disease and controls.



5. Box plot comparing ADC values of orbital fat of patient with active and inactive disease and controls.

DISCUSSION

Thyroid eye disease occurs due to a complex interaction among orbital fibroblasts, immune cells, cytokines, auto - antibodies, genetics and environmental factors.[4,5] The orbital fibroblasts and autoreactive lymphocytes play key roles in the initiation and propagation of TAO. Insulin like growth factor-1 receptor (IGF-1R) expressed on the cell surface of orbital fibroblasts serves as an auto-antigen to mediate activation of B and T cells. Activated B cells produce autoantibodies and T cells secrete cytokines which in turn stimulate orbital fibroblast proliferation and secretion of hydrophilic glycosaminoglycans. In addition, activation of IGF-1R also stimulates orbital fibroblasts to secrete chemokines for T-cell recruitment.[5]

The clinical symptoms and signs result from the increased volume of the swollen orbital tissues in fixed volume bony orbit. The expanded soft orbital tissues displace the globe forward and impede venous outflow from the orbit.[6] The clinical activity score reflects the inflammatory activity at a particular stage.

The enlargement of the extraocular muscles results from an accumulation of hydrophilic glycosaminoglycans within the perimysial connective tissues with edema. In the later stages of the disease, the resolving inflammatory process within the muscles may leave them fibrotic and with ocular misalignment. MRI establishes the degree of extraocular muscles and orbital fat enlargement.[3]

Apparent diffusion coefficient (ADC) is the quantitative parameter of Diffusion weighted imaging (DWI). It is predictive of relative water content within tissues, which is a predictor of outcome of inflammation. Thus, ADC is used as a parameter of inflammatory activity at the tissue level. (3) Its additional importance over MRI in the radiological assessment of clinical disease is highlighted by the observation that the extraocular muscles that appeared similar on conventional MRI in all cases of mild TAO and controls, showed higher values on ADC assessment in mild TAO in comparison to controls. In the study, the ADC maps were calculated using DICOM software.

There were no significant differences between the mean muscle thickness on conventional MRI between mild cases and controls. However, the mean muscle thickness values of cases in moderate-severe and sight threatening stages showed a significant difference in both the eyes as compared to controls. The Inferior rectus muscle was the most frequently involved in the study. This pattern is corroborated by previous studies.[3,7]

The ADC values were increased in both the orbits in the cases. The amount of increase is proportionate to the clinical stage of the disease. On comparison of ADC values in both eyes between the mild, moderate- severe and sight threatening group, it was observed that there were significant differences between the ADC values of

the extraocular muscles and orbital fat among the three groups in both eyes. Thus, showing that the ADC values are directly proportional to the severity of TAO.

A differential pattern was observed in the ADC values among extra ocular muscles and orbital fat. In the active phase of all stages, all orbital tissues had increased ADC value as compared to controls. However, the amount of decrease in ADC that occurred in the inactive stage was quantitatively different among the three tissues. Extraocular muscles showed the maximum decrease in ADC values in inactive phase of the disease. The ADC values of the extraocular muscles showed statistically significant differences between the active and inactive phases in all the stages. All the muscles had the same pattern, Inferior rectus being most affected.

The change in ADC values is an indicator of the resolution of the edema. This dynamism being maximally demonstrated in extraocular muscles. The ADC values increased in the active stage of orbital fat but there were no statistically significant differences in the ADC values of orbital fat in the active and inactive phases of mild disease stage. Thus, demonstrating that once the disease has reached moderate or severe stages, changes occurring in orbital fat are irreversible.

The results of our study suggested that EOM damage begins at a very early stage. Even in patients with mild TAO, ADC values can demonstrate the extraocular muscles and orbital fat involvement. A differential pattern is observed in various stages of TAO. Thus, the quantitative estimation by ADC opens new horizons for early diagnosis of TAO and compels us to hypothesize that the severity of the disease is more closely related to the extraocular muscles, as compared to the other orbital tissues.

The differential pattern also suggests that the inflammatory edema associated with TAO is maximally reversible in the extraocular muscles. In comparison, the changes occurring in the orbital fat is more irreversible.

The above study, in addition to demonstrating the superiority of ADC over conventional MRI in mild TAO, also shows that the maximum dynamism lies in the extraocular muscles. It emphasizes the importance of treating mild TAO, which are usually given symptomatic supportive therapy only as per the standard treatment guidelines, rather than any intensive anti-inflammatory therapy.[7] As it is one of the most crucial stages of the disease where the changes are maximally reversible, the clinician has to intensify the therapy in the mild stage itself to prevent the further progression of the disease.

Authors' contributions

All the authors contributed significantly to this research; Study conceptualization, design, review of literature: SA,AK; Drafting of manuscript: SA,AK,MK,MM,VS, SKS,SS,AM; Critical. Revisions: SA, AK. All authors agree to be accountable for all aspects of the work. All authors have read and approved the final manuscript.

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