Extra-orbital muscle T2 relaxation time and clinical activity in thyroid eye disease

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Introduction. Thyroid Eye Disease (TED) is an inflammatory autoimmune condition of the orbit. It is clinically apparent in 25-50% of people with Graves' hyperthyroidism, which affects an estimated 400,000 people in the UK[1]. TED is characterised by orbital inflammation, proliferation of orbital fat and enlargement of extra-ocular muscles (clinically manifest as proptosis, eyelid oedema and diplopia)[2] and results in both facial disfigurement and visual disability[3]. The treatment of TED is controversial due to conflicting evidence in the literature[4]. Precise, objective and reproducible measures of treatment response are needed to replace the currently available clinical scoring systems. Magnetic Resonance Imaging (MRI) is the ideal tool for generating such objective measures, but MRI has not yet been validated as an outcome measure for studies of interventions in TED. To validate a new MRI-derived outcome measure it needs to be shown to correlate well with the current clinically-assessed 'gold-standard'. The Clinical Activity Score (CAS), is the 'gold-standard' measure of disease activity, considered to reflect the degree of orbital inflammation[5]. The sensitivity of T2-weighted images to changes in tissue water content enables proxy measures of orbital inflammation to be derived[6]. Therefore, the aim of this study was to evaluate T2-maps of extra-orbital muscles as objective outcome measures by correlation with CAS.

Methods. 15 TED patients (12 females) were recruited as a subgroup of the randomised controlled treatment trial Combined Immunosuppression and Radiotherapy in Thyroid Eye Disease (CIRTED). MRI data were acquired on a 1.5T GE MRI system, with an 8-channel coil, from: all patients at baseline and 6 of the 15 patients also an average of 7 months after the baseline scan. Dual-echo data were acquired perpendicular to the AC-PC line with TE1/TE2/TR=25.8/93.8/3000ms, 16 contiguous 3mm-thick coronal slices and 0.5x0.5mm^2 in-plane resolution. All patients underwent a clinical assessment on either the same day of the MRI scan or approximately one month earlier or later. Data analysis was performed with the Jim software (Jim 1.5.0_01, Xinapse, www.xinapse.com) and Microsoft Excel. Regions of interest (ROIs) outlining five extra-orbital muscles for each eye were drawn on the short-TE images (cross-sectional ROIs) (a scheme of the identified muscles is drawn in fig.1). When the superior rectus was identified (R4 and L4 in fig.1), it was evaluated together with the levator palpebrae superioris because of their close proximity. The ROIs were then overlayed on the calculated T2-maps. Smaller ROIs (or 'hotspots') delineating areas of high T2 inside the muscles were also delineated. The size of the smaller ROIs varied from 2.9 to 78% of muscle cross-sectional area. The analysis was then performed in three steps. First three measures were performed for each ROI: (i) average T2 of the cross-sectional ROIs, (ii) average T2 of the 'hotspots', (iii) maximum T2 value of the cross-sectional ROIs. The second step consisted in identifying the maximum of each of the measures (i), (ii) and (iii), for each muscle and for all the muscles together. Finally the results of the second step were correlated to the CAS measures.

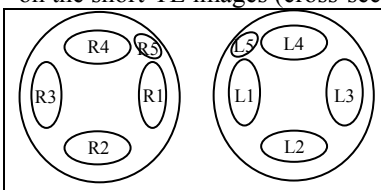

fig1. Schematic drawing of the identified extra-orbital muscles.

Results and Discussion The CAS value ranged from 2 to 6. Results of the correlation between T2 maps and CAS values in the three cases identified in the 'method' section, for each muscle and for all the muscles together are reported in the table. The strongest correlation was found between the maximum across all muscles of the maximum T2 value of the cross-sectional ROIs ((iii) in the method section; data in blue in the table).

Muscles (as in fig.1)		R1	R2	R3	R4	R5	L1	L2	L3	L4	L5	All muscles
Max of average cross-sectional T2	r^2	0.009	0.026	0.114*	0.002	0.001	0.043*	0.054*	0.006	0.003	0.0002	0.009
	Fdist	0.68	0.49	0.14*	0.86	0.87	0.37*	0.31*	0.73	0.83	0.95	0.68
Maximum of 'hotspot' T2	r^2	0.0009	0.024	0.141*	0.011	0.006	0.049*	0.136*	0.088*	0.007	0.004	0.101*
	Fdist	0.90	0.50	0.09*	0.65	0.74	0.33*	0.10*	0.19*	0.72	0.78	0.16*
Max of maxT2 in cross-sect. ROIs	r^2	0.006	0.069*	0.003	0.002	0.077*	0.171*	0.084*	0.051*	0.014	0.150	0.245*
	Fdist	0.74	0.25*	0.82	0.83	0.22*	0.06*	0.20*	0.33*	0.61	0.83	0.02*

r^2 is the coefficient of determination. It compares estimated and actual T2-values, and ranges in value from 0 to 1. If it is 1, there is a perfect correlation in the sample— there is no difference between the estimated T2-value and the actual T2-value.
Fdist represents the probability of an F value higher than the F value obtained by the correlation occurring by chance.
* indicates significant correlation

Conclusions. T2 relaxation times correlate with CAS in patients with thyroid eye disease. This is especially true when sites of higher muscular inflammation ('hotspots' and maximum T2 value) are taken into account. Measures of T2 relaxation are more robust than previously reported measures of signal intensity ratio (SIR)[7]. T2 maps can therefore be used as indicators of orbital inflammation.

Acknowledgements. The Queen Square Imaging Centre (QSIC) for performing the MRI scans.

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