

## Contrast sensitivity function and extraocular muscles thickness in patients with early stage Graves' ophthalmopathy

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**crossref** <http://dx.doi.org/10.5755/j01.u.66.3.658>

### Abstract

The aim of this study was to determine the value of the ultrasonography measurements of extraocular muscles in early stage Graves' ophthalmopathy (GO) and compare the contrast sensitivity function in patients and healthy control eyes. We examined 25-65 years old patients with early stage GO (20 eyes) and age matched healthy subjects (16 eyes). All participants underwent complete ophthalmic examination. The measurements of rectus extraocular muscles were performed by A/B mode Mentor™ Advent ultrasonic diagnostic imaging system. We evaluated thickness (mm) of each extraocular muscle, compared with normal values, calculated the sum of the muscles thickness in a given eye. Contrast sensitivity (CS) was assessed by a Ginsburg Functional Acuity Contrast Test (FACT, Vision Sciences Research Corp.) chart, under day and night lighting conditions at five spatial frequencies (cpd). Inferior rectus muscle enlargement (thickness  $\geq 3,6$  mm) was found in 14 eyes (70 percent) of patients,  $p=0.008$ . Patients CS results differ significantly from those of the control group ( $p<0.05$ ; power 0.65-0.87), except the 6 cpd range under night lighting conditions ( $p=NS$ ). The relation between the sum of the muscles thickness and CS thresholds are pronounced for the medium (6cpd) and high (12cpd) spatial frequency ranges (Spearman correlation coefficient 0.6,  $p=0.032$  and 0.7;  $p=0.012$ , respectively). Even if visual acuity was intact and proptosis was not pronounced, CS impairment and extraocular muscles enlargement were detected in patients with early stage of GO

**Key words:** Graves' ophthalmopathy, extraocular muscle, ultrasonography, contrast sensitivity.

### Introduction

Graves' ophthalmopathy (GO) is associated with thyroid dysfunction and is characterised by disfiguring proptosis, pain, redness and swelling of the eyelids, grittiness of the eyes, diplopia and, at times, a chronic debilitating infiltrative eye disease that in some situations can be associated with blindness [1]. Diagnosis of GO is clear if the typical eyelid symptoms, such as Dalrymple's sign, Graefe's sign, Griffice's sign, and Enroth's sign, are detected [2], but those can still be quite obscure in early stages of the disease.

As the symptoms and signs of dysthyroid ophthalmopathy described above are caused by extraocular muscles and orbital tissues lymphocytic infiltration, edema or fibrosis [3,4], imaging techniques that enable visualization of the orbit contents and evaluation of extraocular muscles are important. Helpful radiologic techniques include orbital ultrasound (US), magnetic resonance imaging and orbital computerized tomography. US is highly informative, non-invasive, poses no risk on the patient [5,6]; it enables differential diagnosis in proptosis and seems to reveal the existing inflammation [7-13]. Ultrasonography may be repeatedly performed in order to evaluate treatment effectiveness or disease progression [5,6,14]. In a clinical practice it allows to measure and evaluate each rectus muscle separately. Foreign scientists suggest to evaluate the sum of muscles thickness in patients with GO [15,16]. Comparison of the difference between the pair rectus muscle thickness and the sum of muscles thickness in the two orbits of the same person may obtain a reliable information to determine the degree of the extraocular muscle involvement in order to choose an appropriate treatment [17].

Furthermore, in evaluation and monitoring disease progression it is important the perceptions of patients of how they feel and how they are able to function in a daily life. Visual acuity is a common measure of visual status. A standard ophthalmic test of the visual acuity, like Snellen chart or other, only tests the ability to identify high contrast, black-on-white targets of progressively smaller size and it often fails to detect early vision loss due to a wide variety of eye diseases [18,19]. Functional acuity contrast sensitivity test offers a more sensitive and comprehensive measure of the functional vision [18,19]. The contrast sensitivity function test more effectively evaluates vision over a range of size and contrast which closely simulates a normal environment [18]. It has proved to be a useful tool for detecting visual disturbances [21-24] and has also been demonstrated in patients with optic neuropathies, including dysthyroid optic neuropathy [20,25-30].

The purpose of our study is to determine the value of the ultrasonography measurements of extraocular muscles in early stage f GO and a compare the contrast sensitivity function in patients and healthy control eyes.

### Subjects and methods

In this study 25-65 years old patients with GO and age matched healthy subjects were included.

All participants underwent a complete ophthalmic examination including best corrected Snellen visual acuity, proptosis measurement by Hertel exophthalmometer, ophthalmoscopy, fundoscopy and assessment of functional acuity contrast sensitivity score. US of the orbit was also performed on each patient.

Patients with a decrease in best corrected visual acuity more than one line or with refractive disorder of more than 1,0 D were excluded. Further, eyes with glaucoma, cataract and a history of other diseases, like amblyopia, trauma, were also excluded.

The group I consisted of patients with GO (20 eyes); the mean age was 45 years (range 25-65 years). The group II consisted of participants without eye diseases (16 eyes); the mean age was 45 years (range 30-69 years).

Non-corrected and the best-corrected visual acuity (measured in decimals from 0.1 to 1.0) was evaluated using Landolt's rings (C optotypes) by Snellen test types at a 5 meter distance from the chart.

The ultrasonography of the orbit and measurements of rectus extraocular muscles (medial, lateral, inferior and superior rectus) were performed by A/B mode Mentor™ Advent ultrasonic diagnostic imaging system with a 7.5 MHz transducer. For each of the four (superior, inferior, lateral and medial rectus) extraocular muscles thickness was measured towards the widest portion of the muscle. Normal values for the rectus muscles have been determined by two different studies: one by McNutt et al. and the second more recent study by Byrne et al. [31]. We evaluated thickness (mm) of each extraocular muscle, compared with normal values, calculated the sum of the muscles thickness in a given eye.

Contrast sensitivity (CS) was assessed with the Ginsburg Functional Acuity Contrast Test (FACT, Vision Sciences Research Corp.) chart, under day and night lighting conditions at five spatial frequencies [1.5, 3, 6, 12, and 18 cycles per degree (cpd)]. The CS is expressed in logarithmic units using the log transformation and was measured with a corrected distance visual acuity.

The results were statistically analyzed using SPSS 18.0. Mann-Whitney U test, Spearman correlation coefficient and the Student's t-test was used. P values less than 0.05 were considered as statistically significant.

**Results**

The mean age of the patients was 45±11.46 years and the controls were age-matched (45±13.87years). Proptosis more than 16 mm was stated in 20 percent of the patients eyes. The mean exophthalmos in the patients group was 16.2±1.64 mm.

The mean thickness of extraocular muscles measured using the ultrasound technique and the ranges of muscles thickness in patients with GO group are showed in Table 1.

Table 1. The mean thickness of extraocular muscles and the ranges of muscles thickness in GO group.

Muscle	Muscle thickness average (mm)	Muscle thickness ranges (mm)
inferior rectus	3,9	2,5-3,5
lateral rectus	3,5	2,7-4,5
medial rectus	3,9	3,1-4,8
superior rectus	3,1	2,5-3,5

Inferior rectus muscle enlargement (thickness ≥ 3,6 mm) was found in 14 eyes (70 percent) of patients, p=0.008. Medial rectus (thickness ≥ 4,7 mm) – in 6 eyes (30 percent), p>0.05. Lateral rectus muscle was enlarged (thickness ≥ 3.8 mm) in 4 patients eyes (20 percent), p>0.05.

The sum of the four (superior, inferior, lateral and medial rectus) extraocular muscles thickness in the patients group ranged from 11.5 to 17.61 mm; the average was 16±1.64mm.

The difference of >1.2mm between the sums of pair eye muscles thickness was noticed in 4 patients eyes (28.6 percent), p = 0.181.

Tested at five spatial frequencies (1.5, 3, 6, 12, and 18 cpd) patients CS results differ significantly from those of the control group (p<0.05; power 0.65-0.87), except of 6 spacial frequency range under night lighting conditions (p>0.05). The results are showed in Fig. 1 and Table 2.

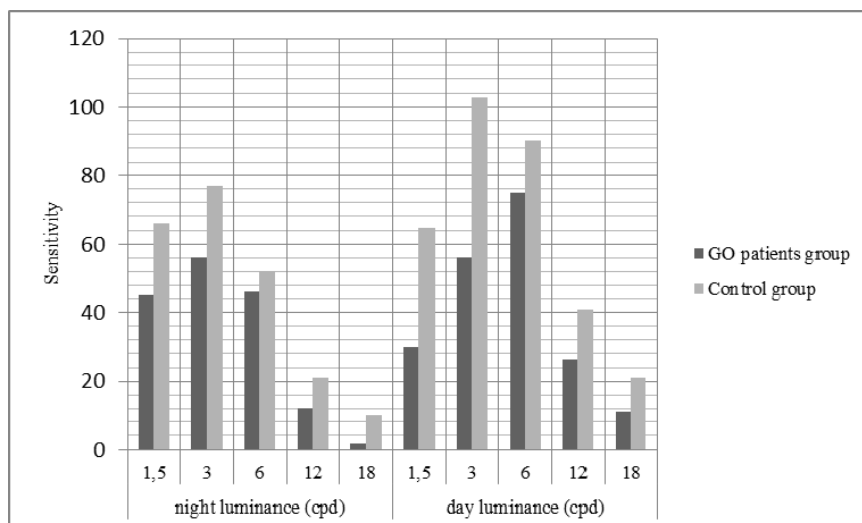


Fig. 1. Functional acuity contrast sensitivity test results

Table 2. Functional acuity contrast sensitivity test results

	Night luminance (cpd)					Day luminance (cpd)				
	1,5	3	6	12	18	1,5	3	6	12	18
GO patients group	45	56	46	12	2	30	56	75	26	11
Control group	66	77	52	21	10	65	103	90	41	21
Sig.	.005	.009	.427	.032	.000	.000	.000	.052	.003	.005

The correlation between the exophthalmos and CS value is weak-medium strong in different spatial frequencies (Spearman correlation coefficient ranges 0.1-0.422) and statistically not significant ( $p=NS$ ).

The relation between the sum of the muscles thickness and CS thresholds are pronounced for the medium (6cpd) and high (12 cpd) spatial frequency ranges (Spearman correlation coefficient 0.6,  $p=0.032$  and 0.7;  $p=0.012$ , respectively).

## Discussion

GO dramatically decreases the patient's quality of life [1] and the correlation among the symptoms, the results of clinical examination and severity of ophthalmopathy may not always be observed [32]. Most patients mild-to-moderate ophthalmopathy usually require no intervention other than restoration of euthyroidism and topical lubricants [32]. For early disease diagnosis sensitive diagnostic methods are necessary. In the present study, we enrolled patients without the pronounced proptosis and with a normal visual acuity. The orbital ultrasound technique for extraocular muscle thickness measurement and contrast sensitivity test in addition to general ophthalmic examination were used.

We found that muscle first affected in GO is inferior rectus (70 percent of cases). Jankauskiene et al. examined patients with more severe disease (active GO) and also confirmed that the majority of patients with infiltrative form of GO had a significant enlargement of the medial rectus muscle (from 5.0 to 5.9 mm in 46.3%, from 6.0 to 6.9 mm in 22.22% of eyes) and the inferior rectus muscle thickness (from 5.0 to 5.9 mm in 33.33%, from 6.0 to 6.9 mm in 24.07% of eyes) [33]. Nagy and colleagues used magnetic resonance imaging for muscle measurement; results are similar to our study, they stated that the inferior rectuses were the most frequently enlarged – at least one in 93% of cases; medial, lateral and superior rectuses were enlarged in 59%, 37% and 34% of the orbits respectively [34]. Dugy et al. evaluated the relationship between the extraocular muscle and the ocular motility in thyroid eye disease in four subpopulations based on age ( $< 40$  or  $\geq 40$  years) and state of thyroid eye disease (active or stable). The inferior rectus and medial rectus were most frequently restricted in their study cohort in all 4 subpopulations. The medial rectus had the strongest trend between the increasing diameter and motility restriction [35]. Villadolid

and colleagues examined two groups of patients with Graves' disease: with clinical ophthalmopathy and without it. Both groups showed the inferior rectus muscle as the most frequently involved (77% and 56% respectively) [36]. In Fledelius and colleagues study all four muscle groups were significantly enlarged in the patients with thyroid associated orbitopathy group than in the healthy control subjects [37]. That may be explained by the fact that research included mainly advanced cases of GO. Fledelius et al. also compared the mean of the sum of all four muscles in the patients and the control group (22.6 vs 16.8 mm). We did not measure muscle thickness in the control group but paid attention to the difference between the sums of the same patient pair eye muscles thickness. The difference of  $\geq 1.2$ mm observed in 28,6 of patients eye, but it is not statistically significant.

Nagy et al [34] and we in our previous study [17] found correlation between the degree of exophthalmos and the sum of muscle thickness for a given eye. In the present study, ophthalmopathy was mild, we did not observe increased proptosis but muscle thickness was increased. That confirms statement that a normal Hertel did not guarantee normal sized muscles [34].

Also, patient's visual acuity was normal but using contrast sensitivity test we detected disturbances in their visual function. It has been shown previously that the contrast sensitivity functions can reveal a visual impairment in optic neuropathies even in patients with normal or near normal Snellen visual acuity [25-28]. Suttorp-Schulten and colleagues measured contrast sensitivity function in two groups of patients with GO: with dysthyroid optic neuropathy and with GO only. Disturbances of the contrast sensitivity function were found in both groups. The eyes affected by dysthyroid optic neuropathy showed pronounced loss of the contrast sensitivity in the low frequency range; threshold values of the group of patients with GO only differ significantly (Wilcoxon U;  $p<.001$ ) from those of the control group for the medium and high spatial frequency ranges [30]. In functional acuity contrast test instruction manual pointed out that losses in 3, 6, 12 spatial frequencies usually indicate early vision problems caused by optic neuropathy or retina region [38]. In our study, the contrast sensitivity values of the GO group differ significantly from those of the control group across the CS spatial frequency range, except 6 cpd under night luminance conditions. We noticed the tendency that in patients with greater proptosis, the CS

function was worse but the difference was not significant statistically. That may be explained by a limited number of cases and early stage of the disease. However, significant conversely correlation was noticed between the sum of extraocular muscles thickness and CS values for the 6 and 12 (medium – high) spacial frequencies under day luminance conditions ( $p < 0.05$ ).

## Conclusion

In early stage of Graves' ophthalmopathy it is not enough to test a visual acuity by a standard ophthalmic test and to measure proptosis. Even if Snellen visual acuity is normal, patients contrast sensitivity perception differ significantly from those of the control group. Furthermore, ultrasound examination shows a marked increase in the volume of the medial and inferior rectus muscle in patients with Graves' ophthalmopathy, while proptosis is still normal or near normal. The functional contrast sensitivity test and ultrasound technique are sensitive methods that help to evaluate early signs of Grave's ophthalmopathy and also may be usefull for disease monitoring.

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#### **Sergančiųjų ankstyvos stadijos Greivso oftalmopatija kontrastinio jautrumo ir akių tiesiųjų raumenų storio pokyčiai**

Reziumė

Darbo tikslas - įvertinti akių pokyčius, kontrastinio jautrumo funkciją ir išmatuoti pacientų, sergančių ankstyvos stadijos Greivso oftalmopatija (GO), akies išorinių tiesiųjų raumenų storį

Į tyrimą buvo įtraukti 25-65 metų amžiaus pacientai, sergantys GO (20 akių) ir atitinkamo amžiaus sveiki tiriamieji (16 akių). Jie buvo išsamiai oftalmologiškai ištirti. Kontrastinio jautrumo funkcija įvertinta funkcinio kontrastinio jautrumo tyrimu (FACT), atliktu pagal dr. Arthuro P. Ginsburgo metodiką OPTEC 6500 aparatu. Pacientams papildomai atliktas ultragarsinis A/B skenavimas. Išmatavus išorinių tiesiųjų akies raumenų storį, duomenys palyginti su normos vertėmis, apskaičiuota raumenų storių suma.

Sergančiųjų GO apatinis tiesusis akies raumuo 70 proc. atvejų buvo sustorėjęs (14 akių,  $p = 0.008$ ); kontrastinis jautrumas mažesnis nei kontrolinės grupės tiriamųjų esant bet kuriam erdviniam dažniui ( $p < 0,05$ ; kriterijaus galia 0,65 – 0,87), išskyrus 6 c/l nakties apšvietimą ( $p = NS$ ). Nustatyta vidutinė ir stipri koreliacija tarp raumenų sumos ir kontrastinio jautrumo: didėjant raumenų sumai, kontrastinis jautrumas statistiškai reikšmingai sumažėja esant vidutiniam (6 c/l) ir aukštam (12 c/l) erdviniam dažniui (Spirmeno koreliacijos koeficientas atitinkamai 0,6,  $p = 0,032$ , ir 0,7,  $p = 0,012$ ).

Daroma išvada, kad netgi ankstyvoje GO stadijoje, kai regos aštrumas nepakitęs ir nėra ryškaus išverstakumo, akių tiesieji raumenys sustorėja ir kontrastinis jautrumas sumažėja.

Pateikta spaudai 2011 09 23