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*Case Report*

# Assessment of Clinical Signs, Retinal Nerve Fiber Layer and Central Macular Thickness in Patients with Graves Ophthalmopathy

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**Abstract**

Purpose: to determine clinical signs, retinal nerve fiber layer and central macular thickness in patients with Graves ophthalmopathy

Objectives: To determine the Clinical Activity Score, best visual acuity, intraocular pressure and exophthalmos in patients with Graves' Ophthalmopathy. To determine Retinal Nerve Fiber Layer (RNFL) and Central Macular Thickness (CMT) by Optical Coherent Tomography (OCT). To determine the relationship between CAS, best visual acuity, intraocular pressure, exophthalmos and RNFL, central macular thickness.

Methods: The retrospective study was done at Lithuanian University of Health sciences Kaunas Clinic of Eye diseases outpatient department. We reviewed the electronic medical records of all patients with Graves' ophthalmopathy seen at the Clinic of Eye diseases between 2021 and 2024, selecting 62 total patients (124 eys). The median age was 49.3 years, ranging from 18.4 years to 74.5 years. All patients had undergone a full ophthalmologic exam, including Best Corrected Visual Acuity (BCVA), Clinical Activity Score (CAS), exophthalmometry with Hertel mirror exophthalmometer, dilated fundus imaging, Schiotz tonometry and OCT imaging (RNFL and CMT). All data were processed using statistical analysis software IBM SPSS 29.0. A statistical significance level of $p<0.05$ was considered.

Results: The mean of CAS of patients was 3,22 ± 0.43, (range 0-7). The mean BCVA was 0.84 ± 0.19. Intraocular eye pressure ranged form 12.3 to 23.5 mmHg, with a mean of 16.83 ± 2.75 mmHg. Exophthalmos results ranged form 13.9 to 23.3 mm. The mean was 18.26 ± 2.07 mm. The mean of RNFL thickness was 96.84 ± 11.27µm and central macular thickness was 271.43± 22.82µm. A statistically significant correlation was found between BCVA and RNFL, CMT thickness ($r=0.376$, $p=0.001$, $r=0.258$, $p=0.026$, respectively). A statistically significant negative correlation was found between CAS and RNFL, CMT ($r=-0.406$, $p<0.001$; $r=-0.233$, $p=0.046$, respectively). These data indicate that the lower the visual acuity and the higher the disease activity, the thinner the RNFL and CMT.

A negative significant correlation was between IOP, exophthalmos and RNFL ($r=-0.348$, $p=0.002$; $r=-0.287$, $p=0.013$, respectively). This shows that the greater IOP and exophthalmos the thinner RNFL. However, there was no significant relationships between IOP, exophthalmos and CMT ($r=-0.14$, $p=0.235$; $r=-0.2$, $p=0.088$, respectively).

Conclusion: A statistically significant correlation was found between Clinical activity score, best corrected visual acuity, intraocular pressure, exophthalmos and RNFL in patients with GO. CAS and BCVA were significantly correlated with central macular thickness. There was no significant relationship between IOP, exophthalmos and CMT. Our study suggests that OCT is useful in diagnosing, monitoring and predicting vision in patients with compressive optic neuropathy in GO.

**Keywords:** Graves Ophthalmopathy; Exophthalmos; Optic Neuropathy; Optical Coherence Tomography; Retinal Nerve Fiber Layer; Central Macular Thickness

**Introduction**

Graves‘ Ophthalmopathy (GO) is an autoimmune inflammatory proliferative process of the orbital fat and extraocular muscles and is the most common extrathyroidal manifestation of Graves' Disease (GD). Clinical features of GD are characterized by Graves‘ Ophthalmopathy (and/or dermopathy). The disease most commonly affects patients between the ages of 30 and 50. The authors describe that the disease tends to be more severe in men, smokers and in older than 50 years [1-3].

Pathology may involve the ocular surface, orbital fat, extraocular muscles and optic nerve [3]. The autoimmune processes lead to 15 proliferation of orbital fibroblasts, adipogenesis and increased production of glycosaminoglycans. The autoimmune processes that occur in Graves' ophthalmopathy, the production of antibodies to TSH and IGF-1 receptors, inflammatory infiltration and the accumulation of glycosaminoglycans cause edematous-infiltrative changes in the periorbital tissues. This leads to the development of edema of the orbital tissues, extraocular muscles and proptosis [1,4-9].

Clinically GO activity is assessed using the Clinical Activity Score (CAS). CAS includes seven inflammatory markers, each of which is scored. GO is active when CAS is ≥ 3/7 points and if CAS is < 3, GO is inactive. CAS is essential for selecting treatment methods for GO [10]. According to the European Graves' Orbitopathy Group (GO) guidelines, clinical signs may lead to corneal exposure, increased tear evaporation, corneal epithelial damage and ulceration [11,12].

More than 50% of patients with GO have mild symptoms. If an accurate diagnosis is not made in time, some cases may progress to severe, visionthreatening form of the disease due to corneal exposure or compressive optic neuropathy. Mechanical compression of the orbit by inflammatory extraocular muscles and expansion of the orbital fat can result in pressure on the optic nerve at the orbital apex. This can lead to optic nerve damage, reduced visual acuity and visual field defects. It is sometimes difficult to assess optic nerve damage in patients suffering from GO [9,13,14].

The prognosis of the disease depends on early diagnosis. Visual acuity tests and perimetry are performed to assess visual function, while biomicroscopy and OCT tests are used to assess changes in eye structure. Early and accurate diagnosis of GO could reduce the number of cases of retinal and optic nerve changes, which would help preserve vision. Optic neuropathy is a rare complication that occurs in 5-6% of people with GO. Optic nerve damage is usually expected in patients with severe Graves' ophthalmopathy. This condition can lead to the death of retinal ganglion cells and blindness [15]. The RNFL, deepest retinal layer, which composed of fibers without myelin, however RNFL thickness can be used to assess axonal loss [16]. OCT is non-invasive method for detecting pathology of the optic nerve and retinae. It is most often used to diagnose these diseases by assessing the RNFL and central macular thickness, disease diagnosis and monitoring. [17]. According to the scientific literature and research data, in Graves' ophthalmopathy, the retina can become thinner due to the loss of the ganglion cell layer, leading to the development of optic neuropathy [18,19].

Tehrani, et al., showed that in active form of GO had significantly lower density of the vessels in central retinae and at peripapillary location compared with inactive GO [20]. Ophthalmological manifestations of GO can affect the patient's quality of life; patients are unable to read, drive, watch television or use a computer [6,14,21].

Studies have shown that patients with GD have visual impairment, exophthalmos, optic neuropathy, corneal ulceration, which is the most clinically severe manifestation of hyperthyroidism and a significantly impaired quality of life. This may cause economic and psychosocial problems [22]. Some authors have observed an increased risk of suicide 15 in patients with Graves' disease and GO compared to patients with Graves' disease without ophthalmopathy [23].

Forte, et al., performed measurements of retinal nerve fibre layer and CMT in people suffering from GO, the authors determined their prognostic value. They found that patients with Graves' ophthalmopathy and ocular hypertension had a reduction in RNFL in the lower and upper quadrants compared with controls. Authors conclude that in Graves‘ ophthalmopathy and ocular hypertension, RNFL thickness assessment using OCT could be an objective diagnostic method for identifying optic neuropathy, peripapillary and macular changes at various stages of GO and helps to monitor disease progression [24]. Little research has been done in the scientific literature showing a correlation between RNFL, CMT and GO activity, exophthalmos, visual acuity and intraocular pressure. In this study, we aimed to evaluate 9 RNFL, CMT measuring by OCT in patients with GO and to determine the correlation between these data and the data mentioned above.

**Materials and Methods**

Our research study was retrospective, including patients (eyes) with Graves' Ophthalmopathy. Between 2021 and 2024, data were collected from the medical records at the Clinic of Eye diseases. Patients were excluded if:: previously suffering from diseases of the orbit, retina and cornea, glaucoma, eye trauma, surgical procedures involving extraocular muscles, eyeball and orbit; amblyopia; keratoconus. The Helsinki Declaration was adhered to during the research and it was approved by the Medical Committee of the Ethics of Lithuanian University of Health Sciences. Best corrected visual acuity (BCVA), Hertel exophthalmometry, intraocular pressure measurements (Schiotz tonometer), OCT data (RNFL and CMT) were collected. CAS was assessed according to the following signs and symptoms: 1. Spontaneous retrobulbar pain, 2. Pain when the patient looks up or down, 3. Palpebral redness, 4. Conjunctival hyperemia, 5. Caruncle edema, 6. Palpebral edema, 7. Conjunctival edema. The active process of Graves' Ophthalmopathy when CAS from 7 signs of the patient was greater than 3.

*Statistical Analysis*

The statistical analysis was performed using the IBM SPSS Statistics 29.0. The mean and Standard Deviation (SD) were calculated. The normal distribution of variables was assessed based on Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U test was applied to compare the distribution of values. To assess the relationship between CAS, BCVA, IOP, exophthalmos and RNFL, as well as the thickness of the central macula, the Spearman correlation coefficient was applied. A P-value of 0.05 or less was statistically significant.

**Results**

Among the 62 participants included, the median age was 49.3 years, ranging from 18.4 years to 74.5 years. 49 (79.03%) were female and 13 (20.97 %) were male. The duration of the disease (GO) was less than six months in patients 12 (19.35 %), from six months to one year in 21 patients (33.87 %), more than one year in 29 patients (46.78 %). The disease activity score at enrollment was active in 39 patients (62.9 %), non-active in 23 patients (37.1 %). The mean of CAS of patients was 3,22 ± 0.43, (range 0-7). The mean BCVA was 0.84 ± 0.19. Intraocular pressure ranged from 12.3 to 23.5 mmHg, with a mean of 16.83 mmHg (Table 1).

| Parameters | Mean | SD |
|---|---|---|
| CAS | 3.22 | 0.43 |
| BCVA | 0.84 | 0.19 |
| IOP(mmHg) | 16.83 | 2.75 |
| Exophthalmos (mm) | 18.26 | 2.07 |
| RNFL (μm) | 96.84 | 11.27 |
| CMT (μm) | 271.43 | 22.82 |
| CAS: Clinical Activity Score; BCVA: Best Corrected Visual Acuity; IOP: Intraocular Pressure; RNFL: Retinal Nerve Fiber Layer; CMT: Central Macular Thickness | | |

**Table 1:** CAS, BCVA, IOP, exophthalmos values and OCT parameters.

Exophthalmos results ranged from 13.9 to 23.3 mm. The mean was 18.26 ± 2.07mm. The mean of RNFL thickness was 96.84± 11.27μm and Central macular thickness was 271.43 ± 22.82μm. A statistically significant correlation was found between BCVA and RNFL, CMT thickness (r=0.376, p=0.001, r=0.258, p=0.026, respectively). A negative significant relationship was between CAS and RNFL, CMT (r=-0.406, p<0.001; r=-0.233, p=0.046, respectively). These data indicate that the lower the visual acuity and the higher the disease activity, the smaller the RNFL and the CMT.

| Parameter | CAS | | BCVA | | IOP | | Exophthalmos | |
|---|---|---|---|---|---|---|---|---|
| | R | P | R | P | r | P | r | p |
| RNFL | -0.406 | <0.001 | 0.376 | 0.001 | -0.348 | 0.002 | -0.287 | 0.013 |
| CMT | -0.233 | 0.046 | 0.258 | 0.026 | - 0.14 | 0.235 | -0.2 | 0.088 |
| CAS: Clinical Activity Score; BCVA: Best Corrected Visual Acuity; IOP: Intraocular Pressure; RNFL: Retinal Nerve Fiber Layer; CMT: Central Macular Thickness; r - Spearman's coeficient correlation; * values represent the best statistically significant results (p < 0.05) | | | | | | | | |

**Table 2:** Correlation between RNFL, CMT and CAS, BCVA, IOP, exophthalmos values.

A negative significant association was between IOP, exophthalmos and RNFL (r=-0.348, p=0.002; r=-0.287, p=0.013, respectively). The changes indicate that the greater IOP and exophthalmos the thinner RNFL. However, there were no statistically significant correlations between IOP, exophthalmos and CMT (r=-0.14, p=0.235; r=-0.2, p=0.088, respectively).

**Discussion**

GO is an autoimmune disease and occurs in most cases in patients with Graves' disease [3,25]. Clinical data for GO vary depending on the location of the affected orbital soft tissue. Approximately 40% GO patients experience extraocular muscles edema. It usually occurs in the elderly, leading to more severe symptoms, including edema of the conjunctiva and eyelids, restriction of eye movement, compression of the optic nerve [26,27].

A study by Eslami, et al., showed that intraocular hypertension was found in men with longterm GO, smokers and patients who had been treated for thyroid disease for a long time [28]. It has been found that patients with active GO often complain of deteriorating vision, since a correlation has been established between the clinical activity 15 of the disease and visual acuity. The results of the authors' studies showed that visual acuity 6 in Graves'Ophthalmopathy patients correlated statistically significantly with disease activity. During the study, the decrease in disease activity may indicate an improvement in the condition of the eye or the effectiveness of treatment, therefore vision improvement may be related to a decrease in inflammation of the orbital tissue and extraocular muscles [29].

There is little scientific literature examining OCT data and the relationship between exophthalmos, Graves' Ophthalmopathy activity and CMT and RNFL. We can compare the results of our research with the data obtained from the global scientific literature. Studies have shown that there is no relationship between RNFL thickness and other GO parameters, either positive or negative correlations.

Wei, et al., studied GO patients who had limited eye movement. They reported that changes in extraocular muscle obtained by computed tomography were not significantly associated with either VA or proptosis or RNFL. According to this sudy visual acuity was not significantly correlated with RNFL thickness [30]. According to some authors, the decrease in the thickness of fiber layer 2 was associated with decreased density of capillars in the peripapillary area [31].

Akpolat, et al., noted that there was no statistically significant difference in central retinal thickness between inactive GO and healthy persons and there was no correlation between central retinal thickness and other parameters in patients with Graves ophthalmopathy. However, a positive correlation was found between the vascular density of the parafoveal segments of these patients. The authors think that optical coherent tomography angiography could be a new and promising non-invasive diagnostic technique for patients with inactive Graves ophthalmopathy to detect changes in foveal and parafoveal vascular density [32].

K Mugdha, et al., showed tha the average RNFL thickness in GO was significantly lower than that of the controls. No relationship was between changes in CAS and RNFL thickness. Assessment of RNFL is very important in Graves' Disease and in cases of severe damage, active intervention may be required [33].

Sayın, et al., assessed that Intraocular pressure and exophthalmos were greater in Graves' ophthalmopathy patients. The authors showed no significant difference in RNFL between patients with GO and healthy control patients., while macular and inferior RNFL thickness was lower compared to healthy controls [34]. Sen, et al., reported that intraocular pressure was greater in GO, the mean thickness of RNFL in GO patients was smaller than in the control group. 3 The authors assume that prolonged hypoxia and ischaemia were associated with optic nerve atrophy and desrease in thickness of RNFL [35]. Meirovitch, et al., indicated that OCT data in patients with GO detect retinal and optic nerve changes earlier and allow for earlier diagnosis and timely treatment to avoid severe visual consequences [36]. Iorga, et al., indicate that OCT is useful for compressive optic neuropathy diagnosis and monitoring treatment by observing the condition of the optic nerve [37]. Park, et al., revealed a reduction 8 in temporal peripapillary RNFL thickness in eyes with chronic optic neuropathy of GO patients compared to eyes with acute optic neuropathy. They found a significant association between inferior peripapillary RNFL thickness and visual acuity. Thicker inferior peripapillary thickness of RNFL was associated with better visual outcomes [38].

Our study found significant relationship between best visual acuity and RNFL thickness and central macular thickness. These data suggest that the lower the visual acuity, the smaller the RNFL and thickness of central macula.

The study of Akkus, et al., assessed significant negative relationship of RNFL measurements with serum TRAb, antiTPO, fT3, fT4 ($p<0.05$). The authors think that baseline serum levels of fT3, fT4 and TRAb in patients with Graves' disease may be a prognostic factor in assessing the nerve fibre layer in patients with GO [39].

In patients with Graves Ophthalmopathy, G Casini, et al., found 2 lower central macular and ganglion cell layer thickness. The authors summarise that these morphology changes indicate the possible influence of the orbital inflammatory process [40]. Furthermore, our study shows significant negative relationship between Clinical activity score and RNFL, as well as CMT. These changes suggest that the higher the disease activity, the thinner the RNFL and CMT.

Based on the results of a study by BE Ogmen, et al., the authors compared the thickness of the retinal layer in patients with Graves‘ ophthalmopathy using spectral optical coherent tomography method. The ganglion cell layer and the inner plexiform layer in GO were thinner than in healthy individuals [41].

Joo, et al., describe OCT data in various optic neuropathies and showed a decrease in RNFL in this pathology. The authors argue that the correlation between the best-corrected visual acuity and internal retina thickness, based on the findings of OCT parameters, helps to assess the aetiology of optic neuropathy [42].

We found a negative significant relationshipr between IOP, exophthalmos and RNFL. The data suggest that the greater IOP and exophthalmos the thinner RNFL. In our study we did not find significant relationship between IOP, exophthalmos and central macular thickness. Some other studies have reported different approaches to RNFL thickness.

Dave, et al., showed that patients with active form of Graves‘ ophthalmopathy had lower peripapillary and macular vascular indexes. They also found that RNFL was greater in patients with active form of Graves‘ ophthalmopathy. In case of inactivity of the disease, these parameters were similar to those of healthy eyes [43].

Cheng, et al., indicated that after orbital decompression surgery, improvement in BCVA, a decrease in RNFL thickness in all patients with GO and optic neuropathy except the nasal quadrant was established [5,26]. Nasal RNFL thickness was an good predictor of postoperative improvement in BCVA. RNFL as measured in OCT correlated with recovery of visual function after decompression surgery in patients with optic neuropathy in GO patients, which may also be a predictor of better vaision prognosis [44].

Ioana, et al., reviewing the literature and scientific studies on retinal changes in Graves' ophthalmopathy, found that the thickness of the TNSS varies depending on the stage and severity of GO. The thickness of RNFL in GO patients did not change statistically significantly in the moderate to low activity stages, but tended to thicken due to optic nerve oedema with the development of dysthyroid optic neuropathy. Subfoveal choroid thickness was greater in active form of GO, it correlated positively with clinical activity score and proptosis, suggesting that it may confirm the disease activity [45].

Some studies have reported that the reduction in RNFL in active GO is related to ischemia caused by orbital soft tissue edema, leading to optic nerve atrophy [35,46-48]. Chu, et al., found that plasma ET-1 levels were higher than normal in patients with thyroid hormone disorders caused by Graves' disease. ET-1, a potent vasoconstrictor, can reduce optic nerve head blood flow. The peripapillary RNFL may be affected by ischemic conditions caused by the vasoconstrictor ET-1 [49,50].

The authors of the study suggested CMT may be useful in the early stages of glaucoma and to monitor disease progression [51]. Poostchi, et al., noted that patients without glaucoma with increased IOP resulted in increased disc area [4,52]. Vascular insufficiency in the peripapillary area, even in the absence of glaucoma, can cause damage to the optic nerve and central macula [53].

A multi-clinic study showed that Graves' ophthalmopathy may progress with increasing TRAb titers and this may have predictive value for activity and development of the disease [54]. Kuebler, et al., describe a positive prognosis for GO patients who have experienced optic nerve compression after treatment [55].

**Conclusion**

In conclusion, our study shows that in patients with Graves' ophthalmopathy, RNFL thickness was significantly correlated with disease activity, visual acuity, intraocular pressure and exophthalmos. CAS and BCVA were significantly associated with CMT. Measuring RNFL thickness may help detect optic nerve damage in GO and prevent the progression of neuropathy. These objective changes of optic nerve and retina require timely and effective treatment by an endocrinologist and an ophthalmologist. Our study has several limitations. It was a retrospective study, which does not allow for control of dynamic OCT and clinical parameters in patients with Graves‘ ophthalmopathy. Furthermore, the number of patients was relatively small, although our results reached a statistically significant level.

**Conflict of Interest**

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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