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Correlation between Intraocular Pressure and Thickness of Extraocular Muscles, the Severity and Activity of Thyroid-associated Orbitopathy

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Aim: To establish the correlation between intraocular pressure (IOP) and thickness of extraocular muscles (EOM), the severity and activity of thyroid-associated orbitopathy (TAO).

Materials and methods: 50 patients with TAO were included in the study. They all underwent a thorough ophthalmic examination, Goldmann tonometry (mm Hg) and computer tomography of the orbits, the muscle thickness sum (MTS) of each eye being measured in millimeters. According to the activity of TAO, the patients were divided into two groups – with and without activity, and according to the severity of the disease – into 6 groups: Group 1 ('O') had only subjective symptoms, group 2 ('S') had soft tissue symptoms, group 3 ('P') – proptosis, group 4 ('E') – ocular motility disorders, group 5 ('C') – corneal damage, and group 6 ('Si') – visual impairment;

Results: TAO activity was registered in 21 patients (42 eyes, 42%) with MTS 23.39 ± 3.81 and IOP 18.43 ± 4.16 . Twenty-nine patients (58 eyes, 58%) with MTS 19 ± 3.21 and IOP 15.98 ± 4.59 showed no TAO activity. The IOP within the groups, in terms of severity, was as follows: group 1 – 19.92 ± 4.05 ; group 2 – 14.5 ± 2.55 ; group 3 – 18.04 ± 4.51 ; group 4 – 18.2 ± 5.05 ; group 5 – 20.5 ± 4.5 ; group 6 – 21.5 ± 4.95 . A correlation between the IOP and MTS was found.

Conclusions: The IOP in patients with TAO depends on the thickness of the EOM, as well as on the activity and severity of the disease.

INTRODUCTION

Thyroid-associated ophthalmopathy (TAO) is an autoimmune disease, linked in most of the cases to the presence of Graves' disease, and to a lesser degree to Hashimoto's thyroiditis.¹ The manifestation of ocular symptoms may occur not only in the hyperthyroid but also in the eu- and hypothyroid phase of the underlying disease. The clinical signs are determined by the development of an autoimmune inflammatory process in the orbital soft tissues and infiltration into the extraocular muscles, which leads to an increase in their volume and the typical fusiform thickening of the muscle bodies. The natural evolution of the disease includes an inflammatory active phase, which passes into an inactive fibrous phase for 6 months to 5 years.

A number of studies show that people with a thyroid disease are at a higher risk of developing ocular hypertension or glaucoma.²⁻⁴

Increased intraocular pressure has been detected in approximately 25% of the TAO patients.⁵ The main reason for this is the increase in intraorbital pressure from the increased volume of soft tissues, which results in disturbances in the venous circulation and an increase in the episcleral venous pressure. Another mechanism which leads to an IOP increase with TAO patients is when the enlarged fusiformly thickened extraocular muscles press the eyeball.⁶ It has been proved that IOP increases on upgaze (the eyeball deviates upwards at an angle of 30°), due to the mechanical compression of the eyeball of the rigid, thickened, inferior rectus muscle.^{7,8} On

the other hand, patients with thyroid dysfunction may develop glaucoma, the reason for this probably being the accumulation of mucopolysaccharides in the trabecular meshwork, which leads to an increase in the drainage resistance of the aqueous humor and elevated IOP. In patients with hypothyroidism, the observed vasculopathy worsens the blood flow and nutrition to the optic nerve, which may be the reason for the development of glaucoma. The presence of ocular hypertension or glaucoma in patients with TAO requires a continuous monitoring of the IOP and refining the therapy. Diagnostically challenging are the cases of severe TAO, with high IOP and visual field defects that necessitate the exclusion of *disthyroid* optic neuropathy. Persistent ocular hypertension can lead to glaucoma with permanent irreversible damage.

The purpose of the present study was to determine the intraocular pressure in patients with TAO and establish a correlation between IOP and the thickness of extraocular muscles, as well as between IOP and the severity and activity of the disease.

MATERIALS AND METHODS

The current prospective study comprised 50 patients (100 eyes) with TAO, examined in the Medical University Eye Clinic between 2012 and 2015. The study included patients diagnosed with TAO based on clinical signs, CT changes and data from clinical laboratory tests. All of the patients not only underwent a thorough ophthalmic examination but

also were consulted by an endocrinologist. Some exclusion criteria were: presence of other inflammatory or space-occupying processes and traumas, increasing the intraorbital pressure; corticosteroid treatment received at the time of the study and up to three months before; orbit decompression or surgical treatment of extraocular muscles (EOM) conducted prior to the study; patients with thyroid disease without TAO.

In order to assess IOP, Goldmann applanation tonometry in the first position of the eyeball was performed, after local anesthesia with proxymetacaine hydrochloride and instilling fluorescein solution into the conjunctival sac. Values up to 21 mm Hg inclusive were accepted as normal, and if greater than 21 mm Hg – for increased IOP.

TAO activity was assessed in accordance with the Clinical Activity Score (CAS, Clinical Activity Score, Mourits, 1989), which is based on determining the classic symptoms of inflammation – pain (2 points), hyperemia (2 points), swelling (4 points), dysfunction (2 points) (**Table 1**).⁹ The presence of 2 or fewer points determined the state as inactive, whereas 3 and more than 3 points indicated an active state.

In order to assess the severity of the disease, NOSPECS classification (S. Werner, 1969) was used, according to which patients were divided into 6 groups (**Table 2**).^{10,11}

Each patient underwent CT of orbits via 16-slice computed tomography (Bright Speed, General Elec-

Table 1. Mourits' clinical activity score

Sign of inflammation	Characteristics	Points
Pain	spontaneous	1
	when moving the eyes	1
Hyperemia	eyelids	1
	conjunctiva	1
Swelling	eyelids	1
	conjunctiva	1
	caruncula	1
	orbital soft tissue / increase in proptosis	1
Dysfunction	decrease in visual acuity during the last 3 months	1
	restriction of the eyeball movement at 8° and more during the last 3 months	1

Table 2. NOSPECS classification of TAO severity

Class	Abbreviation	Clinical Signs
0	No signs or symptoms	No complaints
1	Only mild symptoms	Irritation, lacrimation, photophobia
2	Soft tissue	Swelling of the eyelids, conjunctiva, caruncula, erythema of the eyelids, chemosis: a) minimal b) moderate c) marked
3	Proptosis	Proptosis (<i>Hertel's exophthalmometry</i> > 20 mm) a) 20-23 mm b) 24-27 mm c) > 28 mm
4	Extraocular	Ocular motility disorders a) slight limitation in one direction of gaze b) expressed in one or more directions c) bulb fixation
5	Corneal	Damage to the cornea a) corneal stippling b) ulceration c) necrosis, perforation, clouding
6	Sight loss	Loss of vision a) swollen papilla, visual field defects, visus 1.0-0.5 b) visual acuity up to 0.1 c) visual acuity below 0.1

tric). On axial slices, the thickness of the horizontal EOM (medial and lateral rectus muscles, MRM and LRM) was measured in millimeters, and on coronal slices – the thickness of the inferior rectus muscle (IRM) and the superior muscle complex (SMC), including the superior rectus muscle (SRM) and the superior oblique muscle (SOM). All muscles were measured from different scans. The one with the greatest value for a particular muscle was selected. The muscle thickness sum (MTS) of each eye (MTS = SMC+MRM+IRM+LRM) was calculated. The CT registered the presence or absence of compression of the optic nerve.

Each patient underwent computed perimetry of both eyes (Humphrey Field Analyzer 30-2, Full Threshold).

Through clinical laboratory tests, the levels of TSH, T3, T4, anti-TG, anti-TRO, TRAb were measured in order to determine the thyroid function at the time of the study.

All patients with TAO involved in the study were Caucasian. They signed an informed consent to participate in the study.

The statistical analysis was performed using SPSS, v.17.0. Descriptive analysis was used to describe the results presented by an arithmetic mean and standard deviation (mean $\pm$ SD); the Kolmogorov-Smirnov test was used to determine the type of distribution of values of quantitative indicators; with the independent samples t-test we compared the average values between two groups, and One-Way ANOVA was used to compare the values in more groups. $P < 0.05$ was considered as a level of significance of the null hypothesis (with a confidence interval of 95%).

RESULTS

The mean age of the studied group of patients with TAO was 50.04 ± 10.24 years (mean $\pm$ SD) (range 26 - 69 years). Nine of the patients were males (18%) (mean age 51.11 ± 7.17 years) and 41 were females (82%) (mean age 49.8 ± 10.85 years). All participants in the study had both eyes affected.

Thirty-three patients (66%) were in euthyroid condition, 16 (32%) were in hyperthyroid condition, and 1 (2%) was in hypothyroid condition.

Twenty-one patients (42%) showed TAO activity with the average IOP being 18.43 ± 4.16 , and 29 patients (58%) showed none with the average IOP being 15.98 ± 4.59 . A statistically significant difference was found in the IOP between the two groups ($p=0.007$, $t=2.735$, independent samples Test). In patients with active TAO the intraocular pressure was higher. Of the patients with active TAO, 10 (47.6%) were in an euthyroid state, 10 (47.6%) – in a hyperthyroid state and 1 (4.8%) – in a hypothyroid state. Of the patients without TAO activity, 23 (79.3%) were in an euthyroid state and 6 (20.7%) – in a hyperthyroid state.

Seventeen eyes (17%) (12 patients) had IOP > 21 mm Hg. Of these, 11 eyes showed activity of TAO and 6 eyes showed none. Eighty-three eyes (83%) had normal IOP (31 – with active and 52 – with inactive TAO). Fourteen eyes had IOP which was normalised by an antihypertensive therapy (10 eyes with active TAO and 4 eyes with inactive TAO).

In the present study, 4 patients (8%) with TAO were diagnosed with glaucoma. The diagnosis was made on the basis of high IOP – above 21 mm Hg or such that returns to normal after antihypertensive therapy; the presence of typical changes in the optic nerve disc, and glaucoma visual field defects.

The distribution of patients (eyes) according to the severity of TAO and the average IOP and MTS values for each group are given in **Table 3**.

The CT showed a fusiform thickening of the bodies of the EOM in all patients. The largest thickness was found in the inferior rectus muscle (**Table 4**).

With patients having active TAO, a greater muscle thickness sum was found (23.39 ± 3.81 mm) compared to the group without activity (19 ± 3.21 mm, $p < 0.0001$, $t = 6.24$, Independent Samples Test). A difference in MTS was also detected with patients belonging to the different severity groups, the greatest MTS being measured in group 6 (**Table 3**). Statistically significant were the differences between group 1 and all other groups ($p < 0.05$, One-Way ANOVA, LSD).

Higher IOP was found in patients with greater muscle thickness sum ($P = 0.001$, $R = 0.32$, Pearson correlation) (**Fig. 1**).

Disthyroid optic neuropathy (DON) of one of the eyes was established in two of the patients (4%), with some accompanying visual field defects, decreased visual acuity, indistinct borders of the optic nerve disc and changes in colour vision. DON corresponds to Class 6 in NOSPECS severity classification of TAO. TAO activity was established in both cases, using the scale of clinical activity. The IOP of the affected eyes, in both cases, was 25 mm Hg and 24 mm Hg, without the application of antihypertensive therapy.

Table 3. Distribution of eyes by TAO severity, IOP and MTS (n=100)

Groups by severity	Number of eyes (n)	IOP (mm Hg)	MTS (mm)
Severity 'O'	26	14.92 ± 4.05	17.29 ± 2.92
Severity 'S'	10	14.5 ± 2.55	20.88 ± 2.29
Severity 'P'	50	18.04 ± 4.51	22.02 ± 4.06
Severity 'E'	10	18.2 ± 5.05	22.32 ± 2.60
Severity 'C'	2	20.5 ± 4.95	24.75 ± 1.62
Severity 'Si'	2	21.5 ± 4.95	25.95 ± 4.31

What is notable here is the fact that the greater the severity of TAO, the higher the IOP. A statistically significant difference in IOP between the different groups of patients was established between groups 1 and 3, 4 and 6 group ($p < 0.05$, One-Way ANOVA, LSD), as well as between groups 2 and 3 ($p=0.02$, One-Way ANOVA, LSD) and between group 2 and group 6 ($p=0.039$, One-Way ANOVA, LSD).

Table 4. EOM in TAO patients

Muscle	Size (mm)
Medial rectus	5.11 ± 1.5
Lateral rectus	4.77 ± 1.1
Superior Muscle Complex	5.33 ± 1.6
Inferior Rectus	6.63 ± 1.7

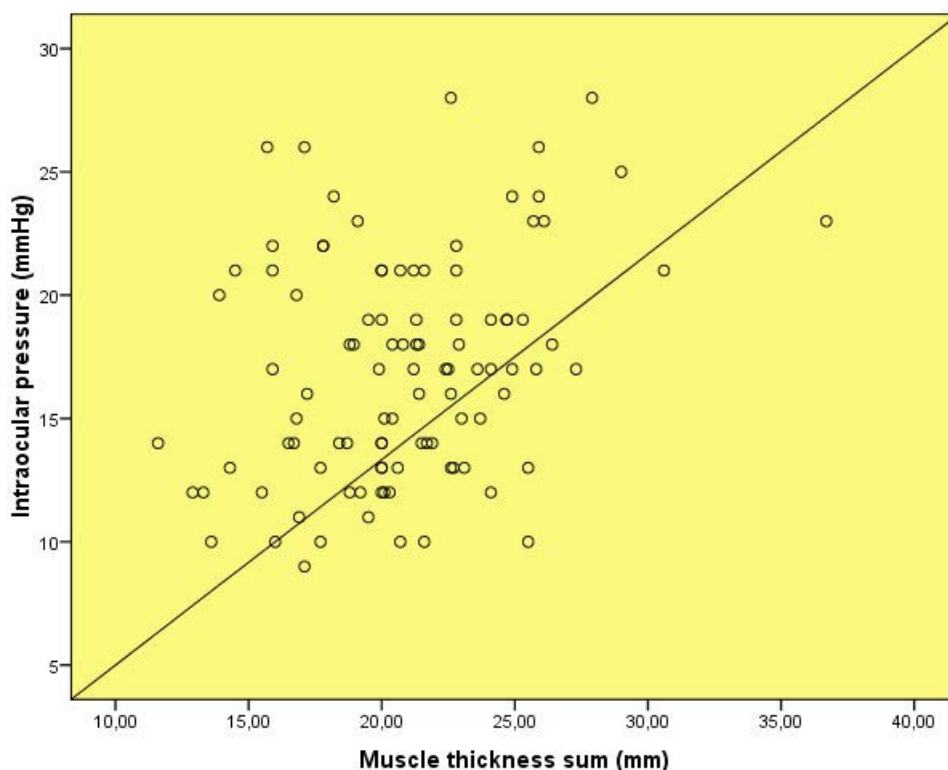


Figure 1. Correlation between IOP and MTS ($p = 0.001$, $R = 0.32$, Pearson correlation).

DISCUSSION

Increased IOP is a common symptom with patients having thyroid-associated ophthalmopathy. During the study, the position of the eyeball is of importance when interpreting the measured values of IOP.^{7,8} In 1918, Wessely was the first to describe higher IOP values on upgaze in patients with TAO.¹¹ Later, a number of studies confirmed an IOP increase when the eyeball deviates at an angle of 30° upwards.^{7,8} In patients with TAO, the enlarged rigid inferior rectus muscle presses the eyeball on upgaze, which leads to elevated IOP. In first position of the gaze, the IOP gets normalized. This necessitates performing tonometry on forward gaze (in the first position of the eyeball) so as to avoid errors and incorrect interpretation of the results, such as ocular hypertension and unnecessary prescription of antihypertensive therapy. During our study, we established thickening of the bodies of all eye-moving rectus muscles, the most pronounced alterations being in the inferior rectus muscle. Higher IOP values were measured in patients with greater MTS, which proves the mechanism of increased IOP due to the enlarged extraocular muscles pressing the eyeball.

The present study shows the correlation between IOP and the activity and severity of TAO. The

clinical activity scale covers 10 signs of inflammation: spontaneous pain in or behind the eyeball, pain upon movement of the eyeball, redness of the eyelids, redness of the conjunctiva, chemosis, swelling of the eyelids, swelling of the caruncula and the semilunar fold, an increase in proptosis by 2 mm and more over the last 3 months, a decrease in visual acuity during the last 3 months, restriction of the movement of the eyeball at 8° and more during the last 3 months. Only 7 of the described features can be diagnosed during primary examination, the other three requiring follow-up observation over time. The choice of treatment depends on the ascertainment of the activity and severity of TAO.¹² Patients with an active disease are prescribed immunosuppressive and corticosteroid therapy, which can influence the values of IOP. In our study, we established higher average IOP values in patients with an active disease. Active inflammation increases the volume of soft tissues of the orbit, including the eye-moving muscles, due to cell infiltration and accumulation of mucopolysaccharides. The increased volume and edema lead to increased intraorbital and episcleral venous pressure which worsens the outflow of the aqueous humor resulting in an IOP increase. Behrouzi

et al.¹³ investigated 117 patients with TAO and found that active forms prevail in patients with ocular hypertension. In the studied group, they established a frequency of ocular hypertension of 8.5%, 2.5% of the cases being with glaucoma. In our study, 4 patients (8%) were with glaucoma, and 12 (24%) – with ocular hypertension, the active TAO forms prevailing in them. In a retrospective study, involving 482 patients with TAO, Kalmann and Mourits detected ocular hypertension in 3.9% of the cases, compared to the general population where the rate is 1.6%.² Other authors indicate a higher incidence of ocular hypertension in patients with TAO – Ohtsuka³ detected 22% and Cockerham⁴ – 24%.

Despite the small number of patients in the severity groups 5 and 6, we found advanced levels of IOP in patients with more severe forms of TAO (higher stages according to NOSPECS). In the cases of high IOP concerning patients with more severe forms of TAO, especially when there are defects in the visual field too, accurate diagnostics is necessary so as to exclude *disthyroid* neuropathy. Optic neuropathy is the most serious complication occurring in 3-6% of all patients with TAO.⁶ The incidence of DON in our group is 4%, high IOP being detected with all patients. In half of the cases, Behrouzi indicates DON in 4.3% with high values of IOP.¹³

Intraocular pressure must be carefully monitored in patients with thyroid-associated orbitopathy during all phases and stages of the disease, and its measurement must be carried out at a standard head position and forward gaze. Patients with ocular hypertension need a detailed examination of the visual field, as well as of the fundus, as persistent ocular hypertension in TAO can lead to glaucoma with permanent disabilities.

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Корреляция между внутриглазным давлением и толщиной экстраокулярных мышц, тяжестью и активностью тиреоид-ассоциированной орбитопатии

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Цель: Установить корреляцию между внутриглазным давлением (ВГД) и толщиной экстраокулярных мышц (ЭОМ), тяжестью и активностью тиреоид-ассоциированной орбитопатии (ТАО).

Материалы и методы: В исследование было включено 50 пациентов с ТАО. Все они прошли подробный осмотр глаз, тонометрию Гольдмана (mm Hg) и компьютерную томографию глазных орбит. Сумма мышечной толщины (СМТ) каждого глаза измеряется в миллиметрах. В соответствии с активностью ТАО пациенты были разделены на две группы - с активностью и без активности, а в соответствии с серьезностью заболевания - на 6 групп: группа 1 («О») с только субъективными симптомами; группа 2 («S») с симптомами гладких мышц; группа 3 («P») – с проптозом; группа 4 («E») – с нарушениями подвижности глазных яблок; группа 5 («C») - с повреждением роговицы; группа 6 («Si») - с нарушением зрения.

Результаты: Активность ТАО была установлена у 21 пациента (42 глаза, 42%) с СМТ $23,39 \pm 3,81$ и с ВГД $18,43 \pm 4,16$. Двадцать девять пациентов (58 глаз, 58%) с СМТ $19 \pm 3,21$ и с ВГД $15,98 \pm 4,59$ не показали активности ТАО. ВГД в группах по степени тяжести было следующим: группа 1 - $19,92 \pm 4,05$; группа 2 - $14,5 \pm 2,55$; группа 3 - $18,04 \pm 4,51$; группа 4 - $18,2 \pm 5,05$; группа 5 - $20,5 \pm 4,5$; Группа 6 - $21,5 \pm 4,95$. Корреляция между ВГД и СМТ была установлена.

Выводы: ВГД у пациентов с ТАО зависит от толщины ЭОМ, а также от активности и тяжести заболевания.