

## DISTHYROID ORBITOPATHY

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A correlation of autoimmune Graves' hyperthyroiditis and mild forms of autoimmune Graves' ophthalmopathy (GO) occurs in approximately 50% of patients, while severe form of autoimmune Graves' ophthalmopathy occurs in 3-7% of all patients. Around 80% of Graves' ophthalmopathy cases occur in association with hyperthyroidism, although not all coincide with the onset of hyperthyroid symptoms. Because an increase in orbital content compresses the eye, elevated intraocular pressure, protrusion of the eye and/or isolated optic nerve neuropathy can be developed. The aim of our work was to demonstrate that autoimmune Graves' disease of the thyroid gland in patients without other autoimmune diseases is in correlation with an increased risk of protrusion of an eye and increased eye pressure.

The research included a group of 42 patients (84 eyes) who were divided into two equal groups. The first group consisted of patients with Graves' disease of the thyroid gland, without other autoimmune diseases, while the second, control group consisted of patients who did not have autoimmune disease. All patients were subjected to a complete ophthalmological and internal examination in the morning hours. The  $\chi^2$  test and Fisher exact test were used in statistical analysis. Patients with Graves' disease of the thyroid gland had statistically higher values of intraocular tension and values of protrusion of patients of control group ( $p < 0.001$ ). Elevated intraocular pressure was measured in 14 eyes of patients with autoimmune hyperthyroidism (16.67%) and 5 eyes of patients of the control group (5.95%). Mild protrusion was found in 12 eyes in the patients with autoimmune hyperthyroiditis (14.29%) and 4 eyes in the control group patients (4.76%). Patients with the disease of thyroid gland have a higher risk of the intraocular pressure increase and protrusion of the eye. Because of that, it is necessary to do a complete ophthalmological and internal examination of patients with Graves' hyperthyroiditis in order to prevent glaucoma.

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**Key words:** Graves' ophthalmopathy, protrusion, increased eye pressure

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### Introduction

The eye disease which has generally been associated with autoimmune thyroiditis has been known by many names: Graves' ophthalmopathy (GO) or von Basedow's disease, thyroid eye disease (TED), or thyroid associated orbitopathy (TAO)(1). These terms indicate that the etiopathogenesis of the con-

dition is not fully elucidated and that the disease has numerous and varied clinical presentations and some features are more sight-threatening than others (2). Around 80% of cases of GO occur in association with hyperthyroidism, although not all coincide with the onset of hyperthyroid symptoms. The rest of 20% of cases of GO occur in association with autoimmune hypothyroidism or autoimmune eutiroidism (3). The most frequent symptoms in the beginning of GO disease are characterized by pain, swelling, redness, watering, retraction of the upper eyelids, conjunctivitis, bulging eyes, double vision and occasionally decreased vision (4). GO has many clinical appearances with more or less important clinical signs (5). Diagnosis and differential diagnosis of Graves' disease (GD) include eye changes, autoimmunity of thyroid gland and exclusion of other autoimmune coexisting diseases such as vitiligo, celiac disease, autoimmune liver disease, myasthenia gravis, sclerosis multiplex, rheumatoid arthritis, systemic lupus erythematosus, Sjögren syndrome and systemic sclerosis (6).

GO may occur before or after the onset of an overt thyroid disease, and it can start suddenly or more slowly (7). Even though some patients undergo spontaneous remission of symptoms within a year, many need treatment (8). The first step of treatment aims to regulate thyroid hormone levels and implement smoking cessation (9). Lubricating eye drops are used to avoid damage to the eye (10). GO is a rare but treatable disease that causes a significant decrease in quality of life (11). The main antigen, which is the same for both thyroid gland and orbit, is called thyrotropin receptor (TR), and it is important for the mechanism involved in the pathogenesis of GO (12). TR-stimulating GD immunoglobulins induce hyaluronan synthesis and enhance adipogenesis by differentiating orbital fibroblasts (13). In active disease, the accumulation of inflammatory cells and interstitial edema of extraocular muscles occurs, in first line m.rectus internus and m.rectus inferior. The muscles may be in increase for two or three times (14). In pathogenesis of glaucoma the most important role was the increase of orbital volume, and compression of bulbus oculi, orbital veins and nervus opticus into the orbital apex. The drainage of anterior chamber fluid is with difficulties (15).

This division allows us a different approach to the treatment of ophthalmopathy (16). The active disease lasts for 18-24 months, especially in patients, younger than 40 years. Signs of the active disease are pain, swelling, redness, watering, retraction of the upper eyelids, conjunctivitis, bulging eyes, and double vision. Signs of inactive disease are proptosis and higher palpebral aperture. In older patients, synthesis of glycosaminoglycans is dominant (17).

## Methods

This study was conducted from December, 2013 to June, 2015. The study included 21 patients with autoimmune hyperthyroiditis from Department of Internal Disease, treated with hormonal therapy and 21 patients without autoimmune diseases from Department of Physical Medicine and Rehabilitation Military Medical Center. All patients were subjected to a detailed internist and ophthalmological examination, including detailed history of previous diseases or injuries, with the aim to exclude any other autoimmune diseases.

The first group consisted of 16 female and 5 male patients, aged from 33 to 65 years. Some of them had other chronic diseases, 15 patients had arterial hypertension, 6 insulin-independent diabetes mellitus and 9 of them were smokers.

The second group of patients served as a control group, consisting of 21 patients, 11 women and 10 men, from 30-65 years. All patients were without autoimmune disease, whereas among other chronic diseases there were 5 smokers, 17 with arterial hypertension and 4 insulin-independent diabetes mellitus patients.

Ophthalmology examinations were performed in the morning and included examination of visual

acuity, color vision, measurement of proptosis with HERTEL-exophthalmometer, examination of eyes motility, upper lid retraction, examination on a slit lamp HAAG-STREIT, intraocular pressure measurement by the contact applanation tonometer, and fundus examination. Measuring with HERTEL-exophthalmometer, with a snug mechanism and preferably a square angle which sits against the orbital rim, was done in a sitting position (18). Pathological values of proptosis were 20mm and higher intraocular pressure (IOP) was 22mmHg and over (19). Values of proptosis from 21 to 23 mm were small, from 24 to 27 were moderate, and values over 28mm were large (20). In a statistical analysis, the  $\chi^2$  test and Fisher exact test were used. During a review with the slit-lamp, the presence or absence of conjunctival plica semilunaris was noted and redness of the caruncula excluded any microbial inflammation. We detected some changes on the optic nerve by fundus examination, using ophthalmoscopy through dilating pupil by the application of the mydriatic agent tropicamide.

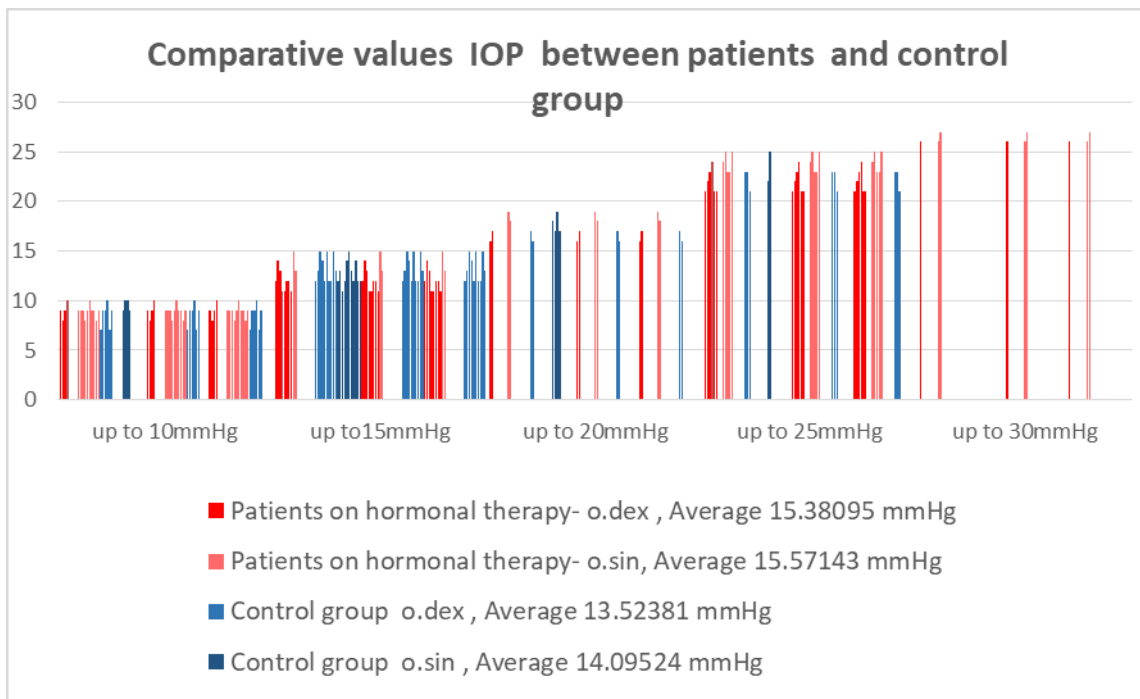
## Results

In a group of 42 patients in total (84 eyes), IOP was increased in 14 eyes on hormonal therapy (16.67%), and in 5 eyes in the control group (5.95%). The average IOP in patients on hormonal therapy was 20.73 mmHg for the right eye and 20.94 mmHg for the left one. In control group, the average IOP was 15.94 mmHg for the right eye and 18.13 mmHg for the left eye (Graph 1).

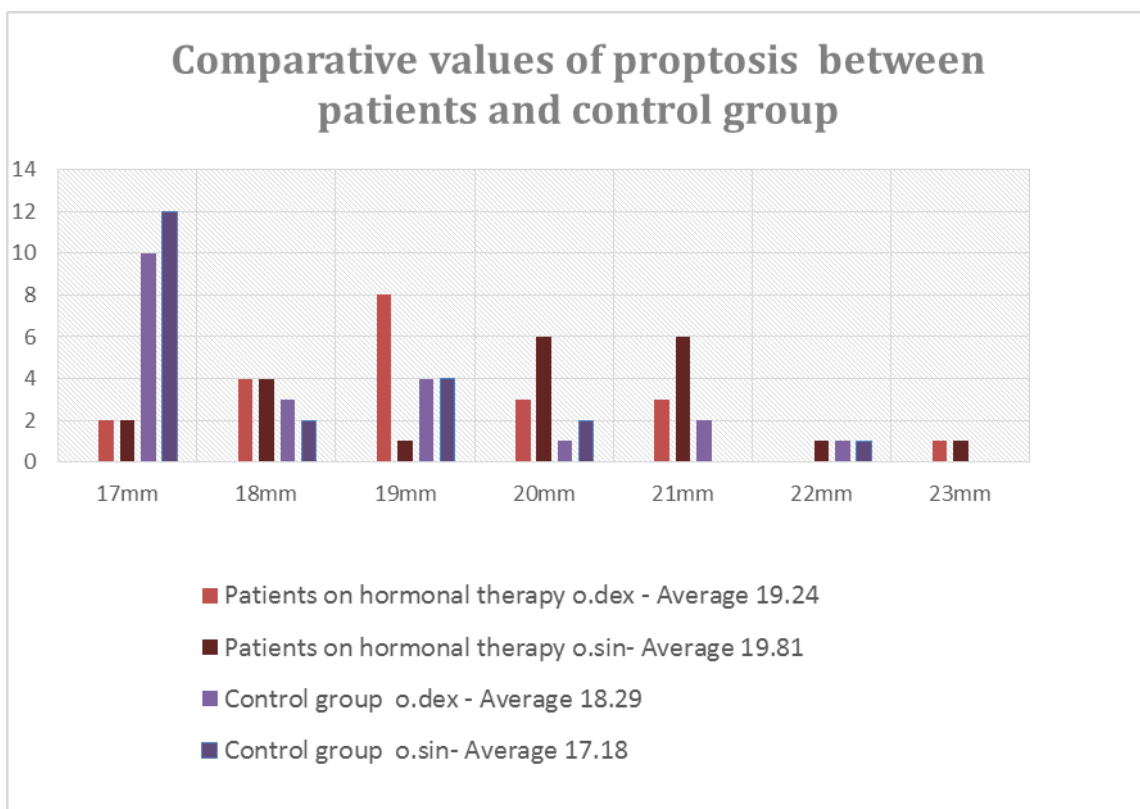
Graph 2 shows the values of proptosis in patients on hormonal therapy and the control group. The average value of proptosis in the patients on hormonal therapy was 19.24 mm for the right eye, and 19.80 mm for the left eye. The average value of proptosis in the patients in control group was 18.29 mm for the right eye, and 18.00 mm for the left eye. Out of the total group of 42 patients (84 eyes) we examined, 12 eyes from the group on hormonal therapy were with mild proptosis (14.29%), while in the control group 4 eyes were with slight proptosis (4.76%).

## Discussion

Hashimoto's thyroiditis - goiter is an autoimmune disease associated with ophthalmopathy, too. In Hashimoto thyroiditis - goiter, changes of the eye are less pronounced, they are slowly progressing and less conspicuous. Goiter is discreet, and it does not indicate a disease (21). Genetics, pregnancy, stress, deficiency of iodine (J) or (Se) in a nutrition, excess of radioactive J, usually entered by therapy per os, various toxins in environment, radioactivity in the living surrounding, cosmic radiation and yersinia enterocolitica are the factors which can be associated with it (22).



**Graph 1.**



**Graph 2.**

Tobacco smoke has a big influence on the level of activity of an autoimmune inflammation, triggering the immune system (23). Smokers are at an increased risk of activating autoimmune processes

(24). Physicians have to be aware of the emotional aspects of patients with Graves' ophthalmopathy, since various kinds of neuroses are frequent (25). In developed countries, a routine thyroid testing of

pregnant women, regular screening of neonates, children and young people is mandatory, because hormone deficiency can lead to brain and organic defects of intrauterine baby, slow growth and slow psychological development (26).

Nowadays, in the modern age, the thyroid gland dysfunctions are diagnosed much earlier, hence endocrinological medical treatment can start immediately at the first sign of proptosis (27). With hormonal therapy conducted on time, from the very beginning of the disease, we are able to suppress autoimmune inflammation (28). If the therapy starts early, a regression of all signs can be accomplished. After Graves' ophthalmopathy has been diagnosed, we should choose an indication for a local medical treatment. Only a few patients (5-10%) develop a severe disease form that requires aggressive treatment. Medical therapy is not effective enough at this stage of the disease (29). Glucocorticoids represent

a major therapeutical modality for severe, active ophthalmopathy (30). For differential diagnosis there are other conditions, such as inflammable ophthalmopathy, orbital cellulitis, myositis, chronic progressive external ophthalmoplegia, orbital tumors, neuro-sarcoidosis, myasthenia gravis, carotid-cavernous fistula and conjunctivitis allergica.

### Conclusion

Patients with GO are exposed to an increased risk of developing proptosis and increased IOP that can lead to glaucoma. Complete ophthalmic examination is necessary for all patients with GO because of the possibility for the development of isolated inflammation localized in the orbital apex, without other signs of proptosis, disturbed ocular motility, or increased IOP.

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## DISTIROIDNA ORBITOPATIJA

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Povezanost autoimunog Grejvsovog hipertiroiditisa i blage forme Grejvsove autoimune oftalmopatije (GO) javlja se kod približno 50% bolesnika, dok se teška forma javlja kod 3-7% bolesnika. Oko 80% slučajeva Grejvsove oftalmopatije povezano je sa autoimunim hipertiroidizmom, iako nije u vezi sa pojavom prvih simptoma bolesti. Zbog uvećanog sadržaja orbite koji vrši kompresiju na oko može se javiti povišen očni pritisak, protruzija oka i/ili kompresivna neuropatija optičkog nerva. Cilj našeg rada bio je da ukažemo da kod bolesnika sa autoimunim Grejvsovom oboljenjem štitne žlezde, bez drugih autoimunih oboljenja, postoji povećan rizik za nastanak protruzije oka i povišen očni pritisak.

Istraživanje je rađeno na grupi od 42 bolesnika (84 oka) podeljenoj u dve jednake grupe. Prvu grupu činili su bolesnici sa Grejvsovom oboljenjem štitne žlezde bez drugih autoimunih oboljenja, dok su drugu, kontrolnu grupu, činili bolesnici koji nemaju autoimuno oboljenje. Svim bolesnicima je urađen kompletan internistički i oftalmološki pregled u preopdnevnom satima. U statističkoj obradi je korišćen  $\chi^2$ -test i Fišerov egzaktni test. Bolesnici sa Grejvsovom oboljenjem štitne žlezde imaju značajno više vrednosti očnog pritiska i izraženiju protruziju očiju od bolesnika kontrolne grupe ( $p < 0,001$ ). Povišen očni pritisak je izmeren kod 14 očiju kod bolesnika sa Grejvsovom oboljenjem štitne žlezde (16,67%) i kod 5 očiju kod bolesnika iz kontrolne grupe (5,95%). Blaga protruzija je nađena kod 12 očiju bolesnika sa Grejvsovom oboljenjem štitne žlezde (14,29%) i kod 4 oka u kontrolnoj grupi (4,76%). Bolesnici sa oboljenjem štitne žlezde imaju veći rizik od nastanka povišenog očnog pritiska i protruzije oka. Zbog toga je kod bolesnika sa Grejvsovom hipertiroidizmom potrebno uraditi kompletna internistička i oftalmološka ispitivanja u cilju prevencije glaukoma.

*Acta Medica Medianae 2018;57(2):60-65.***Ključne reči:** Grejvsova oftalmopatija, protruzija, povišen intraokularni pritisak