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COMPARISON OF THYROID STIMULATING HORMONE RECEPTOR ANTIBODY (TRAB) IN GRAVES' DISEASE PATIENTS WITH AND WITHOUT OPHTALMOPATHY

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Abstract

Background: *Ophthalmopathy Graves' is one of the serious complications of Graves' diseases, that can decrease the quality of life of the patient. The pathogenesis is not well understood, resulting in less effective therapy and resulting in permanent eye function impairment.*

Objective: *To determine the ratio of thyroid stimulating hormone receptor antibody (TRAb) between Graves' disease patients with and without ophtalmopaty.*

Methods: *This is a cross-sectional study involving 50 patients with Graves' active disease, who underwent treatment at Endocrine and Metabolic Unit of Internal Disease, Outpatient Installation of Dr. Soetomo General Hospital Surabaya. Graves' ophthalmopathy was determined when extracted eksoftalmus or eyelid retraction with thyroid dysfunction was found. Levels of thyroid-stimulating hormone (TSH) and FT4 were measured using the ELISA method. Meanwhile, TRAb level was measured using third generation thyroid binding inhibiting immunoglobulins (TBII) with ELISA method.*

Results: *There were 25 (50%) patients in the active Graves' patient group with and without ophthalmopathy, respectively, with age ranging from 20 to 65 years old. The median value of TRAb patients with Graves 'disease with ophthalmopathy was 3.21 IU/l, which is higher and statistically significant (p = 0.001) than TRAb levels of patients with Graves' disease without ophthalmopathy, with median value of 1.81 IU/l.*

Conclusion: *Higher levels of TRAb were found and statistically significant in Graves 'disease patients with ophthalmopathy than Graves' patients without ophthalmopathy.*

Keywords: *graves' disease, ophthalmopathy, TRAb thyroid antibody*

Introduction

Ophthalmopathy Graves' is an autoimmune disease that attacks the orbital and periorbital tissues associated with Graves' disease, one of the serious complications of Graves' disease that can degrade the patient's quality of life due to cosmetic disorders and the impairment or even loss of vision [*Paravina M., 2012*]. Understanding the low pathogenesis of ophthalmopathic Graves' resulting in the treatment of this disease has not achieved satisfactory results resulting in impairment and impaired function and anatomy of the eye [*Griepentrog G, Garrity J, 2009*].

The incidence of Graves' ophthalmopathy in the United States reaches 16 cases per 100,000 population per year in women, and 2.9 cases per 100,000 population per year in men [*Wiersinga W, Bartalena L, 2002*]. Ophthalmopathy occurring in

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about 50% of patients with Graves' disease can cause pain in orbit in 30% of patients, diplopia in 17.5% of patients, lacrimation or photophobia in 15-20% of patients, blurred vision 75% of patients, proptosis in 60% patients, restrictive extraocular myopathy in 40% of patients, eyelid retraction in 90% of patients and loss of vision in 5% of patients [*Khalilzadeh O. et al., 2011*]. Between Graves 'disease with Graves' ophthalmopathy there is a clinical association, in general ophthalmopathy occurs in hyperthyroid patients.

In Graves' disease, Thyroid Stimulating Hormone Receptor (TSH-R) is the main autoantigen. TSH-R bonding with TSH-R receptor autoantibodies (TRAb) may affect the metabolic activity of the thyroid gland resulting in hyperthyroidism. Recent years have found evidence of an increase in TSH-R expression in the orbital tissue of the Graves' ophthalmopathic patient [*Bahn R, 2003*]. The presence of a bond between TRAb and TSH-R in orbital fibroblasts is thought to result in edema, adipogenesis, and fibrosis of connective tissue and intraorbitous fat tissue so that extraocular muscle volume and intraorbitic adipose tissue increase.

These histopathologic changes correspond to typical Graves' ophthalmopathic features with clinical manifestations of eyelid retraction, proptosis, optic neuropathy, or extraocular myopathy [*Eckstein A et al., 2006*]. The study demonstrated a strong correlation between TRAb levels and Graves 'clinical severity of Graves' stalmopathy as measured by NO SPECS classification [*Gerding MN., 2000*]. Similarly, there was no significant difference in TRAb levels between Graves' patients with and without ophthalmopathy [*Myint KS., 2007*].

There are several methods of examination of TRAb levels known today. The examination of using TSH Binding Inhibitor Immunoglobulin (TBII) method was considered quite sensitive, applicative, and useful for research and clinical purposes. The third-generation TBII examination has a high sensitivity and specificity level of 95% and 100%. The degree of sensitivity and specificity is also influenced by the ethnic variation of the examining subjects [*Ajjan R, Weetman A, 2008, Jang S et al., 2013*]. This study aims to determine the TRAb level comparison of patients with Graves' disease with and without ophthalmopathy.

Material and methods

This research is an observational analytic research with cross sectional. The study sample was Graves' disease patients who fulfilled inclusion and exclusion criteria in Endocrine Polyclinic Metabolic Disease, Outpatient Installation dr. Soetomo General Hospital, Surabaya in April - August. Sampling was done by consecutive sampling technique. The inclusion criteria in this study were 20-65 years old patients aged 20 to 65 years old who received active propylthiouracil (PTU) treatment for 8 weeks or more and were willing to be involved in the study and signed informed consent.

Active Graves' disease patients receiving methimazole (MMI) treatment, history of thyroidectomy, radioiodin, intraocular steroids, systemic steroids, intraorbitant radiation, eye reconstruction surgery and intraorbitic trauma, Graves' patients with diabetes mellitus who received Thiazolidinebdiones (glitazone) treatment at this or previous history of therapy, smokers, pregnant women, critical condition patients such as thyroid crisis, septic shock, or cardiogenic shock are excluded.

Graves' Ophthalmopathy is an autoimmune disease that affects extraocular muscles and connective tissue around the orbit of Graves' disease. Diagnosis based on anamnesis and physical examination that is, if there is a disease Graves' hyperthyroidism either at this time or previous history accompanied by eye disorders eksoftalmus and or retraction eyelids [*Bartley G, Gorman C, 1995; Bartalena L, Tanda M, 2009; Chong K, 2010*]. From the results of the examination, patients were classified as patients with and without ophthalmopathy. Graves' disease is an autoimmune disease that affects the thyroid gland, caused by the formation of autoantibodies against TSH-R in the thyroid (TRAb) [*DeGroot LJ., 2012*].

Active Graves' patients, who underwent treatment at Dr. Soetomo Hospital Polyclinic Surabaya and meet the criteria of the study conducted profile data collection, anamnesis and physical examination. Patients also performed blood sampling to determine TRAb level, then subjects were classified into two groups of active Graves' disease patients with and without ophthalmopathy. The study sample was taken by using consecutive sampling technique and matcing of age and sex variables between the two groups of research subjects . After

the sufficient number of subjects met the minimum number required, the data were then processed and analyzed and research reports were prepared. Data were processed using SPSS software version 17.0 (SPSS, Inc., Chicago, IL.). The collected data were analyzed using descriptive statistical analysis, numerical comparative statistical analysis. Results of analysis were considered significant when p <0.05.

Results

There were 119 patients who came and diagnosed with Graves' disease. After anamnesis, physical examination, laboratory examination, and matching of age and sex variables, there were 50 patients with active Graves 'disease consisting of 25 patients with ophthalmopathy and 25 patients without ophthalmopathy. Characteristics of patients with Graves' disease were distinguished by general characteristics, clinical characteristics , and laboratory characteristics.

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Based on the duration of the patient suffering from Graves' disease, most experienced for 1 - 5 years in both groups. In the Graves 'patient group without ophthalmopathy 4 patients (16%) developed Graves' disease for less than 1 year, 12 patients (48%) for 1 - 5 years, 6 patients (24%) for 5-10 years, 3 patients (12%) for more than 10 years. In the Graves' patient group with ophthalmopathy, 8 patients (32%) developed Graves' disease for less than 1 year, 9 patients (36%) for 1 - 5 years, 5 patients (20%) for 5-10 years, and 3 patients (12%) for more than 10 years. The general characteristics data of research subjects can be seen in table 1.

Clinical characteristics of study subjects, classified into diffuse struma, dermopathy, and acropaki. From the results of physical examination, diffuse diffuses were obtained in the Graves' patient group group without the ophthalmopathy as follows, degree 0 in 7 patients (28%), 1 degree

Table 1.

Subjects' general characteristics

Category	Ophthalmopathy				P value
	Without		With		
	n	%	n	%	
Gender					
Male	8	16%	7	14%	0.5
Female	17	34%	18	36%	
Age (year)					
Mean ± St Dev	43.64 ± 13.36	-	43.44 ± 12.36	-	0.956
Range (min-max)	20 s/d 64	-	21 s/d 65	-	
Graves' disease duration					
< 1 year	4	8%	8	16%	0.604
1 – 5 years	12	24%	9	18%	
5 – 10 years	6	12%	5	10%	
>10 years	3	6%	3	6%	

in 15 patients (60%), and 2 degrees in 3 patients (12%). There were no diffuse diffuses of degree 3 in this group. Whereas in the Graves' disease group group with ophthalmopathy the diffuses were obtained at all levels, ie, degre 0 in 4 patients (16%), 1st degree in 13 patients (52%), 2nd degree in 7 patients (28%), and 3rd degree in 1 patient (4%).

Thyroid dermopathy was obtained in 3 patients (6%), in the Graves' disease group with ophthalmopathy. In patients with thyroid dermopathy, there is a picture of gray-colored discoloration, accompanied by hyperkeratosis on both upper and lateral backs. The clinical features of struma, thyroid dermopathy obtained in some research subjects as shown in Figure 1. Thyroid acropacin in this study was obtained in 3 patients (6%), i.e. in

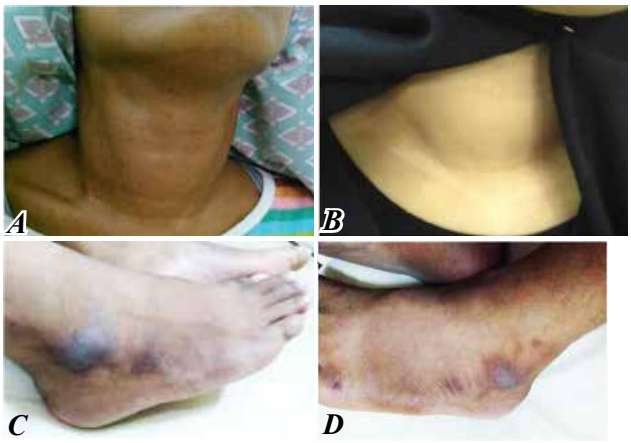

Figure 1*.Struma diffuse Degree 1 (**A**) Degree 2 (**B**); Thyroid dermopathy (**C, D**)*

the Graves' disease group with ophthalmopathy. In these three patients we also obtained a picture of thyroid dermopathy on both legs. Description of thyroid acropaces obtained in the form of swelling of several fingers with pigmentation and hyperkeratosis at the fingertips, without fingers, as shown in Figure 2. Clinical characteristics of the study subjects, as shown in table 2. In the laboratory results, the patient group of Graves' tanpa ophthalmopathy disease has a median value of FT4 level of 1.27 *ng/dl* with a minimum value range up to a maximum of 0.90-9.85 *ng/dl*. The median value of FT4 levels for the Graves' disease group with ophthalmopathy was 1.68 *ng/dl*, with a minimum to maximal range of values of 0.90 - 5.50 *ng/dl*.

FIGURE 2. *Thyroid acids*

The subjects in the Graves' patient group without ophthalmopathy had a median value of 0.036 uIU/mL TSH, with a minimum to maximum range of 0.001 to 4,000 *uIU/mL*. The median values of TSH group of patients with Graves' disease with ophthalmopathy were 0.011 *uIU/mL*, with a minimum range up to a maximum of 0.001 to 4.500 *uIU/mL*.

TABLE 2.

Subjects' clinical characteristics

Category	Ophthalmopathy Without n	Without %	With n	With %
Struma diffuse				
Degree 0	7	14%	4	8%
Degree 1	15	30%	13	26%
Degree 2	3	6%	7	14%
Degree 3	0	0%	1	2%
Thyroid dermopathy				
Negative	25	50%	22	44%
Positive	0	0%	3	6%
Thyroid acropachy				
Negative	25	50%	22	44%
Positive	0	0%	3	6%

Laboratory characteristics of the study subjects were shown in table 3. Graves' ophthalmopathic patients have special characteristics, i.e., varying patient complaints. In this study obtained as many as 12 patients (48%) showed initial complaints that reflect the symptoms and tirahipertiroid, with complaints of pounding and fatigue. A total of 5 patients (20%) changes in eye shape. The rest, as many as 8 patients (32%) said that both complaints, both eye disorders and symptoms and signs of hyperthyroidism occur together.It is illustrated in Fig. 3.

TABLE 3.

Characteristics of laboratory research subjects

Category	Ophthalmopathy Without	With	P value
FT4 (*ng/dl*)			
Range (min-max)	0.90 s/d 9.85	0.90 s/d 5.50	0.269
Median	1.27	1.68	
TSH (*Niu/mL*)			
Rentang (min-max)	0.001 s/d 4.000	0.001 s/d 4.500	0.294
Median	0.036	0.011	

Changes in eye shape obtained in the subjects of this study varied. There are several images of ophthalmopathy found, i.e. as many as 11 (44%) of patients exhibited eksoftalmus manifestation with eyelid retraction, 2 (8%) of patients showed only ecophysical manifestations alone, and 12 (48%) patients showed only eyelid retracted manifestations. Characteristics of abnormalities eyes in Graves' patients with the ophthalmopathy shown above as shown in figure 4.

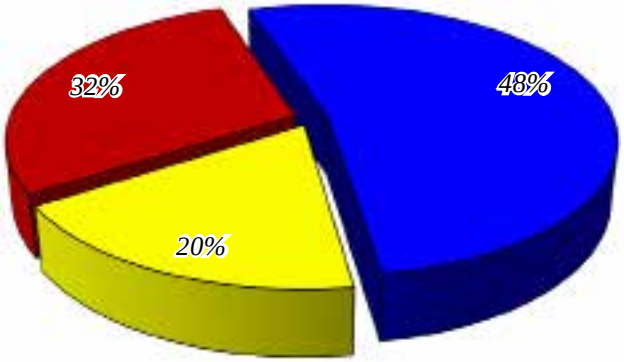

FIGURE 3. *Initial complaints of Graves' disease patients with ophthalmopathy. ■ symptoms and signs of hyperthyroidism, ■ Eye impairment, ■ symptoms and signs of hyperthyroidism and eye impairment*

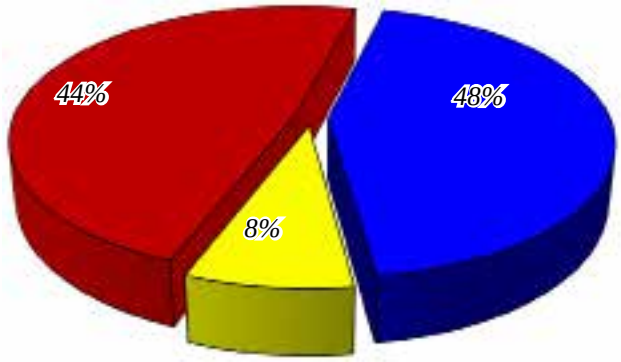

Figure 4. *The ophthalmic characteristics of the study subjects. ■ Retracting eyelids + eksoftalmus 44%, ■ Retracting eyelids, 48%, ■ Eksoftalmus 8%.*

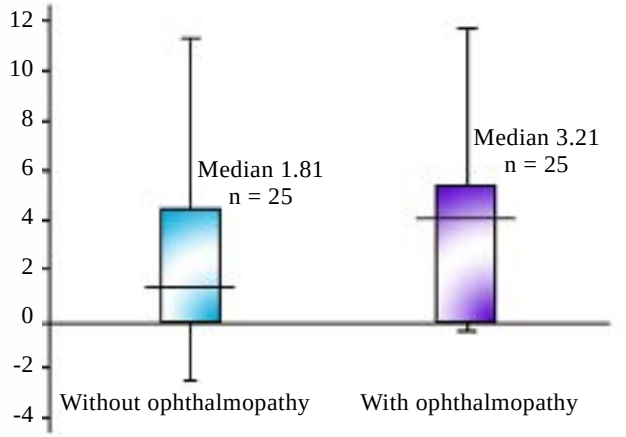

Figure 5. *Distribution and TRAb rate mean*

To find the description of TRAb levels, the subjects were classified into two groups, the Graves' disease group with ophthalmopathy and the Graves' disease group without ophthalmopathy. The mean TRAb rate in the Graves' disease group with ophthalmopathy was 5.47 ± 5.71 *IU/l*, with a median value of 3.21 *IU/l*, a minimum value of 1.79 *IU/l* and a maximum score of 28.9 *IU/l*. While the Graves' patient group without ophthalmopathy had an average TRAb rate of 4.32 ± 6.45 *IU/l*, with a median value of 1.81 *IU/l*, a minimum value of 1.03 *IU/l* and a maximum value of 26.8 *IU/l*. The descriptive descriptive value of TRAb values based on the Graves' patient group of patients as shown in table 4 below.

The TRAb values distribution shows a very high level of diversity. This is as indicated by the standard deviation values of TRAb levels in both groups which are much larger when compared to the mean values of TRAb in each group. The TRAb values distribution can be described as shown in figure 5.

To assess the TRAb rate comparison between the Graves' disease patients group with and without ophthalmopathy, we first tested the data distribution first. The test used is Saphiro-Wilk test because the number of samples used in this study is small. If in this test obtained p value less than 0.05, then the distribution of data is said not normal, and vice versa. In this test obtained the value of p in both groups smaller than 0.05, it can be concluded that the value of TRAb on both groups have abnormal data distribution.

Table 4.

Characteristics of TRAb value of research subjects

TRAb (*IU/l*)	Mean	Min	Max	Median	St. Dev
Without ophthalmopathy	4.32	1.03	26.8	1.81	6.45
With ophthalmopathy	5.47	1.79	28.9	3.21	5.71

The test result on the comparison of TRAb values between the two study subjects was obtained p value of 0.001. Thus, it can be concluded that the comparison of TRAb values between the Graves' disease patients group with and without ophthalmopathy showed statistically significant differences.

Discussion

This study involved 50 patients, consisting of 15 people with male sex (30%) and 35 people (70%) with female gender. The ratio of patients with graves' disease between women and men was obtained consecutively at 3: 1 and 2.9: 1 [*Malabu U et al., 2008; Subekti I et al., 2012*]. In the Graves' disease group with ophthalmopathy, were 18 (72%) female patients and 7 (28%) male patients. These results are not much different from epidemiological studies which say the risk of Graves' ophthalmopathy in women is higher than that of men ranging from 3: 1 to 10: 1 [*Paravina M, 2012; Petrovic M et al., 2012*].

In this study, subjects the Graves' patients group without olfamopati had an average age of 43.64 ± 13.36 years. Whereas, the Graves' patient group group with ophthalmopathy had mean of 43.44 ± 12.36 years. This condition is consistent with the characteristics of Graves' disease patients where incidence increases in adulthood with peak incidence between the ages of 40-60 years [*Brent G, 2008*].

Graves' disease patients have other distinctive clinical characteristics, ie diffuse struma, dermopathy, and thyroid acrophoses. Struma diffuse is a characteristic feature of Graves' disease as a dif-

fuse enlargement of the thyroid gland including isthmus and lateral lobes, without separate nodules [*Brent, 2008*]. Struma is seen in the thyroid gland with normal or abnormal function. In this study we obtained the most diffuse diffuse size in degree I, i.e. 15 (30%) patients in the Graves 'patient group without ophthalmopathy and 13 (26%) patients in the Graves' disease group with ophthalmopathy.

Thyroid dermopathy is a manifestation of Graves' disease in the skin that is quite rare. In this study, obtained 3 (6%) patients with Graves' disease with thyroid dermopathy. In one of the study subjects, there was a description of thyroid dermopathy on the back of the foot, this may be related to the patient's habit of sitting cross-legged on the floor, increasing friction frequency with the floor. In the present study, a description of thyroid dermopathy in the lateral part of the foot was associated with the patient's habit of daily shoe use. In this study, thyroid dermopathy was obtained in three patients (12%) in the Graves' disease group with ophthalmopathy.

Thyroid dermopathy is a manifestation of Graves' disease that arises at an advanced stage, which occurs after the manifestation of ophthalmopathy and thyrotoxicosis. Thus, in patients with thyroid dermopathy is almost always accompanied by Graves' ophthalmopathy [*Schwartz KM., 2002, Fatourechi, 2005, Reddy S et al., 2014*]. Thyroid dermopathy is used as a marker of severe ophthalmopathy and active autoimmune processes [*Fatourechi V, 2005*]. Similarly, patients with thyroid dermopathy in the subjects of this study, in these patients obtained positive thyroid autoantibody results and obtained in the group of patients with Graves' disease with ophthalmopathy alone.

Thyroid acids are a very rare clinical presentation of Graves' disease, with a prevalence rate of 0.8 to 1% [*Paravina M., 2012*]. In this study, we found 3 (6%) patients with Graves' disease with thyroid acids, with images of soft tissue swelling of fingers, pigmentation, and hyperkeratosis, without fingers. Although the thyroid acropachy frequency obtained in this study was higher than in other studies, but in all thyroid acropachy patients, there was also a picture of thyroid dermopathy and ophthalmopathy.

In this study we obtained median values of FT4 levels in the Graves 'patients group without ophthalmopathy of 1.27 *ng/dl* and median group of patients with Graves' disease with ophthalmopathy of 1.68 *ng/dl*. This shows that the median value of FT4 levels of both groups in the normal range range, which means both groups have reached eutyroid. FT4 levels are inversely proportional to levels of TSH. In this study, median TSH levels in both groups were below the normal range of 0.036 *uIU/mL* in the Graves' tanpaoftalmopati and 0.011 *uIU/mL* group of patients with ophthalmopathy.

The TSH level remained low in the study subjects despite having received antithyroid drugs, which is caused by the suppression of the pituitary gland by long-standing thyroid hormones. TSH levels will remain low for several weeks or months, although thyroid hormone levels have reached normal levels with antithyroid drugs [*Decroli E et al., 2014*]. TSH levels can not be used as monitoring in therapy [*Cooper SC, 2005*]. There was no data profile of TSH content of research subjects found prior to therapy. Therefore, how changes in TSH levels of the study subjects before and after antithyroid administration remains unknown.

In this study, patients with ophthalmopathic Graves' most came due to hyperthyroidism, reaching 12 (48%) people. Most hyperthyroid complaints are chest pounding and tired easily. Complaints of ophthalmopathy and hyperthyroidism occur together, which reaches 8 (32%) people. The rest, as many as 5 (20%) of patients come with initial complaints of ophthalmopathy, with most eye complaints in the form of swelling or bulging.

The diagnosis of Graves' ophthalmopathy can be easily established by physical examination including eyelid retraction, ocophthalmus, optic nerve dysfunction, and extraocular muscle involvement [*Bartley GB, Gorman CA., 1995*]. The results obtained in this study showed that eyelid retraction was the most common with 12 (48%) patients, followed by eyelid and eksoftalmus retraction in 11 (44%) patients, and eksoftalmus in 2 (8%) patients.

The study involved patients with positive TRAb. This suggests that the subjects in both groups were still undergoing an active autoimmune process. Thus, the study subjects have a quite high risk of experiencing relapse, although the levels of FT4 have reached normal numbers. Many retrospective studies suggest that patients with severe hyperthyroidism, large goitre size, high TRAb levels, and a T3 to serum T4 ratio of up

to 20 will find it difficult to achieve remission after treatment [*Cooper SC, 2005*]. Antithyroid treatment is recommended for 12-18 months [*Abraham B et al., 2004*].

The Graves' patient group without ophthalmopathy had a median value of TRAb of 1.81 *IU/l* with a minimum value of 1.03 *IU/l* and a maximum of 26.8 *IU/l*. The ophthalmopathic group had a median TRAb level of 3.21 *IU/l* with a minimum value of 1.79 *IU/l* and a maximum of 28.9 *IU/l*. Research conducted by Jang et al. also mentions that patients of Graves 'hyperthyroid ophthalmopathy have higher TRAb levels than Graves' ophthalmopathic patients who have reached eutyroid [*Jang S et al., 2013*]. This can be explained because hyperthyroidism has a direct effect on the immune system and on the interactions between the immune system and the thyroid antigen. Therefore, the occurrence of hyperthyroidism will worsen autoimmune conditions, resulting in thyroid autoantibodies. The presence of thyroid autoantibodies will again aggravate hyperthyroidism, resulting in an unbreakable cycle [*Laurberg P et al., 2014*].

The pathogenesis of Graves 'ophthalmopathy-suspected TRAb has a role as in Graves' disease. In this study, median values of TRAb levels in the Graves' group of patients with higher ophthalmopathy were 3.21 *IU/l*, compared with no ophthalmopathy group of 1.81 *IU/l*. Differences between the two groups showed statistically significant values with $p < 0.05$. This proves that TRAb has a role to the occurrence of ophthalmopathy in Graves' disease patients.

This study shows that there is a significant difference in TRAb levels between Graves' disease patients with and without ophthalmopathy. TRAb examination with third generation TBII method is able to differentiate the autoimmunity process occurring within orbital patients of Graves' disease with and without ophthalmopathy in this study population.

Conclusion

There was a significant difference between TRAb levels of patients with Graves' disease without and with ophthalmopathy with $p = 0.001$. Higher TRAb levels were found in patients with Graves' disease with ophthalmopathy than patients without ophthalmopathy.

REFERENCES

1. *Abraham P, Avenell A, Watson WA, Park CM, Bevan JS.* Antithyroid Drug Regimen for Treating Graves' Hyperthyroidism. Cochrane Database Syst Rev: 2004. Cd003420.
2. *Ajjan RA, Weetman AP.* Techniques to Quantify TSH Receptor Antibodies. Nat Clin Pract Endocrinol Metab. 2008; 4: 461-468.
3. *Bahn RS. Clinical Review 157:* Pathophysiology of Graves' Ophthalmopathy: The Cycle of Disease. J Clin Endocrinol Metab. 2003; 88: 1939-1946.
4. *Bartalena L, Tanda ML.* Clinical Practice. Graves' Ophthalmopathy. N Engl J Med. 2009; 360: 994-1001.
5. *Bartley G, Gorman C.* Diagnostic Criteria for Graves' Ophthalmopathy. American Journal of Ophthalmology. 1995; 119: 792-795.
6. *Brent GA.* Clinical Practice. Graves' Disease. N Engl J Med. 2008; 358: 2594-2605.
7. *Chong K. Thyroid Eye Disease:* A Comprehensive Review. The Hong Kong Medical Diary. 2010; 15: 4-10.
8. *Cooper S.* Drug Therapy: Antithyroid Drugs. The New England Journal of Medicine. 2005; 352: 905-917.
9. *Decroli E, Manaf A, Syahbuddin, S.* Immunologic and Hormonal Effects of Prophylthiouracil Treatment Using Maintenance Dose in Graves' Disease Patients. Acta Med Indones. 2014; 46: 314-319.
10. *1Degroot L.* Graves' Disease and The Manifestations of Thyrotoxicosis. 2012.
11. *Eckstein AK, Plicht M, Lax H, Neuhauser M, Mann K., et al.* Thyrotropin Receptor Autoantibodies Are Independent Risk Factors for Graves' Ophthalmopathy and Help to Predict Severity and Outcome of the Disease. J Clin Endocrinol Metab. 2006; 91: 3464-3470.
12. *Fatourechi V.* Pretibial Myxedema: Pathophysiology and Treatment Options. Am J Clin Dermatol. 2005; 6: 295-309.
13. *Gerding M, V van der Meer JW, Broenink M, Bakker O, Wiersinga W, Prummel M.* Association of Thyrotrophin Receptor Antibodies with The C Linical Features of Graves' Ophthalmopathy. Clinical

Endocrinology (Oxford). 2000; 52: 267-270.

14. *Griepentrog GJ, Garrity JA.* Update On the Medical Treatment of Graves' Ophthalmopathy. Int J Gen Med. 2009; 2: 263-269.
15. *Jang SY, Shin DY, Lee EJ, Lee SY, Yoon JS.* Relevance of TSH-Receptor Antibody Levels in Predicting Disease Course in Graves' Orbitopathy: Comparison of The Third-Generation Tbii Assay and Mc4-Tsi Bioassay. Eye (Lond). 2013; 27: 964-971.
16. *Khalilzadeh O, Noshad S, Rashidi A, Amirzargar A.* Graves' phthalmopathy: A Review of Immunogenetics. Curr Genomics. 2011; 12: 564-575.
17. *Laurberg P, Nygaard B, Andersen S, Carle A, Karmisholt J, Krejbjerg A, Pedersen IB, Andersen SL.* Association Between TSH-Receptor Autoimmunity, Hyperthyroidism, Goitre, And Orbitopathy in 208 Patients Included in The Remission Induction and Sustenance in Graves' Disease Study. J Thyroid Res. 2014, 165487.
18. *Malabu UH, Alfadda A, Sulimani RA, Al-Rubeaan KA, Al-Ruhaily AD, Fouda MA, Al-Maatouq MA, El-Desouki MI.* Graves' Disease in Saudi Arabia: A Ten-Year Hospital Study. J Pak Med Assoc. 2008; 58: 302-304.
19. *Myint KS, Shankargall AG, Macfarlane I, Gurnell M, Wood D, Chatterjee K, Simpson H.* Use of Anti Thyroid Hormone Receptor Antibody (Trab) In Graves' Disease. Endocrine. 2007; 13: 81.
20. *Paravina M, Stanojević M, Veličković M, Petrović S, Milosavljević M. A* Triad of Exophtalmos, Pretibial Myxedema and Acropachy in A Patient with Graves' Disease. Serbian Journal of Dermatology and Venereology. 2012; 4: 85-91.
21. *Petrovic MJ, Sarenac T, Sreckovic S, Petrovic M, Vulovic D, Janicijevic K.* Evaluation of The Patients with Grave's Ophthalmopathy After the Corticosteroids Treatment. Vojnosanit Pregl. 2012; 69: 249-252.
22. *Reddy SV, Jain A, Yadav SB, Sharma K, Bhatia E.* Prevalence of Graves' Ophthalmopathy in Patients with Graves' Disease Presenting to A Referral Centre in North India. Indian J Med Res. 2014; 139: 99-104.
23. *Schwartz KM, Fatourechi V, Ahmed DD, Pond GR.* Dermopathy of Graves' Disease (Pretibial Myxedema): Long Term Outcome. The Journal of Clinical Endocrinology and Metabolism. 2002; 87: 438-446.
24. *Subekti I, Boedisantoso A, Moeloek ND, Waspadji S, Mansyur M. Association of TSH Receptor Antibody,* Thyroid Stimulating Antibody, and Thyroid Blocking Antibody with Clinical Activity Score and Degree of Severity of Graves Ophthalmopathy. Acta Med Indones. 2012; 44: 114-121.
25. *Wiersinga WM, Bartalena L. Epidemiology and Prevention of Graves' Ophthalmopathy. Thyroid. 2002; 12: 855-860.*