CLINICAL STUDY

Neutrophil-to-lymphocyte ratio in thyroid ophthalmopathy

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ABSTRACT

PURPOSE: To evaluate the neutrophil-to-lymphocyte ratio (NLR) levels to predict the severity of inflammation in thyroid ophthalmopathy (TO).

METHODS: Fifty-six patients with TO and 40 healthy subjects were included in this study. TO patients were divided into two groups according to clinical activity score (CAS). Group 1 included 24 active TO patients and Group 2 included 32 inactive TO patients. The thyroid status, white blood cell (WBC), neutrophil, and lymphocyte counts were performed. NLR was calculated by dividing the neutrophil count by the lymphocyte count.

RESULTS: The mean age was 53.6 ± 5.4 in active TO group, 54.2 ± 5.6 in inactive TO group, and 52.7 ± 5.2 in the control group. The WBC, neutrophil, lymphocyte and NLR levels were higher in patients with TO than in the control group ($p < 0.05$). A significant difference in NLR was found between the inactive and active TO groups ($p < 0.05$).

CONCLUSION: NLR values were found to be higher in patients with TO than in controls. NLRvalues were also found higher in active TO patients than in inactive TO patients *(Tab. 3, Ref. 26)*. Text in PDF *www.elis.sk*.

KEY WORDS: neutrophil-to-lymphocyte ratio, thyroid ophthalmopathy, Graves' ophthalmopathy, inflammation, biomarker.

Introduction

Thyroid ophthalmopathy (TO) is an autoimmune inflammatory disease which leads to proptosis, conjunctival pain and hyperemia, extraocular muscle involvement and vision loss by affecting the orbital tissues (1). Although the exact mechanism of TO has not been clarified yet, it has been considered to be associated with the orbital infiltration of T cells which are essentially recognized by thyroid follicle cells and activated with similar antigens in orbital tissues. These activated T cells secrete many cytokines such as interleukin-1, tumor necrosis factor alpha and interferones (2). While the orbital infiltration is generally mild to moderate, severe ophthalmopathy can be seen in 3–5 % of all cases (3). Hyperthyroidism is commonly accompanied with TO but in some cases hypothyroidism develops due to Hashimoto's disease and euthyroidism can occur (4).

Neutrophil-to-lymphocyte ratio (NLR) has been recently used as a novel inflammatory marker to assess the severity of inflammation (5). The relationship between NLR values and various systemic diseases such as diabetes mellitus, cardiovascular diseases, hypertension and malignancies were studied in the last research (5, 6). Moreover, investigations with NLR levels and some ocular diseases have been previously reported particularly for the ophthalmology audience (5–7).

In the current study, we aimed to evaluate the NLR levels to assess the inflammatory process in TO patients. To the best of our knowledge, this is the first clinical study to investigate the inflammatory relationship between TO and NLR values.

Materials and methods

Patients

This study was approved by the ethics committee and was conducted in accordance with the Declaration of Helsinki. The details of the study were explained to the patients and written informed consents were obtained.

Fifty-six participants with TO and 40 healthy subjects were enrolled in this clinical study. Twenty-four patients had active TO (Group1), and 32 patients had inactive TO (Group 2). Clinical activity was graded according to the Clinical Activity Score (CAS) (Tab. 1). Active TO was defined as CAS ≥ 3 (8).

Detailed history, including family history, duration and progression of the disease and smoking were obtained. The patients with acute or chronic infection, inflammatory ocular or systemic diseases, ocular surgery or trauma history during the past 12 months, ocular or systemic drug use, steroid use in the past 6 months, malignancy history and hematologic disorders were excluded from the study.

Best corrected visual acuity, anterior and posterior segments examination and intraocular pressure measurement were applied to all participants.

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Tab. 1. Clinical Activity Score (CAS).

Spontaneous retrobulbar pain
Ocular pain with eye movement
Redness of the eyelids
Swelling of the eyelids
Redness of the conjunctiva
Chemosis of the conjunctiva
Swelling of the caruncle

*1 point is given for each item present.

Laboratory analyses

Complete blood count (CBC) values were obtained from all the participants. Venous blood samples were obtained from the antecubital vein and CBC measurements were performed by blood cell counter (ABX Pentra DF 120, Horiba, Japan. The white blood cell (WBC), neutrophil, and lymphocyte counts were recorded. The NLR levels were calculated from neutrophil and lymphocyte parameters. Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxine (FT4) values were also performed to assess the thyroid status of the patients.

Statistical analysis

All statistical analyses were performed by using the Statistical Package for Social Science version 16.0 software (SPSS, Chicago, IL). Data were expressed as mean± standard deviation. The Kolmogorov–Smirnov test was used to analyze normality of the groups. Comparisons of non-parametric values among groups were performed using one-way ANOVA. Comparisons between the groups were performed by using Mann– Whitney U-test. P values less than 0.05 were considered significant.

Results

Demographic features of participants with active TO, inactive TO and control group are shown in Table 2. The mean age was 53.6 ± 5.4 in the active TO group (n = 24), 54.2 ± 5.6 years in the inactive TO group (n = 32) and 52.7 ± 5.2 in the control group (n = 40). There were 11 men (42 %) and 13 women (58 %) in the active TO group; 15 men (44 %) and 17 women (56 %) in the inactive TO group; 20 men (50 %) and 20 women (50 %) in the control group. There were no significant differences among groups in terms of age and gender distribution.

The thyroid status was proved to be euthyroid in all of the 40 healthy subjects. Hyperthyroid status was found in 21 of 24 TO patients (88 %), 2 TO patients (8 %) were euthyroid and 1 TO patient (4 %) was hypothyroid in the active TO group while 26 of 32 TO patients (81 %) were hyperthyroid, 2 TO patients (12 %) were euthyroid and 1 TO patient (6 %) was hypothyroid in the inactive TO group (p = 0.62, p = 0.46, p = 0.32, respectively).

The NLR and WBC levels were higher in both TO groups when compared with the control group.

A significant difference in NLR was found between the inactive and active TO groups (p = 0.012). The WBC, neutrophil and lymphocyte levels were also higher in active group than in inactive group (p = 0.038, p = 0.026, p = 0.036, respectively) (Tab. 3).

Tab. 2. The demographic features and laboratory parameters of TO patients and control group (mean ± SD).

	TO patients (n=56)	Control group (n=40)	p
Age	53.9±5.5	52.7±5.2	0.665
Gender (M/F)	26/32	20/20	0.542
WBC ($10^3/\mu l$)	8.06±1.72	6.62±1,55	0.042
Neutrophil ($10^3/\mu l$)	4.48±1.68	3.64±1.24	0.037
Lymphocyte ($10^3/\mu l$)	2.18±0.66	1.84±0.52	0.048
NLR	2.12±0.72	1.74±0.48	0.039

Tab. 3. The demographic features and laboratory parameters of active and inactive TO groups (mean ± SD).

Variable	Active TO	Inactive TO	p
Age	53.6±5.4	54.2±5.6	0.625
Gender (M/F)	11/13	15/17	0.764
WBC ($10^3/\mu l$)	9.86±1.84	6.76±1.68	0.038
Neutrophil ($10^3/\mu l$)	5.98±1.76	3.71±1.52	0.026
Lymphocyte ($10^3/\mu l$)	2.38 ±0.64	1.89±0.56	0.036
NLR	2.72 ±1.2	1.98±0.54	0.012

Discussion

TO commonly presents during 4th-5th decades. While the female-to-male ratio is 5–10/1 in Graves' Disease, it is about 2–5/1 in TO. The probability of thyroid ophthalmopathy increased in HLA-B8, HLA-DR3 and HLA-DAW3 haplotypes in the white race (9). As an autoimmune course, antithyroglobulin which is an autoantibody responsible for the disease is directed against thyroid-derived thyroglobulin and attacks extraocular muscles. Mononuclear infiltration and glycosamioglican accumulation leads to the swelling of orbital tissues (10).

IL-17-secreting T cells play a critical role in the pathogenesis of organ-specific autoimmune diseases. These cells stimulate the production of inflammatory cytokines such as IL-1b, IL-6 and TNF-alpha and also promote inflammatory chemokines that induce the production of neutrophils and macrophages (11). Kim et al found the serum levels of Th17 cells in patients with Graves' ophthalmopathy to be higher than in controls and the serum levels of IL-17 in active Graves' ophthalmopathy patients were higher than those in inactive Graves' ophthalmopathy patients. They concluded that serum IL-17 concentration had a significant correlation with the disease activity (12).

In recent years, NLR has been thought to be a simple, inexpensive and easily-reached predictor to evaluate systemic inflammation. This WBC-derived parameter has been used in several tumoral, cardiac, inflammatory and autoimmune diseases (13–15). WBC subgroups play a critical role in inflammation and cytokine release. Tissue damage, stress, and inflammation result in neutrophilia and lymphopenia (16). It was reported that NLR not only evaluates the inflammatory response, it also predicts the prognosis of the disease (13–15).

The relationship between NLR and ocular diseases such as diabetic retinopathy, glaucoma, keratoconus, non-arteritic ischemic optic neuropathy and age-related macular degeneration were studied in literature previously. Ulu et al reported that increased

NLR level was associated with the presence of diabetic retinopathy and diabetes mellitus. The authors pointed out that the grade, as well as the severity of diabetic retinopathy is also correlated with NLR levels (17). Subsequently, Wang et al studied the NLR and brachial-ankle pulse wave velocity among the diabetic patients without diabetic retinopathy, patients with diabetic retinopathy and healthy subjects. They found out that both parameters were significantly higher in patients with diabetes mellitus and diabetic retinopathy (18).

The relationship between NLR and age-related macular degeneration (AMD) was also discussed by researchers. Ilhan et al studied NLR levels in 81 patients with dry AMD, 84 patients with wet AMD, and 80 healthy age- and sex-matched controls. They found out that patients with AMD had higher NLR values compared with controls, and NLR was correlated with disease severity. Therefore, the authors concluded that NLR may be used as a biomarker of inflammation in AMD (19). In another study, increased NLR value is found to be independently associated with neovascular AMD (20).

Guclu et al studied 42 patients with acute optic neuritis and 40 healthy subjects to investigate the relationship between NLR and acute optic neuritis episodes. They reported that there was a significant relation between NLR and number of episodes; therefore, higher NLR can be a useful marker for predicting recurrent episodes (21).

Non-arteritic ischemic optic neuropathy (NAION) was also evaluated in terms of NLR relationship. The authors recommended NLR as a new inflammatory marker for the assessment of severity of inflammation in NAION patients (22).

Retinal vein occlusion (RVO) is another disease which was researched for investigating the relation between NLR and RVO. In a study on 40 RVO patients and 40 healthy volunteers, it was found out that high NLR values were related to the development of RVO (23).

Karaca et al evaluated NLR in patients with progressive and non-progressive keratoconus and they reported that NLR was higher in patients with progressive keratoconus than in the non-progressive group and controls (24).

Two consecutive researches about glaucoma and NLR were reported more recently (25, 26). In the first study, the authors evaluated the NLR levels in patients with primary open-angle glaucoma and they found a significant difference in NLR levels between POAG and control groups (25). Subsequently, the second study assessed the levels of NLR in patients with pseudoexfoliation syndrome (PEX), pseudoexfoliation glaucoma (PXG) and healthy controls. NLR was found to be higher in both, PEX and PXG groups; therefore, NLR may be useful for predicting the prognosis of PEX patients and progression to PXG (26).

In our study, we investigated the relationship between the NLR levels and the severity of inflammation in TO patients. As far as we know from the outcomes of previous research, NLR was associated with the disease activity in several inflammatory diseases. On the basis of this, we also evaluated the NLR levels both in active and inactive TO patients. Our results provide evidence that NLR values are higher in active TO patients compared to inactive patients. An elevated NLR value is thought to result from high thyroid levels in the active TO group but we did not found a significant difference between the active and inactive TO groups in terms of thyroid status. This is the first study investigating the relationship between NLR and TO in literature. The only limitation of our study is a relatively small sample size.

In conclusion, we suggest that NLR can be a useful, reliable, inexpensive and easily-measured biomarker to predict both TO and the disease activity. Further research based on larger groups of participants will contribute to literature.

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