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Investigation of the neutrophil/lymphocyte and monocyte to high-density lipoprotein cholesterol ratios in differentiated thyroid cancers

Diferansiye tiroid kanserlerinde nötrofil/lenfosit oranı ve monosit/ yüksek dansiteli lipoprotein kolesterol oranının araştırılması

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ABSTRACT

Introduction: Thyroid cancers are the most common malignant tumors of endocrine origin. They are classified depending on their histopathological and clinical behaviors. Papillary and follicular cancers are classified as differentiated thyroid carcinomas (DTCs). The neutrophil/lymphocyte ratio (NLR) and the monocyte to high-density lipoprotein cholesterol ratio (MHR) have recently been shown to be powerful markers of oxidative stress and systemic inflammation, and the MHR has been revealed as a potent marker of mortality in coronary heart disease associated with coronary atherosclerosis. The aim of this study was to evaluate these markers in patients diagnosed with DTC.

Material and Method: One hundred twenty-five patients newly diagnosed with DTC and a 75-member control group consisting of entirely healthy individuals were included in the study. The patient and control groups were evaluated by investigation of cholesterol and hematological parameters following 12-h fasting.

Results: Significant differences were determined between the patient and control groups in terms of mean NLR (3.2±2.8 vs 2.4±1.3, respectively, p=0.013) and MHR (0.102±0.079 vs, 0.038±0.052 respectively, p<0.001) values. In the correlation analysis, positive correlation was determined between the NLR and white cell count (r=0.530, p<0.001), neutrophil count (r=0.293, p<0.001) and C reactive protein (CRP) (r=0.371, p=0.005), while negative correlation was determined between the NLR and lymphocyte count (r=-0.271, p=0.001).

Conclusion: The study data show that DTCs increase systemic inflammation.

Keywords: Differentiated thyroid carcinoma, neutrophil/lymphocyte ratio, monocyte to high-density lipoprotein cholesterol ratio

ÖZ

Amaç: Tiroid kanserleri endokrin kökenli en yaygın malign tümörlerdir. Tiroid kanserleri histopatolojik ve klinik davranışlara göre sınıflandırılır. Papiller ve foliküler kanserler diferansiye tiroid kanserleri (DTK) olarak sınıflandırılırlar. Son zamanlarda nötrofil/lenfosit oranı (NLO) ve monosit/yüksek dansiteli lipoprotein kolesterol oranı (MHO) oksidatif stres ve sistemik inflamasyonun güçlü göstergeleri olduğu ve MHO' nun koroner ateroskleroz ile ilişkili koroner kalp hastalığında mortalitenin güçlü göstergeleri olduğu ortaya konuldu. Bu çalışmamızda DTK tanısı konulmuş olan hastalarımızda bu belirteçleri değerlendirmeyi amaçladık.

Gereç ve Yöntem: Çalışmamıza DTK tanısı yeni konulan 125 hasta ve tamamen sağlıklı kişilerden oluşan 75 kişi kontrol grubu olarak dahil edildi. Hasta ve kontrol grubunun 12 saatlik açlık sonrası kolesterol parametreleri ve hematolojik parametreleri çalışılarak değerlendirmeye alındı.

Bulgular: Hasta ve sağlıklı grubun sırası ile NLO ortalaması (3,2±2,8 ve 2,4±1,3 p=0,013) ve MHO (0,102±0,079 ve 0,038±0,052, p<0,001) şeklinde tespit edildi ve aralarında istatistiki açıdan anlamlı bir fark olduğu tespit edildi. Yapılan korelasyon analizinde ise NLO ile sırası ile beyaz küre (r=0,530, p<0,001), nötrofil (r=0,293, p<0,001) ve C reaktif protein (CRP) (r=0,371, p=0,005) arasında pozitif korelasyon tespit edilirken, NLO ile lenfosit arasında (r=-0,271, p=0,001) negatif korelasyon tespit edildi.

Sonuç: Bu çalışma ile elde edilen verilere göre diferansiye tiroid kanserlerinin sistemik inflamasyonu artırdığı gözlenmektedir.

Anahtar kelimler: Diferansiye tiroid kanserleri, nötrofil/lenfosit oranı, monosit/yüksek dansiteli lipoprotein kolesterol oranı

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INTRODUCTION

Papillary and follicular cancers arising from thyroid follicular cells are classified as differentiated thyroid carcinomas (DTCs), and the prognosis is generally good. DTCs comprise 90% of thyroid cancers (1), and their incidence is growing worldwide (2,3). Thyroid cancer is currently the third fastest- growing cancer diagnosis in the USA, and the incidence has doubled in the last 30 years (4).

Numerous studies have shown that chronic inflammation plays an important role in the development of various cancers (5,6). One such association is between thyroid malignancies and autoimmune thyroiditis and high inflammation marker levels. Patients with autoimmune thyroiditis are at a significant risk of developing well-differentiated carcinomas (7,8).

The neutrophil-to-lymphocyte ratio (NLR) has recently been identified as a powerful indicator of oxidative stress and systemic inflammation (9). Studies have also showed elevated NLR in many types of cancer, such as colorectal, gastric, and biliary tract cancers (10,11,12). Monocyte count and high-density lipoprotein (HDL)-cholesterol ratio are important hallmarks of atherosclerosis, in the development of which inflammation again plays an important role (13). A high monocyte count and low HDL cholesterol levels may be related to a pro-inflammatory state in atherosclerosis. However, no previous research has investigated the association between MHR and cancer development, which is strongly associated with chronic inflammation, as described above.

The aim of the present study was to evaluate the levels of these simple, inexpensive, and readily available inflammation markers (NLR and MHR) in patients with DTC.

MATERIAL AND METHOD

One hundred twenty-five DTC patients (47 papillary, 46 micropapillary and 32 follicular) and 75 healthy controls were recruited into the study. Erzurum Regional Training and Research Hospital records were screened from December 2014 to December 2018, and individuals diagnosed of DTC based on histopathological examination were enrolled. Cases with hematological disease, ongoing infection, and chronic inflammatory disease were excluded from the study. All the controls were selected from the same hospital's internal medicine outpatient department. All the controls and patients were over 18 years old. All procedures were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 **Helsinki Declaration** and its later amendments or comparable ethical standards. All lipid and hematological parameters in the patient and control groups were evaluated after 12-h fasting.

Statistical Analysis

All statistical analyses in this study were performed on SPSS version 17.0 (SPSS, Chicago, IL, USA) for Windows software. The Mann–Whitney U Test or the Independent Sample-t Test were used following analysis of variance. Unless otherwise stated, the results were expressed as mean ± standard deviation, and p values <0.05 were considered statistically significant.

Ethical Declaration

The study was approved by the Health Sciences University, Region Training and Research Hospital Local Ethical Committee, Erzurum, Turkey (2018/05-32).

RESULTS

Sociodemographic characteristics, complete blood count, and biochemical parameters for both groups are summarized in Table 1. No significant difference was determined between the patient and control groups in terms of mean age or mean body mass index (p=0.106 and p=0.589, respectively). The 125 DTC cases consisted of 47 papillary, 46 micropapillary, and 32 follicular carcinomas. Liver and kidney tests exhibited no significant difference between the patients and controls. TSH values were higher in the controls than in the cancer cases, while free-T3 and free-T4 values were significantly higher in the cancer cases than in the controls. Mean MHR and NLR values both differed significantly between the patient and control groups (p<0.000 and p=0.013, respectively). Lymphocyte,and monocyte counts also differed significantly between two groups **(Table 1).**

Table 1. The demographic, clinical and biochemical features of the patients with and without differentiated thyroid cancer

Characteristics	DTC Patients* (n=125) Mean±SD	Controls (n=75) Mean±SD	p
Age (years)	45.9±14.7	48.2±7.7	0.106
BMI (kg/m^2)	28.0±4.7	27.2±3.3	0.589
Hemoglobin (gr/dl)	14.0±1.6	14.0±2.0	0.854
White blood cell (x10.e3/uL)	8.4±2.8	8.2±2.7	0.552
Neutrophil (x10.e3/uL)	5.6±2.5	6.7±6.8	0.001
Lymphocytes (x10.e3/uL)	2.0±0.7	3.0±1.4	<0.001
Monocyte (x10.e3/uL)	0.5±0.5	6.3±1.6	<0.001
Monocyte/HDL-cholesterol ratio	0,102±0,079	0.038±0.052	<0.001
Neutrophil-to-lymphocyte ratio	3.2±2.8	2.4±1.3	0.013
C-reactive protein (mg/dl)	8.2±26.0	2.7±1.9	<0.001
Total cholesterol (mg/dl)	199±46	193±44	0.485
LDL-cholesterol (mg/dl)	132±77	121±36	0.419
HDL-cholesterol (mg/dl)	48±14	50±13	0.275
Triglycerides (mg/dl)	158±71	151±113	0.018
TSH (mIU/L)	1. 3±1.3	1.5±1.3	0.305
Free T_3 (pg/ml)	3.2±0.77	2.7±0.66	<0.001
Free T_4 (ng/dl)	1.20±0.30	1.1±0.27	<0.001
Creatinine (mg/dl)	0.90±1.67	0.85±0.92	0.761
Alanine aminotransferase (U/L)	21±11	23±14	0.629
Aspartate aminotransferase (U/L)	22±6	24±9	0.342

The DTC cases consisted of 47 papillary, 46 micropapillary, and 32 follicular carcinomas.
BMI: Body Mass Index, TSH: Thyroid Stimulating Hormone, T_3: Triiodothyronine, T_4: Thyroxine,

The NLR exhibited positive correlation with the inflammatory markers C-reactive protein (CRP) (r=0.371, p=0.005), white blood cell count (r=0.530, p<0.001), and neutrophil count (r=0.293, p<0.001), and negative correlation with lymphocyte count (r=- 0.271, p=0.001). **(Table 2).**

Table 2. Correlation findings between NLR and other parameters

Characteristics	Correlation Coefficient	p
White blood cell	0.530	<0.001
Neutrophil	0.293	<0.001
C-reactive protein	0.371	0.005
Lymphocytes	-0.271	0.001

The MHR exhibited positive correlation with CRP (r=0.346, p=0.017), monocyte count (r=0.494, p<0.001) and neutrophil count (r=0.268, p=0.001).

DISCUSSION

The findings of this study showed that DTC increased systemic inflammation. NLR and MHR are indices that can be easily calculated with routine laboratory tests and that show the systemic inflammatory response. MHR has also recently emerged as a cardiovascular prognostic marker.

Oxidative stress and inflammation are closely linked pathophysiological processes. Oxidative stress is known to play a key role in several chronic diseases (14,15). Chronic inflammation has been associated with various diseases, such as diabetes mellitus (16), cardiovascular diseases (17), pulmonary diseases (18) and different types of cancer (19).

A relationship has also long been reported between thyroid carcinoma and inflammatory processes (20,21). In the physiological process of hormonogenesis, thyroid cells are exposed to high levels of reactive oxygen species (ROS) capable of involvement in the pathogenesis of thyroid cancer or of exhibiting cytotoxic effects (22). Oxidative stress has therefore been described as capable of impacting on thyroid malignancy.

Studies concerning the use of the NLR in various types of thyroid cancer have reported that the ratio cannot replace biopsy in diseases of the thyroid but that it may be a useful clinical marker.

In their study of histologically diagnosed cases of lymphocytic thyroiditis (LT), multinodular goiter (MNG), papillary thyroid carcinoma with lymphocytic thyroiditis (PTC-LT), and papillary thyroid carcinoma, Koçer et al. observed significantly higher NLR values in PTC and LT-PTC cases than in the other two groups, and suggested that this might be a useful guide in differentiating between benign and malignant thyroid diseases (23).

Studies examining the relationships between the clinicopathological characteristics of papillary thyroid carcinomas and the NLR have emphasized that perioperative high NLR values may be associated with tumor size and extrathyroidal extension (24), and also with extra-thyroidal invasion, presence of bilateral location and multifocal tumor, and lymph node positivity (25). Lee et al. reported that a high NLR was associated with an incomplete treatment response in DTCs (26).

We also observed a significant difference in NLR values between cases of DTC and the control group Our scan of the literature revealed no studies investigating the value of the MHR in cases of DTC. Similarly to the NLR, we also observed a significant difference in MHR values between the two groups.

The relationship between thyroid functions and the cardiovascular system is well known. The cardiovascular effects of abnormal thyroid functions, and particularly on atherosclerotic processes, such as adverse impacts on cardiac contractility, systolic and diastolic hypertension, a poor LDL cholesterol profile, and a tendency to cardiac arrhythmias, have been described in the literature (27,28). MHR has recently been described as a novel marker in adverse cardiovascular outcomes. In the present study, we observed significantly higher MHR values in cases of DTC compared to the control group. Research and clarification with more detailed studies of MHR in DTC patients are needed.

Also, we detected in our study, TSH values were higher in the controls than in the cancer cases, while free-T3 and free-T4 values were significantly higher in the cancer cases than in the controls. TSH, the major growth factor for thyroid cells, is a thyroid function regulator (29) and independent predictor for the diagnosis of thyroid malignancy in patients with nodular thyroid disease. In addition, preoperative serum TSH concentrations are higher in patients with more aggressive tumors (30) and advanced tumor stages (31), and this suggests a potential role for TSH in the progression of different thyroid cancers (30).

We attribute the lower mean TSH level in the DTC group in this study than that in the control group, although the difference was not statistically significant, and the significantly higher FT3 and FT4 values to our patients having had diseases requiring L-thyroxine therapy, such as Hashimoto thyroiditis and multinodular goiter, in the period prior to diagnosis of DTC and to their receiving L-thyroxine therapy at the time of diagnosis.

The limitation of this study is that our DTC group patients were not divided into subgroups based on the type of thyroid disease before diagnosis, if present, and on L-thyroxine use. Another limitation is that statistical evaluations have not been made according to these subgroups.

In conclusion, we think that this may be significant as an inflammatory index showing an increased inflammatory response in DTCs.

DECLARATION OF INTEREST STATEMENT

The authors declare that they have no conflict of interest. No financial support was received.

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