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RESEARCH ARTICLE

MONOCYTE-TO-HDL CHOLESTEROL RATIO AS A NEW PARAMETER OF SYSTEMIC INFLAMMATION AND DISEASE SEVERITY IN TREATMENT-RESISTANT CHRONIC SPONTANEOUS URTICARIA

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ABSTRACT

Purpose: Chronic spontaneous urticaria (CSU) is characterized by inflammation and increased oxidative stress in its pathogenesis. The study aims to evaluate new inflammatory markers indicating systemic inflammation in resistant CSU and to determine their relationship with disease activity.

Material and Methods: The files of CSU patients and matched healthy volunteers were reviewed and compared in terms of demographics, medical history, clinical features, laboratory parameters, and new inflammatory markers [NLR:neutrophil-lymphocyte ratio, MLR: monocyte-lymphocyte ratio, MHR:monocyte-to-high-density lipoprotein cholesterol (HDL-C)].

Results: Sixty-one CSU patients and 50 healthy controls were evaluated (female: male ratio=1.9:1, mean age=43.97 ± 14.88 years). The median erythrocyte sedimentation rate, C-reactive protein (CRP), white blood cell, monocyte count, and MHR were higher in the CSU group; in contrast, the mean HDL-C level was lower. The median NLR and MLR were also higher in the CSU group but were not statistically significant. There was a positive correlation between urticaria activity score 7 (UAS7) and MHR and a negative correlation between UAS 7 and HDL-C. MHR was positively correlated with MLR, CRP, and UAS7.

Conclusion: MHR might serve as an indicator of inflammation intensity and predisposition to MS in CSU patients. It might also be used as an objective tool for evaluating disease severity and treatment response in CSU

Keywords: Chronic spontaneous urticaria, C-reactive protein, inflammation, metabolic syndrome, monocyte-to-HDL ratio

INTRODUCTION

Chronic spontaneous urticaria (CSU) is an inflammatory disorder characterized by hiveslasting longer than six weeks. Although the etiology of CSU is not clear, it is known that autoantibodies against IgE and/or IgE receptors stimulate histamine release, and histamine is the primary mediator in the formation of symptoms. In this context, second-generation antihistamines (sg-AH) are recommended as the first-line treatment. Anti-IgE antibody omalizumab (OMZ) is preferred in cases resistant to sg-AH therapy at doses up to 4 times higher (1).

Recently, interest in novel practical and cheap inflammatory markers, especially in inflammatory disorders associated with metabolic syndrome (MS) and its components, has increased. In this context, hematological parameters like neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) are new parameters associated with chronic inflammatory disorders and disease severity (2,3).
Monocyte-to-high-density lipoprotein cholesterol (HDL-C) ratio (MHR)is also one of the new inflammatory markers of interest. Monocytes are pro-inflammatory cells that are the main source of oxidative stress (4). HDL-C is one of the most important proteins that suppress inflammation and oxidative stress (5). In this context, MHR is considered to be a marker of inflammation which has been shown in many inflammatory disorders (6-8).
Since inflammation and oxidative stress are involved in the pathogenesis of CSU and coexist with various inflammatory disorders1, NLR, MLR, and MHR might also serve as important parameters for CSU. This study aimed to evaluate the relationship between these parameters and antihistamine resistance in patients with CSU.

MATERIAL AND METHODS

This comparative retrospective study, approved by Canakkale Onsekiz Mart University Ethics Committee (16.11.2022, 2022/14-15), evaluated the sg-AH treatment-refractory CSU patients and age-gender matched health control group.
Treatment-resistant CSU patients were selected from patients receiving OMZ treatment by looking at the hospital registry data. Individuals under the age of 18, patients with a history of diabetes mellitus, hypertension, cardiovascular diseases (CVDs), myocardial infarction, or another inflammatory disorder,and active smokers were excluded from the study.
The medical files of both the patient and the healthy control groups were evaluated in terms of demographic characteristics (age, sex), medical history (comorbidities), laboratory findings, including serum glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, HDL-C, low-density lipoprotein (LDL), total cholesterol, triglyceride (TG), complete blood count (CBC) erythrocyte sedimentation rate (ESR), C-reactive protein (CRP). In addition, clinical features (presence of angioedema, disease duration, disease activity), serum total Ig-E level, and anti-thyroid peroxidase (TPO) of patients with CSU were recorded. The disease activity was evaluated with an urticaria activity score 7 (UAS7) (1). Clinical and laboratory findings before OMZ treatment were evaluated in the patient group. The NLR, MLR, and MHR values of all participants were calculated. All results were compared between the two groups.

Statistical analysis

Continuous data were presented as mean, standard deviation (SD), median, and range using the Kolmogorov-Smirnov test, and categorical variables were expressed as percentages. The Chi-square test compared the categorical data of CSU patients and healthy controls, and the Mann-Whitney U test was used to evaluate non-normal distribution parameters. Relationships between variables were evaluated with the Pearson correlation test. A p-value lower than 0.05 was accepted as statistically significant. All analyzes were performed using SPSS 14.0 (Chicago, IL, USA) statistical software package.

Table 1. Demographic and clinical characteristics of the chronic spontaneous urticaria patients

Number of patients, n (%)	**61 (100)**
Sex, n (%)	
Female	39 (63.9)
Male	22 (36.1)
Age (years), mean ±SD	47.33±15.28
Disease duration (month), median (range)	14 (6-60)
UAS7, mean ±SD	33.21±6.13
Presence of angioedema, n (%)	23 (37.7)
Total IgE, median (range)	280 (2-2730)
Anti-TPO, median (range)	12.93 (0.87-346)
Anti-TPO/ Total IgE, median (range)	0.10 (0.00-18.82)

SD: standard deviation, TPO:thyroid peroxidase, UAS7: urticaria activity score 7

Table 2. Comparison of chronic spontaneous urticaria patients and healthy controls according to demographic features and laboratory parameters

	CSU n=61	**Control n=50**	***p-value***
Sex, n (%)			
Female	39 (63.9)	34 (68)	*0.190*
Male	22 (36.1)	16 (32)	
Age (years), mean ±SD	47.33±15.28	39.88±13.43	*0.007*
Serum glucose, mean ±SD	100.46±21.04	103.79±31.37	*0.534*
ALT, median (range)	14.00 (5-44)	20.50 (8-59)	*<0.001*
AST, median (range)	17.00 (8-43)	25.00 (12-39)	*<0.001*
Creatinin, mean ±SD	0.73±0.15	0.83±0.16	*0.002*
HDL-C, mean ±SD	43.59±10.07	51.80±14.29	*0.001*
LDL, mean ±SD	133.52±36.01	119.66±38.11	*0.053*
Total cholesterol, mean ±SD	208.16±42.14	192.18±41.86	*0.049*
TG, mean ±SD	172.85±73.70	114.92±40.84	*<0.001*
ESR, median (range)	22.00 (3-59)	12.00 (2-22)	*<0.001*
CRP, median (range)	14.00 (5-44)	14.00 (5-44)	*<0.001*
TSH, median (range)	1.60 (0.42-17)	1.67 (0.04-7.39)	*0.767*
WBC, mean ±SD	8.64±3.00	7.31±1.83	*0.07*
Neutrophil, median (range)	4.50(2.40-12.60)	4.65 (1.59-6.61)	*0.740*
Lymphocyte, median (range)	2.40 (0.97-5.80)	2.30 (1.20-4.37)	*0.910*
Monocyte, median (range)	0.60 (0.30-1.80)	0.50 (0.20-0.90)	*0.029*
NLR, median (range)	0.60 (0.30-1.80)	1.85 (0.84-4.08)	*0.850*
MLR, mean ±SD	0.27±0.12	0.23±0.10	*0.054*
MHR, median (range)	0.142 (0.005-0.033)	0.009 (0.003-0.026)	*0.002*

ALT: alanine aminotransferase, AST: aspartate aminotransferase, CRP: C-reactive protein, CSU: chronic spontaneous urticaria, ESR: erythrocyte sedimentation rate, HDL-C: high-density lipoprotein cholesterol, LDL: low-density lipoprotein, MHR: monocyte-to-high-density-lipoprotein ratio, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, SD: standard deviation, TG: triglyceride,TSH: tiroid stimulating hormon, WBC: white blood cell

RESULTS

Sixty-one CSU and 50 healthy controls were included in the study. The female:male ratio was 1.9:1. The mean age of the individuals was 43.97 ± 14.88 years. Noneof the participants had a history of MS or its components. Table 1 summarizes the demographic and clinical data of patients with CSU.As shown in Table 2,and the median ESR, CRP, WBC, monocyte count, and MHR were significantly higher in the CSU group than in the control group, while the mean HDL-C was lower than in the control group. Although the median NLR and the mean MLR were higher in the CSU group, this difference was not statistically significant. The median ALT and AST levels were higher in the control group but clinically insignificant, as they were within normal limits in both groups. The other parameters did not differ between the two groups.

In the CSU group, disease severity (UAS7) correlated positively with MHR and negatively with HDL-C.

ESR was positively correlated with the disease duration, and MHR was positively correlated with MLR, age, CRP, and disease severity (UAS7) (Table 3).

Table 3. Parameters correlated with disease severity and monocyte-to-high-density-lipoprotein ratio

	UAS7		MHR	
	r	***p***	***r***	***p***
MHR	0.333	0.009		
HDL-C	-0.307	0.016	-0.605	<0.001
MLR			0.482	<0.001
CRP			0.487	<0.001

CRP: C-reactive protein,HDL-C: high-density lipoprotein cholesterol, MHR: monocyte-to-high-density-lipoprotein ratio, MLR: monocyte-to-lymphocyte ratio, UAS7: urticaria activity score

DISCUSSION

The etiopathogenesis of CSU has not been fully elucidated, whereas the roles of low-grade chronic inflammation and oxidative stress have been established. Inflammatory markers such as CRP and parameters indicating coagulation disorders were shown to be increased in the sera of CSU patients in correlation with the disease severity. In previous studies, MS, which has common pathogenesis comprising low-grade chronic inflammation, oxidative stress, and coagulation system activation, has been demonstrated to coexist with CSU, especially in patients with severe disease (9-11). ESR and CRP are generally used as inflammation markers. On the other hand, these are primarily the markers of MS and its complications. Thus, there is an ongoing need for practical, inexpensive, and more specific markers. NLR, MLR, and MHR are new markers that have been shown to be associated with several inflammatory disorders as well as MS and its components (2,3,6-8). In the present study, monocyte count and MHR were significantly higher in antihistamine-resistant CSU patients compared to the control group. In addition, MHR in the CSU group was correlated with disease severity (UAS7) and CRP. Demirbaş et al. reported a similar positive correlation between the disease severity and MHR in vitiligo, a disorder in which oxidative stress, inflammation, and autoimmunity play a role (6). Similarly, it has been shown that MHR was correlated with disease severity in psoriasis, a chronic inflammatory disorder commonly associated with MS (7,8). Monocytes and macrophages are proinflammatory cells. They release inflammatory cytokines and activate T cells and platelets, particularly when they transform into foam cells4.HDL-C suppresses monocytes by inhibiting CD11b activation and downregulating monocyte-chemotaxis protein 1 expression. In such a manner, it reduces inflammation and oxidative stress (5). Thus, the elevated monocyte count and MHR show increased inflammation and oxidative stress. HDL-C has been reported to be low in individuals with autoimmune disorders, and reduced HDL-C level was indicated as a risk factor for autoimmune disorders (12). Considering the autoimmune pathogenesis underlying CSU, lower HDL-C levels in our CSU patients compared to controls was not an unexpected finding.

The parameters expected to be elevated in MS and its complications, total cholesterol, TG, ESR, and CRP, were significantly higher in CSU patients compared to the control group in our study. Similarly, in a study conducted on 11261 CSU patients evaluating the relationship between MS and CSU, dyslipidemia was detected to be more frequent in CSU patients (13). The severe inflammation was held responsible for the increased likelihood of MS in treatment-resistant CSU patients (11). In the present study, the CSU patients were exclusively sg-AH-resistant patients scheduled for OMZ therapy. Moreover, the positive correlation between MHR, CRP, and disease severity further supports the elevated risk of MS in our treatment-resistant CSU patients due to chronic inflammation.

Although not statistically significant, NLR and MLR were higher in our CSU patients. These two parameters were detected at high levels in chronic inflammatory disorders and considered poor prognostic signs (2,3,14). Ertaş et al. similarly detected a higher NLR in the CSU patient group despite the lack of statistical significance (15). The authors have also shown the reduction of NLR in CSU patients under OMZ therapy (15). In light of these findings, it might be speculated that these parameters would not only determine the current inflammation but alsohelp monitor OMZ treatment's efficacy in CSU.

Patients with resistant CSU often require short-term systemic corticosteroid therapies administered in the emergency departments or dermatology outpatient clinics until their disease is under control. It is well known that systemic corticosteroid treatment increases the risk of MS and causes deterioration in the lipid profile (16). The intermittent systemic corticosteroid use might also contribute to the lipid profile changes observed in our CSU patients.

The main limitation of our study was its retrospective nature and the limited number of patients. The exclusion of sg-AH-responsive CSU patients and patients with MS-related comorbidities were responsible for the latter. On the other hand, this is the first study investigating the association between MHR and CSU to the best of our knowledge.

CONCLUSION

Since the scales evaluating the disease severity in patients with CSU are subjective parameters based on the patient's complaints, more objective markers such as MHR, which may be correlated with disease severity, are needed. If supported by large-scale studies, MHR might be a parameter for evaluating disease severity and monitoring the treatment efficacy in CSU. Furthermore, MHR might be a practical marker in CSU patients for detecting susceptibility to MS and its complications at an early stage and taking the necessary precautions.

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REFERENCES

1. Zuberbier T, Abdul Latiff AH, Abuzakouk M, et al. The international EAACI/GA²LEN/ EuroGuiDerm/APAAACI guideline for the definition, classification, diagnosis, and management of urticaria. Allergy. 2022;77(3):734-766.
2. Imtiaz F., Shafique K., Mirza S.S., Ayoob Z., Vart P., Rao S. Neutrophil to lymphocyte ratio as a measure of systemic inflammation in prevalent chronic diseases in Asian population. Int Arch Med. 2012;5:2.
3. Asahina A., Kubo N., Umezawa Y., Honda H., Yanaba K., Nakagawa H. Neutrophil–lymphocyte ratio, platelet-lymphocyte ratio and mean platelet volume in Japanese patients with psoriasis and psoriatic arthritis: response to therapy with biologics. J Dermatol. 2017;44:1112–1121.
4. Ghattas A., Griffiths H.R., Devitt A., Lip G.Y., Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? J Am Coll Cardiol. 2013;62:1541–1551.
5. Murphy AJ, Westerterp M, Yvan-Charvet L,Tall AR. Anti-atherogenic mechanisms of high density lipoprotein: effects on myeloid cells. Biochim Biophys Acta 2012;1821, 513–521.
6. Demirbaş A, Elmas ÖF, Atasoy M, Türsen Ü, Lotti T. Can monocyte to HDL cholesterol ratio and monocyte to lymphocyte ratio be markers for inflammation and oxidative stress in patients with vitiligo? A preliminary study. Arch Dermatol Res. 2021;313(6):491-498.
7. Sirin MC, Korkmaz S, Erturan I, et al. Evaluation of monocyte to HDL cholesterol ratio and other

inflammatory markers in patients with psoriasis. An Bras Dermatol. 2020;95(5):575-582.
8. Aktaş Karabay E, Demir D, Aksu Çerman A. Evaluation of monocyte to high-density lipoprotein ratio, lymphocytes, monocytes, and platelets in psoriasis. An Bras Dermatol. 2020;95(1):40-45.
9. Kolkhir P, Andre F, Church MK, Maurer M, Metz M. Potential blood biomarkers in chronic spontaneous urticaria. Clin Exp Allergy. 2017;47(1):19-36.
10. Vena GA, Cassano N. The link between chronic spontaneous urticaria and metabolic syndrome. Eur Ann Allergy Clin Immunol. 2017;49(5):208-212.
11. Ye YM, Jin HJ, Hwang EK, et al. Co-existence of chronic urticaria and metabolic syndrome: clinical implications. Acta Derm Venereol. 2013;93(2):156-160.
12. Madsen CM, Varbo A, Nordestgaard BG. Low HDL cholesterol and high risk of autoimmune disease: two population-based cohort studies including 117341 individuals. Clin Chem. 2019;65(5):644-652.
13. Shalom G, Magen E, Babaev M, et al. Chronic urticaria and the metabolic syndrome: a cross-sectional community-based study of 11 261 patients. J Eur Acad Dermatol Venereol. 2018;32(2):276-281.
14. Feng F, Tian Y, Liu S, et al. Combination of PLR, MLR MWR, and tumor size could significantly increase the prognostic value for gastrointestinal stromal tumors. Medicine (Baltimore). 2016;95:e3248.
15. Ertaş R, Özyurt K, Karakükçü Ç, et al. Evaluation of platelet parameters and neutrophil/lymphocyte ratio during omalizumab treatment in patients with severe chronic spontaneous urticaria. Turk J Med Sci. 2018;48(6):1255-1262.
16. Liu D, Ahmet A, Ward L, et al. A practical guide to the monitoring and management of the complications of systemic corticosteroid therapy. Allergy Asthma Clin Immunol. 2013;9(1):30.