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ORIGINAL ARTICLE – OPEN ACCESS

Evaluation of Monocyte to High-Density Lipoprotein Cholesterol and Neutrophil to High-Density Lipoprotein Cholesterol Ratios as Indicators of Inflammation in Patients with Celiac Disease

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ABSTRACT

Objective: Celiac disease (CD) is an autoimmune disease with multisystemic manifestations that may be consequences of autoimmunity, inflammation, or malabsorption. The monocyte to high-density lipoprotein cholesterol ratio (MHR) and the neutrophil to high-density lipoprotein cholesterol ratio (NHR) are recent markers of inflammation. The aim of the present study was to analyze the relationship between the MHR, NHR, and CD and to examine whether these measures might be used as inflammatory markers in CD.

Materials and Methods: This cross-sectional, retrospective study included 153 participants. The data of 50 patients with CD and 103 healthy individuals enrolled as a control group were evaluated. Receiver operating characteristic (ROC) analysis and the corresponding area under the curve (AUC) calculation were performed to assess the discriminatory ability of the MHR and the NHR.

Results: The MHR and the NHR were both high in the study participants with CD ($p<0.001$). ROC analysis revealed an AUC value of 0.725 (95% confidence interval [CI]: 0.639–0.811) for the MHR and 0.695 (95% CI: 0.598–0.792) for the NHR ($p<0.001$). The cut-off value for MHR was 9.312 (sensitivity: 76.7%, specificity: 65%) and 77.79 for NHR (sensitivity: 67.4%, specificity: 65%). No statistically significant correlation was seen between the MHR and NHR values and the modified Marsh scores of the patients with CD.

Conclusion: The current study is believed to be the first in the literature to explore and demonstrate that the MHR and the NHR may be indicators in patients with CD. The MHR and the NHR may be promising diagnostic markers for CD.

Keywords: Celiac disease, high-density lipoprotein cholesterol, inflammation, monocyte, neutrophil

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INTRODUCTION

Celiac disease (CD) is an autoimmune disorder triggered by gluten exposure in individuals with a genetic sensitivity (1). CD can have multisystemic manifestations; some are direct consequences of autoimmunity, while others may be related to malabsorption or inflammation.

Inflammation has been shown to be associated with an elevated monocyte count and decreased high-density lipoprotein cholesterol (HDL-C) level (2). Multiple studies have used the monocyte to HDL-C ratio (MHR) to investigate whether inflammation and atherosclerosis have an impact in the development of cardiovascular diseases (3, 4). The research has indicated that the MHR is a predictor of inflammation, reflecting a shift in the pro-inflammatory and anti-atherogenic balance, as seen in atherosclerosis (5).

Neutrophils also play a unique role in the pathogenesis of atherosclerosis. Neutrophils are found in atherosclerosis plaques, where they cause inflammatory response (6). Similar to the MHR, a new marker of inflammation was developed using the neutrophil count to HDL-C ratio (NHR). It has recently been shown that the NHR may be a useful predictor for cardiovascular events (7).

Although there are studies examining the MHR in various inflammatory conditions, to the best of our knowledge, the relationship between the MHR, NHR, and CD is yet to be examined. The objective of the present study was to evaluate the MHR and NHR in individuals with CD.

MATERIALS and METHODS

The present study was approved by the local ethics committee of Hitit University Faculty of Medicine on May 05, 2020 (no: 2020/211) and performed in accordance with the principles of the Declaration of Helsinki.

Table 1. The demographic and laboratory results of the celiac disease patients and the control group

Variable	Celiac disease (n=43)	Control (n=103)	p
Gender (male/female)	9/34	20/83	0.823
Age (years)	42.37±11.92	40.46±12.65	0.387
WBC (10^6/L)	6787.67±1705.00	6720.00±1391.69	0.819
Hemoglobin (g/dL)	12.36±1.71	13.70±1.49	<0.001
Platelets (10^6/L)	306790±92108	262417±61028	0.005
ALT (U/L)	26 (20–34)	15 (12–19)	<0.001
AST (U/L)	26 (21–39)	18 (16–21.5)	<0.001
Creatinine (mg/dL)	0.57±0.16	0.68±0.16	<0.001
FPG (mg/dL)	88.63±8.77	87.85±7.82	0.650
LDL-C (mg/dL)	96.84±26.83	123.09±36.39	<0.001
TG (mg/dL)	95 (70–149)	85 (66–128)	0.341
T-CHOL (mg/dL)	161.39±34.14	195.91±48.22	<0.001
HDL-C (mg/dL)	42.25±8.21	55.97±12.33	<0.001
Monocyte/HDL-C ratio	10.61 (9.32–14.17)	8.22 (6.67–10.93	<0.001
Neutrophil/HDL-C ratio	96.71±36.32	72.65±26.71	<0.001

The mean±SD was used for distributed values and median (25–75% percentiles) for non-normally distributed values. WBC: White blood cell; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; FPG: Fasting plasma glucose; LDL-C: Low-density lipoprotein cholesterol; TG: Triglyceride; T-CHOL: Total cholesterol; HDL-C: High-density lipoprotein cholesterol

Table 2. Receiver operating characteristic analysis of MHR and NHR variables for celiac disease

	ROC analysis					
Variables	**AUC**	**Sensitivity, %**	**Specificity, %**	**NPV, %**	**PPV, %**	**p**
MHR	0.725	76.7	65	87	48.8	<0.001
NHR	0.695	67.4	65	82.7	44.6	<0.001

ROC: Receiver operating characteristic; AUC: Area under the curve; NPV: Negative predictive value; PPV: Positive predictive value; MHR: Monocyte to high-density lipoprotein cholesterol ratio; NHR: Neutrophil to high-density lipoprotein cholesterol ratio

This cross-sectional, retrospective study included 153 patients. The data of 50 patients with CD and 103 healthy subjects enrolled as a control group were compared. Patients who were older than 18 years of age and had available file records were included in the analysis. Patients with insufficient data or with any known disease or conditions such as diabetes mellitus, thyroid dysfunction, coronary heart disease or other cardiovascular disease, hypertension, malignancies, cirrhosis, chronic hepatitis for any reason, pregnancy, chronic renal failure, asthma, chronic obstructive respiratory disease, other autoimmune disorders, connective tissue disease, or hematological disease were excluded. Patients taking any medications were also excluded. A total of 43 CD patients with complete clinical data and follow-up information were analyzed with the data of 103 healthy individuals.

The diagnosis of CD was based on a combination of CD clinical features, serology testing and histopathological evaluation of a duodenal biopsy (1, 8). After the measurement of tissue transglutaminase antibodies and an antiendomysial antibody test, biopsy sampling was performed during a gastroscopy. Multiple biopsy samples of the duodenum (at least 4) were obtained (8). The samples were evaluated by a senior pathologist according to the modified Marsh classification (9, 10). Venous blood samples were also obtained from the patients after 12 hours of fasting. All of the laboratory examinations were performed to confirm a diagnosis of CD before initiating a gluten-free diet. A complete blood count was performed with standard tubes containing ethylenediaminetetraacetic acid (Sarstedt AG & Co., Nümbrecht Germany). Biochemical analysis was performed with standard tubes and the total cholesterol, triglyceride, and HDL-C levels were analyzed using assay kits (Abbott Laboratories Inc., Abbott Park, IL, USA) and an autoanalyzer (Aeroset; Abbott Laboratories Inc., Abbott Park, IL, USA). The low-density lipoprotein cholesterol (LDL-C) value was calculated using the lipid panel results. The MHR and NHR were computed manually by dividing the monocyte count by the HDL-C value and the neutrophil count by the HDL-C, respectively. Fasting plasma glucose, blood urea nitrogen, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were also analyzed using the autoanalyzer. Patients with a white blood count of >11000 (106/L) or <4000 (106/L), a creatinine level of >1.20 mg/dL, and patients with an

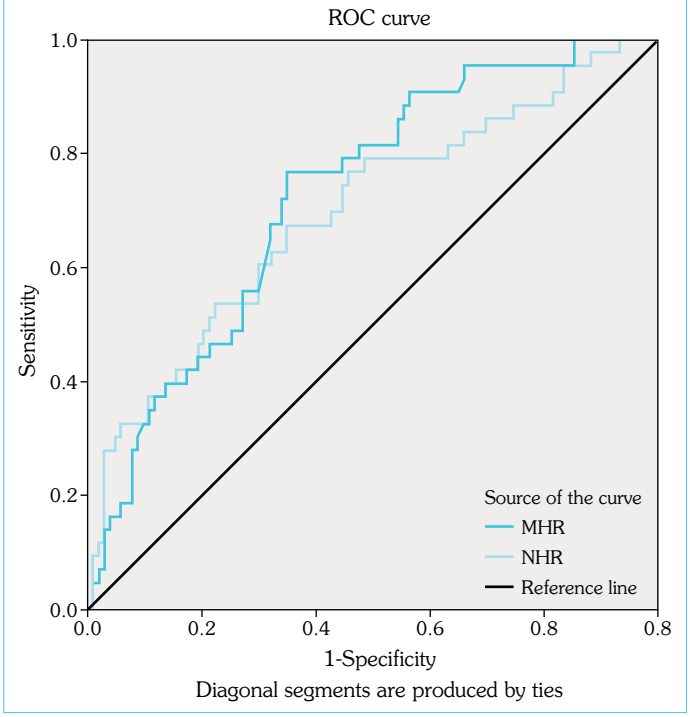

Figure 1. Receiver operating characteristic curve plot of MHR and NHR for celiac disease

ROC: Receiver operating characteristic; MHR: Monocyte/high-density lipoprotein ratio; NHR: Neutrophil/high-density lipoprotein ratio

AST or ALT level >2 times the normal limit were not included in the statistical analysis.

Statistical analyses to compare the study groups were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA). Categorical variables were expressed with number and percentage values, and compared with a chi-squared test. The Kolmogorov-Smirnov test was used to assess the normality of the data. Quantitative variables with and without normal distribution were expressed as the mean±SD and median (interquartile range), respectively. An independent 2-sample t-test and the Mann-Whitney U test were used to compare quantitative variables with and without normal distribution, respectively. Pearson's correlation coefficient was used to measure the correlation between continuous variables and the Eta coefficient was calculated for the categorical and continuous variables. MHR and NHR cut-off values to detect CD were derived using receiver operating characteristic (ROC) curve analysis and a 95% confidence interval (CI) for the Youden Index. A p value <0.05 was considered significant.

RESULTS

The present study included 50 CD patients and 103 control subjects. Seven patients with CD were excluded from the statistical analysis due to additional conditions. Demographic and laboratory parameters of the groups are summarized in Table 1. The MHR and the NHR were statistically significantly higher in the CD group than in the control group (p<0.001).

ROC analysis revealed area under the curve (AUC) values of 0.725 (95% CI: 0.639–0.811) for the MHR and 0.695 (95% CI: 0.598–0.792) for the NHR (p<0.001) (Table 2, Fig. 1). The cut-off value for the MHR was 9.312 (sensitivity: 76.7%, specificity: 65%, positive predictive value: 48.8%, negative predictive value: 87%) and 77.79 (sensitivity: 67.4%, specificity: 65%, positive predictive value: 44.6%, negative predictive value: 82.7%) for the NHR.

Correlation analysis showed no statistically significant relationship between the MHR/NHR and the Marsh scores of the patients. The Eta value for the MHR and the NHR was 0.083 and 0.075, respectively. The MHR was significantly positively correlated with the NHR, creatinine, and ALT values, whereas the NHR was significantly positively correlated with the MHR, thrombocyte count, AST, and ALT. The NHR was negatively correlated with age (Table 3).

DISCUSSION

This research was designed to examine whether the MHR or the NHR might be associated with CD. The findings indicated that the MHR and the NHR values were higher in patients with CD.

Many studies have reported that the MHR and the NHR could serve as prognostic indicators of inflammation and cardiovascular disease (4, 11). Our study is believed to be the first to assess a potential association between the MHR and the NHR and CD.

Inflammation is an important component in the development of atherosclerosis (12). Chronic and generally low-grade inflammation, including cells of the innate and adaptive immune systems are characteristic of the disease. Monocytes and neutrophils both take part in this inflammatory response. Monocytes enter the subendothelial space, differentiate into macrophages and catch LDL-C particles. This process results in the formation of foam cells that induce cytokine and chemokine production, leading to increased inflammation (12). Neutrophils are found in atheroscle-

Table 3. Correlation analysis of MHR and NHR and other laboratory variables

	MHR	NHR	Age	Hgb	PLT	Creatinine	AST	ALT	CRP	MMS
MHR		r:0.537	r: –0.090	r:0.071	r:0.145	r:0.171	r:0.187	r:0.283	r:–0.111	r:0.344
		p<0.001	p:0.278	p:0.395	p:0.081	p:0.042	p:0.083	p<0.001	p:0.858	p:0.646
NHR	r:0.537		r:–0.197	r:0.104	r:0.191	r:0.051	r:0.268	r:0.241	r:0.876	r:0.248
	p<0.001		p:0.017	p:0.216	p:0.021	p:0.548	p:0.012	p:0.003	p:0.051	p:0.566

MHR: Monocyte to high-density lipoprotein cholesterol ratio; NHR: Neutrophil to high-density lipoprotein cholesterol ratio; Hgb: Hemoglobin; PLT: Platelet; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; CRP: C-reactive protein; MMS: Modified Marsh score

rotic plaques and also induce an inflammatory response (6). These findings drew attention to the role of inflammation in patients with cardiovascular diseases.

Monocytes are a marker for systemic inflammation and important in the first step of atherogenesis (13). Lipoprotein uptake by monocyte-derived macrophages leads to the development of foam cells, which is a step in the development of atherosclerosis (14).

HDL-C promotes reverse cholesterol carriage from the arterial wall, including the lipid-rich macrophages (15). HDL-C has antioxidant, anti-inflammatory, and antithrombotic effects, which are protective factors against cardiovascular diseases (16). The important role of a high monocyte level and a low HDL-C value in atherosclerosis generated interest in the MHR. The MHR has become a practical and highly predictive marker of cardiovascular disease and in addition, offers an economic advantage over other inflammatory markers (4, 17, 18). Similar to the MHR, the NHR is also a cardiovascular marker. A high neutrophil and low HDL-C level is now seen as a marker of atherosclerosis (6, 15). The NHR may predict inflammatory status and cardiovascular risk (7).

Cardiovascular risk in CD is a subject of discussion. It was noted in a large cohort study from Sweden that cardiovascular disease was the leading cause of mortality in CD (19). Adherence to a gluten-free diet typically led to significant improvement in symptoms and mucosal healing, which is associated with decreased risk of cardiovascular disease (8). Santoro et al. (20) noticed that there may be an increased risk of atherosclerosis and cardiovascular disease in patients with CD. The authors proposed that the etiopathogenic foundation of this association was related to the presence of a systemic pattern of subclinical inflammation (20). The authors also proposed the use of instrumental techniques to detect atherosclerosis in the subclinical stage, such as noninvasive methods. The findings of this study may provide new perspectives on noninvasive methods. Tetzlaff et al. (21) demonstrated that patients with CD showed small modifications in lipoprotein and carbohydrate metabolism, which would contribute to a pro-inflammatory status and increase the risk of atherosclerosis and cardiovascular disease. Other research has indicated no increased cardiovascular risk in CD (22).

CD is a gastrointestinal inflammatory disorder characterized by chronic inflammation driven by persistent antigenic challenges due to dietary gluten (23). Our findings suggest new indications for the inflammatory and cardiovascular role of CD.

One of the interesting findings of the current study was that there was no correlation between the MHR/NHR and the modified Marsh scores. This may suggest that the level of mucosal damage might have less effect on inflammation. Similarly, Ensari et al. (24) reported that the modified Marsh score was not a very successful means to determine the level of CD and the authors suggested that the subclassifications offered little aid in diagnosis, treatment, or prognosis. Our findings may provide important support for this view.

Limitations

The limitations of the study include the retrospective and single-center, cross-sectional design, which prohibited causality assessment between factors, as well as the small sample size. Nevertheless, the results are significant and appear to demonstrate a potentially valuable relationship between the MHR and the NHR and CD.

CONCLUSION

The current study results indicated that the MHR and the NHR were elevated in patients with CD. Both the MHR and the NHR can be easily calculated and are already used for many conditions, such as cardiovascular disease. To the best of our knowledge, this study is the first to evaluate the potential use in CD. The MHR and the NHR may be useful new markers. Additional prospective cohort studies would provide valuable data.

Ethics Committee Approval: The Hitit University Faculty of Medicine Clinical Research Ethics Committee granted approval for this study (date: 05.05.2020, number: 2020/211).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – TD, DK, HK; Design – TD, DK, HK; Supervision – TD, DK, HK; Resource – TD, DK, HK; Materials – TD, DK, HK; Data Collection and/or Processing – TD, HK; Analysis and/or Interpretation – TD, HK; Literature Search – TD; Writing – TD; Critical Reviews – TD, DK, HK.

Conflict of Interest: The authors have no conflict of interest to declare.

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