ORIGINAL ARTICLE

AG-2021-24
doi.org/10.1590/S0004-2803.202100000-80

Monocyte/HDL ratio in non-alcoholic hepatic steatosis

Ahmet **YOZGAT**[1], Nergis **EKMEN**[2], Benan **KASAPOGLU**[3], Yasemin **UNSAL**[4], Fevzi Coskun **SOKMEN**[5] and Murat **KEKİLLİ**[2]

Received: 3 February 2021
Accepted: 15 June 2021

ABSTRACT – **Background** – Non-alcoholic hepatic steatosis (NAS) is characterized by excess fat accumulation in hepatocytes, causing portal and lobular inflammation and hepatocyte injury. **Objective** – We aimed to evaluate the alterations in monocyte count to high-density lipoprotein cholesterol ratio (MHR) in patients with grade 2 or 3 fatty liver disease and the association of this marker with liver function tests and insulin resistance. **Methods** – In this retrospective analysis; patients diagnosed and followed for the grade 2 or 3 fatty liver disease were included in the patient group and the patients who had undergone abdominal ultrasound for any reason and who were not having any fatty liver disease were included in the control group. **Results** – Totally 409 cases were included in the study. Among participants, 201 were in the control group, and 208 were in the NAS group (111 were having grade 2 and 97 were having grade 3 steatosis). The monocyte/HDL ratio was significantly higher in the NAS group compared with the healthy controls (P=0.001). There was a significant positive correlation between the monocyte/HDL ratio and age (r=0.109; P=0.028), ALT (r=0.123, P=0.014) and HOMA-IR (r=0.325, P=0.001) values. **Conclusion** – In conclusion, the monocyte to high-density lipoprotein ratio significantly increases in fatty liver disease and correlates with insulin resistance. Since it was suggested as a prognostic marker in atherosclerotic diseases, elevated MHR values in fatty liver disease should be evaluated cautiously.

Keywords – Monocyte/HDL ratio; hepatosteatosis; non-alcoholic hepatic steatosis; insulin resistance.

INTRODUCTION

Nonalcoholic hepatic steatosis (NAS) is characterized by excess fat accumulation in hepatocytes, causing portal and lobular inflammation and hepatocyte injury. Its prevalence is continuously increasing in developed countries. Cardiovascular complications are the main life-threatening co-morbidities associated with the NAS. NAS is closely associated with insulin resistance; and metabolic syndrome[1-3]. Very recently the name of the NAS has been suggested to be changed as metabolic associated fatty liver disease (MAFLD). In diagnosis of NAS, the exclusion of concomitant liver diseases and alcohol consumption was the main point. However, the diagnosis of MAFLD depends mainly on the intrahepatic triglyceride content ≥5% with the presence of overweight/obesity, diabetes, or two other metabolic risk factors, in the presence or absence of concomitant liver diseases[4,5].

Macrophages and monocytes are the most important cell types that mainly secrete proinflammatory and pro-oxidant cytokines. On the other hand, high-density lipoprotein cholesterol (HDL-C) has been shown to have both anti-inflammatory and antioxidant actions, by protecting endothelial cells against the unfavorable effects of low-density lipoprotein (LDL) and preventing LDL oxidation. Recently, monocyte count to HDL-C ratio (MHR) has been shown to be a new prognostic marker in atherosclerotic cardiovascular diseases[6-8].

Based on this information, we aimed to evaluate the alterations in MHR in patients with grade 2 or 3 fatty liver disease and the association of this marker with liver function tests and insulin resistance.

METHODS

In this multi-centric retrospective study, patients who were admitted to the gastroenterology outpatient clinic of the Gazi University and Health Sciences University, Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital, between January 2020 and June 2020 were evaluated. Patients diagnosed and followed for the grade 2 or 3 fatty liver disease were included in the patient group. The patients who had undergone abdominal ultrasound for any reason (for non-specific abdominal pain mainly) and who were not having any fatty liver disease, or any chronic metabolic diseases such as diabetes mellitus or hypertension were included in the control group. Patients younger than 18 years and older than 65 years of age, patients under treatment for hyperlipidemia or hypertriglyceridemia, patients having any other known liver diseases, hyperthyroidism, hypothyroidism, pregnant women, patients diagnosed or treated for any kind of infections in last month, malignancy, any kind of rheumatologic diseases or inflammatory bowel disease were excluded from the study. The study was approved by local Ethics Committee.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Ufuk University, Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey. [2] Gazi University, Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey. [3] Lokman Hekim University, Faculty of Medicine, Department of Gastroenterology, Ankara, Turkey. [4] Gazi University, Faculty of Medicine, Department of Internal Medicine, Ankara, Turkey. [5] Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Internal Medicine, Ankara, Turkey.
Corresponding author: Ahmet Yozgat. E-mail: a_yozgat@yahoo.com

Demographic features, and any medications used were recorded. All patients underwent a hepatobiliary ultrasound to determine the presence of fatty liver disease[9]. Patients with grade 1 hepatosteatosis were not included in the study.

Blood samples were obtained from the patients in the morning, after 8 hours of fasting. Laboratory data including complete blood count, plasma glucose level, fasting insulin level, total serum cholesterol, triglyceride, and HDL and LDL cholesterols were recorded. HOMA-IR was calculated. HOMA-IR was calculated according to the formula: fasting insulin (μU/L) x fasting glucose (nmol/L)/22.5[10].

Monocyte count to HDL-C ratio was defined as blood monocyte count to high-density lipoprotein cholesterol concentration ratio[11].

Statistical analysis

The normality of the distribution of the data was analyzed with the Kolmogorov-Smirnov test. Data were presented as mean ± standard deviation, or count, percentage. Two independent sample *t*-test was performed to compare the continuous data between groups. Chi-square test was used to compare the categorical data between groups. Pearson correlation analysis was performed to determine the association of MHR with the liver function tests, age and the insulin resistance. Statistical analyzes were performed using SPSS 21.0 (IBM SPSS Statistics 19, SPSS Inc, an IBM Co, Somers, New York). The significance level was set at $P<0.05$.

RESULTS

Totally 409 cases were included in the study. Among participants, 201 were in the control group, and 208 were in the NAS group (111 were having grade 2 and 97 were having grade 3 steatosis). The mean age of the study participants was 51.79±14.49 years in the control group and 53.74±12.42 years in the NAS group (P=0.23). The mean ALT levels were 27.97±15.85 and 38.03±18.24 (P=0.012) in the control group and in the NAS group respectively. Comparison of demographic features of study participants are summarized in TABLE 1. Monocyte/HDL ratio was significantly higher in the NAS group compared with the healthy controls (P=0.001) (FIGURE 1).

TABLE 1. Comparison of demographic features and laboratory data of the study participants.

	Control group (n=201)	NAS group (n=208)	*P*
Gender (female/male)	117/84	120/88	0.92
Age (years)	51.79±14.49	53.74±12.42	0.23
AST	24.56±16.77	28.74±17.84	0.091
ALT	27.97±15.85	38.03±18.24	0.012
GGT	38.36±44.68	48.23±44.87	0.13
ALP	92.98±44.31	97.01±45.71	0.57
HDL	51.38±11.245	35.27±6.274	0.001
LDL	118.82±51.173	125.10±44.567	0.24
Monocyte/HDL ratio	9.94±4.63	15.10±5.92	0.001
HOMA-IR	2.07±0.44	3.30±0.59	0.001

NAS: non-alcoholic steatohepatitis; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; ALP: alkaline phosphatase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance.

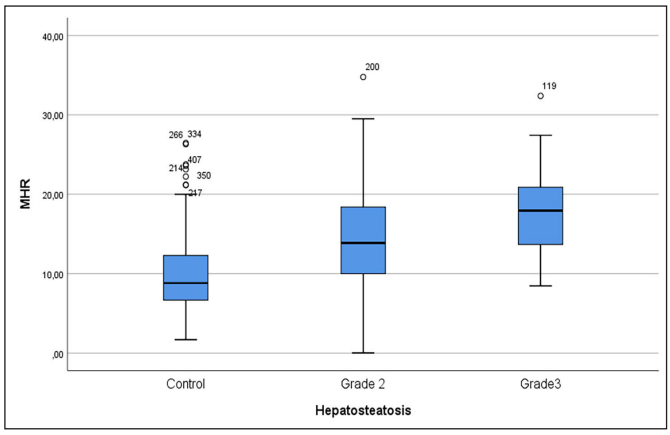

FIGURE 1. Distribution of monocyte/HDL-C ratio (MHR) between hepatosteatosis groups and controls.

The results of correlation analysis performed between the monocyte/HDL ratio and liver function tests, HOMA-IR and NLR values are summarized in TABLE 2. There was a significant positive correlation between the monocyte/HDL ratio and age (r=0.109; P=0.028), ALT (r=0.123, P=0.014) and HOMA-IR (r=0.325, P=0.001) values.

TABLE 2. The results of correlation analysis.

	Monocyte / HDL ratio	
	r	*P*
Age	0.109	0.028
AST	0.062	0.217
ALT	0.123	0.014
GGT	0.074	0.144
HOMA-IR	0.325	0.001

HDL: high-density lipoprotein; r: correlation coefficient; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma-glutamyl transferase; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance.

DISCUSSION

In this study, we determined a significant increase in monocyte/HDL ratio in NAS patients compared with the healthy controls which correlated with the age, HOMA-IR and ALT levels, significantly. To the best of our knowledge, this is the first study in literature evaluating the monocyte/HDL ratio, which is shown to be a predictor of cardiovascular diseases, in NAS patients.

In atherosclerotic diseases, the main pathological mechanisms were shown to be the systemic inflammation and lipid accumulation[12,13]. Monocytes are the major source of proinflammatory cytokines. Monocytes differentiate into the macrophages that ingest oxidized LDL cholesterol. High-density lipoprotein-cholesterol is known with its anti-inflammatory and anti-oxidant effects by inhibiting the activation of monocytes, migration of macrophages and LDL oxidation. Moreover, HDL molecules also increase endothelial nitric oxide expression and improve vasorelaxation[14-16].

In recent literature, monocyte to HDL ratio was studied in many atherosclerotic diseases and defied as a prognostic marker. Bolayir et al. reported that the MHR was significantly higher in patients with

acute ischemic stroke and moreover, it was a significant independent variable of 30-day mortality in these patients[17]. Karatas et al. reported that the MHR in patients with diabetic nephropathy was significantly higher than that of both the normoalbuminuric diabetic patients and the healthy controls and this ratio was independently correlated with urine albumin to creatinine ratio. The authors suggested this ratio as a biomarker for diabetic nephropathy[18]. In a large cohort, Wang et al. reported a linear relation between MHR levels and the ischemic stroke[19]. The role of MHR in predicting the outcomes of cardiovascular diseases is highly important in clinical practice. NAS was defined to be independently associated with both prevalent and incident cardiovascular diseases[20] and in that aspect; MHR may be suggested as a helpful marker in determining the cardiovascular outcomes in NAS patients.

We determined a significant association of MHR with the age and insulin resistance. Insulin resistance is known to be the main pathogenetic mechanism in NAS and some other metabolic diseases. In a cross-sectional study, Dincgez Cakmak et al. reported significantly higher MHR values in patients with polycystic ovary syndrome, which was also determined as an independent predictor of metabolic syndrome[21]. Similarly, Uslu et al. also reported higher MHR values in patients with metabolic syndrome and a significant correlation between the severity of metabolic syndrome and MHR[22]. Battaglia et al. defined MHR as a determinant of metabolic syndrome, which significantly correlated with the body mass index, waist circumference, C-reactive protein, and erythrocyte sedimentation rate[23]. All these data also support our findings reporting the association of MHR with the insulin resistance.

In recent literature, elevated serum gamma-glutamyl transferase (GGT) levels have been associated with increased risk of cardiovascular disease[24,25]. However, some studies did not define any relationship of serum GGT levels with the cardiovascular diseases' presence or outcomes[26]. In this study, though we defined a significant correlation between MHR and ALT levels, there was not any association between MHR and GGT levels.

There are some limitations of this study. First is that NAS was diagnosed with the ultrasound, not with the biopsy. For that reason, this study may be regarded as the preliminary evaluation of MHR in NAS and further studies with biopsy proven NAS patients may give more information regarding this association. Secondly, in this retrospective study, we did not analyze the association of body mass index with MHR, since this was a retrospective study and the data regarding the body mass index was not present in the patient records.

In conclusion, monocyte to HDL ratio significantly increases in fatty liver disease and correlates with the insulin resistance. Since it is suggested as a prognostic marker in atherosclerotic diseases, elevated MHR values in fatty liver disease should be evaluated cautiously. Since this is a non-invasive, inexpensive and simple calculation, further studies are warranted to determine the role of this ratio in predicting outcomes of fatty liver disease and to promptly treat patients with high cardiovascular disease risk.

Authors' contribution

Study design: Yozgat A, Kasapoglu B, Kekilli M. Data collection: Yozgat A, Ekmen N, Unsal Y, Sokmen FC. Data analysis: Yozgat A, Ekmen N, Unsal Y, Sokmen FC. Manuscript preparation: Yozgat A, Kasapoglu B, Kekilli M.

Orcid

Ahmet Yozgat: 0000-0002-4414-9929.
Nergis Ekmen: 0000-0002-7291-3169.
Benan Kasapoglu: 0000-0003-3858-0103.
Yasemin Unsal: 0000-0003-2413-7733.
Fevzi Coskun Sokmen: 0000-0002-5621-8274.
Murat Kekilli: 0000-0002-3063-8748.

Yozgat A, Ekmen N, Kasapoglu B, Unsal Y, Sokmen FC, Kekilli M. Relação monócito/HDL em esteatose não hepática. Arq Gastroenterol. 2021;58(4):439-42.

RESUMO – **Contexto** – A esteatose não hepática (ENH) é caracterizada pelo acúmulo de gordura nos hepatócitos, causando inflamação portal e lobular e lesões ao hepatócito. **Objetivo** – Avaliar as alterações na contagem de monócitos em relação à proporção de lipoproteína de colesterol de alta densidade (MHR) em doentes com doença hepática gordurosa de grau 2 ou 3 e a associação deste marcador com testes de função hepática e de resistência à insulina. **Métodos** – Nesta análise retrospectiva os pacientes diagnosticados e seguidos para a doença hepática gordurosa de grau 2 ou 3, foram incluídos no grupo de doentes e os indivíduos que tinham sido submetidos a ecografia abdominal por qualquer motivo e que não tinham qualquer doença hepática gordurosa foram incluídos no de controle. **Resultados** – Foram incluídos 409 pacientes no estudo. Entre os participantes, 201 estavam no grupo controle e 208 estavam no grupo ENH (111 caracterizados como grau 2 e 97 com esteatose de grau 3). A relação monócito/HDL foi significativamente maior no grupo ENH em comparação com os controles saudáveis (*P*=0,001). Verificou-se correlação positiva significativa entre a relação monócitos/HDL e a idade (r=0,109; *P*=0,028), e valores de ALT (r=0,123; *P*=0,014) e HOMA-IR (r=0,325; *P*=0,001). **Conclusão** – A razão entre monócitos e a lipoproteína de alta densidade aumenta significativamente na doença hepática gordurosa e correlaciona-se com a resistência à insulina. Uma vez que foi sugerido como um marcador prognóstico em doenças ateroscleróticas, os valores elevados de MHR na doença hepática gordurosa devem ser avaliados com cautela.

Palavras-chave – Relação monocito/HDL; hepatosteatose; esteatose não hepática; resistência à insulina.

REFERENCES

1. Brunt EM, Wong VW, Nobili V, Day CP, Sookoian S, Maher JJ, et al. Non-alcoholic fatty liver disease. Nat Rev Dis Primers. 2015;1:15080. doi:10.1038/nrdp.2015.80.
2. Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology. 2014;59:713-23. doi:10.1002/hep.26672.
3. Salgado AL, Carvalho L, Oliveira AC, Santos VN, Vieira JG, Parise ER. Insulin resistance index (HOMA-IR) in the differentiation of patients with non-alcoholic fatty liver disease and healthy individuals. Arq Gastroenterol. 2010;47:165-9. doi:10.1590/s0004-28032010000200009.
4. Wai-Sun Wong V, Lai-Hung Wong G, Woo J, Abrigo JM, Ka-Man Chan C, She-Ting Shu S, et al. Impact of the New Definition of Metabolic Associated Fatty Liver Disease on the Epidemiology of the Disease. Clin Gastroenterol Hepatol. 2020;S1542-3565:31504-4. doi:10.1016/j.cgh.2020.10.046.
5. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020;73:202-9. doi:10.1016/j.jhep.2020.03.039.
6. Kundi H, Kiziltunc E, Cetin M, Cicekcioglu H, Cetin ZG, Cicek G, et al. Association of monocyte/HDL-C ratio with SYNTAX scores in patients with stable coronary artery disease. Herz. 2016;41:523-9. doi:10.1007/s00059-015-4393-1.
7. Cagdas M, Karakoyun S, Yesin M, Rencuzogullari I, Karabag Y, Uluganyan M, et al. The Association between Monocyte HDL-C Ratio and SYNTAX Score and SYNTAX Score II in STEMI Patients Treated with Primary PCI. Acta Cardiol Sin. 2018;34:23-30. doi:10.6515/ACS.201801_34(1).20170823A.
8. Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, et al. The Role of Monocyte to High-Density Lipoprotein Cholesterol Ratio in Prediction of Carotid Intima-Media Thickness in Patients With Type 2 Diabetes. Front Endocrinol (Lausanne). 2019;10:191. doi:10.3389/fendo.2019.00191.
9. Ferraioli G, Soares Monteiro LB. Ultrasound-based techniques for the diagnosis of liver steatosis. World J Gastroenterol. 2019;25:6053-62. doi:10.3748/wjg.v25.i40.6053.
10. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28:412-9. doi:10.1007/BF00280883.
11. Kanbay M, Solak Y, Unal HU, Kurt YG, Gok M, Cetinkaya H, et al. Monocyte count/HDL cholesterol ratio and cardiovascular events in patients with chronic kidney disease. Int Urol Nephrol. 2014;46:1619-25. doi:10.1007/s11255-014-0730-1.
12. Woollard KJ, Geissmann F. Monocytes in atherosclerosis: subsets and functions. Nat Rev Cardiol. 2010;7:77-86. doi:10.1038/nrcardio.2009.228.
13. Libby P. Inflammation in atherosclerosis. Arteriosclerosis, thrombosis, and vascular biology. 2012;32:2045-51. doi:10.1161/ATVBAHA.108.179705.
14. Ganjali S, Gotto AM, Jr., Ruscica M, Atkin SL, Butler AE, Banach M, et al. Monocyte-to-HDL-cholesterol ratio as a prognostic marker in cardiovascular diseases. J Cell Physiol. Dec 2018;233:9237-46. doi:10.1002/jcp.27028.
15. Ghattas A, Griffiths HR, Devitt A, Lip GY, Shantsila E. Monocytes in coronary artery disease and atherosclerosis: where are we now? J Am Coll Cardiol. 2013;62:1541-51. doi:10.1016/j.jacc.2013.07.043.
16. Murphy AJ, Woollard KJ. High-density lipoprotein: a potent inhibitor of inflammation. Clin Exp Pharmacol Physiol.2010;37:710-8. doi:10.1111/j.1440-1681.2009.05338.x.
17. Bolayir A, Gokce SF, Cigdem B, Bolayir HA, Yildiz OK, Bolayir E, et al. Monocyte/high-density lipoprotein ratio predicts the mortality in ischemic stroke patients. Neurol Neurochir Pol. 2018;52:150-5. doi:10.1016/j.pjnns.2017.08.011.
18. Karatas A, Turkmen E, Erdem E, Dugeroglu H, Kaya Y. Monocyte to high-density lipoprotein cholesterol ratio in patients with diabetes mellitus and diabetic nephropathy. Biomark Med. 2018;12:953-9. doi:10.2217/bmm-2018-0048.
19. Wang HY, Shi WR, Yi X, Zhou YP, Wang ZQ, Sun YX. Assessing the performance of monocyte to high-density lipoprotein ratio for predicting ischemic stroke: insights from a population-based Chinese cohort. Lipids Health Dis. 2019;18:127. doi:10.1186/s12944-019-1076-6.
20. Adams LA, Anstee QM, Tilg H, Targher G. Non-alcoholic fatty liver disease and its relationship with cardiovascular disease and other extrahepatic diseases. Gut. 2017;66:1138-53. doi:10.1136/gutjnl-2017-313884.
21. Dincgez Cakmak B, Dundar B, Ketenci Gencer F, Aydin BB, Yildiz DE. TWEAK and monocyte to HDL ratio as a predictor of metabolic syndrome in patients with polycystic ovary syndrome. Gynecol Endocrinol. 2019;35:66-71. doi:10.1080/09513590.2018.1490401.
22. Uslu AU, Sekin Y, Tarhan G, Canakci N, Gunduz M, Karagulle M. Evaluation of Monocyte to High-Density Lipoprotein Cholesterol Ratio in the Presence and Severity of Metabolic Syndrome. Clin Appl Thromb Hemost. 2018;24:828-33. doi:10.1177/1076029617741362.
23. Battaglia S, Scialpi N, Berardi E, Antonica G, Suppressa P, Diella FA, et al. Gender, BMI and fasting hyperglycaemia influence Monocyte to-HDL ratio (MHR) index in metabolic subjects. PloS one. 2020;15:e0231927. doi:10.1371/journal.pone.0231927.
24. Ndrepepa G, Colleran R, Kastrati A. Gamma-glutamyl transferase and the risk of atherosclerosis and coronary heart disease. Clinica chimica acta; international journal of clinical chemistry. 2018;476:130-8. doi:10.1016/j.cca.2017.11.026.
25. Tu WJ, Liu Q, Cao JL, Zhao SJ, Zeng XW, Deng AJ. gamma-Glutamyl Transferase as a Risk Factor for All-Cause or Cardiovascular Disease Mortality Among 5912 Ischemic Stroke. Stroke. 2017;48:2888-91. doi:10.1161/STROKEAHA.117.017776.
26. Ndrepepa G, Kastrati A. Gamma-glutamyl transferase and cardiovascular disease. Ann Transl Med. 2016;4:481. doi:10.21037/atm.2016.12.27.