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The Potential Use of Monocyte-to-High-Density Lipoprotein Ratio as a Chronic Inflammatory Marker in Major Depressive Disorder

Onur Öztürk[1], Ayşe Pınar Doğru Balakbabalar[2], Muhammed Okuyucu[3], Muhammed Emin Göktepe[4]

[1]Department of Family Medicine, Samsun University, Faculty of Medicine, Samsun, Turkey; [2]Department of Psychiatry, Samsun Education and Research Hospital, Samsun, Turkey; [3]Department of Internal Medicine, Ondokuz Mayıs University, Faculty of Medicine, Samsun, Turkey; [4]Department of Family Medicine, Giresun Training and Research Hospital, Giresun, Turkey

ABSTRACT

Background: Monocytes secrete pro-inflammatory and pro-oxidant cytokines as part of inflammatory reactions. High-density lipoproteins have anti-inflammatory and antioxidant effects. This study investigated the potential use of the monocyte-to-high-density lipoprotein ratio in the follow-up of major depressive disorder.

Methods: The study group was composed of patients with newly diagnosed or preexisting major depressive disorder who applied to a psychiatric clinic and did not receive antidepressant treatment in the last 2 weeks. These patients were tested for the monocyte-to-high-density lipoprotein ratio in the psychiatric outpatient clinic both in the first interview and at their follow-up at 2 months. The control group, on the other hand, consisted of subjects who presented to the checkup clinic without any complaints.

Results: The study included a total of 98 individuals aged between 18 and 62 years, including 66 women and 32 men. The proportion of women in the study group was higher than that in the control group ($P = .002$). Patients in the study group had higher first high-density lipoprotein levels than healthy controls ($P = .026$). Beck's Depression Inventory scores of the study group decreased significantly from the first to the second interview ($P < .001$). There was no significant correlation between the percentage of change in Beck's Depression Inventory scores and the percentage of change in the monocyte-to-high-density lipoprotein ratio ($P = .271$).

Conclusion: The high-density lipoprotein levels in healthy controls were not higher than those in the group with major depressive disorder; monocyte levels did not differ between the groups and the monocyte-to-high-density lipoprotein ratio was not superior to Beck's Depression Inventory and could not be used in prognosis.

ARTICLE HISTORY

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INTRODUCTION

The incidence of major depressive disorder (MDD) is rising and is resulting in an increased use of antidepressants. This increase in MDD incidence has led to increased numbers of studies that investigate the causes of this disease and associated comorbidities in recent years and led to new hypotheses. Based on a report from the World Health Organization (WHO), depression will be the single biggest cause of ill health in the world by 2030.[1,2]

Changes in biochemical parameters, such as stress hormones, cytokines, neopterin, and brain-derived neurotrophic factor in MDD, indicate the presence of an association between MDD and inflammatory pathways. It has been claimed that MDD increases inflammation and inflammation increases MDD. It has been shown that some antidepressants reduce inflammation and some anti-inflammatory drugs reduce the severity of MDD.[2,3]

Inflammatory markers include C-reactive protein, procalcitonin, erythrocyte sedimentation rate, interleukins, interferon-γ, and tumor necrosis factor-α. Some studies conducted in recent years have found other potential inflammatory markers such as neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, red cell distribution width-to-platelet ratio, eosinophil -to-lymphocyte ratio, and mean platelet volume.[4,5]

Monocytes secrete pro-inflammatory and pro-oxidant cytokines as part of inflammatory reactions, directly

Corresponding author: Muhammed Okuyucu, e-mail: muhammedokuyucu55@gmail.com

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affecting platelets and endothelial cells.[2] High-density lipoproteins (HDLs) have been shown to protect endothelial cells against the harmful effects of low-density lipoproteins (LDLs) and prevent the oxidation of LDL molecules. Thus, HDL has anti-inflammatory, antioxidant, and antithrombotic effects.[6] Decreased HDL levels and increased count of monocytes have been shown to be associated with inflammation. Therefore, monocyte/HDL ratio has been suggested as a potential novel inflammatory biomarker in tobacco addiction, schizophrenia, bipolar disorder, cardiovascular disease, obstructive sleep apnea, mesenteric embolism, and acute appendicitis.[2,7-12]

This study investigated the usefulness of the monocyte-to-HDL ratio in the follow-up of MDD.

MATERIAL AND METHODS

This was a prospective, controlled, and analytic study. The study group consisted of patients with newly diagnosed or preexisting MDD (provided that diagnosis was established by the same psychiatrist based on DSM-5) who presented to the psychiatric clinic of Samsun Education and Research Hospital between August 15, 2021 and October 15, 2021 and had not received antidepressant treatment in the last 2 weeks (to rule out the antidepressant discontinuation syndrome).[13] These individuals were reevaluated for the purpose of follow-up 2 months after presentation (between October 15, 2021 and December 15, 2021).

Patients in the study group were tested for the monocyte-to-HDL ratio and were assessed using Beck's Depression Inventory (BDI) both at the first interview and at follow-up at 2 months. These individuals were started on treatment as judged appropriate by the psychiatrist who was a member of the research team. Researchers examined the effect of the treatment on the monocyte-to-HDL ratio and the association of any possible change in BDI scores at different time points with the monocyte-to-HDL ratio.

Inclusion criteria were having age between 18 and 65 years and MDD diagnosis. Exclusion criteria were having any acute and/or chronic comorbidity (respiratory infection, hypertension, diabetes, schizophrenia, fibromyalgia, migraine, cancer, COVID-19 history, hypercholesterolemia, and thyroid dysfunctions), acute and/or chronic drug use (nonsteroidal anti-inflammatory drugs, immunosuppressive agents, and antibiotics), smoking or using alcohol, history of potentially deadly trauma, and failure to meet any of the inclusion criteria.

The control group consisted of individuals aged between 18 and 65 years of age who presented to the checkup clinic at the same hospital without any complaints during the same 4-month period and who volunteered to participate in the study. These individuals underwent an assessment, and those who were found to have any acute and/or chronic comorbidity, history of previous MDD, and acute and/or chronic drug use, those who smoked and used alcohol, and those with a history of potentially deadly trauma were excluded. Since the guidelines did not have an advice on follow-up in the same year for healthy individuals, these people were tested for the monocyte-to-HDL ratio by the family physician at the clinic only once.

Tools

Participants' sociodemographic data, including sex and age, were recorded. Confidential data were not shared.

The monocyte-to-HDL ratio was calculated using a statistical software suite based on the data extracted from complete blood counts and HDL measurement. The monocyte-to-HDL ratio was tested before noon and after fasting for at least 8 hours for all participants in line with the recommendation of the American Diabetes Association.[14]

Levels of serum HDL cholesterol were measured using a Cobas 8000 modular analyzer (Roche Diagnostics GmbH, Mannheim, Germany) using a photometric method.

Complete blood counts including monocytes were performed using a Mindray BC-6800 automatic hematology analyzer (Mindray Building, Shenzhen, P.R. China) using impedance and laser light technology.

We obtained venous blood samples from all participants following overnight fasting. Serum samples were stored at −80°C before the collection of measurements.

Beck's Depression Inventory is used to measure the levels of symptoms of depression in both clinical and nonclinical samples. This scale has been developed by Beck et al based on clinical observations and was updated later. The scale consists of 21 items scored between 0 and 3 points and the total score was obtained by the sum of scores from each item. A higher total score indicates a more severe depressive mood. A meta-analysis of the BDI's internal consistency estimates yielded a mean coefficient alpha of 0.86 for psychiatric patients and 0.81 for nonpsychiatric subjects.[15] The validity and reliability study for the Turkish version of the inventory was conducted by Hisli. The maximum possible score from the inventory is 63 and the lowest possible score is 0. Split-half reliability coefficient was 0.78 for the student sample and 0.61 for the patient sample. Test–retest reliability for the student sample was 0.65 with a 2-week interval.[16] All procedures in the study were designed in accordance with the Helsinki Declaration and guidelines for Good Clinical Practice.

MAIN POINTS

- High-density lipoprotein (HDL) levels were significantly higher in the patients than in the healthy controls.
- Monocyte levels did not differ between the groups.
- The monocyte-to-HDL ratio was not superior to Beck's Depression Inventory and could not be used in prognosis.

Statistical Analysis

Sample size calculation was conducted using G Power 3.1.9.7 (Franz Faul, Germany), using data provided by Sahpolat et al[2] in their study, and effect size was assumed to be 0.767. The calculation done with the specified effect size, 80% power and 5% margin of error showed that the study should include a total of at least 56 subjects, including 28 patients and 28 healthy controls.

Statistical analysis was performed using the Statistical Package for the Social Sciences version 25.0 (IBM SPSS Corp.; Armonk, NY, USA). The variables were checked for normality of distribution using the Kolmogorov–Smirnov test. Descriptive statistics of the data are presented with n (%) and non-normalized variables (for nonparametric tests) are shown as "median (interquartile range)." Percentages of change were calculated as [(last measurement − first measurement)/first measurement] × 100. Categorical variables were compared using the Pearson's chi-squared test. The Mann–Whitney *U*-test was used to evaluate nonparametric variables without normal distribution between 2 groups. The Wilcoxon signed-rank test was used when repeated measurements are concerned. The Spearman correlation coefficient was used for correlation. Observations with a *P*-value below .05 were interpreted as statistically significant.

Ethical Approval

This study was approved by the local Ethics Committee of Samsun Education and Research Hospital, approval no GOKA/2021/6/6, dated March 24, 2021. Participants' informed consent was acquired.

RESULTS

A total of 98 people aged between 18 and 62 years, including 66 (67.3%) women and 32 (32.7%) men, participated in the study. The proportion of women in the study group (87.88%; female = 29, male = 4) was higher than that in the control group (56.92%; female = 37, male = 28; *P* = .002). In addition, the median age of the patients in the study group 41 (35-47) was higher than that of healthy controls 32 (25-39) (*P* = .002).

The groups were compared in terms of first HDL levels, first monocyte value, first monocyte percentage (MP), monocyte value-to-HDL level, and monocyte percentage-to-HDL level. Results showed that the first HDL levels were higher in patients in the study group than in the healthy controls (*P* = .026; Table 1).

The researchers also analyzed the change in BDI scores, HDL levels, monocyte value, monocyte percentage, monocyte value-to-HDL level, and monocyte percentage-to-HDL levels. Results show that the study group's BDI scores decreased significantly (*P* < .001; Table 2).

There was no significant correlation between the percentage of change in BDI scores and the percentage of change in monocyte-to-HDL and monocyte percentage-to-HDL ratios (*P* = .271, *P* = .196, respectively; Table 3, Figures 1 and 2).

Table 1. Blood Test Results of the Groups

First	Study Group [Median (IQR)]	Control Group [Median (IQR)]	*P*
Female			
HDL level (mg/dL)	60 (49-65)	56 (44-60)	.109
Monocyte value (10^9/L)	0.4 (0.4-0.5)	0.4 (0.4-0.5)	.941
Monocyte percentage (%)	6.7 (6.1-8.4)	7.1 (6-8.4)	.747
Monocyte value-to-HDL level	0.008 (0.006-0.009)	0.008 (0.006-0.012)	.289
Monocyte percentage-to-HDL level	0.11 (0.1-0.161)	0.138 (0.109-0.159)	.190
Male			
HDL level (mg/dL)	49 (41.5-56)	46 (43.5-55)	.774
Monocyte value (10^9/L)	0.4 (0.35-1.95)	0.5 (0.4-0.6)	.597
Monocyte percentage (%)	6.55 (5.5-23.3)	7.55 (6.15-8.75)	.628
Monocyte value-to-HDL level	0.01 (0.007-0.04)	0.01 (0.008-0.011)	.887
Monocyte percentage-to-HDL level	0.163 (0.105-0.486)	0.154 (0.135-0.192)	1.000
Total			
HDL level (mg/dL)	57 (47-64)	51 (44-59)	**.026**
Monocyte value (10^9/L)	0.4 (0.4-0.5)	0.4 (0.4-0.5)	.641
Monocyte percentage (%)	6.7 (5.9-8.4)	7.3 (6-8.5)	.415
Monocyte value-to-HDL level	0.008 (0.006-0.009)	0.009 (0.007-0.012)	.065
Monocyte percentage-to-HDL level	0.114 (0.1-0.165)	0.149 (0.12-0.169)	.055

Mann–Whitney *U*-test.
HDL, high-density lipoprotein; IQR, interquartile range.Bold values show significant P value.

Table 2. Study Group's Measurements in the First and Second Interviews

Study Group	First [Median (IQR)]	Second [Median (IQR)]	*P*
Female			
BDI score	25 (19-32)	15 (5-23)	**<.001**
HDL level (mg/dL)	60 (49-65)	60 (54-67)	.332
Monocyte value (10^9/L)	0.4 (0.4-0.5)	0.4 (0.4-0.5)	.812
Monocyte percentage (%)	6.7 (6.1-8.4)	7.2 (6.1-8.2)	.746
Monocyte value-to-HDL level	0.008 (0.006-0.009)	0.008 (0.006-0.009)	.905
Monocyte percentage-to-HDL level	0.11 (0.1-0.161)	0.114 (0.108-0.144)	.738
Male			
BDI score	24.5 (22.5-32.5)	18 (14-22.5)	.068
HDL level (mg/dL)	49 (41.5-56)	47 (44-64)	.465
Monocyte value (10^9/L)	0.4 (0.35-1.95)	0.55 (0.5-0.6)	.713
Monocyte percentage (%)	6.55 (5.5-23.3)	8.3 (6.5-9.2)	1.000
Monocyte value-to-HDL level	0.01 (0.007-0.04)	0.012 (0.009-0.013)	.715
Monocyte percentage-to-HDL level	0.163 (0.105-0.486)	0.155 (0.11-0.196)	1.000
Total			
BDI score	25 (20-32)	15 (5-23)	**<.001**
HDL level (mg/dL)	57 (47-64)	59 (50-67)	.187
Monocyte value (10^9/L)	0.4 (0.4-0.5)	0.5 (0.4-0.5)	.626
Monocyte percentage (%)	6.7 (5.9-8.4)	7.5 (6.1-8.9)	.661
Monocyte value-to-HDL level	0.008 (0.006-0.009)	0.008 (0.006-0.011)	.714
Monocyte percentage-to-HDL level	0.114 (0.100-0.165)	0.115 (0.108-0.161)	.611

Wilcoxon signed-rank test.
BDI: Beck's Depression Inventory; HDL, high-density lipoprotein; IQR, interquartile range.Bold values show significant P value.

DISCUSSION

An increasing number of studies are investigating the association between metabolic variables and psychopathologies, followed by studies examining the association between inflammatory markers and antidepressant treatment, so much so that fluvoxamine, a selective serotonin reuptake inhibitor, is believed to have a potential use in the treatment of COVID-19 due to its anti-inflammatory effect.[17] Indeed, there are very few prospective and control studies that have investigated inflammatory markers in depressive disorder. Recently, the monocyte-to-HDL ratio has been put forward as having a potential value in monitoring chronic diseases, but to the best of our knowledge, the present study is the first to examine the association between MDD and the monocyte-to-HDL ratio.

Table 3. Percentages of Changes

	% Change in BDI score	
	% Change in MP-to-HDL	% Change in MP-to-HDL
r	−0.197	−0.231
P	.271	.196

Spearman correlation coefficient.
BDI, Beck's Depression Inventory; HDL, high-density lipoprotein; MP-to-HDL, monocyte percentage-to-high-density lipoprotein.

Various depression screening and diagnostic tests are available for different age groups and patients. There are 2 types of tests: self-rating tests and clinician-administered tests. Beck's Depression Inventory and the Zung Depression Scale are examples of self-rating tests. The Hamilton Depression Rating Scale and the Montgomery–Asberg Depression Rating Scale are clinician-administered tests.[18] These tests have high reliability (80%-90%) but moderate sensitivity (70%-80%). They fail

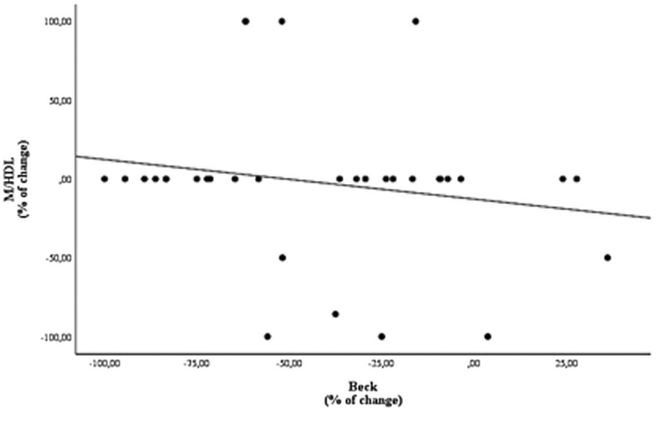

Figure 1. Association between changes in BDI scores and monocyte-to-HDL. BDI, Beck's Depression Inventory; M/HDL, monocyte-to-high-density lipoprotein.

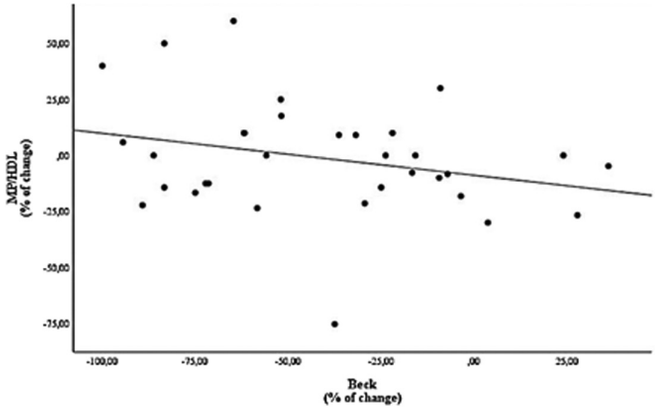

Figure 2. Association between changes in BDI scores and monocyte percentage-to-HDL. BDI, Beck's Depression Inventory; MP/HDL, monocyte percentage-to-high-density lipoprotein.

to provide an objective and standardized result because they depend on self-assessment. The present study found no significant correlation between the change in BDI scores and the monocyte-to-HDL ratio, a potentially more objective measurement in patients receiving psychiatric treatment. It was concluded that the comparison between this ratio, which is an extremely topical parameter for chronic inflammation, and the reliability of BDI is still at a hypothetical stage. Furthermore, based on current parameters, the present study rejected the hypothesis that depression is an inflammatory process.

A 7-year study from India investigating cholesterol lipoproteins and lipids has found higher HDL cholesterol levels among women in all age groups compared with men.[19] Higher HDL is protective against depression-mediated inflammation.[20] In addition, low HDL may predict new-onset MDD in the elderly population.[21] However, elevated levels of HDL in our study group are not sufficient to produce an anti-inflammatory effect. Indeed, according to general characteristics of participants in the "The Maastricht Study," a population-based cohort study investigating the association of inflammation with MDD, there was no difference in age, gender distribution, and HDL values between those with and without depressive disorder.[22] Some other studies have found significantly lower levels of HDL in patients with MDD compared with healthy controls.[23,24] A study by Eker et al[25] found that HDL levels in patients with depression increased with antidepressant treatment but remained lower than those in healthy controls. In line with the results of our study, a study by Ekinci and Ekinci that compared inflammatory parameters and blood lipid values found higher HDL values in patients with depression compared with healthy controls.[12] There was no consensus in the literature about the role of HDL in MDD.

Some studies on monocyte levels in MDD have found increased monocyte gene expression in patients with MDD with childhood trauma.[26] Beumer et al[27] have reported that increased expression of immunity genes in psychiatric patients and overproduction of macrophage-related cytokines resulted in increased numbers of monocytes. Downregulation of the p11 protein in monocytes and NK cells during antidepressant treatment is associated with a subsequent decrease in the severity of depression.[28] However, a population-based study examining the association between circulating cytokine concentrations and MDD found that gender, age, and cytokines had no effect on the diagnosis of MDD.[29] The present study found no significant change in the values and percentage of monocytes, and also does not have a design that examines the etiology of MDD. More studies are required to further investigate "monocyte levels in MDD," a problem for which no consensus exists in the literature.

The common feature of all these studies is the presence of comorbidities as a confounding factor, and these conditions may have affected the association between the examined parameters. The most powerful aspect of this study is its attempt to fully rule out comorbidities.

This study has some limitations. Since the study was single-centered, the number of participants was relatively low and the data cannot be generalized. During the 2-month follow-up, the drugs used for treatment were not standardized, which may have affected the results. Detailed markers of inflammation such as cytokines and acute phase reactants had not been investigated. Parameters such as demographic data and body mass index were not compared with inflammation. In addition, Cronbach's alpha value was not calculated.

It was observed that HDL levels were significantly higher in the patients than in the healthy controls, monocyte levels did not differ between the groups, and the monocyte-to-HDL ratio was not superior to BDI and could not be used in prognosis.

Data Availability Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Data Management and Sharing: Data sharing requests would be available on reasonable request.

Ethics Committee Approval: This study was approved by the Samsun Education and Research Hospital Ethics Committee (Approval number: GOKA/2021/6/6, Date: March 24, 2021).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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