Original Article
https://doi.org/10.9758/cpn.2021.19.1.112 pISSN 1738-1088 / eISSN 2093-4327
Clinical Psychopharmacology and Neuroscience 2021;19(1):112-116

Elevated Monocyte to High-density Lipoprotein Ratios as an Inflammation Markers for Schizophrenia Patients

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Objective: Monocyte to high density lipoprotein ratio (MHR) is a new instrument for giving notice inflammation, which plays a main role in schizophrenia. Thus, in this study, our goal was to investigate the possible association between MHR and schizophrenia.
Methods: The participants of this study consisted of 75 schizophrenia patients and 74 healthy individuals (control group). The Positive and Negative Syndrome Scale was used to collect data from the patient group. Complete blood count parameters and lipid profile were analyzed in all study participants.
Results: The patients with schizophrenia had higher MHR values (15.04 ± 3.31 in schizophrenia patients and 12.62 ± 2.99 in controls; $p = 0.001$). Monocyte counts and MHR of the schizophrenia patients were significantly higher than the control group. There was a significant and positive correlation between age, body mass index, severity of disease and MHR.
Conclusion: To our knowledge, this study was the first to demonstrate inflammatory markers such as MHR levels in schizophrenia patients. Both monocyte counts and MHR values in schizophrenia patients were higher than the control group. MHR might be an available and useful inflammatory marker to evaluate inflammation in schizophrenia patients.

KEY WORDS: High density lipoprotein; Inflammation; Monocyte; Schizophrenia.

INTRODUCTION

Schizophrenia is a progressive and chronic psychiatric illness influencing roughly 1% of whole population worldwide [1,2]. The average life span of individuals who are diagnosed with schizophrenia is almost 20 years less than healthy individuals without this disorder [1,2]. Unfortunately, there is not sufficient information explaining etiology of schizophrenia in the strict sense. One of the important hypotheses to clarify its etiopathogenesis is about immune dysfunction and inflammation [1-3]. Components such as increment in proinflammatory cytokines, increment in autoantibodies, increment oxidative stress products, and maternal infection in prenatal period strengthen this hypothesis [1-3]. The prevalence of risk factors for cardiovascular disease (CVD), cardiovascular morbidity, and an increasing mortality due to CVD in schizophrenia patients is higher than the general population [2,3]. In addition, metabolic syndrome (MetS) and its related factors are major risk factors for the development of cognitive impairment [4,5]. In the study conducted by Zhang and colleagues [6], it was found that schizophrenia patients with MetS had poorer cognitive functions than those without MetS. In addition, same study's results revealed that immune-inflammation might play a major role in this association [6]. Previous studies also indicated the inflammation in MetS had a significant role on cognitive impairment [7]. Hence, identifying biomarkers for inflammation and CVD in schizophrenia patients, and to diminish its occurrence remains as a critical goal.

Monocytes are sources of several cytokines and directly

Received: March 29, 2020 / **Revised:** May 30, 2020
Accepted: June 8, 2020
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affect platelets and endothelial cells, which induces pro-inflammatory and prothrombotic pathways. Monocytes conduct also as an important source of pro-inflammatory species during atherosclerosis process [8-10]. High density lipoprotein (HDL) displays antithrombotic, anti-inflammatory and antioxidant effects [8]. HDL also protects the endothelial tissue from the harmful effects of low-density lipoprotein (LDL), and also prevents the oxidation of LDL [8,9]. Decreased HDL levels and increased monocyte counts were also showed to be related with inflammation. So, the monocyte to HDL ratio (MHR) was recommended to be used as a new inflammatory biomarker [9,10]. Recent studies showed that MHR might be a new marker of inflammation and oxidative stress. In addition, it was also closely associated to the presence and prognosis of some CVDs [10-12]. As reported in the literature, inflammatory process may be part of etiology of schizophrenia [10-12]. In this study, our goal was to investigate the possible association between MHR and schizophrenia.

METHODS

This study included a total of 75 schizophrenia patients and 74 randomly selected healthy volunteers admitted to a psychiatric outpatient clinic. The first group consisted of schizophrenia patients diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders 5th edition criteria. The second group consisted of healthy volunteer individuals (control group). The control group was selected by simple random sampling method. Exclusion criteria included: presence of other chronic diseases such as hyperlipidemia, hypertension, DM, asthma, presence of active infection, myocardial infarction, congestive heart failure, or neurological disorders, being over the ages of 18−65, presence of pregnancy.

Socio-demographic datas and body mass index (BMI) were collected. The Positive and Negative Syndrome Scale (PANSS) was used to evaluate the severity of schizophrenia in the patient group [13]. The study protocol was approved by the Institutional Ethics Committee (IRB no. 2020/05). Our study was conducted in accordance with the ethical standards of the responsible committee on human experimentation and the Helsinki Declaration.

Venous blood samples of the individuals were obtained after a fasting period of 12 hours; HDL levels, monocyte counts determined. MHR value was calculated by dividing the monocyte count to HDL level.

Statistical Analysis

Statistical analysis was performed using the IBM SPSS Statistics 24.0 (IBM Co., Armonk, NY, USA). Descriptive data were expressed as the mean, standard deviation, frequency, and rate. Kolmogorov−Smirnov test was used to test the normality. The independent sample t test for the inter-group comparison of normally distributed quantitative variables was used. Normally distributed qualitative variables were compared using the Pearson's chi-square tests. Pearson's method was used for correlation analysis. p values of < 0.05 were considered statistically significant.

RESULTS

The study included 75 (36 females, 39 males) schizophrenia patients with a mean age of 36.91 ± 10.71 years and 74 (35 females, 39 males) control individuals with a mean age of 36.65 ± 6.34 years ($p > 0.05$) (Table 1).

Table 1. The demographic and biochemical characteristics of two groups

Variables	Schizophrenia patient group (n = 75)	Healthy control group (n = 74)	Significance	p value
Age (yr)	36.91 ± 10.71	36.65 ± 6.34	0.871*	0.385
Sex (female/male)	36/39	35/39	0.007**	0.932
BMI (kg/m^2)	24.90 ± 3.98	24.78 ± 3.01	0.220*	0.827
Smoking (yes/no)	36/39	31/43	0.562**	0.454
PANSS total score	87.71 ± 12.16	-	-	-
Monocyte (×10^3/μl)	636.57 ± 98.55	542.97 ± 96.14	5.867*	0.001
HDL (mg/dl)	43.49 ± 7.71	43.97 ± 6.40	−0.415*	0.697
Monocyte/HDL	15.04 ± 3.31	12.62 ± 2.99	4.660*	0.001

Values are presented as mean ± standard deviation or number only.
BMI, body mass index; PANSS, Positive and Negative Syndrome Scale; HDL, high density lipoprotein.
*Independent Sample t test, **Pearson's chi-square test, $p < 0.05$ is signifiant.

The mean monocyte counts were 636.57 ± 98.55 $\times 10^3/\mu l$ in schizophrenia patients and 542.97 ± 96.14 $\times 10^3/\mu l$ in control group, statistically significant difference was found between both groups in terms of mean monocyte counts ($p = 0.001$ and $p < 0.05$). Although HDL cholesterol levels were lower in schizophrenia patients, but no statistically significant difference was found between both groups ($p = 0.697$). MHR of the control group was 12.62 ± 2.99 while it was 15.04 ± 3.31 in schizophrenia patients. MHR values were found to be statistically significantly higher in schizophrenia patients than control group ($p = 0.001$ and $p < 0.05$) (Table 1).

In addition, MHR of both groups were significantly and positively correlated with age, BMI and PANSS total scores (r = 0.170, $p = 0.038$; r = 0.178, $p = 0.030$ and r = 0.260, $p = 0.025$, and $p < 0.05$, respectively). No statistically significant relationship was found between smoking and MHR in both groups ($p > 0.05$).

DISCUSSION

Schizophrenic patients are under a high risk of CVD when compared to normal population. Moreover, those patients experience more DM and are at risk of being twice as obese as the normal population. The association between schizophrenia patients and sudden cardiac death has been reported; however, the underlying mechanisms are not sufficiently understood [1,3]. The previous studies reported association between schizophrenia and inflammation for a long time [1-3]. The findings related to correlations between schizophrenia and proinflammatory cytokine increase, various infectious diseases, MetS, CVDs and autoimmune diseases have supported the inflammation hypothesis of schizophrenia [1-3].

The main findings of our study were: 1) Elevated MHR was found to be significantly higher in schizophrenia patients, 2) MHR of both groups were significantly and positively correlated with age and BMI, and 3) Significantly positive correlation was found between MHR and severity of disease (PANSS total scores) in schizophrenia patients.

The MHR as a new prognostic factor in CVD has been suggested to be used as an indicator of inflammation. Studies have also indicated that elevated MHR levels were associated with obesity, smoking and muscular bridge diagnoses with coronary anjiography [14-16]. In our study, there was not an evidence of relationship between smoking and MHR. However, MHR was significantly and positively correlated with BMI. The activation of monocytes is important and they can be in different forms in the lipid-laden machropages. Both the activated monocytes and these machropages have a significant role promoting the immune system and driving inflammation and CVD [11,17,18]. Acikgoz *et al.* [19] indicated that there was a high and negative relationship between MHR and flow-mediated dilatation. Hence, increased MHR might be a useful tool reflecting impaired endothelial function and systemic inflammation. Johnsen *et al.* [20] reported that an increased monocyte count may be used as an independent predictor of future plaque improvement in already plaque-free arteries. It was stated that the MHR was a significant marker of increased cardiovascular events in chronic renal failure patients, and to be related with a poor prognosis for cardiovascular mortality [21].

Monocytes migrate into tissue macrophages in interaction with platelets and endothelium, which aggravates inflammation [22,23]. The number of monocytes has been shown to predict the premature occurrence of coronary activities, and the activation of monocytes has been a significant process in the onset of atherosclerosis [22-24]. The HDL displays antioxidant, antiinflammatory, and antiplatelet effects by several pathways, such as inhibition of endothelial adhesion protein expression, including contribution to the cholesterol outflow from macrophages, and encouraging reverse transport of oxidized molecules [23-25]. Thus, HDL reduces inflammation via inhibition of monocyte activities and interruption of alteration of monocytes to macrophages [24,25]. As a result, combining measurements of HDL and monocyte counts as the MHR might represent the basic inflammatory process.

Studies demonstrated that schizophrenia has increased macrophage/monocyte inflammatory activation pattern. It includes especially monocytosis, high levels of proinflammatory and anti-inflammatory monocyte/macrophage derived cytokines [26-29]. The stimulation of the inflammatory response system can give an idea for activation of microglia cells, as they are the macrophages of the brain [26,27]. Another important finding of the study was the prevalence of hypertriglyceridemia and low HDL levels in schizophrenia patients. We found that the prevalence of hypertriglyceridemia (35.2%) and low HDL levels (42.6%) in these patients were higher than in the healthy individuals [28]. Moreover, it was reported that

acute-phase schizophrenia patients had poorer lipid profiles, such as higher LDL and lower HDL, which are associated with the risk of improving CVD and inflammation [29]. For these reasons, we can say that MHR might be used as an indicator of inflammation in schizophrenia patients.

This study had important findings, which was the first study to investigate MHR values in schizophrenia patients, but there were also some limitations. First, the study included a cross-sectional and retrospective data, and reflected experience of only one psychiatric service. Another limitation was the lack of controlling for antipsychotics used. Therefore, we were unable to compare the effects of antipsychotics drugs on MHR. We believe that the analysis of inflammatuar cytokinesis, such as cortisol, interleukin-6 as well as MHR would better elucidate the complex relationship between them.

Consequently, to our knowledge, our study was the first to demonstrate inflammatory markers such as MHR levels in schizophrenia patients. Both monocyte counts and MHR values in schizophrenia patients were higher than control individuals in our study population. MHR is a basic, inexpensive instrument that ought to be used for giving notice the systemic inflammatory events in schizophrenia patients.

■ Acknowledgments

The authors would like to thank the participants.

■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Musa Sahpolat and Mustafa Ari. Data acquisition: Musa Sahpolat. Formal analysis: Musa Sahpolat and Mustafa Ari. Funding: Musa Sahpolat, Duygu Ayar, Mustafa Ari, and Mehmet Akif Karaman. Supervision: Musa Sahpolat, Duygu Ayar, Mustafa Ari, and Mehmet Akif Karaman. Writing—original draft: Musa Sahpolat, Duygu Ayar, Mustafa Ari, and Mehmet Akif Karaman. Writing—review & editing: Musa Sahpolat, Duygu Ayar, Mustafa Ari, and Mehmet Akif Karaman.

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