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

Musa Sahpolat¹, Duygu Ayar², Mustafa Ari³, Mehmet Akif Karaman⁴

¹Department of Psychiatry, Kilis State Hospital, ²Yusuf Serefoglu Faculty of Health Sciences, Kilis 7 Aralık University, Kilis, ³Department of Psychiatry, Mustafa Kemal University Tayfur Ata Sokmen Faculty of Medicine, Hatay, ⁴Department of Psychological Counseling and Guidance, Kilis 7 Aralık University, Kilis, Turkey

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
Elevated Monocyte to High-density Lipoprotein Ratios in Schizophrenia Patients

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/m²)              | 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 (×10³/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 significant.
The mean monocyte counts were $636.57 \pm 98.55 \times 10^3/\mu l$ in schizophrenia patients and $542.97 \pm 96.14 \times 10^3/\mu l$ 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 $12.62 \pm 2.99$ while it was $15.04 \pm 3.31$ 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 angiography [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 macrophages. Both the activated monocytes and these macrophages 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
Elevated Monocyte to High-density Lipoprotein Ratios in Schizophrenia Patients

José Luis P. Gálvez-Rodríguez, MD, PhD, et al.

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 inflammatory cytokines, 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.

ORCID

Musa Sahpolat https://orcid.org/0000-0002-0022-2389

Duygu Ayar https://orcid.org/0000-0003-3781-7914

Mustafa Ari https://orcid.org/0000-0002-8003-1661

Mehmet Akif Karaman https://orcid.org/0000-0001-7405-5133

REFERENCES

1. Karadag F, Sengul CB, Enli Y, Karakulah K, Alacan H, Kaptanoglu B, et al. Relationship between serum bilirubin levels and metabolic syndrome in patients with schizophrenia spectrum disorders. Clin Psychopharmacol Neurosci 2017;15:153-162.
2. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry 2011;70:663-671.
3. Correll CU, Solmi M, Veronese N, Bortolato B, Rosson S, Santonastaso P, et al. Prevalence, incidence and mortality from cardiovascular disease in patients with pooled and specific severe mental illness: a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls. World Psychiatry 2017;16:163-180.
4. Qiu C, Fratiglioni L. A major role for cardiovascular burden in age-related cognitive decline. Nat Rev Cardiol 2015;12:267-277.
5. Kaifashian S, Dugavot A, Elbaz A, Shipley MJ, Sabia S, Kivimäki M, et al. Predicting cognitive decline: a dementia risk score vs. the Framingham vascular risk scores. Neurology 2013;80:1300-1306.
6. Zhang C, Fang X, Yao P, Mao Y, Cai J, Zhang Y, et al. Metabolic adverse effects of olanzapine on cognitive dysfunction: a possible relationship between BDNF and TNF-alpha. Psychoneuroendocrinology 2017;81:138-143.
7. Mackenzie NE, Kowalchuk C, Agarwal SM, Costa-Dookhan KA, Caravaggio F, Gerrets P, et al. Antipsychotics, metabolic adverse effects, and cognitive function in schizophrenia. Front Psychiatry 2018;9:622.
8. Barter PJ, Nicholls S, Rye KA, Anantharamaiah GM, Navab M, Fogelman AM. Antiinflammatory properties of HDL. Circ Res 2004;95:764-772.
9. Negi G, Kumar A, Joshi RP, Sharma SS. Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: old perspective with a new angle. Biochem Biophys Res Comm 2011;408:1-5.
10. Abacioglu OO. Monocyte to high-density lipoprotein ratio: a prognostic factor for mitral valve prolapse? Bratisl Lek Listy 2020;121:151-153.
11. Cepelopolu U, Çetin EH, Četin S, Aydin S, Akboga MK, Yayla C, et al. Association of monocyte-to-HDL cholesterol ratio with slow coronary flow is linked to systemic inflammation. Clin Appl Thromb Hemost 2016;22:476-482.
12. Kaplan IG, Kaplan M, Abacioglu OO, Yavuz F, Saler T. Monocyte/HDL ratio predicts hypertensive complications.
13. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261-276.

14. Enhos A, Cosansu K, Huyut MA, Turna F, Karacop E, Bakshaliyev N, et al. Assessment of the relationship between monocyte to high-density lipoprotein ratio and myocardial bridge. Arq Bras Cardiol 2019;112:12-17.

15. Vahit D, Akboga MK, Samet Y, Huseyin E. Assessment of monocyte to high density lipoprotein cholesterol ratio and lymphocyte-to-monocyte ratio in patients with metabolic syndrome. Biomark Med 2017;11:535-540.

16. Yilmaz M, Kayanciçek H. A new inflammatory marker: elevated monocyte to HDL cholesterol ratio associated with smoking. J Clin Med 2018;7:76.

17. Dogan A, Oylumlu M. Increased monocyte-to-HDL cholesterol ratio is related to cardiac syndrome X. Acta Cardiol 2017;72:516-521.

18. Kundi H, Gok M, Kiziltunc E, Cetin M, Ciccioglu H, Cetin ZG, Karayigit O, Ornek E. Relation between monocyte to high-density lipoprotein cholesterol ratio with presence and severity of isolated coronary artery ectasia. Am J Cardiol 2015;116:1685-1689.

19. Acikgoz N, Kurtoglu E, Yagmur J, Kapicioglu Y, Cansel M, Ernis N. Elevated monocyte to high-density lipoprotein cholesterol ratio and endothelial dysfunction in Behçet disease. Angiology 2018;69:65-70.

20. Johnson SH, Fosse E, Joakimsen O, Mathiesen EB, Stensland-Bugge E, Njolstad I, et al. Monocyte count is a predictor of novel plaque formation: a 7-year follow-up study of 2610 persons without carotid plaque at baseline the Tromsø Study. Stroke 2005;36:715-719.

21. Kanbay M, Solak Y, Ural 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;46:1619-1625.

22. Barter PJ, Baker PW, Rye KA. Effect of high-density lipoproteins on the expression of adhesion molecules in endothelial cells. Curr Opin Lipidol 2002;13:285-288.

23. Açikgoz SK, Açikgoz E, Sensoy B, Topal S, Aydogdu S. Monocyte to high-density lipoprotein cholesterol ratio is predictive of in-hospital and five-year mortality in ST-segment elevation myocardial infarction. Cardiol J 2016;23:505-512.

24. Murphy AJ, Woollard KJ, Hoang A, Mukhamedova N, Stirzaker RA, McCormick SP, et al. High-density lipoprotein reduces the human monocyte inflammatory response. Arterioscler Thromb Vasc Biol 2008;28:2071-2077.

25. Cetin EH, Cetin MS, Canpolat U, Aydin S, Topaloglu S, Aras D, et al. Monocyte/HDL-cholesterol ratio predicts the definite stent thrombosis after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction. Biomark Med 2015;9:967-977.

26. Bergink V, Gibney SM, Drexhage HA. Autoimmunity, inflammation, and psychosis: a search for peripheral markers. Biol Psychiatry 2014;75:324-331.

27. Drexhage RC, van der Heul-Nieuwenhuijsen L, Padmos RC, van Beveren N, Cohen D, Versnol MA, et al. Inflammatory gene expression in monocytes of patients with schizophrenia: overlap and difference with bipolar disorder. A study in naturally treated patients. Int J Neuropsychopharmacol 2010;13:1369-1381.

28. Huang MC, Lu ML, Tsai CJ, Chen PY, Chiu CC, Jian DL, et al. Prevalence of metabolic syndrome among patients with schizophrenia or schizoaffective disorder in Taiwan. Acta Psychiatr Scand 2009;120:274-280.

29. Huang TL, Chen IJ. Serum lipid profiles and schizophrenia: effects of conventional or atypical antipsychotic drugs in Taiwan. Schizophr Res 2005;80:55-59.