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Investigation of the Monocyte to High Density Lipoprotein Ratio as an Inflammatory Marker in Schizophrenia

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ABSTRACT

Objective: The purpose of this study is to investigate the potential relationship between MHR and schizophrenia.

Methodology: This case control study was conducted at the psychiatry department of a tertiary care hospital of a private medical college from 1/11/2022 to 31/04/2023, involving 60 subjects, with thirty diagnosed with schizophrenia according to DSM-5 criteria and thirty healthy controls. The Positive and Negative Syndrome Scale (PANSS) was employed in the patient group to gauge the severity of schizophrenia. Peripheral venous blood was collected from all participants for the analysis of complete blood count parameters, including MHR, and the lipid profile (HDL cholesterol). Pearson's correlation co-efficient was used for correlation analysis, P values of < 0.05 were considered as statistically significant.

Results: Patients with schizophrenia exhibited higher MHR values (15.25±3.16 in schizophrenia patients and 11.50±2.65 in controls; P = 0.001). Both monocyte counts and MHR in schizophrenia patients were significantly elevated compared to the control group. A noteworthy positive correlation was observed between age, body mass index, severity of disease, and MHR. Statistical analyses, including independent sample t-tests, chi-square tests, and Pearson's correlation coefficient, were employed to explore relationships between study variables and calculate P values.

Conclusion: The utilization of the novel parameter MHR enabled the demonstration of an association between low-grade systemic inflammation and schizophrenia. This study underscores the validation of MHR as a valuable marker in psychiatric patients with schizophrenia, warranting further research to explore the utility of this simple and cost-effective instrument.

Key words: High-density lipoproteins, Inflammation, Monocytes, Schizophrenia.

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Introduction

Monocyte-to-high-density lipoprotein ratio (MHR) serves as an innovative parameter indicating low-grade systemic inflammation. Its significance has been established in various medical conditions such as coronary artery disease, rheumatoid arthritis, endocrine disorders, and cancer. There is a growing body of evidence linking inflammation to the pathophysiology of psychiatric disorders, including schizophrenia. Schizophrenia is a major mental disorder which has serious consequences in the biological, psychological and social domains. With a global prevalence of 1%, schizophrenia is a multi-system disease and is one of the fifteen leading causes of disability.[1] A disorder of thought and behavior, schizophrenia includes hallucinations, delusions, disrupted speech and thought patterns as well as, cognitive symptoms such as deficits in working memory and executive functioning.[2] Commonly, the onset of the disorder is in early adulthood and males and females are affected equally. The disorder runs a chronic course and as the illness progresses there is physical worsening, psychological deterioration and cognitive decline.[3] The etiology and pathogenesis of schizophrenia are largely

unknown, but recently the inflammatory hypothesis has been forwarded to elucidate the disease's psychiatric manifestations and medical comorbidities.[4]

Schizophrenia has positive, negative and cognitive symptoms and is associated with increased morbidity and mortality.[5] The latter is mainly derived from cardiovascular causes, such as coronary artery disease; further, patients with schizophrenia have increased incidence of the metabolic syndrome with such accompanying complications as diabetes mellitus, hypertension and atherosclerotic disease .[6] The net result is that patients with schizophrenia have decreased lifespan of about 10 to 15 years as compared to the unaffected individuals.[7] Based on research which spans at least 2 decades, the myriad manifestations of schizophrenia have been explained on the basis of a pro inflammatory state in the body. Numerous original studies, systematic reviews and meta-analyses have investigated this issue, and increase in different inflammatory markers has been found.[8] These include C-reactive protein, cytokines, chemokines, platelet factors, components of the complement and coagulation cascades. More recently, research has been conducted on peripheral blood leucocytes (monocytes, lymphocytes and neutrophils) and lipoproteins (low density lipoproteins, high density lipoproteins) as inexpensive and readily obtainable markers of inflammation in schizophrenia, particularly in assessing the risk of cardiovascular morbidity in such patients. [9]

A novel marker indicating subclinical inflammation is monocyte to high density lipoprotein ratio (MHR). In several systemic diseases such as coronary artery disease, cancer and auto-immune disorders MHR has been examined and high values have been linked to increased disease severity, treatment resistance and worse prognosis.[10] Researchers have turned their attention to neuropsychiatric disorders and investigated MHR as an easily available marker, monitoring the course of major depressive disorder, bipolar disorder and schizophrenia. In this regard, MHR can provide valuable information regarding the severity and physical comorbidities of schizophrenia, which is an intractable mental disorder.[11] With this background, the aim of this study was to investigate the possible association between MHR and schizophrenia.

Methodology

This case-control study was carried out at the Psychiatry Department of a tertiary care hospital affiliated with a private medical college from November 1, 2022, to April 30, 2023. The study received approval from the medical college's Ethical Review Board. The study sample was enrolled using convenience sampling. The sample size was determined with a 90% confidence interval, a margin of error of 10%, and the equation for an unlimited population. A total of 60 participants were included, with 30 individuals diagnosed with schizophrenia, encompassing both cases of first-episode psychosis and established patients with the disorder. These were compared to 30 matched healthy controls who were free from both medical and psychiatric disorders.

According to the inclusion criteria the ages of participants were between 18 and 65 years. Informed consent was obtained from all the subjects and the cases were diagnosed as suffering from schizophrenia according to the DSM-5 criteria. Patients with chronic diseases like hyperlipidemia, hypertension, DM, coronary artery disease, active infection, immunological disorders and comorbid substance abuse were excluded. We used the instrument Positive and Negative Syndrome Scale (PANSS) in the schizophrenia group. PANSS measures the severity of symptoms in schizophrenia and has 3 sub-scales – positive scale, negative scale and general psychopathology scale. The instrument is considered the "gold standard" for the assessment of schizophrenia and related psychotic disorders and is widely used in research work. A demographic proforma was given to the subjects and included the calculation of the body mass index (BMI) of all the participants. Venous blood samples of the participants were obtained after a fasting period of 12 hours and HDL levels and monocyte counts were determined. MHR value was obtained by dividing the absolute monocyte count with the HDL level. Statistical analysis was performed using the IBM SPSS Statistics, version 24.0. Descriptive data were expressed as frequency, mean, standard deviation, and rate. Inter group comparison of normally distributed quantitative variables was done with the help of sample t test and normally distributed qualitative variables itself were compared with the help of chi-square test. Pearson's correlation co-efficient was used for correlation analysis, P values of < 0.05 were considered as statistically significant.

Results

Table 1 gives the demographic characteristics of the 2 study groups. The schizophrenia group and the control group were matched for demographic variables and there was no significant difference between them.

In schizophrenia patients the mean monocyte count was 655.16 ± 99.27 ×103/ml, whereas in the control group it

was 512.35 ± 53.14 $\times 10^3$/ml. Statistically significant difference was found between both groups in terms of the mean monocyte counts (P = 0.001). Although HDL cholesterol levels were lower in schizophrenia patients, no statistically significant difference (P = 0.697) was found between both groups. (Table II)

MHR of the control group was 11.50±2.65 while it was 15.25±3.16 in schizophrenia patients. MHR values were found to be significantly higher in schizophrenia patients than control group (*P* = 0.001).

In addition, MHR of both groups were significantly and positively correlated (Pearson's correlation co-efficient) 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). (Table III)

Discussion

In schizophrenia there is increased stimulation of the monocyte-macrophage system, and an inflammatory activation pattern has been demonstrated. There is a monocytosis, with high levels of pro inflammatory cytokines derived from the triggering of the monocyte-macrophage system.[13] The integrity of the blood-brain barrier is compromised and peripheral inflammatory response leads to the activation of microglial cells which serve as the macrophages of the brain. [14] The stimulated microglia secrete inflammatory mediators and lead to neuro inflammation, manifested as increased symptom severity and poor treatment response.[15]

The current conceptualization of schizophrenia is of a systemic disease with affliction of the brain as well as the peripheral organs. In this regard an association has been found between schizophrenia and the metabolic syndrome.[16] These patients have obesity, higher body mass index, glucose intolerance and dyslipidemias, with the metabolic abnormalities leading to atherosclerotic disease, cardiovascular morbidity and decreased lifespan.[17]

The composite inflammatory indicators such as monocyte-to-high-density lipoprotein ratio, neutrophil-to-lymphocyte ratio, systematic immune-inflammation index and systemic inflammation response index are novel parameters based on peripheral blood cell count and calculated by combining different biochemical parameters to give an idea about the inflammatory status in systemic as well as psychiatric disorders.[18] The MHR as a new prognostic factor in CVD has been suggested to be used as an indicator of inflammation.[19] Circulating monocytes as a source of various cytokines and pro-inflammatory molecules interact with platelets and endothelial cells leading to triggering of the pro-thrombotic pathways. High-density lipoprotein cholesterol counteracts these pro-inflammatory and pro-oxidant effects of monocytes by inhibiting the migration of macrophages and oxidation of the low-density lipoprotein cholesterol molecules, as well as promoting the efflux of cholesterol from endothelial cells.[20] Because of this, monocyte to high density lipoprotein ratio could show the inflammatory status of a patient. Studies have shown that elevated MHR levels

Table I: Demographic features of the participants.

Variable	Schizophrenia group (n = 30)	Control group (n = 30)	Significance	*P* value
Age	35.25±10.56	36.68±7.85	0.832*	0.726
Sex (female/male)	12/18	14/16	0.714**	0. 279
BMI (kg/m^2)	26.38±5.37	25.94±4.73	0.729*	0.418
Smoking (Yes/no)	17/13	11/19	0.714**	0.826
PANSS total score	85.58±13.93	-	-	-

Table II: Biochemical characteristics of the study groups.

Variable	Schizophrenia group (N = 30)	Control group (N = 30)	Significance	P value
Monocyte (x 10^3/ml)	655.16 ± 99.27	512.35 ± 53.14	5.867*	0.001
HDL (mg/dl)	42.94 ± 8.15	44.53 ± 7.24	0.415*	0.697
Monocyte/HDL	15.25±3.16	11.50±2.65	3.994*	0.001

*Independent Sample *t* test

Table III: Relationship between study variables and MHR scores (Controls + Cases)

Variable	MHR (control)	MHR (schizophrenia)	P value
Age	11.50±2.65	15.25±3.16	0.038
BMI	11.50±2.65	15.25±3.16	0.030
Smoking	11.50±2.65	15.25±3.16	0.351
PANSS Score	11.50±2.65	15.25±3.16	0.017

were associated with obesity, smoking and positive findings in coronary angiography. In our study, there was not an evidence of relationship between smoking and MHR. However, MHR was significantly and positively correlated with the BMI in both schizophrenia and control groups.[21]

The value of MHR in neuropsychiatric disorders is increasingly being recognized. A recently published study examined aggressiveness in schizophrenia patients and possible association with MHR as well as other potential peripheral blood cell markers. In this cross-sectional study it was found that there was a statistically significant association between increased symptoms of aggression in schizophrenia and the MHR. The study concluded that MHR, a cheap and simple test may be useful as a clinical tool for risk stratification, and may direct clinicians' prevention and treatment plans in the course of ordinary clinical care. Another study investigated MHR as a novel instrument for demonstrating inflammation in schizophrenia. In this case-control study it was revealed that both monocyte counts and MHR were higher in the schizophrenia group compared to the control group, such that MHR may be an available and useful marker to evaluate inflammation in schizophrenia patients.[22] A retrospective, naturalistic, cross-sectional study investigated systemic immune-inflammation index, neutrophil/high-density lipoprotein ratio, lymphocyte/high-density lipoprotein ratio, and monocyte/high-density lipoprotein ratio as indicators of inflammation in patients with schizophrenia and bipolar disorder. The study highlighted the role of systemic inflammation in the pathophysiology of main neuropsychiatric disorders. Further, an association between inflammation and lipid metabolism was demonstrated, and it was seen that the inflammation and lipid metabolism indicators showed different variation patterns in schizophrenia, bipolar mania and depression.[23] Lastly, another recently published cross-sectional, case-control study showed elevated MHR in schizophrenia patients and indicated the role that inflammation plays in the pathophysiology of the disorder. The authors concluded that recommendations such as diet and exercise, in the treatment approaches might be beneficial in protecting schizophrenia patients against cardiovascular diseases and early death.[24]

Limitations:

i) The study included a cross-sectional design and reflected experience of only one psychiatric service.
ii) The sample size was small and derived by convenience sampling.
iii) Lack of controlling for antipsychotic medications so that we were unable to compare the effects of these drugs on MHR.
iv) The analysis of other inflammatory mediators and stress hormones such as serum cortisol, interleukin-6, etc, as well as MHR would better elucidate the complex relationship between them.

Conclusion

Monocyte to high density lipoprotein ratio is an innovative marker of systemic inflammation and a growing body of literature supports its utility in medical as well as psychiatric disorders. Its use as a prognostic marker is being increasingly recognized. In this study both monocyte counts and MHR values were significantly higher in schizophrenia patients as compared to healthy controls. In neuropsychiatric disorders MHR values indicate underlying inflammation and further research is needed to elucidate the biological characteristics of this marker. Since it is a basic and inexpensive instrument more studies could contribute in clarifying the real value of MHR in the management of psychiatric patients.

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