ORIGINAL ARTICLE

Schizophrenia is linked to dyslipidemia with minimal alterations in the inflammatory biomarkers - an experience from Saudi Arabia

Razan Ahmed Alyoubi[1]*, Sawsan Hassan Mahassni[1]

ABSTRACT

Background and Objective: Schizophrenia (SZ) is a chronic mental illness that is associated with increased inflammation, adverse effects on the immune system, and abnormal concentrations of biochemical molecules. This study is the first to determine the concentrations of C-reactive protein (CRP) and some proinflammatory and anti-inflammatory cytokines, the differential complete blood count (CBC), and the lipid profile in Saudi patients with SZ.

Methods: Blood samples were collected from 45 randomly chosen male in-patients with chronic SZ and 29 healthy males, with an age range of 28-47 years. The concentrations of CRP, IL-6, IL-4, TNF-α, and IFN-γ; body mass index (BMI); CBC; and the lipid profile were determined through standard guidelines and compared between the patients and controls.

Results: The results showed that there were no significant differences in the CRP and cytokines' concentrations for the patients compared with those of the controls. Patients, however, had significantly higher red blood cell (RBC) distribution width. Additionally, patients had significantly lower BMI, basophil and RBC counts, basophil-lymphocyte and eosinophil-lymphocyte ratios, hemoglobin, cholesterol, and low-density lipoprotein concentrations.

Conclusion: In conclusion, patients with SZ in local population showed slight inflammation and the immune system was minimally affected. Additionally, patients had dyslipidemia and were possibly more prone to anemia.

Keywords: Schizophrenia, body mass index, C-reactive protein, cytokines, immune response, inflammation, lipid profile.

Introduction

Affecting around 20 million people worldwide,[1] schizophrenia (SZ) is a chronic mental illness that is characterized by severe symptoms such as delusion, hallucination, and paranoia. In Saudi Arabia in 2019, 34% of Saudis were diagnosed with a mental disorder with 40% being in the age range 25-34 years.[2]

Recent research studies [3,4] found that inflammation has a role in SZ since abnormal levels of cytokines and C-reactive protein (CRP) are found in patients with SZ. It is generally accepted that CRP is a marker for general inflammation [5] and in mental disorders.[6] Tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) are pro-inflammatory cytokines, while interleukin-4 (IL-4) is an anti-inflammatory cytokine, and finally IL-6 may be either a pro-inflammatory or anti-inflammatory cytokine.[7] Thus, the measurement of the concentrations of these cytokines and CRP is an accessible way to determine the inflammatory status in a subject.

Compared to healthy controls, some studies have found that serum levels of many cytokines, such as IL-6, IL-4, IFN-γ, and TNF-α in patients with SZ are abnormal. [4,8-10] In addition, CRP levels are associated with a high risk of SZ where previous results showed that patients with SZ had significantly higher levels of high-sensitivity CRP (hs-CRP) than the controls.[3,11]

It has been shown that patients with SZ have abnormal counts of blood cells, [12] which lead to the possibility that the immune system may be affected adversely. These effects may be attributed to low counts of blood cells of the innate (basophils, eosinophil, monocyte, and neutrophil) and/or acquired (lymphocytes) immune systems both.[13] White blood cells (WBCs) are related to inflammation and higher than normal counts may indicate the presence of abnormal

levels of inflammation in the body.[14] Other indicators or markers of inflammation are the ratios of some WBC, such as neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), and platelets-lymphocyte ratio (PLR), [15] which have been found to be elevated in patients with SZ.[16]

Lipids are one of the important groups of molecules that have an important role in the development of psychiatric disorders, especially SZ, depression, and bipolar disorders.[17] In fact, it has been found that the levels of lipids in serum have a role in the pathophysiology of SZ.[18]

There are no studies yet published that elucidate the effects of SZ on the counts of immune system cells, concentrations of inflammatory markers, and the lipid profile in Saudi Arabian patients with the exception of only one study [9] that determined the levels of inflammatory markers, TNF-α, IL-6, and IFN-γ, only. Therefore, this study was planned to determine whether patients with SZ in the local community have immunological and/or biochemical differences compared to normal healthy controls by determining the concentrations of CRP, IL-6, IL-4, TNF-α, and IFN-γ; the differential complete blood count (CBC); the lipid profile; and the body mass index (BMI).

Methods

Subjects

This study was carried out among 45 male in-patients with SZ, randomly chosen from the Eradah Complex Mental Health Services, Jeddah, Saudi Arabia, and 29 randomly chosen healthy male subjects with no SZ or any other mental disorders. All subjects resided in Jeddah, Saudi Arabia, had an age range 28-47 years, none had any diseases other than SZ, and none were taking any medications other than the antipsychotic medications for the patients. Two inclusion criteria for the control subjects were not having had any lifetime diagnosis of any mental disorder or exposure to any antidepressant, antipsychotic, and mood stabilizer medications. The study was conducted from October 2020 to January 2021. Ethical approval for this study was granted by the Directorate of Health Affairs, Jeddah, Saudi Arabia (Institutional Review Board Approval Number: A00857). All subjects filled a consent form. Access was granted to the hospital files of the patients from which most of the lifestyle information and some test results were obtained.

Blood collection

Blood samples were collected, after fasting for a minimum of 10 hours, from both the patients and controls. Serum blood samples were collected in gel serum separator vacutainer tubes and that were separated by centrifugation at a speed of 4,400 rpm for 3 minutes, for the determination of the lipid

profile, and the concentrations of the CRP and cytokines. Serum samples were collected from 27 patients only, as remaining patients were discharged from the hospital. Blood samples were also collected in ethylene diamine tetraacetic acid vacutainer tubes for the determination of the differential CBC.

Determination of CRP and cytokines concentrations

The CRP, TNF-α, IL-6, IL-4, and IFN-γ concentrations were measured by using human enzyme-linked immunosorbent assay kits (ElabScience, Houston, Texas, United States) and the results were read using a microplate reader (BioTek Instruments, Inc., Winooski, VT) at King Fahad Center for Medical Research, Jeddah, Saudi Arabia. The serum samples were applied neat on the plates for all cytokines, whereas the CRP was diluted 1:2000 before applying to the wells.

Determination of the differential CBC and lipid profile

The lipid profile and the differential CBC of the patients' samples were done at the Eradah Complex Mental Health Services Laboratory, Jeddah, Saudi Arabia, on a D × H 500 and UniCel D × C 600 instruments, respectively (Beckman Coulter Inc., Brea, CA). The samples of the healthy control group were analyzed on a CELL-DYN instrument (Abbott, Abbott Park, IA) for the differential CBC while the lipid profile was done on an ARCHITECT instrument (Abbott, Abbott Park, IA) at King Abdulaziz University Hospital, Jeddah, Saudi Arabia.

Statistical analysis

Data were analyzed using the MegaStat program version 9.4 (Butler University, Indianapolis, IA). Data were summarized as mean, SD (±SD), SE of the mean (±SE), maximum (max) value, and minimum (min) value. The p-value was calculated and used to determine the statistical differences between the patients and the control groups for each parameter. The Student t-test was used for the normally distributed parameters while the Mann-Whitney U test was used for the non-normally distributed parameters.

Results

The age ranges for the control and patient groups were similar, as shown in Table 1. The mean age for the patients was significantly higher than that for the control. The range of weights for the control subjects was higher for both the minimum and maximum compared to those for the patients' range. In addition, the mean body weight for the patients was significantly lower than that for the controls. The height range for the controls was narrower than for the patients with the patients having a higher minimum and maximum. The mean height for the patients was not significantly different than for the controls. Finally, the BMI results for

the controls were compared with the previously published results for the patients.[19] The minimum and maximum and the mean BMI for the control subjects were higher than for the patients The lifestyle questionnaire results are shown in Table 2 where most of the patients had a duration of illness from 1 to 10 years.

Using the Mann-Whitney U test (Table 3), there were no significant differences for the mean concentrations of CRP, IL-6, TNF-α, and IFN-γ for the patients with SZ compared to the healthy control subjects. Using the t-test (Table 3), there was no significant difference for the mean concentration of IL-4 between the patients and the controls.

Using the t-test (Tables 4 and 5), there were no significant differences between the patients with SZ and control subjects for the mean total WBC counts; lymphocyte, monocyte, neutrophil, and eosinophil counts; NLR and MRL for counts and percents; and eosinophil-lymphocyte ratio (ELR) for counts. Additionally, using the Mann-Whitney U test, there was no significant difference for the mean PLR for counts for the patients compared to the controls. On the other hand, using the t-test, the mean basophil count and percent, mean basophil-lymphocyte ratio (BLR) for counts and percents, and mean ELR for percents were significantly lower for the patients compared to the controls.

As shown in Table 6, using the t-test, the mean red blood cell (RBC) counts, hematocrit (HCT), and the mean hemoglobin concentration were significantly lower for the patients compared to the controls. Also using the t-test, the mean corpuscular hemoglobin concentration (MCHC) and the mean volume of RBC distribution width-standard deviation (RDW-SD) was significantly higher for the patients compared with the controls. There were no significant differences, using the t-test, for the mean platelet counts and mean platelets volume (MPV) between the patients and the controls. On the other hand, using the Mann-Whitney U test, the MCH and RDW-coefficient of variation (RDW-CV) percents for the

patients were significantly higher compared to the same for the controls. There was no significant difference, using the Mann-Whitney U test, for the mean corpuscular volume (MCV) for the patients compared to the controls.

Using the t-test (Table 7), the mean cholesterol and low-density lipoprotein (LDL) concentrations for the patients with SZ were significantly lower as compared to the healthy controls. On the other hand, there were no significant differences between the patients and control group for the mean high-density lipoprotein (HDL) concentrations. Compared to the respective levels for the controls, using the Mann-Whitney U test, the patients had significantly lower cholesterol:HDL and LDL:HDL concentrations, while there were no significant difference for the mean triglycerides (TG) and TG:HDL concentrations between the groups.

Discussion

To the best of authors' knowledge, this is the first study to measure the CRP and IL-4 concentrations, differential CBC, and the lipid profile in Saudi patients with SZ and to compare these parameters with the healthy controls. There is only one research study [9] that measured the concentrations of TNF-α, IL-6, and IFN-γ in patients with SZ.

The mean weight and BMI for the patients was significantly lower as compared to the healthy controls. These results are in contradiction with the previous findings by other researchers [20,21] who found that patients with SZ are more likely to have an overweight or obese BMI as compared to the healthy controls. Additionally, other studies [22,23] found no significant difference for the BMI between the patients and controls, in disagreement with the current findings. On the other hand, in agreement with the current results, a study from USA [24] found lower BMI ($p < 0.01$) for patients with SZ as compared to healthy subjects.

The mean CRP, IL-6, IL-4, TNF-α, and IFN-γ concentrations showed no significant differences between patients with SZ

Table 1. *Comparison of the mean age, weight, height, and the BMI for the patients and controls. The results for the mean BMI for the patients have been previously reported.*[19]

Parameters	Groups	N	Min	Max	Mean	±SD	±SE	*p*-value
Age (year)	Control	29	28	47	36	5	1	0.049[S]
	Patient	45	28	47	38	4	1	
Weight (kg)	Control	29	58	120	84	17	3	0.001[HS]
	Patient	45	50	110	71	15	2	
Height (cm)	Control	29	160	184	173	6	1	0.103[NS]
	Patient	44	155	188	171	8	1	
Mean BMI (kg/m²)	Control	29	19.3	42.5	28.2	5.8	1	0.007[HS]
	Patient	45	16.1	37.2	24.6	5.1	0.7	

t-test was used for the significance testing
HS: Highly significant ($p < 0.01$); NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$).

Table 2. *Characteristics of the patients with SZ and the control subjects.*

Factors	Controls N (%)	Patients N (%)
Number of subjects	29%	45%
Duration of illness		32 (100%)
1-10 years	-	17 (53%)
11-20 years	-	13 (41%)
21-30 years	-	2 (6%)
Education		
Elementary/middle	-	14 (31%)
High school	2 (7%)	19 (42%)
College/diploma	27 (93%)	12 (27%)
Employment status		
Unemployed	-	31 (69%)
Employed	29 (100%)	7 (16%)
Retired	-	7 (16)
Marital status		
Single	-	34 (76%)
Married	29 (100%)	5 (11%)
Divorced	-	6 (13%)
Smoking		
Yes	8 (29%)	36 (80%)
No	20 (71%)	9 (20%)
Substance abuse		
Yes	-	29 (64%)
No	-	16 (36%)
Family history of mental disorders		
Yes	1 (3%)	16 (36%)
No	28 (97%)	29 (64%)

and healthy subjects. These results are in contradiction with the findings of previous researchers [3,4,9,10,25,26] who reported significantly abnormal levels of serum CRP, IL-6, IL-4, TNF-α, and IFN-γ in patients with SZ when compared to the healthy subjects. On the other hand, the current findings are in agreement with those of Okasha et al.[27], and Hope et al.[28] where the levels of CRP for patients with SZ showed no significant differences with that of controls.

It has been shown [29,30] that a higher weight or BMI is related to a higher level of inflammation in the body and conversely lower weight or BMI is associated with a lower level of inflammation. In addition, it has been found [31-33] that patients with SZ show significant differences in the levels of cytokines before and after treatment with antipsychotic medications. The current results do not support the presence of an inflammatory condition in patients with SZ due to the unchanged levels of CRP, IL-6, IL-4, TNF-α, and IFN-γ compared to the controls. These findings may be explained by the fact that the patients had lower BMI compared to the controls, all had chronic SZ, were taking antipsychotic medications, and were all hospitalized (thus, medication compliance was high), which are all factors that may be associated with a lower inflammatory status.

The significantly lower mean basophil count in the patients is the only difference between the patients and the controls for the counts of WBC and their types. When the counts of basophil are less than the normal range in the blood, this condition is known as basopenia. [34] Reductions in the counts of basophil cells is found in acute hypersensitivity, acute stress, hyperthyroidism, and anxious depression. [34,35] Therefore, the patients of the current study may be more

Table 3. *Comparison of the mean concentrations of CRP and cytokines for the controls and the patients.*

Parameters	Groups	N	Mean	±SD	±SE	p value
CRP[ab] (ng/ml)	Control	27	5.47	6.02	1.16	0.682[NS]
	Patient	23	6.41	7.56	1.57	
IL-6[ab] (pg/ml)	Control	26	2.59	7.08	1.39	0.239[NS]
	Patient	25	1.72	2.85	0.57	
IL-4[A] (pg/ml)	Control	26	0.13	0.06	0.01	0.966[NS]
	Patient	24	0.13	0.07	0.01	
TNF-α[ab] (pg/ml)	Control	29	1.98	4.58	0.85	0.862[NS]
	Patient	26	1.89	3.20	0.62	
IFN-γ[ab] (pg/ml)	Control	27	16.3	32.2	6.20	0.112[NS]
	Patient	21	7.77	15.1	3.30	

[A]*t*-test and [ab]Mann-Whitney *U* test were used for the significance testing
NS: Not significant ($p > 0.05$).

Table 4. *Mean total and differential WBC counts in patients and controls.*

Cells	Groups	Cell count (×10³/µl)				Cell%		
		N	Mean	±SD	p value	Mean	±SD	p value
WBC	Control	29	6.83	1.90	0.372[NS]	-	-	-
	Patient	45	7.26	2.07		-	-	
Lymphocyte	Control	29	2.81	0.78	0.585[NS]	42.4	10.9	0.099[NS]
	Patient	45	2.71	0.80		38.3	10.1	
Monocyte	Control	29	0.59	0.24	0.154[NS]	8.65	2.56	0.225[NS]
	Patient	45	0.67	0.22		9.41	2.64	
Neutrophil	Control	29	3.10	1.30	0.147[NS]	45.5	10.8	0.141[NS]
	Patient	45	3.61	1.57		48.6	11.0	
Eosinophil	Control	26	0.25	0.20	0.928[NS]	3.53	2.08	0.864[NS]
	Patient	42	0.26	0.16		3.62	2.07	
Basophil	Control	26	0.07	0.03	0.000[HS]	1.18	0.58	0.000[HS]
	Patient	42	0.02	0.01		0.29	0.10	

The *t*-test was used for the significance testing.
HS: Highly significant ($p < 0.01$); NS: Not significant ($p > 0.05$)

Table 5. *Mean differential WBC and platelets ratios in patients and controls.*

Ratios	Groups	Count (×10³/µl)				Cell%		
		N	Mean	±SD	p value	Mean	±SD	p value
NLR[A]	Control	29	1.18	0.61	0.108[NS]	1.20	0.60	0.137[NS]
	Patient	45	1.46	0.76		1.45	0.76	
MLR[A]	Control	29	0.21	0.08	0.075[NS]	0.21	0.08	0.072[NS]
	Patient	45	0.27	0.14		0.27	0.13	
BLR[A]	Control	26	0.02	0.01	0.000[HS]	0.47	0.29	0.000[HS]
	Patient	42	0.00	0.00		0.00	0.00	
ELR[A]	Control	26	0.09	0.06	0.766[NS]	1.33	0.84	0.000[HS]
	Patient	42	0.09	0.05		0.09	0.05	
PLR[ab]	Control	29	103	34.3	0.876[NS]	-	-	-
	Patient	45	111	49.8		-	-	

[A]*t*-test and [ab]Mann-Whitney *U* test were used for the significance testing.
HS: Highly significant ($p < 0.01$); NS: Not significant ($p > 0.05$).

prone to basopenia due to their underlying condition. The present study is the first to find a low count of basophil, BLR, and ELR for patients with SZ, therefore we were unable to compare the current results with those of others. It may be assumed that the low count of basophil cells in patients with SZ may be due to stress and anxiety as found previously in patients with anxious depression. [35] Additionally, a low count of eosinophil cells was found in acute stress conditions. [34] Therefore, further studies with a larger number of patients may lead to the finding of lower eosinophil counts, in addition to the current finding of lower basophil counts in patients, since the ELR was lower for them.

For the lipid profile, there were significantly lower concentrations for the mean cholesterol, LDL, cholesterol:HDL, and LDL:HDL ratios for the patients compared to the levels for the controls. On the other hand, mean TG and TG:HDL ratio showed no significant differences between patients with SZ and healthy subjects. These results disagree with the previous studies that found higher levels of cholesterol, TG, LDL, cholesterol:HDL, and LDL:HDL, and low levels of HDL [18,25,36,37] for patients with SZ as compared to healthy subjects. Additionally, the current results are contradictory with those of previous studies that found no significant differences for the levels of cholesterol and LDL [25,37] for patients with SZ compared to healthy controls. Finally, the current results

Table 6. *Mean hemoglobin concentrations and RBC and platelets counts and indices in patients and controls.*

Parameters	Groups	N	Mean	±SD	±SE	p value
RBC[A] (×10^6/µl)	Control	29	5.47	0.57	0.11	0.000[HS]
	Patient	45	5.00	0.50	0.12	
Hemoglobin[A] (g/dl)	Control	29	14.7	1.15	0.25	0.045[S]
	Patient	45	14.1	1.35	0.47	
Platelets[A] (×10^3/µl)	Control	29	274	58.6	17.9	0.862[NS]
	Patient	45	277	85.4	25.3	
HCT[A] (%)	Control	29	44.7	3.3	0.61	0.000[HS]
	Patient	45	41.9	3.5	0.52	
MCV[ab] (fl)	Control	29	82.2	6.20	1.15	0.102[NS]
	Patient	45	84.2	6.89	1.02	
MCH[ab] (pg)	Control	29	27.1	2.33	0.43	0.005[HS]
	Patient	45	28.4	2.91	0.43	
MCHC[A] (g/dl)	Control	29	32.9	1.19	0.22	0.012[S]
	Patient	45	33.7	1.21	0.18	
RDW-CV[ab] (%)	Control	29	13.1	1.42	0.26	0.005[HS]
	Patient	45	14.6	1.83	0.27	
RDW-SD[A] (fl)	Control	22	38.5	3.17	0.67	0.007[HS]
	Patient	45	41.3	2.99	0.44	
MPV[A] (fl)	Control	28	9.83	1.45	0.27	0.059[NS]
	Patient	45	9.28	1.02	0.15	

[A]*t*-test and [ab]Mann-Whitney *U* test were used for the significance testing.
HS: Highly significant ($p < 0.01$); NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$).

Table 7. *Mean lipid profile and lipid ratios in patients and controls.*

Parameters (mg/dl)	Groups	N	Mean	±SD	±SE	p-value
Cholesterol[A]	Control	29	214	50	9	0.000[HS]
	Patient	43	161	40	6	
TG[ab]	Control	29	133	93	17	0.099[NS]
	Patient	42	109	75	12	
HDL[A]	Control	28	51.6	28.4	5.3	0.463[NS]
	Patient	20	46.6	12.8	2.8	
LDL[A]	Control	28	137	54.7	10.3	0.003[HS]
	Patient	19	92.7	35.7	8.2	
Cholesterol:HDL[ab]	Control	28	5.34	4.9	0.9	0.014[S]
	Patient	20	3.62	1.2	0.2	
TG:HDL[ab]	Control	28	3.40	3.7	0.7	0.391[NS]
	Patient	19	2.36	1.6	0.3	
LDL:HDL[ab]	Control	28	3.67	4.1	0.7	0.012[S]
	Patient	18	2.19	1.1	0.2	

[A]t-test and [ab]Mann-Whitney *U* test were used for the significance testing.
HS: Highly significant ($p < 0.01$); NS: Not significant ($p > 0.05$); S: Significant ($p \leq 0.05$)

agree with the previous studies that found no significant differences in the levels of TG and HDL [22,36,37] between patients with SZ and healthy subjects.

In summary, compared with the control subjects, patients with SZ had no differences in the CRP and cytokines levels, while they had significantly lower mean BMI, basophil, and BLR for counts and percents, and ELR percent. Additionally, patients had significantly lower mean RBC counts and hemoglobin and HCT concentrations compared to the controls, which may indicate the prevalence of anemia among the patients. Significantly higher mean RDW (indicating the presence of inflammation) were found for the patients in the current results compared with controls, which agree with previous findings.[38] Significantly higher or lower mean MCH concentration and MCHC were found in the patients compared with the same in controls. Finally, significantly lower mean cholesterol and LDL concentrations, and cholesterol:HDL and LDL:HDL ratios were found for patients with SZ compared to the same for the controls.

Conclusion

It may be concluded that patients with SZ in the Saudi Arabian population have dyslipidemia with minimal alterations in the immune system cells count and the levels of inflammatory biomarkers. These findings may be attributed to the fact that the patients have lower BMI, good dietary lifestyle, and compliance to the medication.

Limitations of the study

This study is a single-center study with a small sample size, thus lesser generalizability. The number of control subjects included in the present study was even lesser than the patients due to difficulties encountered in recruitment related to the ongoing COVID-19 epidemic and the refusal of many prospective control subjects to fast for 10 hours for the lipid profile. It is recommended that future large-scale studies should be carried out to measure the levels of stress and anxiety and thyroid hormones in patients with SZ, since they have been linked to lower basophil counts, as also found in the current study.

List of Abbreviations

BLR — Basophil-lymphocyte ratio
BMI — Body mass index
CBC — Complete blood count
CRP — C-reactive protein
ELR — Eosinophil-lymphocyte ratio
HCT — Hematocrit
HDL — High density lipoprotein
IFN-γ — Interferon-γ
IL-4 — Interleukin
LDL — Low density lipoprotein
MCHC — Mean corpuscular hemoglobin concentration
MCV — Mean corpuscular volume
MPV — Mean platelets volume
MLR — Monocyte-lymphocyte ratio
NLR — Neutrophil-lymphocyte ratio
PLR — Platelets-lymphocyte ratio
RDW-CV — RDW-coefficient of variation
RBC — Red blood cell
SZ — Schizophrenia
TG — Triglycerides
TNF-α — Tumor necrosis factor-α
WBC — White blood cells

Authors' contributions
RAA, SHM: Conception and design of study, acquisition and analysis of data, drafting of the manuscript with critical intellectual input and approval of the final version of the manuscript to be published.

Authors' Details
Razan Ahmed Alyoubi[1], Sawsan Hassan Mahassni[1]
1. Department of Biochemistry, Faculty of Science, King Abdulaziz University, Jeddah, Saudi Arabia

References
1. World Health Organization. Schizophrenia. 2019. [cited 2020 Dec 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia
2. King Salman Center for Disability Research. Saudi national mental health survey: 2019; technical report. [cited 2020 Nov 23]. Available from: http://www.healthandstress.org.sa/
3. Miller BJ, Kandhal P, Rapaport MH, Mellor A, Buckley P. Total and differential white blood cell counts, high-sensitivity C-reactive protein, and cardiovascular risk in non-affective psychoses. Brain Behav Immun. 2015;(45):28–35. https://doi.org/10.1016/j.bbi.2014.12.005
4. Shahraki A, Sarabandi R, Kianpour M, Zakeri Z. Elevated serum interleukin-23 and interleukin-6 levels in schizophrenic patients compared to those in healthy controls. Shiraz E-Med J. 2016;17(6):e38984. https://doi.org/10.17795/semj38984
5. Windgassen EB, Funtowicz L, Lunsford TN, Harris LA, Mulvagh SL. C-reactive protein and high-sensitivity C-reactive protein: an update for clinicians. Postgrad Med. 2011;123(1):114–9. https://doi.org/10.3810/pgm.2011.01.2252
6. Fond G, Lançon C, Auquier P, Boyer L. C-reactive protein as a peripheral biomarker in schizophrenia. An updated systematic

review. Front Psychiatry. 2018;(9):392–404. https://doi.org/10.3389/fpsyt.2018.00392

7. Opal SM, DePalo VA. Anti-inflammatory cytokines. CHEST. 2000;117(4):1162–72.

8. O'Brien SM, Scully P, Dinan TG. Increased tumor necrosis factor-alpha concentrations with interleukin-4 concentrations in exacerbations of schizophrenia. Psychiatry Res. 2008;160(3):256–62. https://doi.org/10.1016/j.psychres.2007.11.014

9. Al-Asmari AK, Khan MW. Inflammation and schizophrenia: alterations in cytokine levels and perturbation in antioxidative defense systems. Hum Exp Toxicol. 2013;33(2):115–22. https://doi.org/10.1177/0960327113493305

10. Al-Hakeim HK, Al-Rammahi DA, Al-Dujaili AH. IL-6, IL-18, sIL-2R, and TNFα proinflammatory markers in depression and schizophrenia patients who are free of overt inflammation. J Affect Disord Rep. 2015;(182):106–14. https://doi.org/10.1016/j.jad.2015.04.044

11. Fawzi MH, Fawzi MM, Fawzi MM, Said NS. C-reactive protein serum level in drug-free male Egyptian patients with schizophrenia. Psychiatry Res. 2011;190(1):91–7. https://doi.org/10.1016/j.psychres.2011.05.010

12. Wasti A, Zahid S, Ahmed N. Antipsychotic drugs induced iron deficiency anemia in schizophrenic patients. Int J Adv Res. 2013;1(10):111–8.

13. Rao D. Overview and compartmentalization of the immune system. Chapter 19. In: Hematology: Basic Principles and Practice. 7th Ed. Elsevier BV. 2018;199–209.

14. Lind L. Circulating markers of inflammation and atherosclerosis. Atherosclerosis. 2003;169(2):203–14. https://doi.org/10.1016/s0021-9150(03)00012-1

15. Gao K, Zhu W, Liu W, Ma D, Li H, Yu W, et al. The predictive role of monocyte-to-lymphocyte ratio in osteoporosis patient. Medicine. 2019;98(34):e16793. https://doi.org/10.1097/MD.0000000000016793

16. Mazza MG, Lucchi S, Rossetti A, Clerici M. Neutrophil-lymphocyte ratio, monocyte-lymphocyte ratio and platelet-lymphocyte ratio in non-affective psychosis: a meta-analysis and systematic review. World J Biol Psychiatry. 2019;21(5):326–38. https://doi.org/10.1080/15622975.2019.1583371

17. Perica MM, Delaš I. Essential fatty acids and psychiatric disorders. Nutr Clin Pract. 2011;26(4):409–25. https://doi.org/10.1177/0884533611411306

18. Gohar SM, Dieset I, Steen NE, Mørch RH, Iversen TS, Steen VM, et al. Association between serum lipid levels, osteoprotegerin and depressive symptomatology in psychotic disorders. Eur Arch Psychiatry Clin Neurosci. 2019;269(7):795–802. https://doi.org/10.1007/s00406-018-0897-z

19. Mahassni S, Alyoubi R. Overweight and obesity in Saudi patients with schizophrenia affects cholesterol concentration and some immune system cells. Asian J Immunol. 2021;5(3):1–14. https://journalaji.com/index.php/AJI/article/view/59

20. Subramaniam M, Lam M, Guo ME, He VYF, Lee J, Verma S, et al. Body mass index, obesity, and psychopathology in patients with schizophrenia. J Clin Psychopharmacol. 2014;34(1):40–6. https://doi.org/10.1097/JCP.0000000000000058

21. Cameron IM, Hamilton RJ, Fernie G, MacGillivray SA. Obesity in individuals with schizophrenia: a case-controlled study in Scotland. BJPsych Open. 2017;3(5):254–6. https://doi.org/10.1192/bjpo.bp.116.003640

22. Petrikis P, Tigas S, Tzallas AT, Papadopoulos I, Skapinakis P, Mavreas V. Parameters of glucose and lipid metabolism at the fasted state in drug-naïve first-episode patients with psychosis: evidence for insulin resistance. Psychiatry Res. 2015;229(3):901–4. https://doi.org/10.1016/j.psychres.2015.07.041

23. Garcia-Rizo C, Casanovas M, Fernandez-Egea E, Oliveira C, Meseguer A, Cabrera B, et al. Blood cell count in antipsychotic-naive patients with non-affective psychosis. Early Interv Psychiatry. 2019;13(1):95–100. https://doi.org/10.1111/eip.12456

24. Moody G, Miller BJ. Total and differential white blood cell counts and hemodynamic parameters in first-episode psychosis. Psychiatry Res. 2018;(260):307–12. https://doi.org/10.1016/j.psychres.2017.11.086

25. Chow V, Reddel C, Pennings G, Scott E, Pasqualon T, Ng AC, et al. Global hypercoagulability in patients with schizophrenia receiving long-term antipsychotic therapy. Schizophrenia Res. 2015;162(1–3):175–82. https://doi.org/10.1016/j.schres.2014.12.042

26. Jacomb I, Stanton C, Vasudevan R, Powell H, O'Donnell M, Lenroot R, et al. C-reactive protein: higher during acute psychotic episodes and related to cortical thickness in schizophrenia and healthy controls. Front Immunol. 2018;(9):2230. https://doi.org/10.3389/fimmu.2018.02230

27. Okasha T, Elgamel O, Ashry H. Acute phase reactants (Proteins) in schizophrenia. Curr Psychiatr. 2006;13(1):71–8. https://doi.org/10.1016/s0165-1781(96)02915-0

28. Hope S, Melle I, Aukrust P, Steen NE, Birkenaes AB, Lorentzen S, et al. Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor. Bipolar Disord. 2009;11(7):726–34. https://doi.org/10.1111/j.1399-5618.2009.00757.x

29. Mahassni SH. Overweight and obesity and the immune system, lipids and C-reactive protein in young and middle-aged Saudi female University worker. J Biochem Technol. 2020;11(1):49-56.

30. Mahassni SH, Bashanfar NO. High levels of inflammatory adipokines and C-reactive protein, and minimal changes in immune cells in overweight and obese Saudi female University students. Int IJPRAS. 2019;8(1):171–83.

31. Borovcanin M, Jovanovic I, Radosavljevic G, Dejanovic SD, Stefanovic V, Arsenijevic N, et al. Antipsychotics can modulate the cytokine profile in schizophrenia: attenuation of the type-2 inflammatory response. Schizophrenia Res. 2013;147(1):103–9. https://doi.org/10.1016/j.schres.2013.03.027

32. Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, et al. Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia. Psychopharmacology. 2014;231(2):319–25. https://doi.org/10.1007/s00213-013-3382-4

33. Ding M, Song X, Zhao J, Gao J, Li X, Yang G, et al. Activation of Th17 cells in drug naïve, first episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2014;(51):78–82. https://doi.org/10.1016/j.pnpbp.2014.01.001

34. Porwit A, McCullough J, Erber W. Blood and bone marrow pathology. 2nd ed. London, UK: Churchill Livingstone; 2011 257 p.

35. Baek JH, Kim H, Fava M, Mischoulon D, Papakostas GI, Nierenberg A, et al. Reduced venous blood basophil count and anxious depression in patients with major depressive

disorder. Psychiatry Investig. 2016;13(3):321–6. https://doi.org/10.4306/pi.2016.13.3.321

36. Mhalla A, Bel Hadj Salah W, Mensi R, Amamou B, Messaoud A, Gassab L, et al. Lipid profile in schizophrenia: case control study. Tunis Medicale. 2018;96(1):22–9.

37. John S, Dharwadkar K, Motagi MV. Study on association between lipid profile values and psychiatric disorders. J Clin Diagn Res JCDR. 2014;8(12):WC04–WC6. https://doi.org/10.7860/JCDR/2014/10383.5301

38. Ayyildiz H, Karabulut N, Kalayci M. Relationship between red blood cell distribution width and schizophrenia. Int J Med Biochem. 2018;1(1):15–9. https://doi.org/10.14744/ijmb.2017.32042