Apolipoprotein serum levels related to metabolic syndrome in patients with schizophrenia

Anastasiia S. Boiko [a], Irina A. Mednova [a], Elena G. Kornetova [a,f], Arkadiy V. Semke [a], Nikolay A. Bokhan [a,b,f], Anton J.M. Loonen [c,d,*], Svetlana A. Ivanova [a,e,f]

[a] Mental Health Research Institute, Tomsk National Research Medical Center of the Russian Academy of Sciences, Aleutskaya str., 4, Tomsk, Russian Federation
[b] National Research Tomsk State University, Lenin Avenue, 36, Tomsk, Russian Federation
[c] University of Groningen, Groningen Research Institute of Pharmacy, PharmacoTherapy, Epidemiology &Economics, Antonius Deusinglaan 1, 9713 AV, Groningen, the Netherlands
[d] GGZ Westelijk Noord-Brabant, Hoofdlaan 8, 4661 AA, Halsteren, the Netherlands
[e] National Research Tomsk Polytechnic University, Lenin Avenue, 30, Tomsk, Russian Federation
[f] Siberian State Medical University, Moscowsky Trakt, 2, Tomsk, Russian Federation

A B S T R A C T

Background: Schizophrenia is associated with a lowered life expectancy due to cardiovascular disease. This is, at least in part, related to an increased vulnerability to the development of metabolic syndrome (MetS) in patients with schizophrenia. The dysregulation of apolipoproteins (Apos) may also play a role in the pathogenesis of schizophrenia via their effect on cerebral cholesterol processing.
Aim: The aim of this study was to investigate serum Apos A1, C3, E, A2 and C2 concentration in schizophrenia patients with or without MetS in comparison to healthy donors.
Methods: After obtaining informed consent, 53 patients with a diagnosis of paranoid schizophrenia according to ICD-10 criteria (F20) were included. Patients were divided into two groups with (N = 26) and without (N = 27) MetS according to the criteria of the International Diabetes Federation. The control group included 20 mentally and physically healthy subjects. Serum Apos A1, A2, C2, C3 and E were measured using xMAP technology (Luminex).
Results: Serum ApoA1 was significantly decreased in patients with schizophrenia compared to healthy subjects (p = 0.002); ApoA2 was lower in patients without MetS in comparison to patients with MetS (p = 0.017) and the levels of ApoC3 and ApoC2 were increased in patients with schizophrenia with MetS in comparison with the control group and also with patients without MetS. No other significant differences were established concerning the other assayed apolipoproteins.
Conclusions: In line with literature data the results of our study suggest that while disturbances in ApoA1 level may play a role in the pathogenesis of schizophrenia, ApoA2, ApoC2, ApoC3 and ApoE may be primarily related to metabolic imbalance.

1. Introduction

Schizophrenia is, without doubt, one of the most important severe mental illnesses (SMIes), and with a median life time prevalence of 6.35 per 1000 persons (25% quartile: 4.10; 75% quartile: 8.72) is among the top 15 leading causes of disability worldwide [1]. Considering 11 studies including 302,691 patients from all inhabitant continents (except for South America) the average for years of potential life lost amounted to 14.5 (95% CI 11.2–17.8) and the average life expectancy was 64.7 years (95% CI 61.1–68.3) [2]. Cardiovascular diseases form a major contributor to the excess of mortality in patients with schizophrenia; a meta-analysis of 13 studies involving over 3.5 million participants found a pooled relative risk for the incidence of cardiovascular disease of 1.53 (CI95% 1.27–1.86) for schizophrenia in comparison with the reference group [3]. Metabolic syndrome (MetS) is generally considered to be a major predictor of cardiovascular disease [4]. In the general population, a diagnosis of MetS has a relative risk of 2-fold for cardiovascular disease over 5–10 years and at least a 5-fold risk for type 2 diabetes [4]. In

patients with schizophrenia the overall rate of MetS was 32.5% (95% CI 30.1%–35.0%); there were only minor differences according to treatment setting (inpatient vs outpatient) and by country of origin; there were no appreciable difference between males and females [5]. Older age, and particularly illness durations, had a strong influence on the prevalence of MetS [5]. This can be related to the usage of psychotropic drugs such as clozapine and second generation antipsychotics. In drug-naïve patients with schizophrenia and related disorders the MetS rate is about 10% [6, 7], while this was found to be about 52% in patients using clozapine [5]. The usage of other antipsychotics is also associated with an increased risk of MetS [5, 8, 9, 10]. Olanzapine appears to have the highest rate of risk, and aripiprazole the lowest [10]. This may correspond to the observed association between their use and type 2 diabetes mellitus in population-based studies [9]. Dyslipidemia (a decreased high density lipoprotein (HDL)-cholesterol and elevated triglycerides), is a major component of MetS [4], which is commonly seen in patients with schizophrenia [5]. Treatment with antipsychotics is associated with these lipid abnormalities and an increased risk of diabetes [6, 11]. In addition, over 20% of the treatment-naïve schizophrenia patients and first-episode patients have a lowered HDL-cholesterol level and a glucose dysregulation/insulin resistance [6, 12]. This percentage corresponds to the figure of 144 un-medicated and antipsychotic-naïve German patients with first episode psychosis (20.2%; 95% CI 13.5%–28.3%), which was higher than in 3995 control persons (13.3%; 95% CI 12.2%–14.4%). It is highly likely, therefore, that the high rate of cardiovascular disorder in patients with schizophrenia is partly associated to a disease-related dyslipidemia which also increases their vulnerability to the effects of treatment with certain antipsychotics. Finding a biomarker which can predict this increased vulnerability could be an important facilitator in selecting the best treatment for these patients.

Cholesterol has an essential role in determining the structure and function of the neuronal system of the brain [13]. Due to its incapacity to pass through the blood-brain barrier, all cerebral cholesterol is synthetized locally by glia cells; this also makes recycling of neuronal cholesterol of critical importance [13]. Apolipoproteins (Apos) have an essential role for lipid transport, peripherally by being the protein component of lipoproteins, but probably also within the central nervous system (CNS). Some of these proteins, such as ApoE (which is found in all plasma lipoproteins), are synthetized mainly within the brain, while others, such as ApoA1 is synthetized peripherally and crosses the blood-brain barrier [13]. The potential role of Apos in both dyslipidemia and cerebral neuronal functioning in schizophrenia make these proteins good candidates for the study of their potential as MetS biomarkers in patients with this disorder.

The major apolipoproteins include ApoE, ApoB, ApoA1, ApoA2, ApoA4, ApoC1, ApoC2, and ApoC3 [14]. ApoA1 is the most important protein component of HDL particles in plasma. This protein, as a component of HDL particles, enables efflux of fat molecules by accepting fats from within cells for transport. ApoA1 is often used as a biomarker for the prediction of cardiovascular diseases. ApoA2 is the second most abundant protein of the high density lipoprotein particles and appears to be a key regulatory factor of HDL metabolism [15]. ApoC2 is a small exchangeable apolipoprotein found on triglyceride-rich lipoprotein particles, such as chylomicrons and very low-density lipoproteins (VLDL), as well as on HDL, particularly during fasting. ApoC2 plays a critical role in triglyceride-rich lipoprotein metabolism by acting as a cofactor of lipoprotein lipase; this is the main enzyme which hydrolyses these triglycerides [16]. ApoC3 also has a critical role in the metabolism of triglyceride-rich lipoproteins; there is evidence supporting this apolipoprotein as an emerging target for hypertriglyceridemia and associated cardiovascular disorders [17]. ApoE is a fat-binding protein that is part of the chylomicron and intermediate-density lipoprotein (IDL) and are essential for the normal processing (catabolism) of triglyceride-rich lipoproteins. In peripheral tissues, ApoE is produced primarily by the liver and macrophages and mediates cholesterol metabolism. In the central nervous system, ApoE is mainly produced by astrocytes and transports cholesterol to neurons via ApoE receptors which are members of the low density lipoprotein receptor gene family. ApoE is the principal cholesterol carrier in the brain [18]. In humans, ApoE exists in three different isoforms: ε2, ε3 and ε4. ApoE ε3 is the most common isoform, while the ε4 isoform confers the greatest genetic risk for Alzheimer's disease. The mechanisms underlying exactly how ApoE contributes to the pathogenesis of this disease, however, are still being debated [19].

The aim of our study is to investigate serum apolipoprotein A1, A2, C2, C3, and E concentration in schizophrenia patients with or without metabolic syndrome and to compare these levels with those of healthy donors.

2. Materials & methods

2.1. Patients

This study was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki 1975, revised in Fortaleza, Brazil, 2013), established for experiments involving humans. We recruited patients from the Mental Health Research Institute Inpatient Department and Psychiatric Hospital located in Tomsk, Tomsk oblast (region) of Siberia, Russia. Recruitment started after the study was approved (protocol N187, 24.04.2018) by the Local Bioethics Committee of the Mental Health Research Institute. Each patient provided written informed consent after a proper explanation was given. The inclusion criteria were a clinical diagnosis of schizophrenia, according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10: F20) and an age of between 18 and 65. Symptom severity was measured with the Positive and Negative Syndrome Scale [20] at the beginning of the observation. Most patients received antipsychotic drugs in anti-relapse and maintenance dosages before admission to the clinic. They were often noncompliant, and were hospitalized in the clinic due to the exacerbation of schizophrenic symptoms.

Patients were divided into two groups, either with or without MetS, according to the criteria of the International Diabetes Federation IDF [4, 21]. According to these criteria, the metabolic syndrome is diagnosed in a patient with central obesity (waist circumference more than 94 cm in men, more than 80 cm in women) and the presence of any two of the following four signs:

- The concentration of triglycerides in serum is higher than 1.7 mmol/L (150 mg/dL), or lipid-lowering therapy is carried out.
- The concentration of high-density lipoprotein in serum is below 1.03 mmol/L (40 mg/dL) in men and 1.29 mmol/L (50 mg/dL) in women.
- The arterial blood pressure level is systolic above 130 mmHg or diastolic above 85 mmHg (or with treatment of previously diagnosed hypertension).
- Serum glucose concentration is greater than 5.6 mmol/L (100 mg/dL) (or previously diagnosed type 2 diabetes).

2.2. Control group

The control group consisted of persons who were recruited from a group of blood donors, hospital staff members, and students, on a voluntary basis. They reported on questioning to be mentally and somatically healthy individuals.

2.3. Blood sampling

Laboratory examination was conducted during the first days of hospitalization. Blood samples were drawn after an 8-h overnight fast into tubes with a clot activator (CAT) to isolate the serum (BD Vacutainer). Blood samples with CAT were centrifuged for 30 min at 2000×g at 4 °C to isolate the serum; the serum was stored at −20 °C (or – 80 °C) until analysis.

2.4. Multiplex analysis

Concentrations of Apos were determined on the MAGPIX multiplex analyzer (Luminex, USA) using xMAP® Technology. To determine the levels of five markers (ApoA1, ApoA2, ApoC2, ApoC3, ApoE) the standard panel APOMAG-62K by MILLIPLEX® MAP (Merck, Darmstadt, Germany) was used. System MILLIPLEX® MAP includes antibodies specific binding with the tests and conjugated with bits xMAP® using the minimum volume of the sample (25 µl). Magnetic bits are added to the test sample then biotinylated detectable antibodies are introduced into the reaction mixture. To complete the reaction, incubation with streptavidin peroxidase conjugate is carried out on each microsphere. Each individual microsphere is identified in a multiplex analyzer and the result of its biological analysis is quantified on the basis of fluorescent signals. The detected information is processed by specialist software (LuminexxPONENT®) with the subsequent export of data to program the MILLIPLEX® Analyst 5.1. Final results on serum apolipoprotein concentrations are presented in mg/dL.

2.5. Statistics

Statistical analyses were performed using the SPSS software for Windows, version 20.0. The data were tested for the normality of the distribution by the Shapiro-Wilk test. Between-group differences were evaluated using the Mann-Whitney U-test for independent samples with non-normal distribution. Results were expressed as median with 25%- and 75%-quartiles (Me [Q1; Q3]). P-values less than 0.05 were considered as significant.

3. Results

We included 53 patients with a diagnosis of paranoid schizophrenia and 25 healthy subjects (Table 1); all patients received antipsychotic treatment in anti-relapse and maintenance dosages before admission to the clinic. All patients were prescribed conventional and atypical antipsychotics for at least 6 weeks, 11 of them (20.8%) used haloperidol, 19 (35.8%) risperidone, 12 (22.6%) olanzapine, and 11 (20.8%) quetiapine. According to IDF-criteria, 26 patients had MetS and 27 patients were without it.

We found a significant decrease in the concentration of ApoA1 in the serum of patients with schizophrenia in comparison to healthy subjects (*p* = 0.002) (Table 2). ApoA2 was significantly decreased in patients without MetS in comparison to patients with MetS (*p* = 0.017) (Table 3). Analysis of the levels of other Apos revealed a significant increase of ApoC3 in patients with MetS in comparison to the controls (p = 0.001) and patients without MetS (p < 0.001). A similar situation was observed with respect to ApoC2: patients with MetS had significantly higher levels than the healthy subjects (p = 0.002) and those patients without MetS (p < 0.001). A significant increase in the level of ApoE was found in patients with MetS (p = 0.001), while at the first point of the study differences in

Table 1
Patient and healthy person characteristics.

	Healthy persons N = 25	Patients with schizophrenia N = 53	p-value
Age, Me [Q1; Q3] years (Min – Max)	31 [28; 41] (19–57)	35 [25.5; 42.5] (22–68)	0.410
Male, n (%)	14 (56%)	27 (51%)	0.109
Female, n (%)	11 (44%)	26 (49%)	
Duration of disease, Me [Q1; Q3] years	N/A	13.5 [4; 20.8]	
BMI, Me [Q1; Q3] value	26.4 [22.4; 31.45]	27 [23.1; 32.1]	0.2946
PANSS, Me [Q1; Q3] total score	N/A	102 [92; 109]	

Comparisons between groups were performed using χ2 test for sex and Mann-Whitney U-test for age. N/A, not applicable.

Table 2
Concentration of apolipoproteins (µg/dL) in the serum of patients with schizophrenia and healthy individuals (Me [Q1; Q3]).

	Healthy persons N = 25	Patients with schizophrenia N = 53	p-value
ApoA1, µg/dL	117.69 [48.81; 190.17]	51.95 [39.53; 66.68]	**0.002***
ApoA2, µg/dL	52.295 [41.835; 65.97]	43.47 [28.26; 68.26]	0.443
ApoC2, µg/dL	13.75 [10.89; 25.36]	20.17 [9.43; 36.3]	0.268
ApoC3, µg/dL	31.66 [23.16; 41.49]	42.55 [20.865; 67.59]	0.216
ApoE, µg/dL	4.655 [3.21; 6.12]	4.6 [3.59; 5.87]	0.911

Abbreviations: ApoA1, ApoA2, ApoC2, ApoC3, ApoE – apolipoproteins A1, A2, C2, C3, E.Comparisons between groups were performed using Mann-Whitney U-test. * - p < 0.05 – statistically significant difference (highlighted in bold).

Table 3
Concentration of apolipoproteins (µg/dL) in the serum of patients with metabolic syndrome and patients without it (Me [Q1; Q3]).

	Patients without MetS N = 27	Patients with MetS N = 26	p-value
ApoA1, µg/dL	55.23 [41; 73.75]	49.41 [37.12; 58.82]	0.266
ApoA2, µg/dL	37.9 [22.96; 60.51]	63.67 [32.6; 75.81]	**0.017***
ApoC2, µg/dL	12.56 [7.22; 20.95]	32.4 [19.955; 49.06]	**<0.001***
ApoC3, µg/dL	24.035 [10.585; 44.34]	59.86 [39.205; 95.13]	**<0.001***
ApoE, µg/dL	4.36 [2.41; 5.33]	5.03 [4.05; 6.03]	0.075

Abbreviations: MetS – metabolic syndrome; ApoA1, ApoA2, ApoC2, ApoC3, ApoE – apolipoproteins A1, A2, C2, C3, E.Comparisons between groups were performed using Mann-Whitney U-test. * – p < 0.05 – statistically significant difference (highlighted in bold).

the groups were at the level of statistical trends. No other significant differences were established concerning the other assayed apolipoproteins.

4. Discussion

Of particular importance may be our finding that serum ApoA1 is significantly lower in patients with schizophrenia in comparison to healthy blood donors, but that the levels barely differ between patients with and without MetS. ApoA1 is the major protein component of HDL [15, 22]; it is believed to be synthetized peripherally and to enter the brain by crossing the blood-brain barrier [13]. Concerning the lowered levels in schizophrenia, our results correspond to literature data [23, 24, 25, 26, 27]. Previous studies have, as far as we know, never discriminated between patients with and without MetS. All our patients with schizophrenia were using antipsychotics and had already been ill for a considerable number of years: this suggests that ApoA1 is primarily associated with a component of the schizophrenic disease process and therefore not with the likelihood of antipsychotic drug-induced MetS. Venkatasubramanian et al. have observed that serum HDL has a significant inverse correlation with negative symptoms in 60 antipsychotic-naïve patients with schizophrenia [28]. The mechanism involved is entirely unknown. Lowered levels of ApoA1 may play a role in the pathogenesis of multiple sclerosis because ApoA1 acts as an anti-inflammatory factor [29, 30]. Inflammation also plays a major role in the pathophysiology of schizophrenia [31, 32]. Study of the interaction between ApoA1, other anti-inflammatory mediators and pro-inflammatory cytokines in the pathogenesis of schizophrenia and MetS definitely deserve priority.

ApoA2 is the second most abundant protein in HDL, accounting for approximately 20% of total HDL protein [33, 34]. Similarly to ApoA1, it has potent anti-inflammatory effects [33], although high serum ApoA2

predicted MetS compared with low ApoA2 concentrations in an elderly Turkish population [34]. This corresponds to our findings, and as a matter of fact would indicate pro-inflammatory instead of anti-inflammatory effects [34]. This finding is not very surprising, as ApoA1 and ApoE are also known to have both pro- and anti-inflammatory effects depending on particular circumstances [35, 36, 37].

In our study, patients with MetS were found to have significantly higher serum ApoC2 and ApoC3 levels than those without MetS. The human ApoCs are found within chylomicrons (very low density lipoprotein, VLDL) and HDL and appear to play a complex role in the processing of triglycerides [38]. Our results correspond to those of Savinova et al. who compared 60 MetS subjects with a sample of 14 age- and sex-matched control subjects and found that total plasma - apoA1 was lower in metabolic syndrome patients in comparison with the healthy controls [39]. Song et al. observed that ApoC3 in particular correlated positively with coronary atherosclerosis (n = 224 with vs. 177 without) [40].

4.1. Strengths and limitations

To our knowledge this is the first paper in which patients with schizophrenia and with or without MetS are compared with healthy controls. As far as is comparable, our results largely correspond to what is found in the literature. The limitations are that we studied a rather restricted number of individuals, who were not characterized/analyzed with respect to the separate components of MetS, alcohol intake and current drug treatment (antipsychotics, lipid-lowering drugs, antidiabetics).

4.2. Conclusions

Our results suggest that disturbances in the level of Apo A1 play a role in the pathogenesis of schizophrenia as well as MetS, while the level of ApoC3 and ApoC2 can reflect the metabolic dis-balance and could be a novel biomarker to predict metabolic side effects associated with antipsychotic treatment. Future studies with a larger sample size, a well-defined control group and a longer study time duration could be of great clinical utility, particularly if these can predict antipsychotic-associated metabolic problems in patients who carry a higher cardiovascular risk. A correlation of serum or CSF ApoA1 levels with those of other pro- and anti-inflammatory mediators (considering specific clinical components), could give more insight into the pathophysiology of schizophrenia.

Declarations

Author contribution statement

Anastasiia S. Boiko: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data.

Irina A.Mednova, Elena G. Kornetova: Performed the experiments.

Arkadiy V. Semke, Nikolay A. Bokhan: Conceived and designed the experiments.

Anton J.M. Loonen: Analyzed and interpreted the data; Wrote the paper.

Svetlana A. Ivanova: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Competing interest statement

The authors declare no conflict of interest.

References

[1] B. Moreno-Kustner, C. Martin, L. Pastor, Prevalence of psychotic disorders and its association with methodological issues. A systematic review and meta-analyses, PLoS One 13 (2018), e0195687.

[2] C. Hjorthoj, A.E. Sturup, J.J. McGrath, M. Nordentoft, Years of potential life lost and life expectancy in schizophrenia: a systematic review and meta-analysis, Lancet Psychiatr 4 (2017) 295–301.

[3] Z. Fan, Y. Wu, J. Shen, T. Ji, R. Zhan, Schizophrenia and the risk of cardiovascular diseases: a meta-analysis of thirteen cohort studies, J. Psychiatr. Res. 47 (2013) 1549–1556.

[4] S.L. Samson, A.J. Garber, Metabolic syndrome, Endocrinol Metab. Clin. N. Am. 43 (2014) 1–23.

[5] A.J. Mitchell, D. Vancampfort, K. Sweers, R. van Winkel, W. Yu, M. De Hert, Prevalence of metabolic syndrome and metabolic abnormalities in schizophrenia and related disorders–a systematic review and meta-analysis, Schizophr. Bull. 39 (2013) 306–318.

[6] A.J. Mitchell, D. Vancampfort, A. De Herdt, W. Yu, M. De Hert, Is the prevalence of metabolic syndrome and metabolic abnormalities increased in early schizophrenia? A comparative meta-analysis of first episode, untreated and treated patients, Schizophr. Bull. 39 (2013) 295–305.

[7] S.M. Reddy, C.T. Goudie, M. Agius, The metabolic syndrome in untreated schizophrenia patients: prevalence and putative mechanisms, Psychiatr. Danub. 25 (Suppl 2) (2013) S94–S98.

[8] R. Bou Khalil, Atypical antipsychotic drugs, schizophrenia, and metabolic syndrome in non-Euro-American societies, Clin. Neuropharmacol. 35 (2012) 141–147.

[9] L. Hirsch, J. Yang, L. Bresee, N. Jette, S. Patten, T. Pringsheim, Second-generation antipsychotics and metabolic side effects: a systematic review of population-based studies, Drug Saf. 40 (2017) 771–781.

[10] D. Vancampfort, B. Stubbs, A.J. Mitchell, M. De Hert, M. Wampers, P.B. Ward, S. Rosenbaum, C.U. Correll, Risk of metabolic syndrome and its components in people with schizophrenia and related psychotic disorders, bipolar disorder and major depressive disorder: a systematic review and meta-analysis, World Psychiatr. 14 (2015) 339–347.

[11] M.Z. Liu, H.Y. He, J.Q. Luo, F.Z. He, Z.R. Chen, Y.P. Liu, D.X. Xiang, H.H. Zhou, W. Zhang, Drug-induced hyperglycaemia and diabetes: pharmacogenomics perspectives, Arch Pharm. Res. (Seoul) 41 (7) (2018) 725–736.

[12] S. Anjum, M. Bathla, S. Panchal, G.P. Singh, M. Singh, Metabolic syndrome in drug naïve schizophrenic patients, Diabetes Metab. Syndr. 12 (2) (2018) 135–140.

[13] A.G. Woods, I. Sokolowska, R. Taurines, M. Gerlach, E. Dudley, J. Thome, C.C. Darie, Potential biomarkers in psychiatry: focus on the cholesterol system, J. Cell Mol. Med. 16 (2012) 1184–1195.

[14] R.W. Mahley, T.L. Innerarity, S.C. Rall Jr., K.H. Weisgraber, Plasma lipoproteins: apolipoprotein structure and function, J. Lipid Res. 25 (12) (1984 Dec 1) 1277–1294.

[15] S.F. Maïga, A.D. Kalopissis, M. Chabert, Apolipoprotein A-II is a key regulatory factor of HDL metabolism as appears from studies with transgenic animals and clinical outcomes, Biochimie 96 (2014 Jan) 56–66.

[16] A. Wolska, R.L. Dunbar, L.A. Freeman, M. Ueda, M.J. Amar, D.O. Sviridov, A.T. Remaley, Apolipoprotein C-II: New findings related to genetics, biochemistry, and role in triglyceride metabolism, Atherosclerosis 267 (2017 Dec) 49–60.

[17] G.D. Norata, S. Tsimikas, A. Pirillo, A.L. Catapano, Apolipoprotein C-III: From pathophysiology to pharmacology, Trends Pharmacol. Sci. 36 (10) (2015 Oct) 675–687.

[18] R.M. Adibhatla, J.F. Hatcher, Altered lipid metabolism in brain injury and disorders, Subcell. Biochem. 49 (2008) 241–268.

[19] L. Mahoney-Sanchez, A.A. Belaidi, A.I. Bush, S. Ayton, The complex role of apolipoprotein E in Alzheimer's disease: an overview and update, J. Mol. Neurosci. 60 (3) (2016 Nov) 325–335.

[20] S.R. Kay, L.A. Opler, A. Fiszbein, The positive and negative syndrome Scale (PANSS) for schizophrenia, Schizophr. Bull. 13 (2) (1987) 261–276.

[21] K.G. Alberti, P. Zimmet, J. Shaw, Metabolic syndrome–a new world-wide definition. A consensus statement from the international diabetes federation, Diabet. Med. 23 (2006) 469–480.

[22] A. Jonas, A review of plasma apolipoprotein A-I interactions with phosphatidylcholines, Exp. Lung Res. 6 (1984) 255–270.

[23] J.T. Huang, L. Wang, S. Prabakaran, M. Wengenroth, H.E. Lockstone, D. Koethe, C.W. Gerth, S. Gross, D. Schreiber, K. Lilley, M. Wayland, D. Oxley, F.M. Leweke, Independent protein-profiling studies show a decrease in apolipoprotein A1 levels in schizophrenia CSF, brain and peripheral tissues, Mol. Psychiatry 13 (2008) 1118–1128.

[24] H. Mabrouk, H. Mechria, A. Mechri, I. Azizi, F. Neffati, W. Douki, L. Gaha, M.F. Najjar, Paraoxonase 1 activity and lipid profile in schizophrenic patients, Asian J. Psychiatr. 9 (2014) 36–40.

[25] J. Sasaki, G. Kumagae, T. Sata, M. Kuramitsu, K. Arakawa, Decreased concentration of high density lipoprotein cholesterol in schizophrenic patients treated with phenothiazines, Atherosclerosis 51 (1984) 163–169.

[26] F. Wen, J. Tan, Effects of phenothiazine drugs on serum levels of apolipoproteins and lipoproteins in schizophrenic subjects, Acta Pharmacol. Sin. 24 (2003) 1001–1005.

[27] Y.J. La, C.L. Wan, H. Zhu, Y.F. Yang, Y.S. Chen, Y.X. Pan, G.Y. Feng, L. He, Decreased levels of apolipoprotein A-I in plasma of schizophrenic patients, J. Neural Transm. 114 (2007) 657–663.

[28] G. Venkatasubramanian, R. Arasappa, N.P. Rao, R.V. Behere, S. Kalmady, B.N. Gangadhar, Inverse relationship between serum high density lipoprotein and negative syndrome in antipsychotic-naive schizophrenia, Clin. Chem. Lab. Med. 48 (2010) 95–98.

[29] L.A. Gardner, M.C. Levin, Importance of apolipoprotein A-I in multiple sclerosis, Front. Pharmacol. 6 (2015) 278.

[30] L. Meyers, C.J. Groover, J. Douglas, S. Lee, D. Brand, M.C. Levin, L.A. Gardner, A role for Apolipoprotein A-I in the pathogenesis of multiple sclerosis, J. Neuroimmunol. 277 (2014) 176–185.

[31] J. Kucerova, Z. Babinska, K. Horska, H. Kotolova, The common pathophysiology underlying the metabolic syndrome, schizophrenia and depression. A review, Biomed. Pap. Med. Fac 159 (2015) 208–214. Univ.Palacky Olomouc. Czech. Repub.

[32] B.E. Leonard, M. Schwarz, A.M. Myint, The metabolic syndrome in schizophrenia: is inflammation a contributing cause? J. Psychopharmacol. 26 (Suppl) (2012) 33–41.

[33] A.T. Remaley, Apolipoprotein A-II: still second fiddle in high-density lipoprotein metabolism? Arterioscler. Thromb. Vasc. Biol. 33 (2013) 166–167.

[34] A. Onat, G. Hergenç, E. Ayhan, M. Uğur, G. Can, Impaired anti-inflammatory function of apolipoprotein A-II concentrations predicts metabolic syndrome and diabetes at 4 years follow-up in elderly Turks, Clin. Chem. Lab. Med. 47 (2009) 1389–1394.

[35] M. Navab, G.M. Ananthramaiah, S.T. Reddy, B.J. Van Lenten, B.J. Ansell, S. Hama, G. Hough, E. Bachini, V.R. Grijalva, A.C. Wagner, Z. Shaposhnik, A.M. Fogelman, The double jeopardy of HDL, Ann. Med. 37 (3) (2005) 173–178.

[36] R. Namiri-Kalantari, F. Gao, A. Chattopadhyay, A.A. Wheeler, K.D. Navab, R. Farias-Eisner, S.T. Reddy, The dual nature of HDL: anti-Inflammatory and pro-Inflammatory, Biofactors 41 (3) (2015 May 6) 153–159.

[37] L. Guo, M.J. LaDu, L.J. Van Eldik, A dual role for apolipoprotein e in neuroinflammation: anti- and pro-inflammatory activity, J. Mol. Neurosci. 23 (3) (2004) 205–212.

[38] M.C. Jong, M.H. Hofker, L.M. Havekes, Role of ApoCs in lipoprotein metabolism: functional differences between ApoC1, ApoC2, and ApoC3, Arterioscler. Thromb. Vasc. Biol. 19 (3) (1999 Mar) 472–484.

[39] O.V. Savinova, K. Fillaus, L. Jing, W.S. Harris, G.C. Shearer, Reduced apolipoprotein glycosylation in patients with the metabolic syndrome, PLoS One 9 (2014), e104833.

[40] X. Song, S.P. Tian, H.Y. Ju, F. Zhang, Y.N. Li, F. Wu, L. Yang, Predictive value of apolipoprotein for coronary atherosclerosis in asymptomatic non-diabetic population, Zhongguo Yi XueKeXue Yuan XueBao 37 (2015) 55–60.