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ORIGINAL RESEARCH

Association Between ApoA1 Gene Polymorphisms and Antipsychotic Drug-Induced Dyslipidemia in Schizophrenia

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Purpose: Dyslipidemia frequently occurs in schizophrenia patients treated with antipsychotic drugs (APDs), especially atypical APDs. Apolipoprotein A1 (ApoA1) plays a key role in lipid metabolism. The aim of this study was to investigate whether ApoA1 gene polymorphisms are associated with APD-induced dyslipidemia in schizophrenia patients.

Patients and Methods: A total of 1987 patients with schizophrenia were enrolled in this study. Serum lipid profiles were determined with a biochemistry analyzer. Genotyping for the rs5072 polymorphism of ApoA1 was performed with TaqMan assay. Logistic regression analysis was carried out to evaluate the relationship between ApoA1 gene polymorphisms and APD-induced dyslipidemia. The effects of drug classification (typical vs atypical APD) and drug regimen (monotherapy vs combination therapy) on serum lipid levels were also analyzed.

Results: A significant association was found between rs5072 and triglyceride (TG) levels in the recessive model of the logistic regression analysis (adjusted odds ratio [OR]=1.50, 95% confidence interval [CI]: 1.03, 2.17; P<0.05). TG level was significantly higher in patients treated with combination therapy (1.03 (0.71, 1.51) mmol/l) compared to monotherapy (0.93 (0.67, 1.43) mmol/l) and was also associated with sex. There were significant differences in TG levels among the three genotypes of ApoA1 rs5072 (GG, GA, and AA) in the whole study population and in patients treated with atypical APDs.

Conclusion: The ApoA1 rs5072 variant is associated with dysregulated TG metabolism in schizophrenia patients treated with APDs, which may increase susceptibility to dyslipidemia.

Keywords: apolipoprotein A1, gene polymorphism, dyslipidemia, schizophrenia, antipsychotic drug

Introduction

Schizophrenia is a complex mental disorder characterized by positive and negative symptoms including delusions, hallucinations, thought disorder, apathy, and avolition as well as cognitive and functional impairment.[1,2] Schizophrenia affects approximately 1% of the world's population[1,3] and the lifetime risk of developing schizophrenia is ~0.7%.[4] Despite its relatively low prevalence, schizophrenia is a significant burden on the healthcare system; in 2016, the global disease burden of schizophrenia was 13.4 (95% uncertainty interval: 9.9–16.7) million years of life lived with disability.[5]

Antipsychotic drugs (APDs) are the first-line treatment for schizophrenia.[4] Chlorpromazine is a representative typical APD; atypical APDs include

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clozapine, olanzapine, risperidone, and quetiapine.[6] Although they are known to be effective in the treated of schizophrenia, these drugs—especially atypical APDs—can cause metabolic dysfunction including dyslipidemia, weight gain, insulin resistance, and glucose intolerance.[7] While monotherapy is the recommended regimen, given the complexity of the disease, combination therapy (ie, concurrent use of two or more APDs) is often prescribed.[8] However, this is associated with increased risks of metabolic syndrome and insulin resistance compared to treatment with a single drug,[9] although the underlying mechanisms are not known.

Dyslipidemia, which is among the most common side effects of APDs in schizophrenia patients,[10] is characterized by abnormal lipid levels such as increases in total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL-C).[11] As most schizophrenia patients require lifelong treatment, the risk of dyslipidemia is a major concern associated with APD maintenance treatment. Sterol regulatory element-binding protein has been implicated in dyslipidemia induced by atypical APDs.[12] Activation of hypothalamic AMP kinase via histamine H_1 receptor was shown to contribute to APD-induced weight gain through modulation of food intake.[13] Additionally, polymorphisms in the promoter region of the 5-HT_{2C} receptor gene were found to be closely related to weight gain in first-episode psychosis.[14]

Apolipoprotein (Apo) A1 is a key component of high-density lipoprotein (HDL), which is involved in reverse cholesterol transport and promotes cholesterol efflux from tissues and excretion in the liver.[15] ApoA1 level was reported to be reduced in schizophrenia patients compared to healthy subjects,[16] and was upregulated following treatment with APDs.[17] However, the precise role of ApoA1 in schizophrenia is poorly understood.

The occurrence of schizophrenia is strongly influenced by genetic factors.[4,18] ApoA1 is encoded by the ApoA1 gene located on chromosome 11q23, which is an area of interest in schizophrenia research;[19,20] single nucleotide polymorphisms (SNPs) of this gene have been identified in patients.[21,22] The present study investigated the relationship between ApoA1 gene polymorphisms and dyslipidemia induced by APDs in schizophrenia.

Patients and Methods

Subjects

A total of 1979 schizophrenia inpatients treated at Huai'an Third People's Hospital in Huai'an, China between 2010 and 2018 were enrolled in this study. Schizophrenia was diagnosed according to the Chinese Classification and Diagnosis of Mental Diseases 3rd Edition. Patients with cardiovascular or cerebral vascular disease, liver disease, nephropathy, and/or immunologic diseases were excluded. A standard questionnaire was administered to collect demographic data on schizophrenia patients such as sex, age, family history, etc. This study was approved by the Research Ethics Committee of Huai'an Third People's Hospital (approval no. 2018003) and was conducted in accordance with the principles of the Declaration of Helsinki. All patients signed the consent form after being informed of the study protocol.

Biochemical Measurements

Venous blood samples were collected from patients between 8 a.m. and 9 a.m. after a 12-h overnight fast. Serum TC, TG, LDL-C, and HDL-C levels were measured by enzymatic methods. ApoA1 and ApoB levels in blood samples were detected with a turbidimetric inhibition immunoassay performed with an Automatic Biochemical Analyzer (AU5800, Beckman Coulter, Inc., Brea, CA, USA).

SNP Selection

The ApoA1 gene (gene ID: 335) is located on chromosome 11q23.3 and spans 2.2 kb (116835751–116837950 bp). SNPs of the ApoA1 gene in the Chinese Han population from Beijing, China (CHB) were searched in the HapMap database. Tagging SNPs (tagSNPs) of ApoA1 were searched in the CHB data of HapMap (dbSNP b126); and 6 SNPs (rs5072, rs2070665, rs10750098, rs632153, rs12718462, and rs12718464) within the region from 2 kb upstream to 1 kb downstream of the ApoA1 gene along with the selected tagSNPs were searched in the Genome Variation Server 147 (http://gvs.gs.washington.edu/GVS147/). All selected tagSNPs met the following criteria: minor allele frequency ≥0.05 and linkage disequilibrium value of $r^2 \geq 0.8$. A candidate screening strategy was used to identify SNPs with functions in transcription, gene regulation, splicing, etc. using the Function Analysis and Selection Tool for Single Nucleotide Polymorphisms web server (http://fastsnp.ibms.sinica.edu.tw). One tagSNP, rs5072, was selected from the genotyping experiments for further analysis (Table S1).

DNA Isolating and Genotyping

Blood samples were collected in ethylenediaminetetraacetic acid-containing tubes. DNA was extracted from peripheral blood leukocytes by proteinase K digestion and the phenol-chloroform method. The TaqMan SNP Genotyping Assay was used for genotyping; we repeated the genotyping for 5% of samples (randomly selected) for quality control. The call rates of the SNPs were >99%.

Statistical Analysis

Data were analyzed with SPSS v19.0 software (SPSS Inc, Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the distribution of variables. Normally distributed data are presented as mean ± standard deviation and were analyzed with a two-tailed Student's *t* test. Quantitative variables with non-normal distribution are expressed as median and interquartile range, and comparisons between groups were performed with nonparametric tests. Categorical variables were analyzed with the chi-squared (χ^2) test or Fisher's exact test. Logistic regression analysis was carried out to evaluate the association between ApoA1 gene polymorphisms and dyslipidemia. A P value <0.05 was defined as statistically significant.

Results

Demographic and Clinical Characteristics of the Study Population

A total of 1979 inpatients (902 males [45.58%] and 1077 females [54.42%]) diagnosed with schizophrenia were included in this study; their demographic and clinical characteristics and biochemical data (serum lipids levels) are shown in Table 1. The mean age was 34.37±12.90 years. A total of 99 (5.00%) patients were treated with typical APDs; 1476 (74.58%) were treated with atypical APDs; and 404 (20.42%) were treated with a combination of typical and atypical APDs. In terms of treatment regimen, 57.91% of patients received antipsychotic monotherapy and 42.09% received combination therapy.

Relationship Between Therapeutic Regimen and Serum Lipid Levels

Serum TG level was higher with APD combinations (1.03 (0.71, 1.51) mmol/l) than with monotherapy (0.93 (0.67, 1.43) mmol/l). There were no significant differences in the levels of other lipids between the groups (Table 2). Stratification by sex revealed that the difference in TG levels between combination therapy and monotherapy was only present in female patients (1.00 (0.70, 1.48) mmol/l vs 0.91 (0.65, 1.39) mmol/l) (Table 3).

Table 1 Demographic and Clinical Characteristics of Cases

Characteristics	Group	Cases (n=1979)
Sex	Male Female	902 (45.58%) 1077 (54.42%)
Age, years		34.37±12.90
Family history	Positive Negative	403 (20.36%) 1576 (79.63%)
Drug regimen	Monotherapy Combination therapy	1146 (57.91%) 833 (42.09%)
Drug classification	Typical Atypical Combined (typical and atypical)	99 (5.00%) 1476 (74.58%) 404 (20.42%)
TC, mmol/l		3.96 (3.39, 4.62)
TG, mmol/l		0.97 (0.68, 1.46)
LDL-C, mmol/l		2.64 (2.13, 3.16)
HDL-C, mmol/l		1.16 (1.00, 1.36)
ApoA1, g/l		1.07 (1.00, 1.20)
ApoB, g/l		0.71 (0.60, 0.85)
ApoA1/ApoB		1.54 (1.28, 1.84)
TC/HDL		3.37 (2.85, 4.03)

Notes: Data are shown as mean ± standard deviation, median (interquartile range) or n (%). Lipid levels showed a skewed distribution according to the Kolmogorov–Smirnov test and are expressed as median (interquartile range).
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; HDL, high-density lipoprotein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 2 Comparison of Serum Lipid Levels Between Patients Treated with Antipsychotic Monotherapy and Combination Therapy

Serum Lipid, mmol/l	Monotherapy (n=1146)	Combination Therapy (n=832)	Z	P [a]
TC	3.94 (3.37, 4.62)	4.00 (3.41, 4.62)	1.11	0.27
TG	0.93 (0.67, 1.43)	1.03 (0.71, 1.51)	2.71	0.01
LDL-C	2.60 (2.12, 3.14)	2.68 (2.15, 3.18)	0.92	0.36
HDL-C	1.17 (1.00, 1.36)	1.15 (1.00, 1.36)	0.45	0.65

Notes: [a]Mann–Whitney U non-parametric testing was used to compare non-normally distributed quantitative variables between antipsychotic monotherapy and combination therapy groups.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 3 Comparison of Serum Lipid Levels Between Patients Treated with Antipsychotic Monotherapy and Combination Therapy Stratified by Sex

Sex	Serum Lipid, mmol/l	Monotherapy	Combination therapy	Z	*P* [a]
Male (548/353)	TC	3.90 (3.35, 4.65)	3.98 (3.38, 4.63)	0.67	0.50
	TG	0.97 (0.69, 1.50)	1.06 (0.75, 1.56)	1.83	0.07
	LDL-C	2.66 (2.17, 3.20)	2.70 (2.17, 3.20)	0.26	0.80
	HDL-C	1.12 (0.99, 1.31)	1.13 (0.98, 1.34)	0.14	0.89
Female (598/479)	TC	3.95 (3.39, 4.59)	4.01 (3.47, 4.58)	0.87	0.38
	TG	0.91 (0.65, 1.39)	1.00 (0.70, 1.48)	2.18	0.03
	LDL-C	2.56 (2.08, 3.08)	2.66 (2.13, 3.15)	1.16	0.24
	HDL-C	1.20 (1.01, 1.42)	1.18 (1.00, 1.38)	1.13	0.26

Notes: [a]Mann–Whitney U non-parametric testing was used to compare non-normally distributed quantitative variables between antipsychotic monotherapy and combination therapy groups.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Relationship Between APD Classification and Serum Lipid Levels

The patients were divided into three groups according to APD classification (ie, typical, atypical, and combined typical and atypical APD). Lipid levels did not differ among the three groups (Table 4) or between the typical and atypical groups (Table 4). Stratification by sex revealed no significant differences (Table 5).

Association Between ApoA1 Polymorphism and Dyslipidemia

Dyslipidemia was defined according to the Guidelines on Prevention and Treatment of Dyslipidemia in Chinese

Table 4 Comparison of Serum Lipid Levels Between Patients Treated with Typical and Atypical Antipsychotic Drugs and Their Combination

Serum Lipid, mmol/l	Typical (n=99)	Atypical (n=1476)	Combined (n=403)	Z	*P* [a]	Z	*P* [b]
TC	4.09 (3.38, 4.78)	3.95 (3.39, 4.60)	3.99 (3.40, 4.63)	0.83	0.66	0.86	0.39
TG	1.01 (0.74, 1.63)	0.96 (0.67, 1.48)	1.00 (0.70, 1.40)	1.14	0.57	1.04	0.30
LDL-C	2.57 (2.26, 3.28)	2.62 (2.12, 3.15)	2.67 (2.15, 3.16)	0.98	0.61	0.74	0.46
HDL-C	1.17 (1.00, 1.34)	1.16 (1.00, 1.35)	1.18 (1.00, 1.41)	1.65	0.44	0.25	0.81

Notes: [a]Brown-Mood non-parametric testing was used to compare non-normally distributed quantitative variables among typical, atypical and combined antipsychotic drug groups. [b]Mann–Whitney U non-parametric testing was used to compare non-normally distributed quantitative variables between typical and atypical antipsychotic drug groups.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 5 Comparison of Serum Lipid Levels Between Patients Treated with Typical and Atypical Antipsychotic Drugs and Their Combination Stratified by Sex

Sex	Serum Lipid, mmol/l	Typical	Atypical	Combined	Z	*P* [a]	Z	*P* [b]
Male (56/665/180)	TC	3.97 (3.36, 4.64)	3.95 (3.37, 4.65)	3.90 (3.31, 4.63)	0.41	0.81	0.24	0.81
	TG	1.03 (0.80, 1.66)	1.00 (0.71, 1.52)	1.01 (0.72, 1.41)	1.12	0.57	1.02	0.31
	LDL-C	2.56 (2.22, 3.29)	2.72 (2.19, 3.20)	2.57 (2.12, 3.19)	1.25	0.53	0.13	0.90
	HDL-C	1.11 (0.95, 1.34)	1.11 (0.99, 1.30)	1.11 (1.00, 1.37)	3.60	0.17	0.22	0.83
Female (43/811/223)	TC	4.26 (3.38, 5.06)	3.94 (3.40, 4.57)	4.06 (3.49, 4.64)	3.30	0.19	1.51	0.13
	TG	0.92 (0.70, 1.32)	0.93 (0.66, 1.43)	0.97 (0.69, 1.39)	0.27	0.87	0.25	0.81
	LDL-C	2.59 (2.26, 3.28)	2.56 (2.07, 3.08)	2.70 (2.15, 3.16)	4.82	0.09	0.96	0.33
	HDL-C	1.22 (1.06, 1.39)	1.19 (1.00, 1.39)	1.19 (1.00, 1.42)	0.78	0.68	0.88	0.38

Notes: [a]Brown-Mood non-parametric testing was used to compare non-normally distributed quantitative variables among typical, atypical, and combined antipsychotic drug groups. [b]Mann–Whitney U non-parametric testing was used to compare non-normally distributed quantitative variables between typical and atypical antipsychotic drug groups.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

Table 6 Association Between the ApoA1 rs5072 Genotype and Serum Lipid Levels

Serum Lipid	Genotype	OR (95% CI)[a]		
	GG/GA/AA	Addictive	Dominant	Recessive
TC < 5.2 mmol/l	876/710/152	1.08 (0.87–1.33)	1.01 (0.76–1.33)	1.38 (0.89–2.16)
TC ≥ 5.2 mmol/l	120/87/27	*P* = 0.50	*P* = 0.95	*P* = 0.15
TG < 1.7 mmol/l	818/656/136	1.15 (0.97–1.37)	1.10 (0.88–1.39)	1.50 (1.03–2.17)
TG ≥ 1.7 mmol/l	178/141/43	*P* = 0.11	*P* = 0.40	*P* = 0.03
LDL-C < 3.4 mmol/l	837/688/148	0.99 (0.81–1.20)	0.92 (0.71–1.18)	1.22 (0.80–1.86)
LDL-C ≥ 3.4 mmol/l	159/109/31	*P* = 0.91	*P* = 0.49	*P* = 0.35
HDL-C ≥ 1.0 mmol/l	235/178/41	1.05 (0.89–1.23)	1.08 (0.87–1.33)	1.01 (0.70–1.45)
HDL-C < 1.0 mmol/l	761/618/138	*P* = 0.58	*P* = 0.49	*P* = 0.97

Note: [a]Logistic regression with adjustment for age, sex, drug classification and drug regimen.
Abbreviations: ApoA1, apolipoprotein A1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; OR, odds ratio; CI, confidence interval.

Adults (2016 Revision)[23] as high TC (≥5.2 mmol/l), TG (≥1.7 mmol/l), and LDL-C (≥3.4 mmol/l) and low HDL-C (<1.0 mmol/l). SNP rs5072 of the ApoA1 gene was significantly associated with TG level after adjusting for covariates in the recessive model (OR=1.50, 95% CI: 1.03, 2.17; P=0.03) (Table 6).

Relationship Between ApoA1 rs5072 and Serum Lipid Levels

In the whole study population, the TG levels with the GG, GA, and AA genotypes of ApoA1 rs5072 were 0.95 (0.67, 1.44) mmol/l, 1.00 (0.70, 1.42) mmol/l, and 1.15 (0.80, 1.68) mmol/l, respectively; the differences among the three groups were statistically significant (Table 7). The TG levels with the GG, GA, and AA genotypes were 0.99 (0.70, 1.43) mmol/l, 1.06 (0.72, 1.53) mmol/l, and 1.24 (0.82, 1.77) mmol/l, respectively, in patients who received combination APD therapy and 0.91 (0.65, 1.47) mmol/l, 0.95 (0.68, 1.37) mmol/l, and 1.08 (0.73, 1.66) mmol/l, respectively, in patients who received monotherapy. Within-group comparisons showed no significant differences in TG levels according to genotype, even after stratification by sex (data not shown).

Lipid levels in each genotype were also compared according to the type of APD. TG levels differed significantly among the three genotypes only in patients treated with atypical APDs (P=0.02), with values of 0.93 (0.67, 1.50) mmol/l, 0.97 (0.67, 1.41) mmol/l, and 1.08 (0.80, 1.67) mmol/l, respectively, for the GG, GA, and AA genotypes (Table 7). Stratification analysis by sex showed that TC levels were significantly among the three genotypes in males treated with typical APDs (P=0.001; data not shown).

Discussion

The available APDs have variable efficacy in patients with schizophrenia. Combination treatment with more than one APD is commonly used[24,25] as many patients with schizophrenia do not demonstrate a satisfactory response to a - monotherapy.[26] However, there is inadequate evidence for the efficacy and safety of APD combinations,[26,27] and few studies have investigated whether the two types of regimen differentially affect lipid metabolism.

In this study we found that APD combinations were more likely to be associated with elevated serum lipid levels than monotherapy, especially in females, suggesting that they increase the risk of dyslipidemia. This is consistent with a previous study demonstrating that TG level was lower with APD monotherapy than with combination therapy (134 ± 81.3 vs 144.6 ± 83.8 mg/dl), although the difference in that study was not statistically significant.[9] The high overall drug dose of APD combinations can increase the incidence of adverse reactions, and drug interactions can lead to variability in serum drug concentrations. Additionally, drug combinations usually contain at least one atypical APD because of the superior efficacy of these drugs, although they are more likely to cause dyslipidemia than typical APDs. Nonetheless, antipsychotic combinations are a good option for patients who do not respond or have contraindications to clozapine. A previous study found that women were at greater risk for adverse reactions to antipsychotics (including dyslipidemia) than men,[28] with a fat transport velocity in blood that was about two times higher and a greater change in TG levels after high-carbohydrate or high-fat feeding.[29] Another possible explanation for the sex difference in susceptibility to increased TG levels is that blood levels of some

Table 7 Comparison of Serum Lipid Levels Across Genotypes

Group	Serum Lipid, mmol/l	Genotype			Z	P [a]
		GG	GA	AA		
Total (996/796/179)	TC	3.97 (3.37, 4.63)	3.95 (3.41, 4.57)	4.00 (3.44, 4.75)	0.58	0.56
	TG	0.95 (0.67, 1.44)	1.00 (0.70, 1.42)	1.15 (0.80, 1.68)	5.54	<0.01
	LDL-C	2.66 (2.13, 3.18)	2.60 (2.15, 3.10)	2.65 (2.07, 3.20)	0.21	0.81
	HDL-C	1.15 (1.00, 1.35)	1.17 (1.00, 1.37)	1.16 (1.00, 1.34)	1.25	0.29
Drug regimen						
Monotherapy (576/462/103)	TC	3.95 (3.35, 4.62)	3.89 (3.39, 4.53)	4.01 (3.34, 4.90)	1.21	0.55
	TG	0.91 (0.65, 1.47)	0.95 (0.68, 1.37)	1.08 (0.73, 1.66)	5.22	0.07
	LDL-C	2.64 (2.11, 3.20)	2.56 (2.14, 3.05)	2.64 (2.04, 3.22)	0.92	0.63
	HDL-C	1.16 (1.00, 1.36)	1.19 (1.00, 1.36)	1.16 (1.00, 1.30)	1.24	0.54
Combination therapy (420/334/76)	TC	3.98 (3.37, 4.63)	4.02 (3.46, 4.62)	3.99 (3.52, 4.60)	0.32	0.85
	TG	0.99 (0.70, 1.43)	1.06 (0.72, 1.53)	1.24 (0.82, 1.77)	5.74	0.06
	LDL-C	2.68 (2.15, 3.17)	2.66 (2.15, 3.17)	2.69 (2.08, 3.20)	0.13	0.94
	HDL-C	1.14 (1.00, 1.35)	1.17 (1.00, 1.38)	1.16 (1.00, 1.37)	1.03	0.60
Drug classification						
Typical (52/39/8)	TC	4.18 (3.56, 4.87)	3.74 (3.18, 4.46)	3.50 (3.00, 5.35)	3.35	0.19
	TG	1.01 (0.72, 1.43)	1.10 (0.76, 1.73)	1.03 (0.59, 4.01)	0.27	0.87
	LDL-C	2.63 (2.28, 3.36)	2.56 (2.21, 3.08)	1.95 (1.53, 3.34)	2.16	0.34
	HDL-C	1.16 (1.00, 1.33)	1.14 (1.00, 1.39)	1.21 (0.98, 1.45)	0.27	0.87
Atypical (731/609/131)	TC	3.95 (3.35, 4.59)	3.94 (3.43, 4.55)	4.01 (3.44, 4.75)	0.91	0.63
	TG	0.93 (0.67, 1.50)	0.97 (0.67, 1.41)	1.08 (0.80, 1.67)	7.88	0.02
	LDL-C	2.67 (2.11, 3.20)	2.57 (2.14, 3.06)	2.64 (2.07, 3.20)	1.30	0.52
	HDL-C	1.14 (1.00, 1.35)	1.17 (1.00, 1.36)	1.16 (1.01, 1.30)	0.83	0.66
Combined (213/148/40)	TC	3.90 (3.33, 4.64)	4.04 (3.40, 4.65)	4.02 (3.53, 4.69)	1.07	0.59
	TG	0.97 (0.65, 1.38)	1.04 (0.73, 1.39)	1.19 (0.82, 1.67)	3.95	0.14
	LDL-C	2.62 (2.14, 3.11)	2.68 (2.17, 3.20)	2.83 (2.15, 3.20)	0.91	0.63
	HDL-C	1.15 (1.00, 1.38)	1.21 (1.00, 1.45)	1.13 (0.97, 1.41)	2.67	0.26

Note: [a]Brown-Mood non-parametric testing was used to compare non-normally distributed quantitative variables across the three genotypes.
Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.

antipsychotics are higher in women than in men, even at the same drug dose.[30]

APDs are classified as typical or atypical based on their ability to cause extrapyramidal side effects;[31] randomized controlled trials comparing the two types of APD in schizophrenia have shown that the latter had similar or slightly superior efficacy and tolerability.[31–34] Typical APDs cause more extrapyramidal side effects than atypical APDs; the latter are associated with higher risk for developing metabolic syndrome, which includes weight gain and dysregulation of glucose and lipid metabolism.[35,36] The mechanism underlying atypical APD-induced dyslipidemia remains unclear, but is thought to involve peroxisome proliferator-activated receptor (PPAR), a transcription factor that regulates lipid and carbohydrate metabolism. As PPAR modulators, glimepiride, rosiglitazone, and fenofibrate showed beneficial TG-lowering effects in atypical APD-treated mice.[37] Previous studies have reported that TG levels showed a greater increase in patients treated with atypical APDs as compared to typical APDs.[36,38] However, no differences were observed in our study. The reason for this discrepancy may be the large difference in group sizes of patients treated with typical (n=99) vs atypical (n=1476) APDs; the latter have greater efficacy and are associated with better treatment adherence and fewer adverse reactions than the former, and are therefore more frequently prescribed by clinicians.

ApoA1 and ApoB mutations were shown to predict the development of cardiovascular disease;[39,40] and patients with schizophrenia have lower expression of ApoA1 compared to healthy subjects.[41] Only a few studies to date

have investigated the effect of APDs on ApoA1 and ApoB. As a matter of interest, ApoA1 and ApoB levels as well as ApoA1/ApoB and TC/HDL-C ratios were also analyzed in this study to explore the differences in safety and efficacy among different medications. But no differences were found (Tables S2–S6).

The ApoA1 gene is a main site regulating lipids and lipoproteins expression,[42,43] and the association between ApoA1 gene polymorphisms and lipid levels has been extensively studied.[44,45] We found a significant association between the rs5072 polymorphism of ApoA1 and serum TG level in schizophrenia. Moreover, patients with the AA genotype had a higher TG level than those with the GG and GA genotypes. Rs5072 is in high linkage disequilibrium with rs2070665 and rs7116797; all three SNPs are located in regions with histone modifications that are characteristic of active promoters, and may regulate plasma TG level by enhancing the expression of ApoA1/C3/A4/A5 gene cluster.[46]

The present study had some limitations. Firstly, we compared lipid levels between patients treated with the two classes of APD but did not evaluate differences within each class (eg, olanzapine vs clozapine). Additional studies with a larger sample size are required to address this point. Secondly, we focused on only one tagSNP in the association study, but should consider others in order to clarify the effect of gene interactions on lipid metabolism. Finally, previous studies have reported an association between ApoA1 gene polymorphisms and lipid levels. Drug therapy is a possible confounding factor in lipid abnormalities caused by ApoA1 variants; without a control group, it is unclear which variable contributed to the high TG levels in the patients. In order to address this issue, a cohort study with a small sample size was carried out to compare TG levels before and after APD treatment in patients with the rs5072 risk genotype (Table S7). The results showed that TG level was increased by the treatment, suggesting that this rs5072 polymorphism increases the risk of dyslipidemia, although a control group is needed to validate our conclusion.

Conclusion

Our results showed that schizophrenia patients are at high risk of developing dyslipidemia, which is influenced by multiple factors including sex and APD treatment regimen. We also identified that rs5072 in ApoA1 was associated with TG level in schizophrenia patients treated with APDs. These findings can guide clinical management strategies (eg, lifestyle modifications and pharmacotherapy) to prevent dyslipidemia in schizophrenia patients harboring this ApoA1 variant.

Data Sharing Statement

The datasets used and/or analyzed in this study are available from the corresponding author on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no conflicts of interest.

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