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Olanzapine-induced Metabolic Syndrome and its Association with -759C>T Polymorphism of the HTR2C Gene in Iraqi Schizophrenic Patients

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Abstract

The hazardous metabolic effects of treating schizophrenia patients with olanzapine comprise serotonin 2C receptor (5-HT2C) antagonists. Metabolic side effects of antipsychotic drugs, including lipid abnormalities, disturbed glucose metabolism, and weight gain, can have a major impact on treating psychiatric patients. The intent of this study was to investigate whether there is an associated link between the genetic polymorphism at -759C>T in the promoter region of the 5-hydroxytryptamine 2C receptor (HTR2C) gene and the metabolic syndrome driven by olanzapine in schizophrenia patients. A cross-sectional study that involved fifty hospitalized patients with schizophrenia. The patients were split into two groups (metabolic and non-metabolic) according to the classification criteria of the metabolic syndrome. The HTR2C promoter region polymorphism was identified through sequencing using the Sanger method after polymerase chain reaction amplification of the extracted deoxyribonucleic acid. Even though none of the genotypes of the -759C>T variant are associated with the propensity to develop metabolic syndrome, there is a significant difference in the -759C>T variant's T allele (p-value = 0.001). The presence of the T allele in the -759 C/T variant was significantly associated with developing metabolic syndrome.
Keywords: Schizophrenic patients, Olanzapine, Genetic polymorphism, 5-hydroxytryptamine 2C receptor (HTR2C) gene, -759C>T.

متلازمة الايض المتسببة من الأولانزبين و علاقتها بتعدد الأشكال الجيني للسيروتونين ـ٧٥٩ في مرضى الفصام العراقيين

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الخلاصة

إن الآثار الأيضية الخطرة لعلاج مرضى الفصام بأولانزابين بما في ذلك مضادات مستقبلات السيروتونين (5-HT2C)و الآثار الجانبية الأيضية للأدوية المضادة للذهان ، بما في ذلك خلل مستوى الدهون في الدم، واضطراب التمثيل الغذائي للجلوكوز ، وزيادة الوزن ، يمكن أن يكون لها تأثير كبير على علاج المرضى النفسيين. إن الهدف من هذه الدراسة هو التحقق مما إذا كان هناك ارتباط بين تعدد الأشكال الجيني عند ـ٧٥٩ T في منطقة لجين مستقبل ٥-هيدروكسي تريبتامين (HTR2C) ومتلازمة التمثيل الغذائي التي يسببها أولانزابين في مرضى الفصام. الدراسة مقطعية شملت خمسين مريضًا مصابًا بالفصام في المستشفى. تم تقسيم المرضى إلى مجموعتين (التمثيل الغذائي وغير الأيضي) وفقًا لمعايير تصنيف متلازمة التمثيل الغذائي. تم تحديد تعدد الأشكال لمنطقة المروج HTR2C من خلال التسلسل باستخدام طريقة Sanger بعد تضخيم تفاعل البلمرة المتسلسل لحمض ديوكسي ريبونوكلييك المستخرج. على الرغم من عدم ارتباط أي من الأنماط الجينية للمتغير ـC٧٥٩> T بالميل لتطوير متلازمة التمثيل الغذائي ، إلا أن هناك فرقًا كبيرًا في أليل T المتغير ـC٧٥٩> T (القيمة p = 0.001). إرتبط وجود الأليل T في متغير ـ٧٥٩ C / T بشكل كبير بتطور متلازمة التمثيل الغذائي.
الكلمات المفتاحية: مرضى الفصام ، أولانزابين ، تعدد الأشكال الجيني ، جين مستقبلات ٥-هيدروكسي تريبتامين ٢ (HTR2C) ، ـT٧٥٩> C.

Introduction

About 25% of people will have mental illnesses at some point in their life, making them prevalent community concerns [1]. Schizophrenia was the most often identified illness among patients [2].

One of the complications associated with olanzapine use is a metabolic syndrome which is defined by the presence of three or more of the following five circumstances increased waist circumference (central obesity), high blood pressure, low high-density lipoprotein cholesterol, hypertriglyceridemia, and hyperglycemia [3]. Nearly 70% and 30% of metabolic diseases are impacted by the interplay of hereditary and environmental variables [4].

Due to various variables, like a sedentary lifestyle, poor food choices, and the adverse effects of antipsychotic drugs, patients with schizophrenia are likelier than non-schizophrenics to experience metabolic dysfunctions [5]. Many studies link atypical antipsychotics to higher risks of hyperglycemia, changed glucose levels, and lipid disturbance, leading to metabolic syndrome development in schizophrenia patients [6].

The 5-HT2C receptor substantially modulates atypical antipsychotics (AAPs)' adverse effects, especially metabolic syndrome [7]. Identifying the association between the genetic polymorphism in the 5-HTR2C gene and the tendency to develop metabolic syndrome can help physicians avoid prescribing olanzapine to high-risk patients.

Although olanzapine significantly affects body weight, serum glucose levels, and lipid profiles in two earlier studies conducted in Iraq [8,9], and a previous study examine the Association Between -697C>G and -997G>A polymorphism of the HTR2C gene and the metabolic syndrome in Iraqi schizophrenic patients [10].

However, no research in Iraq has examined the relationship between metabolic syndrome and the -759 C/T variant polymorphism in the HTR2C gene in Iraqi schizophrenia patients.

Iraqi citizens experienced war, which is commonly thought to have enhanced the population's vulnerability to psychiatric disorders [11].

In order to determine whether there is a link between genetic variation in the promoter region of the 5-HTR2C gene at-759C>T variants and the propensity to develop metabolic syndrome in a sample of olanzapine-treated Iraqi schizophrenia patients.

Patients and Methods

Study design

A cross - sectional study was conducted at two mental hospital facilities in Baghdad, Iraq (Ibn Rushd Psychiatric Training Hospital and Al-Rashad Hospital for Mental Health).

Inclusion criteria

* According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) diagnostic criteria for schizophrenia [12], adult patients between the ages of (18 and 70) have been diagnosed with schizophrenia.

* The patients had to be treated with an atypical antipsychotic (olanzapine) for at least a last one year, taking (5-20) mg every day.

Exclusion criteria

* Patients who hadn't been taking olanzapine for a year or more.
* Patients have psychotic disorders as a result of general ailment or mental disability.
* Patients with conditions known to have an impact on the brain or diseases needing treatment with drugs having psychotropic effects.
* Patients who are taking drugs interact with olanzapine, for example, pregabalin, and Vitamins such as B12, C, and D3.
* Women who are pregnant or nursing.
* Patients have DM, hyperlipidemia, hypertension, or obesity when starting treatment with antipsychotic drugs.
* Patients taking mood stabilizers (sodium valproate, carbamazepine and lithium).

Patient's groups

Two groups of patients have been identified based on the metabolic syndrome criteria. [13].

50 patients are included in the trial and are split into two groups as follows.:

Group A (n=30): schizophrenic patients have metabolic syndrome.

Group B (n=20): schizophrenic patients didn't have metabolic syndrome.

All patients have had their medical histories taken, and each has undergone thorough clinical examinations that include filling out specific questionnaires for the following information: gender, age, education, occupation, place of residence, marital status, height, waist size, weight, family history, medical history (including diabetes, hypertension, dyslipidemia, cardiovascular disease, and psychiatric disease), duration of sickness, length of olanzapine treatment, current medication, smoking, blood pressure, and pulse rate. The study design is presented in the following Figure 1.

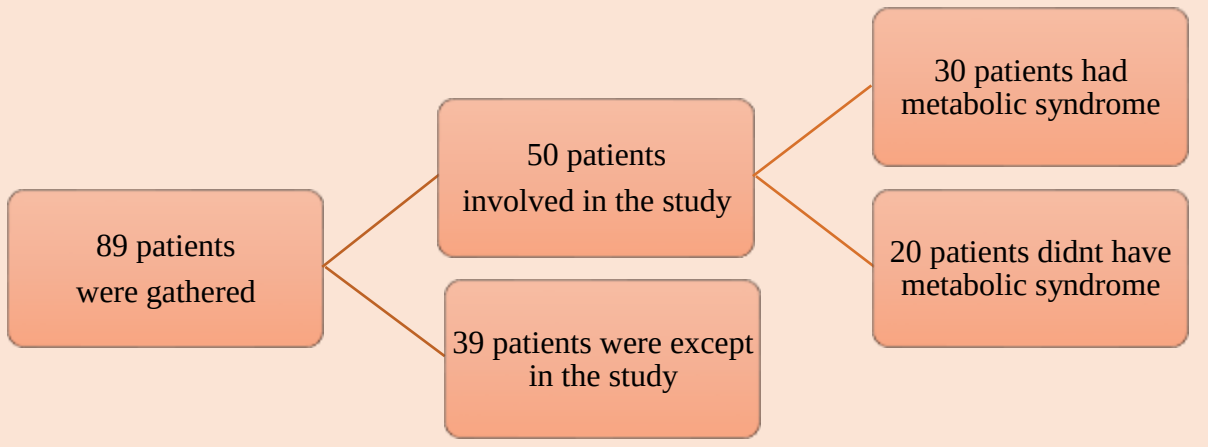

Figure 1. Flow chart of the study.

Data collection

Using an already assembled data collection sheet, information were gathered on demographic and anthropometric details like gender, age, education, occupation, place of residence, marital status, height, waist size, weight, family history, medical history (including diabetes, hypertension, dyslipidemia, cardiovascular disease, and psychiatric disorders), length of illness, length of olanzapine treatment, current medications, smoking, blood pressure, pulse rate, weight, and length of the disease. Fasting Blood Sugar (FBS) and lipid profiles (cholesterol, triglycerides, HDL, and VLDL) have been evaluated in the lab.

Sample collection and preparation

Each patient's forearm vein was pierced to get 5 ml of venous blood. For the purpose of extracting DNA, two milliliters of blood were transferred into an ethylenediaminetetraacetic acid (EDTA) tube. The serum was obtained by centrifuging the remaining three milliliters of the drawn blood sample for ten minutes at (4000 rpm) in a gel tube. When the sample was collected, the separated serum was maintained in Eppendorf tubes and frozen at (-20 °C).

DNA extraction

DNA from blood samples can be efficiently purified using the Promega ReliaPrepTM Blood gDNA Miniprep System for Genomic DNA (Promega Corp., WI, USA). Enzymatic amplification was done using the Master Taq polymerase enzyme and a hybrid thermal cycler via the polymerase chain reaction (PCR).

The primer

The DNA sequences for the HTR2C gene were retrieved from the NCBI GenBank repository. With annealing temperatures of (56, 58, and 60°C), primer lengths of (18 to 23 nucleotides), and PCR amplicon lengths of (800 to 1000 base pairs), PCR primers were created using Premier 3 software.

Table 1. The sequences, Annealing temperature, and Product size (bp) of the primer

Primer name	Sequence	Annealing Temp. (°C)	Product size (bp)
HTR2C-F	AAGGATGGGGAGACAAGGAT	56	837
HTR2C-R	ACCTCCAGCATCTCTGCACT		

HTR2C-F: the forward primer. HTR2C-R: the reverse primer.

Primer optimization and PCR amplifications

To find the best primers, we amplified the DNA template using the same primer pair (Forward) (Reverse) at 56, 58, and 60°C annealing temperatures. As shown in Figure 2, the ideal annealing temperature for the primer was 56°C. The PCR amplifications were carried out in quantities of 25 µL. The PCR protocol employs 2xEasyTaq® PCR SuperMix. All PCR calculations and reactions were carried out in a 25 µl final volume and according to the manufacturer's instructions, as seen in Tables 2 and 3.

Table 2. The components and volumes of a PCR reaction.

Component	**Volume 25** µl
2xEasy*Taq*® PCR SuperMix	12.5µl
Forward primer	1 µl
Reverse primer	1 µl
DNA	4µl
Nuclease free water	6.5µl

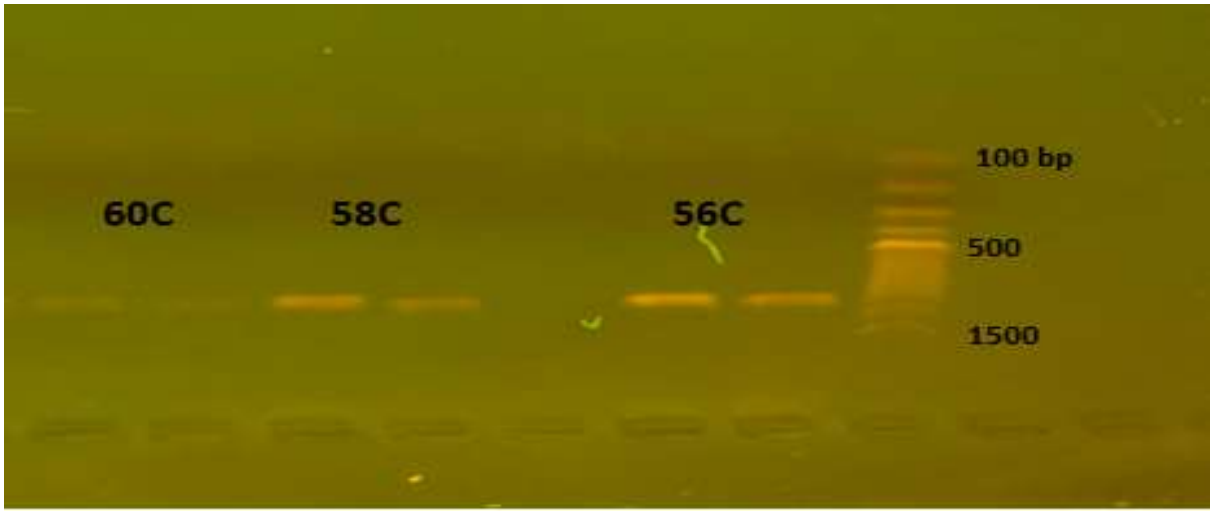

Figure 2. Primer optimization at annealing temperatures of 56, 58, and 60°C

Table 3. PCR program.

Step	**Temperature (**ºC**)**	**Time**	**Cycle**
Denaturation	94	5 min	1
Denaturation	94	30 sec	**35**
Annealing	56	30 sec	
Extension	72	1 min	
Final extension	72	10 min	**1**

Agarose gel electrophoresis

After ethidium bromide staining, the extracted DNA fragments, after the amplification by PCR, were separated on an agarose gel and then seen under UV light to identify the desired band.

Sequencing of PCR products

Analyzer for DNA, ABI3730XL from "Macrogen Corp., Seoul, South Korea" was used to sequence the PCR product using the Sanger technique. The findings were collected by electronic mail, and Geneious Prime software version 2021.1.1 "Biomatters Ltd., Auckland, New Zealand; www.geneious.com" was used to analyze them.

Statistical analysis

The "IBM SPSS" for Windows version 26.0 software from "IBM Corp., Armonk, NY, USA" and "GraphPad Prism" from "GraphPad Software, CA, USA" were used to conduct the statistical analysis. The mean and standard deviation (m±SD) expressed continuous variables. Genotypes and alleles were shown in terms of frequency and number. The Shapiro-Wilk test was employed to examine the results' normality. The findings showed that all variables had a normal distribution (P. Value > 0.05); thus, the unpaired t-test was employed to identify if there were statistically significant differences in the demographic traits and parameters between the two groups. The chi-square test or Fisher exact test was applied to examine proportional differences across groups. The association between each genotype and the risk of developing the metabolic syndrome was calculated using the phi correlation coefficient (phi) and binary logistic regression. A p-value below 0,05 was regarded as statistically significant.

Results

Demographic and basic descriptive data

The demographic information for each participant is included in Tables 4A and 4B. Hospitalized individuals (n=50), of both sexes (22 women (44%) and 28 men (56%) were selected for the research as a convenient sample. The research group's average age was 47.60 years (SD: 9.293), ranging from 24-69 years. Eight patients taking carbamazepine, seven taking sodium valproate, four

had pre-existing hypertension, one taking thyroxine, seven missing baseline glucose levels (before starting olanzapine treatment), and twelve missing baseline lipid profiles (3 triglycerides, five cholesterols, and four HDL) have been excluded from the study.

Table 4A. Demographic and clinical data for qualitative parameters of the study groups.

		Metabolic N=30		Non-Metabolic N=20		Total N=50		P value
		N	%	N	%	N	%	
Gender	**Male**	18	36.0%	10	20.0%	28	56.0%	[a] **0.485**
	Female	12	24.0%	10	20.0%	22	44.0%	
Occupation	**Unemployed**	23	46.0%	15	30.0%	38	76.0%	[b] **0.575**
	Employed	7	14.0%	5	10.0%	12	24.0%	
Marital Status	**Divorced**	6	12.0%	7	14.0%	13	26.0%	[b] **0.171**
	Single	19	38.0%	9	18.0%	28	56.0%	
	Married	5	10.0%	2	4.0%	7	14.0%	
	Widow	0	0.0%	2	4.0%	2	4.0%	
Residence	**Baghdad**	13	26.0%	11	22.0%	24	48.0%	[b] **0.443**
	Karbalaa	2	4.0%	2	4.0%	4	8.0%	
	Diyala	5	10.0%	0	0.0%	5	10.0%	
	Qadsiea	1	2.0%	0	0.0%	1	2.0%	
	Karkuk	1	2.0%	1	2.0%	2	4.0%	
	Mosul	1	2.0%	1	2.0%	2	4.0%	
	Basra	1	2.0%	2	4.0%	3	6.0%	
	Najaf	1	2.0%	3	6.0%	4	8.0%	
	Wasit	1	2.0%	0	0.0%	1	2.0%	
	Dhi qar	1	2.0%	0	0.0%	1	2.0%	
	Babylon	2	4.0%	0	0.0%	2	4.0%	
	Maysan	1	2.0%	0	0.0%	1	2.0%	
Family History of schizophrenia	**Yes**	19	38.0%	12	24.0%	31	62.0%	[a] **0.812**
	No	11	22.0%	8	16.0%	19	38.0%	
Education	**Illeteracy**	13	26.0%	3	6.0%	16	32.0%	[b] **0.088**
	Primary	11	22.0%	8	16.0%	19	38.0%	
	Middle school	3	6.0%	7	14.0%	10	20.0%	
	Bachelor	1	2.0%	1	2.0%	2	4.0%	
	Diploma	2	4.0%	1	2.0%	3	6.0%	
Smoking status	**No**	9	18.0%	3	6.0%	12	24.0%	[b] **0.317**
	Yes	21	42.0%	17	34.0%	38	76.0%	
Medical History	**Nill**	28	56.0%	17	34.0%	45	90.0%	[b] **0.517**
	IHD	2	4.0%	1	2.0%	3	6.0%	
	Stroke	0	0.0%	1	2.0%	1	2.0%	
	Asthma	0	0.0%	1	2.0%	1	2.0%	
Dose of olanzapine	**5mg daily**	2	4.0%	1	2.0%	3	6%	[b] **0.792**
	10mg daily	11	22.0%	5	10.0%	16	32%	
	20mg daily	17	34.0%	14	28.0%	31	62%	

Results are reported as [a] Chi-square test. [b] Fisher-exact test. * Significant difference between the groups) $p < 0.05$ was statistically significant) . IHD: ischemic heart disease, Nil: nothing, cm: centimeter, Kg: kilogram

Table 4B. Demographic and clinical data for quantitative parameters of the study groups.

	Metabolic		Non-Metabolic		P value
	Mean	SD	Mean	SD	
Age(yrs)	47.40	9.25	47.90	9.59	0.995
Height (cm)	167.43	8.51	166.75	8.12	0.761
Waist Circumference (cm)	119.53	10.32	102.10	21.13	**0.001**
Weight(kg)	97.57	15.40	91.95	25.32	0.057
BMI (kg/m^2)	34.47	4.05	32.98	8.07	**0.001**
Duration of disease(yrs)	9.03	6.55	7.45	3.93	0.410
Duration of olanzapine treatment(yrs)	8.60	5.46	6.85	3.27	0.234
BP (systolic) mmHg	147	19	121	16	٠.668
BP (Diastolic) mmHg	92	16	79	10	٠.053
Pulse Rate	88	21	90	20	٠.798

Results are reported as means ±SD. ($p< 0.05$ was statistically significant).[a] **Independent Samples Test, BMI: body mass index, BP: blood pressure**

Types of adjuvant therapy used with olanzapine.

Table 5 shows that just three individuals utilized olanzapine alone to treat their schizophrenia, whereas other adjuvant medications were also administered. However, the usage of Fluphenazine ampule and Procyclidine tablet was the only notable distinction between the two groups.

Table 5. Adjuvant therapy used with olanzapine

No.	Type of adjuvant therapy	Metabolic N=30	Non-metabolic N=20	**P. Value**
1	Fluphenazine ampule	27	12	**0.017***
2	Fluoxetine capsule 20mg	3	1	**0.64**
3	Quetiapine tablet 200mg	1	2	**0.55**
4	Procyclidine tablet 5mg	26	11	**0.02***
5	Escitalopram	0	1	**0.4**
6	Haloperidol ampule	0	1	**0.4**
7	Diazepam tablet 5mg	2	4	**0.20**
8	Amitriptyline tablet 25mg	4	1	**0.63**
9	Nothing else	1	2	**0.55**

The Fisher Exact Test was used to calculate the P.value. *: significant differences between the two groups ($p< 0.05$ was statistically significant).

Prevalence of genotypes and alleles for all patients

Figure 3 demonstrates the CC genotype was more predominant in 88% of patients with –759C>T, with a high frequency of the C allele (92 %) and a low proportion of the T allele (8 %).

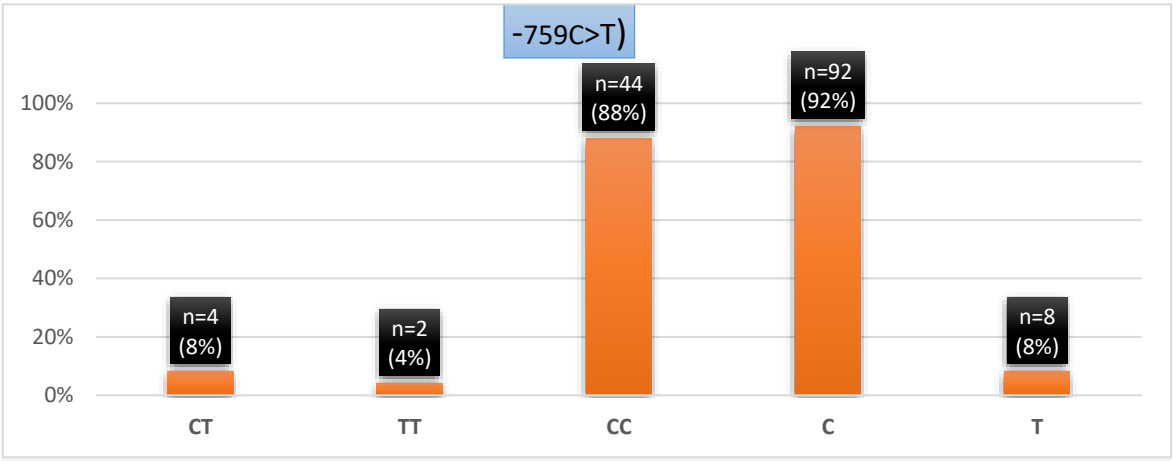

Figure 3. Proportion of genotypes and alleles for -759C>T **in schizophrenic patients (n=50).**

Regarding the difference in allele frequencies between the metabolic and non-metabolic, the results show a significant difference in the T allele of -759C>T SNP, as prescribed in Table 6.

Table 6. Difference in genotype frequencies between metabolic and non-metabolic groups.

SNP	Genotype	Metabolic		Non-Metabolic		*P value
		N	%	N	%	
-759C>T	**CT**	2	6.7%	2	10.0%	[a] 1.000
	TT	2	6.7%	0	0.0%	-
	CC[o]	26	86.7%	18	90.0%	[a] 0.228
	C	54	90%	38	95%	[a] 0.367
	T	6	10%	2	5%	[a] **0.001**

[a] Fisher exact test was used to identify the statistical difference between the groups. [b] chi-square. *: Significant difference between the groups(p< 0.05 was considered statistically significant) .
[o]: the wild genotype.

Association between the variant's genotype and the likelihood of metabolic syndrome

Binary logistic regression analysis was used to predict the influence of having a genotype other than the wild type on another genotype on the tendency to be metabolic syndrome for each variant, Table 7 displays that.

Table 7. Binary logistic regression analysis of genotypes to predict the tendency to have metabolic syndrome.

	Coefficient	OR	P-Value
-759 C>T	0.368	1.444	0.725
CG	.000	1.000	1.000
CC	0.368	1.444	0.230

Likewise, phi-coefficient analysis was used to investigate the correlation between genotype and the tendency to be metabolic syndrome. Table 8 highlights that genotype exhibited either a positive or negative correlation, none was statistically significant.

Table 8: Correlation between each genotype and the likelihood of having metabolic syndrome.

SNP	Genotype	Phi-coefficient	*P value
-759	**CT**	-0.048	0.735
	TT	0.173	0.219
	CC	-0.065	0.647

The phi-correlation coefficient was used to find the correlation between each genotype and the likelihood of metabolic syndrome.

Discussion

Identifying markers to monitor metabolic syndrome occurrence in antipsychotic-treated schizophrenia patients is crucial because of the greater prevalence of metabolic syndrome in these patients compared to the general population [(14)]. Different doses and durations of olanzapine use in Iraqi schizophrenic patients negatively impact glycemic control, blood pressure, and lipid profiles [(15)].

The study's demographics, the variables of age, sex, employment, marital status, residence, family history , education , and smoking status, did not show any significant difference between the two groups (P > 0.05). The current results were similar to the Daray F *et al.* [(16)] study involving 48 Caucasian women in Argentina , and these characteristics were also determined to be independent.

The prevalence of MS among men was higher than among women with schizophrenia in the current study; MS was 64% and 54%, respectively. In contrast, Cohn *et al.* [(17)] found that the prevalence of MS among men and women with schizophrenia was 42.6% and 48.5%, respectively.

Evidence supports sex variations in serotonin neurotransmission and mental diseases brought on by hormonal irregularities, genetic influences, and serotonin system abnormalities [(18)].

Regarding the duration of illness and duration of olanzapine use in the current study. The results showed that there was a no-significant difference between metabolic and non-metabolic groups (p > 0.05), which is not consistent with the findings of Diana Z. *et al*. [(19)] study, which recruited 475 patients from several Siberian regions (Russia) with a clinical diagnosis of schizophrenia and stated that the duration of illness in patients with metabolic

syndrome was considerably longer than in patients without metabolic syndrome (p = 0.001).

Several adjuvant treatments were administered alongside olanzapine in the current study. However, the consumption of the procyclidine medication and fluphenazine ampule was the only significant distinction between the two groups. The current study's findings can be explained by the fact that fluphenazine utilization is linked to a 37% increase in weight gain. According to research by Maslov *et al.* [20], this may be a risk factor for developing metabolic syndrome, especially when combined with olanzapine.

Although procyclidine usage has been associated with Parkinsonism [21], no earlier studies have connected procyclidine use to metabolic syndrome.

In this study, Abnormal waist circumference was the most prevalent observation in the patients with metabolic syndrome (significant difference between metabolic and non-metabolic groups, P value 0.001). These findings support those of Kato *et al.* [22] who realized that the most typical MS criteria were abnormal waist circumference, finding that the mean body mass index (BMI) was significantly higher in patients with metabolic syndrome in our study than in those with the non-metabolic syndrome (P value = 0.001).

In his study, Kuzman MR *et al.* [23] deduced that the greatest increase in waist circumference was significantly associated with the absence of the -759 C allele of the 5-HT2C genotype.

The current study shows no correlation between metabolic and non-metabolic groups, regardless of the dose of olanzapine tablets (5, 10, or 20 mg daily). This is consistent with the findings of Arzu Gunes *et al* [24], who found no correlation between the daily doses of antipsychotics and any of the studied metabolic parameters.

In the case of the -759C>T variant, the present study findings indicated that the wild genotype CC was the most prevalent (88%) of the patients, followed by the CT genotype (8%) and the lowest one, homozygote TT (4%). Regarding allele distribution, the C allele was the most prevalent in about 92% of patients, whereas the T allele occurred in only 8% of patients.

In comparison, the Kuzman *et al.* [23] study found that the proportion of CC, CT, and TT of -759CT 5-HT2C were 54,38 and 8, respectively.

This study found a non-significant association between the -759C>T genetic polymorphism and the tendency to get MS, in contrast to previous reports [25,26] associating the rs3813929 (-759 C/T) polymorphism with olanzapine-induced metabolic syndrome, especially weight gain.

The current study results are similar to the study by AJ Risselada *et al.* [27], a cross-sectional study that found no association between the HTR2C -759 C/T polymorphism and metabolic syndrome.

The outcomes of the current research found that T allele carriers were associated significantly with MS, contrastingly to Arzu Gunes *et al.* [24], who ascertained that patients who carry the HTR2C -759T alleles seem to be less likely to develop metabolic abnormalities compared with patients not carrying these alleles.

Conclusion

The wild genotype CC was the most prevalent genotype, followed by the CT genotype and the lowest homozygote TT. Regarding allele distribution, the C allele was the most prevalent. The presence of the T allele in the -759 C/T variant was significantly associated with developing metabolic syndrome.

Conflicts of Interest

The Authors declare that there is no conflict of interest.

Funding

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Ethics Statements

Approval for the current study was obtained from the Ethical and Scientific Committee of the College of Pharmacy, University of Baghdad (REAFUBLP 16112021 on 29/1/2022).
Additionally, the Ministry of Health / Ibn Rushd Psychiatric Training Hospital and Al-Rashad Hospital for mental health in Baghdad, Iraq, also approved the study (Ref. No. AS 6751 in 6-11- 2022 & Ref. No. AS 6752 in 6-11- 2022) respectively.

Author Contribution

The authors confirm their contribution to the paper as follows: study conception and design: Both authors; data collection: the first author; analysis and interpretation of results: Both authors; draft manuscript preparation: Both authors. All authors reviewed the results and approved the final version of the manuscript.

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