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The Association Between -697C>G and -997G>A polymorphism of the HTR2C Gene and the Metabolic Syndrome in Iraqi Schizophrenic Patients

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ABSTRACT

Background: Serotonin 2C receptor (5-HT2C) antagonisms play a role in the metabolic adverse effects induced by olanzapine treatment of schizophrenic patients.

Objectives: This study aimed to determine if there is an association between the genetic polymorphisms of -697G/C and -997G>A in the promoter region of the 5-hydroxytryptamine 2C receptor (HTR2C) gene and olanzapine-induced metabolic syndrome in patients with schizophrenia.

Patients and Methods: A cross-sectional study involving 50 hospitalized patients (28 males, 22 females, mean age: 47.60 years with schizophrenia. The patients were divided into two groups according to metabolic syndrome classification criteria. Following polymerase chain reaction amplification of the extracted deoxyribonucleic acid, sequencing by the Sanger method was performed to identify the polymorphism at the HTR2C promoter region.

Results: Olanzapine significantly increases the waist circumferences and body mass index in the metabolic syndrome group (P value 0.001). The GG genotype and G allele of the -697C>G were significantly present in the metabolic syndrome group. The study failed to find any association between the genotypes of -997G>A and the tendency to have metabolic syndrome.

Conclusion: The presence of the GG genotype or G allele in the -697C>G variant was significantly associated with the metabolic syndrome group. None of the -997G>A genotypes were associated with an increased risk of developing metabolic syndrome.

Keywords: *Olanzapine, Genetic polymorphism, -697C>G , -997G>A ,Schizophrenic patients,5-hydroxytryptamine 2C receptor (HTR2C) gene*

INTRODUCTION

Schizophrenia is a complex, heterogeneous behavioral and cognitive syndrome that seems to originate from disruption of brain development caused by genetic or environmental factors, or both(1).

Patients with schizophrenia are at a greater risk for metabolic dysfunctions than other individuals due to a number of reasons, including an inactive lifestyle, poor dietary choices as well as the side effects of antipsychotic medications(2).

Genetic factors are thought to play a role in individual response to antipsychotic drugs—both in terms of benefits from the treatment and susceptibility to side effects. Variations in gene sequence, called polymorphism, might influence the proprieties of encoded proteins, and result in individual response to drugs(3).

metabolic side effects of antipsychotic drugs including lipid abnormalities, disturbed blood glucose , blood pressure and weight gain can have a major impact on the treatment of psychiatric patients(4).

The mechanism behind the metabolic abnormalities is unclear. The highly divergent prevalence in different populations suggests that genetic makeup is a modulating factor. One of the potential genetic determinants is genetic variation in the serotonin 2C (5-HT2C) receptor encoded by the X-chromosomal 5-hydroxytryptamine (serotonin) receptor 2C (HTR2C) gene. The 5-HT2C receptor is of interest because showing genetic association with obesity and eating disorders in patients with and without psychiatric disorders(5).

It is essential to study the effect of genetic variation on olanzapine treatment because , unlike other variables that can influence and modulate the olanzapine response , genetic determinants are stable throughout a patient's lifetime(6).

Multiple research articles describe a correlation between variants of the HTRC2 gene and olanzapine response. Multiple loci are statistically associated with weight gain (rs498207; G997A, rs3813928; C759T, rs3813929) and metabolic syndrome (rs1414334; G697C, rs518147)(7,8,9).

Two previous studies in Iraq demonstrated that olanzapine has significant effects on serum glucose concentration and lipid profile in addition to its effect on body weight (10)(11), but no study has evaluated the association between metabolic syndrome and HTR2C polymorphism in patients with schizophrenia.

Therefore, the present investigation aimed to assess the association between genetic polymorphism in the promoter region of 5-HTR2C gene at-697G/C and -997G>A variants and the tendency to develop metabolic syndrome in a sample of Iraqi schizophrenic patients receiving olanzapine.

PATIENTS AND METHODS
Study design
A cross-sectional study was conducted at two mental institution centers (Ibn Rushd Psychiatric Training Hospital and Al-Rashad Hospital for mental health) in Baghdad, Iraq.

Inclusion Criteria
 * Adult Patients with age range of (18-70) years diagnosed with schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders (DSM)-V   diagnostic criteria for schizophrenia (12).

 * The patients must have received atypical antipsychotic treatment (olanzapine dose of 10 mg/day) for at least one year.

Exclusion criteria
* patients who used olanzapine for less than one year.
* Patients have psychotic disorder due to general condition, or mental retardation.
* Patients with medical conditions are known to affect the brain or medical condition requiring treatment with medication that has psychotropic effects.
* Patients who are taking drugs interact with olanzapine, for example, pregabalin, Vitamins such as B12, C, and D3.
* Pregnant or lactating women.
* Patients have hypertension, DM, hyperlipidemia, or obesity when starting treatment with antipsychotic drugs.
* Patients taking mood stabilizers (carbamazepine, sodium valproate and lithium).

Patients' groups
The patients were classified into two groups according to metabolic syndrome criteria(13).

The study includes 50 patients divided into two groups as follows:

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

Group B (n=20): schizophrenic patients without metabolic syndrome.

The medical history of all patients has been taken, and detailed clinical checks with a particular questionnaire formula occupied for each patient contain:

Gender, age, education, occupation, residence, marital status, height, waist size, weight, family history, medical history (diabetes, hypertension, dyslipidemia, cardiovascular disease, psychiatric disease), duration of disease, duration of olanzapine treatment, current medication, smoking, blood pressure, pulse rate. The study design is presented in the following Figure 1.
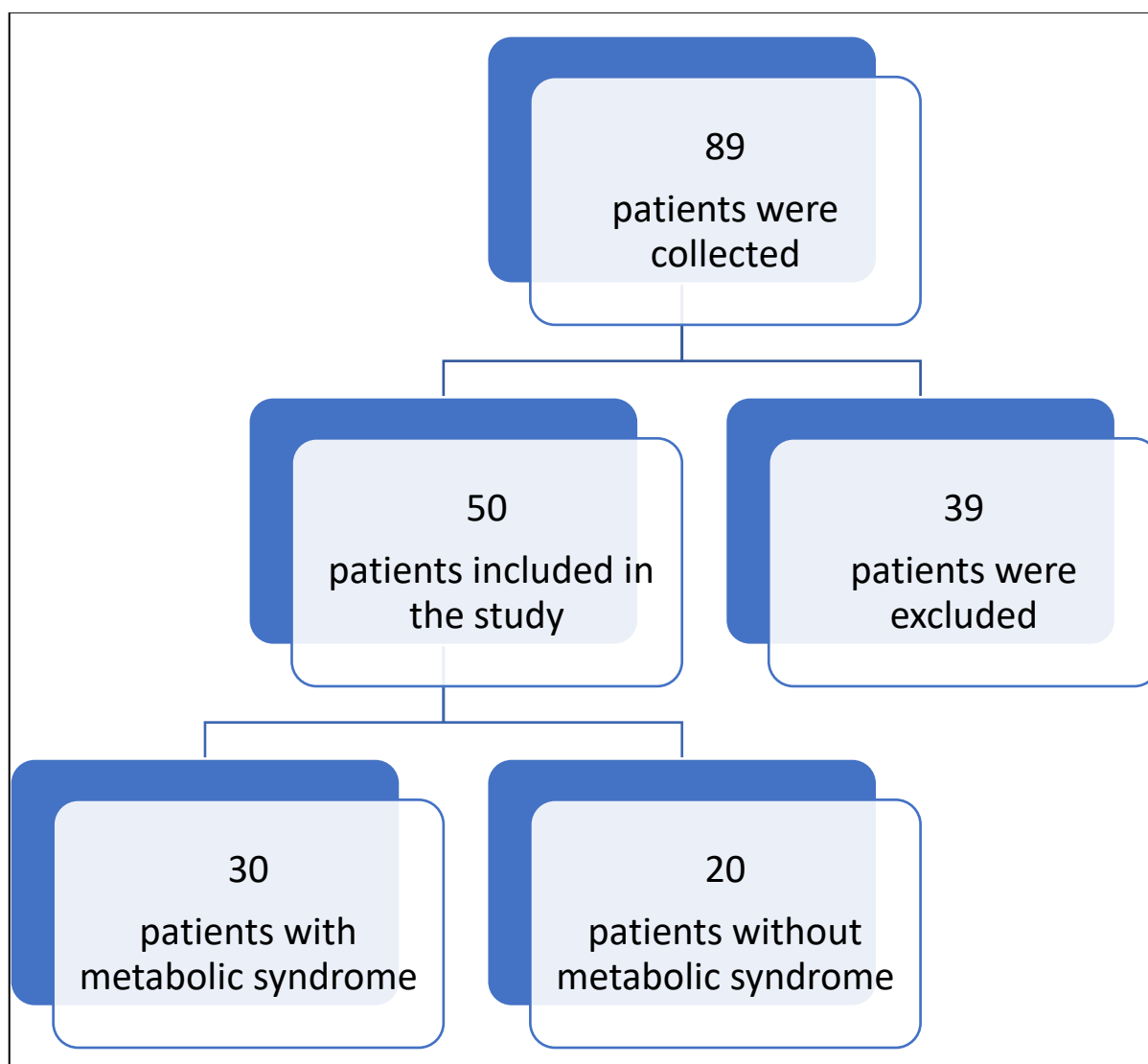

FIGURE 1: Total number of patients who participated in the current study.

Data collection
By using predesigned data collection sheet ,Data on demographic characteristics such as gender, age, education, occupation, residence, marital status, height, waist size, weight, family history,

medical history (diabetes, hypertension, dyslipidemia, cardiovascular disease, psychiatric disease), duration of disease, duration of olanzapine treatment, current medication, smoking, blood pressure, pulse rate, weight,

disease duration. laboratory data such as FBS, and lipid profile (cholesterol, triglycerides, HDL,VLDL) were measured.

Sample collection and preparation

forearm vein of each patient was punctured to get 5 mm of the venous blood. Two milliliters of the blood converted into an ethylenediaminetetraacetic acid (EDTA) tube for deoxyribonucleic acid (DNA) extraction. The remaining Three milliliters of the collected blood specimen were transferred to a gel tube and then centrifuged for ten minutes at (4000 rpm) to get serum. Then the separated serum was kept in an Eppendorf tube and frozen at (-20 °C) until samples collection finished.

DNA extraction

The Promega ReliaPrepTM Blood gDNA Miniprep System for Genomic DNA (Promega Corp., WI, USA) provides a practical approach for purifying DNA from blood samples. Polymerase chain reaction (PCR) was used for enzymatic amplification with the Master Taq polymerase enzyme and a hybrid thermal cycler.

The Primer

The HTR2C gene DNA sequences were taken from the NCBI GenBank database. Primer Premier 3 software was used to generate PCR primers (Table 1), with a melting temperature of (56 , 58 , 60°C), a primer length of (18 to 23) nucleotides, and a PCR amplicon length of (800 to 1000) base pairs.

TABLE 1: The sequences, Annealing temperature, 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 determine the optimal annealing temperature for primers, we amplified the DNA template using the identical primer pair (Forward) (Reverse) at annealing temperatures of 56, 58, 60°C. The best annealing temperature for the primer was 56°C as seen in Figure 2. The PCR amplifications were performed with 20 μL volumes.
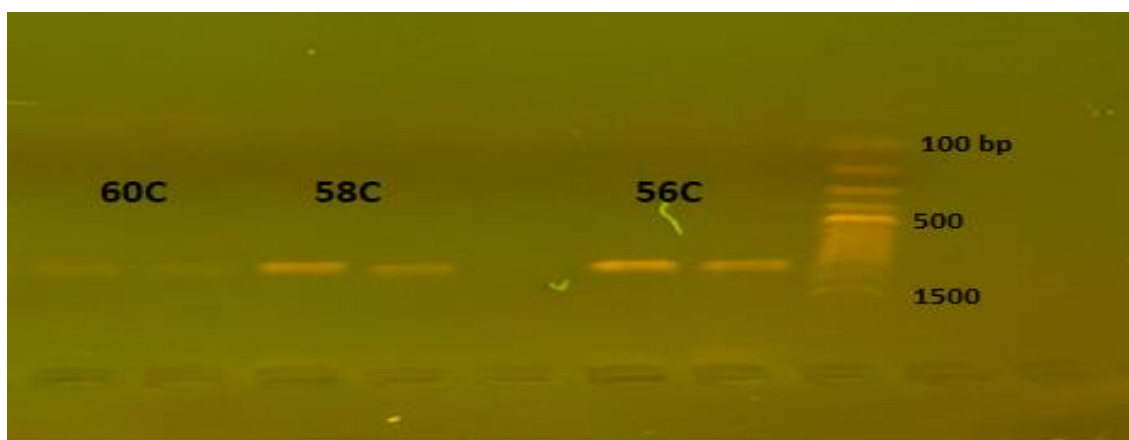

FIGURE 2: Primer optimization at annealing temperatures of 56, 58 and 60°C

Sequencing of PCR products

The PCR product was sequenced by the Sanger method of sequencing using a DNA analyzer (ABI3730XL) "Macrogen Corp., Seoul, South Korea". The results were obtained by electronic mail and analyzed with the use of Geneious Prime software version 2021.1.1 "Biomatters Ltd., Auckland, New Zealand; www.geneious.com".

Statistical analysis

Statistical analysis was performed using the "IBM SPSS" for Windows version 26.0 software "IBM Corp., Armonk, NY, USA" and GraphPad Prism "GraphPad Software, CA, USA". Continuous variables were expressed in mean ± standard deviation. Allele and genotypes were presented in number and frequency. The Shapiro-Wilk test was used to test the normality of the results. Since the results demonstrated a normal distribution for all variables (P.Value > 0.05), the unpaired t-test was used to determine a significant difference in demographic characteristics and parameters between the two groups. One-way analysis of variance (ANOVA) was used to analyze the difference between the means of more than two groups. Then, a post hoc analysis was used whenever a significant difference between three sample means was revealed by the ANOVA. The chi-square test or Fisher exact test was used to test group differences in proportions. The phi correlation coefficient (phi) and binary logistic regression were used to measure the correlation between each genotype and the likelihood of developing a metabolic syndrome. A p-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Basic Descriptive Data

Demographic data for all participants were demonstrated in Tables 2A & 2B. The study recruited a convenient sample of hospitalized patients (n=50) of both sexes (22 women (44%) and 28 men (56%)). The mean age of the study group was 47.60 years (SD=9.293), with a range of 24–69 years.

In this study, 39 patients have excluded: 8 patients on carbamazepine, 7 patients on sodium valproate, 4 patients with pre-existing hypertension, 1 patient on thyroxin, 7 patients for lack of baseline glucose levels (prior to starting olanzapine treatment), and 12 patients for lack of baseline lipid profile (3 triglycerides, 5 cholesterols, 4 HDL) prior to starting olanzapine treatment.

TABLE 2A: 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	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 2B: Demographic and clinical data for quantitative parameters of the study groups.

	Metabolic		Non Metabolic		P value
	Mean	SD	Mean	SD	
Age	47.40	9.25	47.90	9.59	0.995
Hight (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	97.57	15.40	91.95	25.32	0.057
BMI	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)	147	19	121	16	0.668
BP (Diastolic)	92	16	79	10	0.053
Pulse Rate	88	21	90	20	0.798

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 3 showed that several adjuvant therapies were given with olanzapine to control schizophrenia, and only three patients used olanzapine alone. However, the only significant difference between the two groups was in the use of Fluphenazine ampule and Procyclidine tablet.

TABLE 3: 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 200mg	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

The Sanger sequencing analysis for the study sample revealed two polymorphic sites at rs518147 (-697C>G) and rs3813928 (-997G>A).

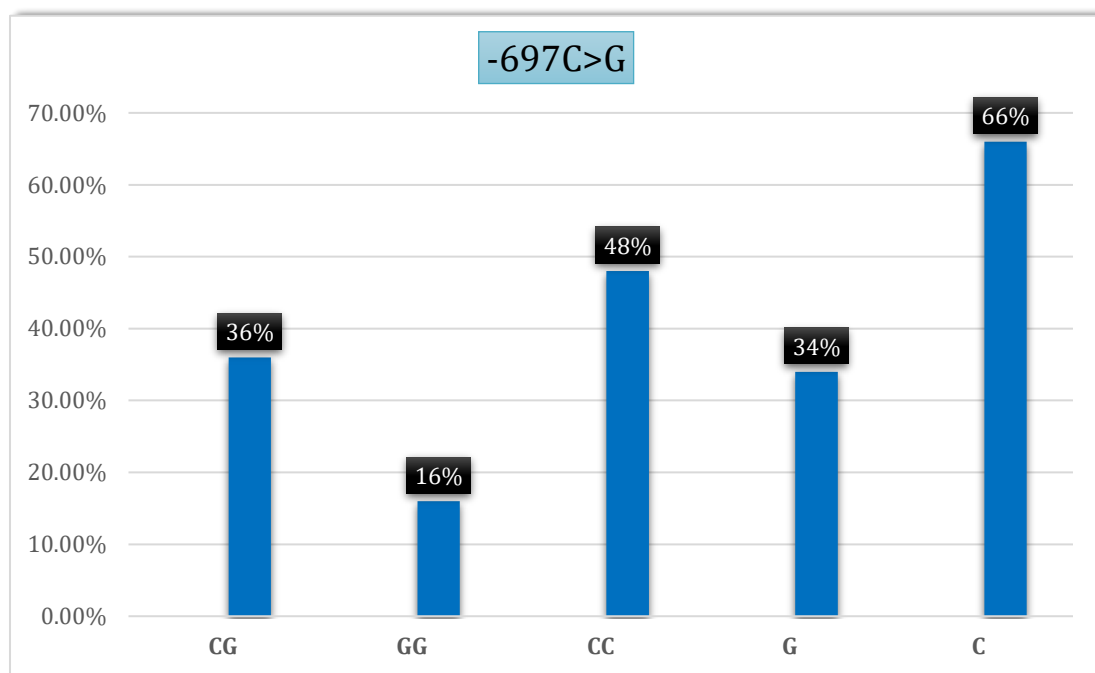Figure 1 demonstrates the high proportions of CC genotypes in the -697C>G.

FIGURE 3: Proportion of genotypes and alleles for -697C>G in schizophrenic patients (n=50).

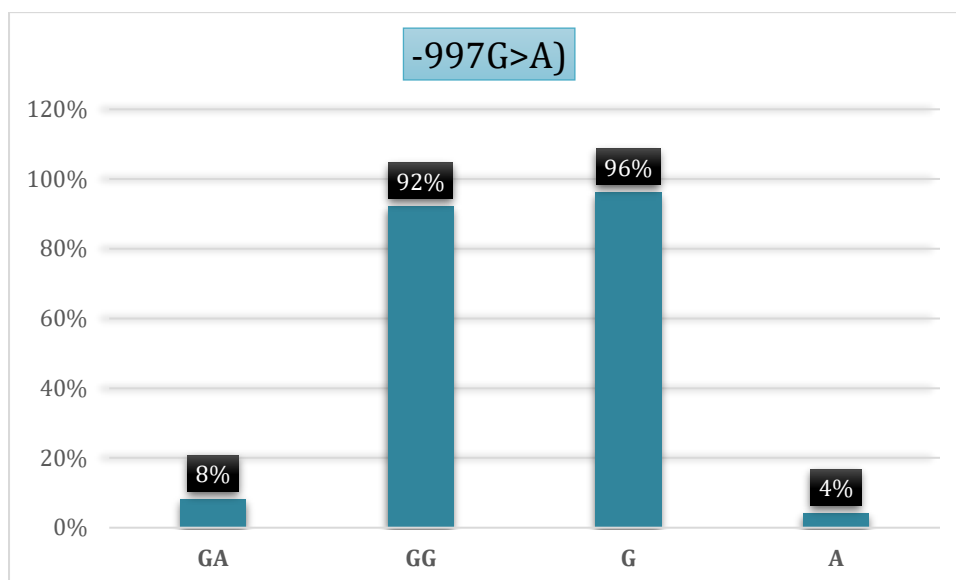Notably, in Figure 2 ,the GG genotype was the most prevalent in -997G>A.

FIGURE 4: Proportion of genotypes and alleles for -997G>A in schizophrenic patients (n=50).

Additionally, the results of this study indicated that there was a significant incidence the CG genotype of -697C>G (p=0.031) in the metabolic syndrome group as mentioned in Table 4.

Regarding the difference in alleles frequencies between the metabolic and non-metabolic, the results show a significant difference in the G allele of -697C>G SNP (Table 4).

TABLE 4: Difference in genotype frequencies between metabolic and non-metabolic groups.

SNP	Genotype	Metabolic		Non-Metabolic		*P value
		N	%	N	%	
-697C>G	CG	14	46.7%	4	20.0%	a 0.031
	GG	6	20.0%	2	10.0%	a 0.289
	CC°	10	33.3%	14	70.0%	b 0.414
	C	34	56.7%	32	80%	b 0.157
	G	26	43.3%	8	20%	b 0.016
-997G>A	GA	2	6.7%	2	10.0%	a 1.000
	GG°	28	93.3%	18	90.0%	b 0.140
	G	58	96.7%	38	95%	b 0.677
	A	2	3.3%	2	5%	a 1.000

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).

°: the wild genotype.

Correlations between the variant's genotypes and the likelihood of metabolic syndrome
The Phi coefficient analysis was used to investigate the correlation between each genotype and the tendency of metabolic syndrome. Table 5 shows that the only genotype that appeared to raise the likelihood of metabolic syndrome was the CG of (-697 C>G) SNP. On the other hand, The CC genotype of -697 C>G was negatively correlated with the tendency for a metabolic syndrome.

TABLE 5: Correlation between each genotype and the likelihood to have metabolic syndrome.

SNP	Genotype	Phi-coefficient	P. value
-697C>G	CG	0.301	0.034*
	GG	0.150	0.288
	CCº	-0.399	0.005*
-997G>A	GA	-0.048	0.735
	GGº	0.048	0.735

Phi-correlation coefficient was used to find the association. P.value < 0.05 was considered statistically significant. º: the wild genotype. *: Significant difference between the groups.

In addition to Phi correlation, the binary logistic regression analysis was used to predict the influence of changing the genotype from the wild type to another genotype on the tendency to get metabolic syndrome, as seen in Table 6. The results clearly showed that changing from the wild genotype to the polymorphic one was not associated with any significant tendency to get metabolic syndrome in schizophrenic patients.

TABLE 6: Binary logistic regression analysis of genotypes to predict the tendency to get metabolic syndrome.

Variant	Coefficient	OR.	P. Value	95% Confidence Interval for Exp(B)	
				Lower Bound	Upper Bound
-697C>G	1.435	4.200	0.117	1.238	19.399
-997G>A	-0.442	0.643	0.672	0.083	4.981

Binary logistic regression analysis. P.value < 0.05 was considered statistically significant.

DISCUSSION

The elevated prevalence of MS in antipsychotic-treated schizophrenic patients compared to the general population highlights the need for regular monitoring of various metabolic parameters in antipsychotic-treated schizophrenic patients [14].

the current study tries to investigate the effect of genetic polymorphism in the promoter region of the HTR2C gene and the tendency to develop MS in the Iraqi schizophrenic patients.

Regarding the study's demographic characteristics, there was no association between the metabolic syndrome (P > 0.05) and the covariates of age, sex, occupation, marital status, residence, family history, education, and smoking status. Uniformly to Daray F et al. [15] study in which, he found these variables were independent in his research for 48 Caucasian women in Argentina.

In the current study, several adjuvant therapies were given with olanzapine. However, the only significant difference between the two groups was in the use of the fluphenazine ampule and procyclidine tablet. The current study result can be explained because fluphenazine use is also associated with an increase in weight gain by 37%, according to Maslov et al. [16] study, which may be considered a risk factor for metabolic syndrome, especially if used with olanzapine.

Although procyclidine use was connected to Parkinsonism [17], no previous study connected the use of procyclidine with metabolic syndrome.

In this study, Regarding the prevalence of metabolic syndrome in men and women of hospitalized patients with schizophrenia was 60% and 40%, respectively. a study by Cohn et al. [18] found that the prevalence of metabolic syndrome in men and women with schizophrenia was 42.6% and 48.5%, respectively. evidence supported sex differences in serotonin neurotransmission and psychiatric disorders caused by disruptions in the serotonin system, hormonal regulation, and genetic effects [19].

The most common findings in our patients with metabolic syndrome were abnormal waist circumference(significant difference between metabolic and non-metabolic groups, P value 0.001) . The mean body mass index (BMI) was significantly higher in patients with

metabolic syndrome in our study than those with non-metabolic syndrome (P value= 0.001) and these results substantiate those by Kato et al. (20), who found that the most common metabolic syndrome criteria were abnormal waist circumference.

The results of this study identified two SNPs in the promoter region of the HTR2C gene in a sample of fifty schizophrenic patients treated with olanzapine: -697C>G and -997G>A. However, no study has evaluated the relationship between these SNPs and metabolic syndrome in Iraqi schizophrenic patients.

Many studies have examined the effect of SNP combination in the HTR2C gene on effect of atypical antipsychotic drugs (21)(7).

For instance, the SNPs -697G>C and -997G>A in the HTR2C gene and their association to the metabolic syndrome were evaluated in 112 hospitalized and 27 non hospitalized psychiatric patients with a chronic psychiatric Disorder (mainly schizophrenia or schizoaffective disorder) taking olanzapine, risperidone or clozapine(3).

The current study confirmed that the wild CC genotype of -697C/G was present in 48% of the participants, followed by heterozygote CG (36%) and the lowest one, homozygote GG(16%). In addition, the C allele was present in 66% of patients, while the G allele was only present in 34% of patients.

Similarly, BR Godlewska et al (22) found that the genotypes distribution of -697 was GC 19/54 (35.2%) and CC 10/54 (18.5%) patients with schizophrenia using olanzapine.

The presence of the CG genotype or the G allele of -697G/C variants is significantly associated with an increase in the risk for metabolic syndrome in olanzapine-treated patients, which is consistent with the findings of a previous study (23) that found the CG genotype to be associated with metabolic syndrome in patients treated with clozapine, olanzapine, or risperidone. In contrast to the current study's finding that the G allele was significantly associated with metabolic syndrome, a meta-analysis conducted by Xiaojie Ma et al. (8) revealed that the HTR2C -697C allele was positively associated with metabolic syndrome.

Two studies have investigated the association between 697C/G (rs518147) and antipsychotic-induced weight gain. In a study of 107 atypical-naive European patients treated with olanzapine, the C allele was found to be protective against increased BMI (23). While the second study (22) consists of 36 antipsychotic-naive patients (P = 0.008) and reaches to the same conclusion.

In addition to the small sample size of the current research, the difference between the current study's results and those of previous studies could be attributed to the ethnic variation between our sample and the samples of other studies. Ethnicity can be a significant confounding variable in genetic research, as the frequency of gene variants can vary between populations. In addition, linkage disequilibrium patterns may differ between ethnicities (22).

In the case of the –997 G/A variant, the present study findings indicated that the GG genotype was the most prevalent (92%) of the patients, followed by the GA genotype (8%). In terms of allele distribution, the G allele was the most prevalent, occurring in more than 96% of patients, whereas the A allele occurred in only 4% of patients.

The current study failed to find an association between the genetic polymorphism and the tendency to get metabolic syndrome, in contrast to previous studies (7,9, 24) that found G allele carriers increase the tendency for weight gain and metabolic syndrome.

The contrast result could be attributed to the small number of patients with metabolic syndrome, but it is more likely attributable to the complex involvement of serotonergic transmission and other neurotransmitters in the mechanisms of the metabolic syndrome's patient components.

The current study was associated with several limitations, such as the unspecified duration of olanzapine use, which may be attributed to the limited number of patients that can be included according to the inclusion criteria. However, the duration of olanzapine use was not significantly different between the metabolic and non-metabolic groups, and no correlation was found with all the studied parameters, meaning its effect was neutralized in the studied sample. Another limitation was that we could not measure the effect of olanzapine alone without the adjuvant treatment used with it because most schizophrenic patients need combination therapy. However, the current study results showed that the only significant difference between the two groups was in the use of Fluphenazine ampule and Procyclidine tablets.

CONCLUSION

The presence of the GG genotype or G allele in the -697C>G variant was significantly associated with the metabolic syndrome group. None of the -997G>A genotypes were associated with an increased risk of developing metabolic syndrome.

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