

Role of D₂ receptor (–141 C Ins/Del) genetic polymorphism on olanzapine-induced adverse drug reaction in schizophrenic patients

Zahra Jawd Mohammed Ali¹, Atheer Majid Rashid Al-juhiashi²

¹ Department of Pharmacology and Toxicology, College of Pharmacy, University of Kerbala, Karbala, Iraq

² Department of Clinical Pharmacy, College of Pharmacy, University of Kerbala, Karbala, Iraq

Corresponding author: Zahra Jawd Mohammed Ali (zahranh2019@gmail.com)

Received 2 September 2023 ♦ Accepted 9 September 2023 ♦ Published 12 January 2024

Citation: Ali ZJM, Al-juhiashi AMR (2024) Role of D₂ receptor (–141 C Ins/Del) genetic polymorphism on olanzapine-induced adverse drug reaction in schizophrenic patients. *Pharmacia* 71: 1–8. <https://doi.org/10.3897/pharmacia.71.e112064>

Abstract

Olanzapine is commonly prescribed for the management of schizophrenia and is associated with many adverse effects like weight gain, hyperglycemia, and hyperprolactinemia, which may increase the risk of other diseases like diabetes mellitus and cardiovascular diseases. Genetic polymorphism of the D₂ receptor may be responsible for the incidence of such adverse effects. This study aimed to assess the role of D₂ receptor–141 C Ins/Del (rs1799732) genetic polymorphism and olanzapine-induced adverse effects in Iraqi schizophrenic patients. The case-control study was performed from October 2022 to April 2023 in Al-Hassan Al-Mojtaba Hospital. A total of 100 schizophrenic patients consisting of both genders, aged between 20 and 65 years, were recruited from the Psychiatry Outpatient Department, and 50 apparently healthy without any disease comprising both genders aged 20 to 63 years, served as a control group and were also enrolled in this study. Plasma level of FBS, HbA1c, lipid profile, and prolactin were measured, and genotyping of D₂ Receptor–141 C Ins/Del (rs1799732) Polymorphisms was detected using the RFLP method. The heterozygous (Ins/Del) and mutant (Del/Del) alleles of D₂ receptor–141 C Ins/Del (rs1799732) was significantly predominated in schizophrenic patient and absent in healthy volunteers. Schizophrenic patients with the deletion allele of D₂ receptor–141 C Ins/Del and who were administered olanzapine (rs1799732) exhibited notably higher susceptibility to metabolic adverse effects induced by olanzapine, such as weight gain, hyperglycemia, dyslipidemia, and hyperprolactinemia. In conclusion, the genetic polymorphism of D₂ receptor–141 C Ins/Del (rs1799732) was significantly associated with olanzapine induce metabolic adverse effects in Iraqi schizophrenic patients.

Keywords

Olanzapine, D₂ receptor, schizophrenia, genetic polymorphism, metabolic disorder

Introduction

Schizophrenia is a crippling mental condition that affects 1% of people worldwide and affects between 0.24 and 4.7% of the population in the Arab world. In Iraq, the prevalence of psychiatric disorders rose from 12% in 2000 to 15% in 2020, with schizophrenia considered

the most common disorder (Ahmed 2022). Effective antipsychotic agents are those that align with the pathology of schizophrenia by either blocking dopamine (D₂) receptors, demonstrating greater selectivity to serotonin (5-HT_{2A}) than D₂ receptors as multi-target antagonists, or acting as partial agonists specifically targeting the D₂ receptor of alpha-type of G-protein-coupled receptors

(Kaczor et al. 2021). Atypical antipsychotic agents are medications that effectively alleviate both positive and negative symptoms of schizophrenia. They have shown efficacy in treating resistant types of schizophrenia and carry a lower risk of extrapyramidal symptoms (EPS) and other movement disorders, such as parkinsonism, akathisia, dystonia, and tardive dyskinesia, which are associated with physical disability and subjective discomfort and distress. However, they may be associated with various adverse effects, including metabolic syndrome (such as weight gain, hyperglycemia, and diabetes), hyperprolactinemia, sedation, sexual dysfunction, cerebrovascular events, and anticholinergic effects (Grinchii and Dremencov 2020). A commonly prescribed atypical antipsychotic agent is olanzapine, which inhibits the action of dopamine at the post-synaptic receptor in the mesolimbic pathway, specifically at the D₂ receptors via binding loosely to these receptors and readily dissociates, thereby allowing normal dopamine neurotransmission to occur. Thus, it leads to a reduction in positive symptoms experienced by patients, such as hallucinations, delusions, and disorganized speech, thought, and behavior (Grinchii and Dremencov 2020). Weight gain, dyslipidemia, hyperglycemia, and hyperprolactinemia are frequently observed side effects of olanzapine in patients with schizophrenia, which may increase the risk of other diseases like diabetes mellitus and cardiovascular diseases, which may reduce the quality of life (Manu et al. 2015; Zhang et al. 2021; Yang et al. 2018). Many studies suggested that D₂ receptor gene polymorphism was associated with olanzapine-induced adverse drug reactions (Miura et al. 2016). The presence of a specific genetic variation in the D2 receptor gene, known as the 141C Insertion/Deletion (Ins/Del) polymorphism (rs1799732), has functional implications by impacting the density of dopamine receptors in the striatum. This genetic variation in the 5'-promoter region of the D2 receptor gene is strongly associated with schizophrenia. The InDel polymorphism rs1799732 is specifically found in the gene promoter. Individuals with the deletion variant tend to experience greater weight gain when treated with olanzapine compared to those without the deletion. This mutation occurring in the promoter region of the D₂ receptor gene may lead to variations in the receptor's responsiveness to the effects of antipsychotic medications regarding reward signals related to satiety and food consumption (Paderina et al. 2022). Another study mentioned that Taq1A is a well-researched polymorphism of the D₂ receptor gene, located downstream of D₂ receptor within a novel kinase gene. It exhibits two different forms, A1 and A2. Patients who possess the A1 allele and receive olanzapine treatment tend to have prolactin levels approximately 40% higher than patients who do not carry this allele (López-Rodríguez et al. 2011). This study aimed to investigate the common adverse effects of olanzapine and its association with D₂ receptor -141 C Ins/Del (rs1799732) gene polymorphism in Iraqi schizophrenic patients.

Subjects, materials, and methods

Subjects

The adult-aged patients or older of both genders were estimated for competence. Patient schizophrenia is diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (Tandon et al. 2013). After completing a written consent form containing a full explanation of the study's objective and a request to complete a specially created questionnaire, all participants were enrolled. Patients receiving 10 mg /day olanzapine from 6 months up to years with no additional disorder were included in this study. Patients with previous hyperglycemia/diabetes, hypotension, weight gain, hyperprolactinemia, or tardive dyskinesia before taking olanzapine or receiving treatment or any other medicine that interacts with olanzapine such as bromocriptine, levodopa, methyldopa were excluded from the study.

Study design

The case-control study was performed from December 2022 to April 2023 in Al-Hassan Al-Mojtaba Hospital. The 100 male and female patients aged between 20 and 65 years were recruited from the Psychiatry Outpatient Department, and 50, apparently healthy without any disease comprising both males and females aged 20 to 63 years, were also enrolled and served as a control group. The scientific and ethical committee approved the study, Kerbala University, College of Pharmacy, and Ministry of Health of Iraq - Karbala health department, with the project being assigned No: 244.

Samples collections

All patients and healthy controls underwent overnight fasting before having blood drawn. The blood was divided into two parts: the first part (2 ml) was kept in an EDTA tube for the HbA1c test and DNA extraction, and the second part (3 ml) was kept in a gel tube for serum isolation for the hormonal and biochemical tests (Sugai et al. 2020).

Determination of body mass index

The Body Mass Index (BMI) is determined by an individual's weight and height measurements. To calculate BMI, one divides the body weight by the square of the body height. The result is expressed as kilograms per square meter (kg/m²), with weight in kilograms and height in meters.

Biochemical assessment

The plasma level of fasting blood sugar (FSB) and lipid profile including total cholesterol (TCHO), triglyceride (TG), high density lipoprotein (HDL) were measured using multipurpose dry chemistry analyzer termed Fujifilm Dri-Chem. NX500 Apparatus and kits (Germany). Low density lipoprotein (LDL) and Low density lipoprotein (VLDL)

can be determined dependent on the values of TCHO, TG, and HDL according to the Friedewald equation:

$$\text{LDL} = \text{TCHO} - \text{HDL} - \text{TG}/5$$

The term TG/5 represents an estimate of VLDL⁽¹²⁾.

While the plasma level of HbA1c and prolactin were assessed according to ichroma biotechnology technic using ichroma HbA1c and prolactin kits and apparatus (Boditech Med Inc. – Korea).

Genotyping for D₂ receptor (–141 C Ins/Del) polymorphisms detection

The genomic DNA was purified from whole blood using the phenol/chloroform method. For the detection of the D₂ receptor gene –141C ins/del polymorphisms, the polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP) method was employed in plate thermal cycles using the Mastercycler gradient system from Eppendorf, Germany. To amplify the target regions, oligonucleotide primers were designed based on the published genomic sequences from GenBank NC_000011.9. The details of the primers, annealing temperature, restriction enzyme used, and fragment sizes can be found in Table 1. Each 25 µL PCR reaction mixture consisted of 2 µL of DNA, 2.5 µL of 10×ExTaq Buffer, 5 µM of each primer, 25 mM MgCl₂, 2.5 mM dNTPs, and 1.25U of ExTaq enzyme from Takara Biotech, Japan. The PCR conditions were as follows: an initial denaturation step at 94 °C for 5 minutes, followed by 30 cycles of 30 seconds at 94 °C, 40 seconds at either 68 °C or 57 °C (depending on the polymorphism being analyzed), and 40 seconds at 72 °C. After PCR amplification, the products were subjected to digestion with appropriate restriction endonucleases. Subsequently, 10 µL portions of both digested and undigested samples were electrophoresed on a 2% agarose gel, and the DNA bands were visualized by staining with ethidium bromide (0.5 µg/mL) and exposed to UV light. Photos were taken using a video camera for documentation. The results were validated by two independent observers. Furthermore, the RFLP findings were cross-verified by DNA sequencing using 10 randomly selected samples.

Table 1. Primers sequences of D₂ Receptor, –141 C Ins/Del (rs1799732) polymorphisms.

Primers	Annealing temperature	Restriction enzyme	Allele	Product Size (bp)
P1:5'ACTGGCGAGCAGACGGTGAGGACCC-3'	68 °C	BstN I	C	C/C: 144, 160
P2:5'-TGCGCGCTGAGGCTGCCGGTTCGG-3'			Del-C	C/-: 303, 144, 160 -/-: 303 bp

Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS 26). Descriptive statistics for the numerical data were present as the mean and standard error of the mean (Mean ± SEM), and the non-numerical data were number and %. Numerical data was analyzed by using an independent sample T-test and a one-way ANOVA-post-hoc-LSD test. Non-numerical data was an-

alyzed by using the Chi-square test. The P values less than 0.05 are considered statistically significant.

Result

Demographic data

The demographic data, including age, gender, BMI, and waist circumference, were assessed in both healthy individuals and volunteers with schizophrenia. There were no significant differences in age and gender ($P > 0.05$) between the healthy volunteers and those with schizophrenia, as shown in Table 2. Schizophrenic patients demonstrated significant weight gain, as evidenced by increased BMI and waist circumference, compared to the healthy individuals ($P < 0.05$), as shown in Table 2.

Table 2. Demographic data of both healthy and schizophrenic volunteers (data present as mean ± S.E and No (%)).

Variables	Volunteer		P – value	
	Healthy (n = 50)	Schizophrenic (n = 100)		
Age (y)	38.98 ± 1.73	39.11 ± 1.44	0.256	
Gender	Male	32 (64%)	18 (36%)	0.190
	Female	55 (55%)	45 (45%)	
BMI	Male	24.43 ± 0.27	28.39 ± 0.62	<0.0001*
	Female	24.79 ± 0.22	30.58 ± 0.83	<0.0001*
Waist Circumference (cm)	Male	85.69 ± 0.90	94.21 ± 1.95	0.002*
	Female	75.72 ± 1.39	95.37 ± 2.04	<0.0001*

*: Significant effect ($P < 0.05$) compared to healthy group.

Prevalence of D₂ Receptor Genes –141 C Ins/Del (rs1799732)

The results of genotype D₂ receptor –141 C Ins/Del (rs1799732) genetic polymorphism were a clear band with a molecular size of 144, 160, and 303 bps (Fig. 1). The wild allele (Ins/Ins) was predominate (100%) in healthy volunteers and about (75%) in schizophrenic patients, while the heterozygous allele (Ins/Del) and mutant allele (Del/Del)

were only presented in schizophrenic individuals with the ratio of 12% and 13% respectively as shown in Fig. 2. The frequencies of the D₂ receptor alleles –141 C Ins/Del (rs1799732) were significantly different between the healthy and schizophrenic volunteers ($P < 0.05$) as shown in Table 3. There were significant differences among both genders of healthy and schizophrenic individuals regarding three different alleles of rs1799732 (141c ins/del) ($P < 0.05$) as explained in Tables 4, 5 and Fig. 3.

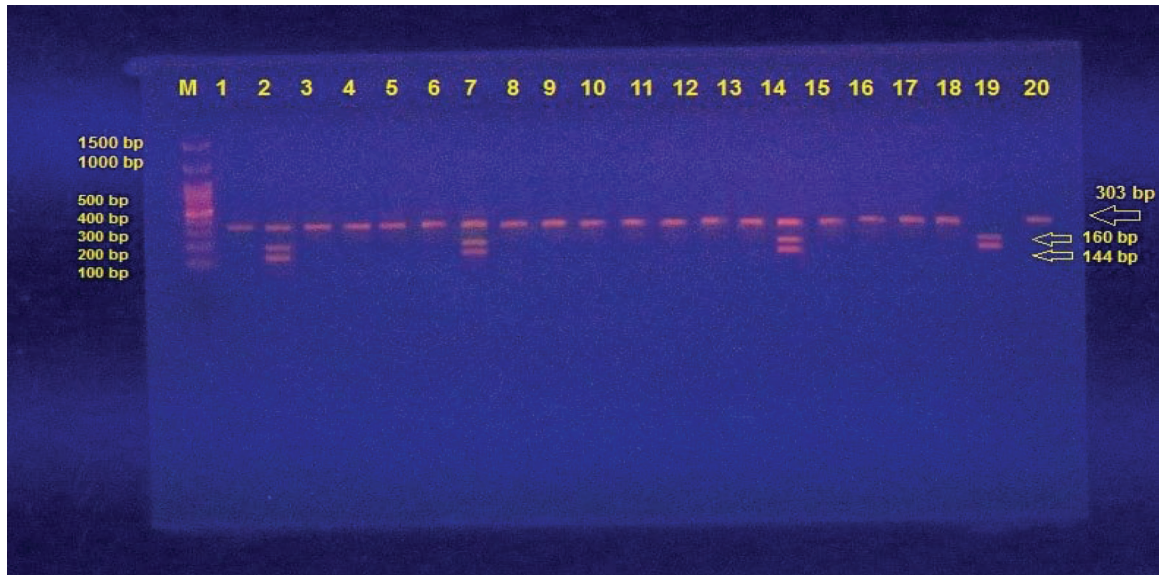


Figure 1. Genotyping of D2 Receptor Genes -141 C Ins/Del (rs1799732).

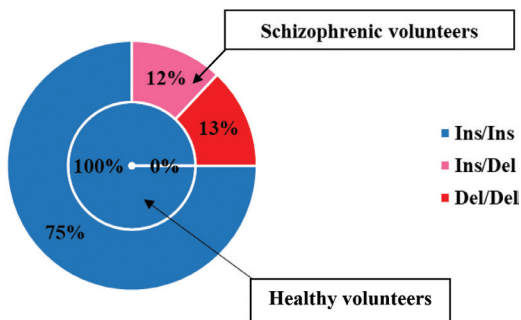


Figure 2. The Prevalence of D2 Receptor alleles rs1799732 (141c ins/del) among volunteers.

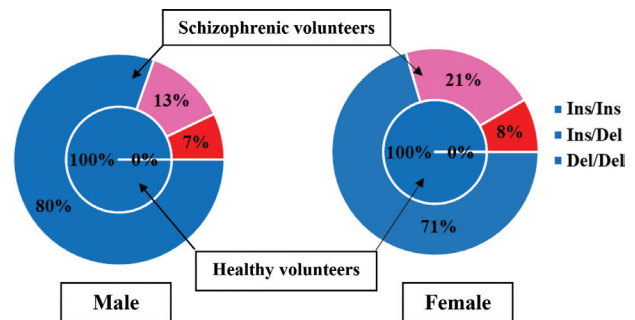


Figure 3. The Prevalence of D2 receptor alleles rs1799732 (141c ins/del) among both male and female volunteers.

Table 3. The Prevalence of D₂ receptor alleles rs1799732 (141c ins/del) among volunteers (data present as No (%)).

Volunteers	Alleles of rs1799732 (141c ins/del)			P - Value
	Ins/Ins	Ins/Del	Del/Del	
Healthy	50 (100%)	0 (0%)	0 (0%)	0.001*
Schizophrenic	75 (75%)	12 (12%)	13 (13%)	

*: Significant effect ($P < 0.05$) compared to healthy group.

Table 4. The Prevalence of D₂ receptor alleles rs1799732 (141c ins/del) among male volunteers (data present as No (%)).

Male volunteers	Alleles of rs1799732 (141c ins/del)			P - Value
	Ins/Ins	Ins/Del	Del/Del	
Healthy	32 (100%)	0 (0%)	0 (0%)	0.028*
Schizophrenic	45 (80.4%)	7 (12.5%)	4 (7.1%)	

*: Significant effect ($P < 0.05$) between all groups.

Table 5. The Prevalence of D₂ Receptor alleles rs1799732 (141c ins/del) among female volunteers (data present as No (%)).

Female volunteers	Alleles of rs1799732 (141c ins/del)			P - Value
	Ins/Ins	Ins/Del	Del/Del	
Healthy	18 (100%)	0 (0%)	0 (0%)	0.025*
Schizophrenic	30 (68.2%)	9 (20.5%)	5 (8.1%)	

*: Significant effect ($P < 0.05$) compared to healthy group.

Effects of D₂ receptor alleles 141c ins/del (rs1799732)² on metabolic parameters

Body weight

Both genders of schizophrenic patients who received olanzapine and had mutation type (Del/Del) of 141c ins/del (rs1799732) significantly increased in BMI as compared to those with schizophrenia and had the wild allele (Ins/Ins) ($P < 0.05$) as presented in the Table 6. There were no significant differences when The two genders of schizophrenic patients with heterozygous (Ins/Del) alleles compared to those with Ins/Ins and Del/Del alleles regarding BMI ($P > 0.05$) as shown in the Table 6. Moreover, the waist circumference of male schizophrenic patients with olanzapine and had either the heterozygous type (Ins/Del) mutant type (Del/Del) of 141c ins/del (rs1799732) were significantly high in comparison to those with schizophrenia and had the wild allele (Ins/Ins) (He et al. 2013). While the female schizophrenic patients who had the mutant type (Del/Del) of 141c ins/del (rs1799732) were significantly elevated as compared to those with schizophrenia and had the wild allele (Ins/Ins) ($P < 0.05$) as presented in the Table 6. There were no significant differences when male schizophrenic patients

Table 6. The effects of D₂ receptor alleles 141c ins/del (rs1799732) on body weight of both healthy and schizophrenic volunteers (data present as mean ± S.E).

Variables		Volunteer				P – value
		Healthy	Schizophrenic			
			Ins/Ins	Ins/Del	Del/Del	
BMI (kg/m ²)	Male	24.43 ± 0.27	27.75 ± 0.71	29.93 ± 0.56	32.88 ± 2.1	0.001 ^{a, b, c}
	Female	24.79 ± 0.22	29.68 ± 1.01	29.62 ± 1.22	33.77 ± 1.69	<0.0001 ^{a, b, c}
Waist Circumference (cm)	Male	85.69 ± 0.9	91.1 ± 2.12	104.86 ± 2.88	110.75 ± 3.92	<0.0001 ^{a, d, e}
	Female	75.72 ± 1.39	93.07 ± 2.6	98.00 ± 4.97	101.67 ± 2.87	<0.0001 ^{a, b, c}

^a: Significant effect ($P < 0.05$) when schizophrenic groups compared to healthy group.

^b: Significant effect ($P < 0.05$) when Del/Del group compared to Ins/Ins group.

^c: No Significant effect ($P > 0.05$) when Ins/Del group compared to Ins/Ins and Del/Del groups.

^d: Significant effect ($P < 0.05$) when Ins/Ins group compared to Ins/Del and Del/Del group.

^e: No Significant effect ($P > 0.05$) when Ins/Del group compared to Del/Del groups.

with Ins/Del alleles compared to those with Del/Del alleles and female schizophrenic patients with Ins/Del alleles compared to those with Ins/Ins and Del/Del alleles regarding BMI ($P > 0.05$) as shown in the Table 6.

Glycemic status

The glycemic status of schizophrenic patient with olanzapine and had wild (Ins/Ins) alleles of 141c ins/del (rs1799732) was no significantly differed from that of the healthy volunteers ($P > 0.05$) as shown in Table 7. The schizophrenic volunteers with olanzapine and had mutation (Del/Del) allele of 141c ins/del (rs1799732) were significantly suffered from diabetic status characterized by highly uncontrolled FBS (168 mg/dl) and elevated HbA1c (8.15%). While, those with heterozygous (Ins/Del) allele were significantly suffered from prediabetic status characterized by elevated FBS (131.08 mg/dl) and HbA1c (6.21%) as compared with healthy and schizophrenic

volunteers who had wild type (Ins/Ins) ($P < 0.05$) as presented in the Table 7.

Lipid profile

The plasma level of TCHO, TG, LDL, and VLDL in schizophrenic volunteers with wild (Ins/Ins) allele of 141c ins/del (rs1799732) were significantly highly as compared to healthy volunteers ($P < 0.05$) as explained in Table 8 (Altalebi et al. 2023). The schizophrenic volunteers with mutant (Del/Del) allele or heterozygous (Ins/Del) allele were significantly suffered from dyslipidemia due to increase the level of TCHO (263.31 mg/dl), TG (219.15 mg/dl), LDL, (180.09 mg/dl), and VLDL (43.83 mg/dl) as compared to those with wild (Ins/Ins) allele. ($P < 0.05$). There were no significant difference between schizophrenic volunteers carry heterozygous (Ins/Del) allele and those carry mutant (Del/Del) allele regarding level of TCHO, TG, and VLDL ($P > 0.05$) as shown in Table 8.

Table 7. The Effects of D₂ receptor alleles 141c ins/del (rs1799732) on glycemic status of schizophrenic volunteers (data present as mean ± S.E).

Variables		Volunteer				P – value
		Healthy	Schizophrenic			
			Ins/Ins	Ins/Del	Del/Del	
Glycemic status	FBS (mg/dl)	103.02 ± 1.33	105.67 ± 2.2	131.08 ± 8.87	168 ± 17.01	0.001 ^{a, b}
	HbA1c (%)	5.36 ± 0.05	5.58 ± 0.09	6.21 ± 0.2	8.15 ± 0.78	0.012 ^{a, b}

^a: No Significant effect ($P > 0.05$) when Ins/Ins group compared to healthy groups.

^b: Significant effect ($P < 0.05$) between three groups of schizophrenic patients.

Table 8. The Effects of D₂ receptor alleles 141c ins/del (rs1799732) on lipid profile of schizophrenic volunteers (data present as mean ± S.E).

Variables		Volunteer				P – value
		Healthy	Schizophrenic			
			Ins/Ins	Ins/Del	Del/Del	
Lipid profile	TCHO (mg/dl)	140.34 ± 4.45	196.84 ± 4.12	225.5 ± 7.79	263.31 ± 9.38	<0.0001 ^{a, b}
	TG (mg/dl)	115.06 ± 4.0	146.45 ± 7.04	202.33 ± 24.7	219.15 ± 16.0	<0.0001 ^{a, c}
	HDL (mg/dl)	47.18 ± 1.28	44.97 ± 1.24	41 ± 2.68	39.38 ± 2.74	0.043 ^{d, e}
	LDL (mg/dl)	70.15 ± 4.58	122.58 ± 3.5	144.03 ± 6.54	180.09 ± 9.54	<0.0001 ^a
	VLDL (mg/dl)	22.67 ± 0.89	29.29 ± 1.41	40.47 ± 4.95	43.83 ± 3.19	<0.0001 ^{a, c}

^a: Significant effect ($P < 0.05$) when all schizophrenic groups compared to healthy group.

^b: No Significant effect ($P > 0.05$) when Ins/Del group compared to Ins/Ins and Del/Del groups.

^c: No Significant effect ($P > 0.05$) when Ins/Del group compared to Del/Del group.

^d: Significant effect ($P < 0.05$) when Del/Del group compared to healthy groups.

^e: No Significant effect ($P > 0.05$) between Ins/Ins, Ins/Del, and healthy groups.

Prolactin level

The prolactin level (9.92 ng/ml) of male schizophrenic volunteers who received olanzapine and carried wild (Ins/Ins) allele of 141c ins/del (rs1799732) did not significantly differ from those (8.91 ng/dl) of the healthy volunteers ($P > 0.05$). While the prolactin level (22.28 ng/dl) of female schizophrenic volunteers who received olanzapine and carried wild (Ins/Ins) allele of 141c ins/del (rs1799732) was significantly high as compared to the healthy volunteers ($P < 0.05$) as presented in Table 9. The prolactin level of both genders of schizophrenic volunteers with heterozygous (Ins/Del) allele or mutant (Del/Del) allele was significantly elevated as compared to those with wild (Ins/Ins) allele ($P < 0.05$) as shown in Table 9. There were significant differences among male schizophrenic volunteers who carried the heterozygous (Ins/Del) allele or mutant (Del/Del) allele regarding prolactin level ($P < 0.05$) (Kumar et al. 2023). While there was no significant difference among female schizophrenic volunteers who carried the heterozygous (Ins/Del) allele or mutant (Del/Del) allele regarding prolactin level ($P < 0.05$), as shown in Table 9.

of 141c ins/del (rs1799732) were significantly suffered from weight gain characterized by high BMI and waist circumference in comparison to those with the wild allele (Ins/Ins). Some research mentioned that the deletion allele of D₂ receptor gene 141c ins/del (rs1799732) significantly gained more body weight over time than those with the insertion allele. The deletion allele of D₂ receptor gene 141c ins/del (rs1799732) was associated with overweight and obesity in schizophrenic females from Northwest Iran. This may be induced by hedonic hunger (Al-hussainy et al. 2022; Aliasghari et al. 2021). This polymorphism may be responsible for increasing the density of D₂ receptors in the striatum, thus olanzapine interacted with more D₂ receptor (Salim Mahmood et al. 2022; Tawfeeq et al. 2022).

This study revealed that the glycemic status of olanzapine taken in schizophrenic patients with wild (Ins/Ins) alleles of 141c ins/del (rs1799732) was not significantly different from that of the healthy volunteers. In contrast, the olanzapine taken in schizophrenic patients with mutation (Del/Del) allele of 141c ins/del (rs1799732) significantly suffered from diabetic status characterized by highly uncontrolled FBS and elevated HBA1c. While those with heterozygous

Table 9. The Effects of D₂ receptor alleles 141c ins/del (rs1799732) on prolactin level of schizophrenic volunteers (data present as mean \pm S.E).

Variables		Volunteer			P - value	
		Healthy	Schizophrenic			
			Ins/Ins	Ins/Del		Del/Del
Prolactin level (ng/dl)	Male	8.91 \pm 0.42	9.92 \pm 0.84	30.08 \pm 1.54	75.64 \pm 1.27	<0.0001 ^{a,b}
	Female	9.48 \pm 0.95	22.28 \pm 1.69	42.26 \pm 1.7	48.64 \pm 1.73	0.0012 ^{c,d}

^a: No Significant effect ($P > 0.05$) when Ins/Ins group compared to healthy groups.

^b: Significant effect ($P < 0.05$) when Ins/Del and Del/Del groups compared to Ins/Ins group.

^c: Significant effect ($P > 0.05$) when three schizophrenic groups compared to healthy group.

^d: No Significant effect ($P > 0.05$) when Ins/Del group compared to Del/Del group.

Discussion

Although olanzapine is the most common atypical antipsychotic agent used in the management of many diseases like schizophrenia, bipolar disorder, anorexia nervosa, and autism, it can induce many adverse effects that may lead to restricted use or discontinuation from the management of chronic psychiatric disorder and the exact mechanism of olanzapine-induced some of these adverse effects remained unknown (Stroup and Gray 2018).

This study explained the present heterozygous (Ins/Del) and mutant (Del/Del) alleles of D₂ receptor alleles 141c ins/del (rs1799732) among both genders of Iraqi schizophrenic patients and not present in healthy volunteers. Some studies mentioned that individuals with deletion alleles of D₂ receptor gene 141c ins/del (rs1799732) most commonly tended to suffer from neuropsychiatric disorders (Kumar et al. 2023). Another study revealed that the D₂ receptor alleles 141c ins/del (rs1799732) is functional and associated with risk of schizophrenia development (Awad et al. 2022).

In this study, both genders of schizophrenic patients who received olanzapine and had mutation type (Del/Del)

(Ins/Del) alleles significantly suffered from prediabetic status characterized by elevated FBS and HBA1c. These results, comparable with other studies, revealed that schizophrenic patients who carried the deletion allele of 141c ins/del (rs1799732) were more disposed to have metabolic syndrome induced by atypical antipsychotics like elevation of FBS. In addition to weight gain, this effect may be related to role of D₂ receptors in pancreatic cells that modulate the release of insulin and glucagon (Aslanoglu et al. 2021; Zubiaur et al. 2021). Moreover, the D₂ receptors assumed a crucial function in facilitating glutamatergic neuroplasticity within the striatum; thus, they played a crucial role in dopamine-dependent neuroplastic effects and had a direct impact on hypothalamic regulatory mechanisms, which has led to its significant involvement in the development of metabolic syndrome (Matikainen-Ankney and Kravitz 2018).

In this study, schizophrenic patients who had taken olanzapine and carried heterozygous or mutant allele of 141c ins/del (rs1799732) significantly suffered from dyslipidemia as compared to those with wild allele and healthy volunteers. The same results mentioned by Paderina et al. revealed that about 64 – 80% of schizophrenic patients who were treated with atypical antipsychotics and had ge-

netic polymorphism of 141c ins/del (rs1799732) suffered from hyperlipidemia and metabolic syndrome (Paderina et al. 2022). Olanzapine could induce hyperlipidemia not associated with obesity that may disappear within a few weeks from discontinuation of olanzapine. This effect may not be full understanding (Zhu et al. 2022). Some studies mention that β -lactotensin and neurotensin could rapidly decline the serum cholesterol level by stimulating mainly D_2 receptors; thus, olanzapine competed with these peptides by blocking D_2 receptors, which may be overexpression in schizophrenic patients with deletion allele of 141c ins/del (rs1799732) (Iwaniak and Mogut 2020).

This study demonstrated that prolactin level was significantly elevated in schizophrenic patient who carried either heterozygous or mutant allele of 141c ins/del (rs1799732) as compared to those with wild allele. A research mentioned that atypical antipsychotic induced hyperprolactinemia a significantly association with polymorphism of the -141C Ins/Del (Sugai et al. 2020). Olanzapine-induced hyperprolactinemia is attributed to blocking of D_2 receptors on the lactotroph cells membranes within the pituitary gland and the deletion allele of 141c ins/del (rs1799732) may be made these G-coupled protein receptor with highly affinity for interacting with olanzapine (Zubiaur et al. 2021; Taima 2023). In another study, Risperidone-induced hyperprolactinemia was identified in 87.2% of the patients, and a substantial relationship of the 141 C deletion with the likelihood of increased prolactin levels was discovered (Charan et al. 2016).

Conclusion

In conclusion, the genetic polymorphism of D_2 receptor-141 C Ins/Del (rs1799732) was significantly associated with olanzapine induce metabolic adverse effects in Iraqi schizophrenic patient.

Reference

- Ahmed D (2022) The study of mental illness in Iraq and its common trends: A systematic review. *Global Psychiatry Archives* 5(1): 26–35. <https://doi.org/10.52095/gp.2022.3774.1026>
- Awad M, Al-Hussainiy HA, Alburghaif AH, Tawfeeq KT (2022) The role of COVID-19 in myopathy: incidence, causes, treatment, and prevention. *Journal of Medicine and Life* 15(12): 1458–1463. <https://doi.org/10.25122/jml-2022-0167>
- Al-hussainiy HA, AL-Biati HA, Ali IS (2022) The effect of Nefopam hydrochloride on the liver, heart, and brain of rats: Acute toxicity and mechanisms of nefopam toxicity. *Journal of Pharmaceutical Negative Results* 13(3): 393–400. <https://doi.org/10.47750/pnr.2022.13.03.061>
- Ali ZJM (2023) supplementary data for Genetic Polymorphism on Olanzapine-Induced Adverse Drug Reaction in Schizophrenic Patients. Zenodo. <https://doi.org/10.5281/zenodo.8335329>
- Aliasghari F, Nazm SA, Yasari S, Mahdavi R, Bonyadi M (2021) Associations of the ANKK1 and DRD2 gene polymorphisms with overweight, obesity and hedonic hunger among women from the Northwest of Iran. *Eating and weight disorders: EWD* 26(1): 305–312. <https://doi.org/10.1007/s40519-020-00851-5>
- Altalebi RR, Al-Hussainiy HA, Al-Tameemi ZS, Al-Zobaidy MA-H, Albu-Rghaif AH, Alkuraishy HM, Hedeab GM, Azam F, Al-Samydai AM, Naji MA (2023) Non-alcoholic fatty liver disease: relation to juvenile obesity, lipid profile, and hepatic enzymes. *Journal of Medicine and Life* 16(1): 42–47. <https://doi.org/10.25122/jml-2022-0091>
- Aslanoglou D, Bertera S, Sánchez-Soto M, Benjamin Free R, Lee J, Zong W, Xue X, Shrestha S, Brissova M, Logan RW, Wollheim CB, Trucco M, Yechoor VK, Sibley DR, Bottino R, Freyberg Z (2021) Dopamine regulates pancreatic glucagon and insulin secretion via adrenergic and dopaminergic receptors. *Translational Psychiatry* 11(1): 59. <https://doi.org/10.1038/s41398-020-01171-z>
- Charan A, Shewade DG, Rajkumar RP, Chandrasekaran A (2016) Relation between serum prolactin levels and antipsychotic response to risperidone in patients with schizophrenia. *Psychiatry Research* 240: 209–213. <https://doi.org/10.1016/j.psychres.2016.04.001>

Author Contributions

Zahra Jawd Mohammed Ali: Conducted all experimental and analytical work, and wrote the manuscript.; Atheer Majid Rashid Al-juhiashi: Provided supervision throughout the project and proofread the manuscript.

Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data sets for this article are available in the Zanodo repository DOI: 10.5281/zenodo.8335329. Under License Creative Commons Attribution 4.0 International (Ali 2023).

Acknowledgments

This study was conducted in Psychiatry Outpatient Department of Al-Hassan Al-Mojtaba hospital. Therefore, we thank all members of the said department, including nurses, service workers, resident doctors, and statistics employees.

This research was undertaken without the support of any external funding agencies or grants. All costs associated with the design, execution, analysis, and manuscript preparation of this study were borne by the authors. We would like to acknowledge our institutional affiliations for providing the necessary infrastructure and resources that enabled the completion of this work, but no direct financial support was received. We are grateful for the internal resources and support that made this research possible.

- Funahashi Y, Yoshino Y, Yamazaki K, Ozaki Y, Mori Y, Mori T, Ochi S, Iga JI, Ueno SI (2019) Analysis of methylation and-141C Ins/Del polymorphisms of the dopamine receptor D₂ gene in patients with schizophrenia. *Psychiatry Research* 278: 135–140. <https://doi.org/10.1016/j.psychres.2019.06.001>
- Grinchii D, Dremencov E (2020) Mechanism of action of atypical antipsychotic drugs in mood disorders. *International Journal of Molecular Sciences* 21(24): 9532. <https://doi.org/10.3390/ijms21249532>
- He M, Yan H, Duan Z-X, Qu W, Gong H-Y, Fan Z-L, Kang J-Y, Li B-C, Wang J-M (2013) Genetic distribution and association analysis of DRD2 gene polymorphisms with major depressive disorder in the Chinese Han population. *International Journal of Clinical and Experimental Pathology* 6(6): 1142–1149.
- Iwaniak A, Mogut D (2020) Metabolic syndrome-preventive peptides derived from milk proteins and their presence in cheeses: A review. *Applied Sciences (Basel, Switzerland)* 10(8): 2772. <https://doi.org/10.3390/app10082772>
- Kaczor AA, Targowska-Duda KM, Stępnicki P, Silva AG, Koszła O, Kędzierska E, Grudzińska A, Kruk-Słomka M, Biała G, Castro M (2021) N-4-[3-(trifluoromethyl) phenyl] piperazin-1-yl propyl)-1H-indazole-3-carboxamide (D2AAK3) as a potential antipsychotic: In vitro, in silico and in vivo evaluation of a multi-target ligand. *Neurochemistry International* 146(3): 105016. <https://doi.org/10.1016/j.neuint.2021.105016>
- Kumar KV, Sree SL, Sree SJ (2023) Cabergoline-Dopamine Receptor Agonist. *Medical and Pharmaceutical Journal* 2(2): 90–98. <https://doi.org/10.55940/medphar202346>
- López-Rodríguez R, Román M, Novalbos J, Pelegrina ML, Ochoa D, Abad-Santos F (2011) DRD2 Taq1A polymorphism modulates prolactin secretion induced by atypical antipsychotics in healthy volunteers. *Journal of Clinical Psychopharmacology* 31(5): 555–562. <https://doi.org/10.1097/JCP.0b013e31822cfff2>
- Manu P, Dima L, Shulman M, Vancampfort D, De Hert M, Correll CU (2015) Weight gain and obesity in schizophrenia: epidemiology, pathobiology, and management. *Acta psychiatrica Scandinavica* 132(2): 97–108. <https://doi.org/10.1111/acps.12445>
- Matikainen-Ankney BA, Kravitz AV (2018) Persistent effects of obesity: a neuroplasticity hypothesis: Neuroplasticity hypothesis of obesity. *Annals of the New York Academy of Sciences* 1428(1): 221–239. <https://doi.org/10.1111/nyas.13665>
- Miura I, Zhang J-P, Hagi K, Lencz T, Kane JM, Yabe H, Malhotra AK, Correll CU (2016) Variants in the DRD2 locus and antipsychotic-related prolactin levels: A meta-analysis. *Psychoneuroendocrinology* 72: 1–10. <https://doi.org/10.1016/j.psyneuen.2016.06.002>
- Paderina DZ, Boiko AS, Pozhidaev IV, Mednova IA, Goncharova AA, Bocharova AV, Fedorenko OY, Kornetova EG, Semke AV, Bokhan NA, Loonen AJM, Ivanova SA (2022) The gender-specific association of DRD2 polymorphism with metabolic syndrome in patients with schizophrenia. *Genes* 13(8): 1312. <https://doi.org/10.3390/genes13081312>
- Salim Mahmood A, Ammoo AM, Ali MHM, Hameed TM, Al-Hussainy HA, Aljumaili AAA, Al-Falooji MHA, Kadhim AH (2022) Antiepileptic effect of neuroaid* on strychnine-induced convulsions in mice. *Pharmaceuticals (Basel, Switzerland)* 15(12): 1468. <https://doi.org/10.3390/ph15121468>
- Stroup TS, Gray N (2018) Management of common adverse effects of antipsychotic medications: World Psychiatry. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)* 17(3): 341–356. <https://doi.org/10.1002/wps.20567>
- Sugai T, Suzuki Y, Yamazaki M, Sugawara N, Yasui-Furukori N, Shimoda K, Mori T, Ozeki Y, Matsuda H, Okamoto K, Sagae T, Someya T (2020) Lower prolactin levels in patients treated with aripiprazole regardless of antipsychotic monopharmacy or polypharmacy. *Journal of Clinical Psychopharmacology* 40(1): 14–17. <https://doi.org/10.1097/JCP.0000000000001158>
- Taima RK (2023) Idiopathic Recurrent Pregnancy Loss related with GP1a gene in Iraqi patient women. *Medical and Pharmaceutical Journal* 2(1): 65–74. <https://doi.org/10.55940/medphar202326>
- Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, Malaspina D, Owen MJ, Schultz S, Tsuang M, Van Os J, Carpenter W (2013) Definition and description of schizophrenia in the DSM-5. *Schizophrenia Research* 150(1): 3–10. <https://doi.org/10.1016/j.schres.2013.05.028>
- Tawfeeq KT, Al-Khalidi GZ, Ha A-H (2022) Neurodevelopmental abnormalities in children associated with maternal use of psychoactive medication: Maternal use of psychoactive medication. *Medical and Pharmaceutical Journal* 1(2): 64–73. <https://doi.org/10.55940/medphar202210>
- Yang F, Chen L, Fang X, Zheng K, Zhu C, Xu C, Zhang C, Tang W (2018) Influence of olanzapine on serum prolactin levels and BMI in female patients with schizophrenia. *Neuropsychiatric disease and treatment*, 14: 3373–3379. <https://doi.org/10.2147/NDT.S180303>
- Zhang Z, Xu L, Xu X (2021) The role of transcription factor 7-like 2 in metabolic disorders. *Obesity Reviews* 22(5): e13166. <https://doi.org/10.1111/obr.13166>
- Zhu Z, Gu Y, Zeng C, Yang M, Yu H, Chen H, Zhang B, Cai H (2022) Olanzapine-induced lipid disturbances: A potential mechanism through the gut microbiota-brain axis. *Frontiers in pharmacology*, 13: 897926. <https://doi.org/10.3389/fphar.2022.897926>
- Zubiaur P, Soria-Chacartegui P, Villapalos-García G, Gordillo-Perdomo JJ, Abad-Santos F (2021) The pharmacogenetics of treatment with olanzapine. *Pharmacogenomics* 22(14): 939–958. <https://doi.org/10.2217/pgs-2021-0051>