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Association Between D2 Receptor Single Nucleotide polymorphisms and Olanzapine Response and Safety in Schizophrenic Patients in Kerbala City

A Thesis

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بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

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Dedication

To my dear family, who have always been an inspiration to me and provided me with unwavering love, courage, and support.

To my mother, sisters, relatives, friends, and coworkers who offered me words of wisdom and motivation to keep going.

To everyone who has supported me and believed in what I have to say and has prayed for me to finish my thesis.

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List of Abbreviations	
A-241G	Adenine- 241 Guanine
AA	Adenine Adenine
ACT	Assertive Community Treatment
AG	Adenine Guanine
AMPK	Adenosine Monophosphate Activated Protein Kinaseb - B
APA	American Psychiatric Association
ATP	Adenosine Triphosphate
B cell	B – Lymphocyte Cell
BL	Binding Buffer
BMI	Body Mass Index
BSA	Bovine Serum Albumin
CB1	Cannabis Activated Cannabinoid Receptors Type-1
CBT	Cognitive Behavioral Therapy
CE	Cholesterol oxidase enzyme
CHOD	Cholesterol Oxidase Enzyme
CI	Confidence Interval
CNS	Central Nervous System
COMT	Catechol-O-Methyl Transferase
CYP1A2	Cytochrome P450 A2 Isozyme
CYP450	Cytochrome P450
D1	Dopamine Receptor 1
D2	Dopamine Receptor 2
D3	Dopamine Receptor 3
D4	Dopamine Receptor 4
D5	Dopamine Receptor 5
DEL/DEL	Deletion/ Deletion
DRD2	Dopamine Receptor D2
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
EDTA	Ethylenediaminetetraacetic Acid
EPS	Extrapyramidal Side Effects
FBS	Fasting Blood Sugar
FDA	Food and Drug Administration
GABA	Gamma- Aminobutyric Acid
GG	Guanine Guanine
H1	Histamine receptors
HbA1c	Glycosylated Hemoglobin
HDL	High-Density Lipoprotein

HPA	Hypothalamic-Pituitary-Adrenocortical
HSV-1	Viral Infections Like Herpes Simplex Virus-1
HSV-2	Viral Infections Like Herpes Simplex Virus-2
HSDAa	Sodium N (2-Hydroxy-3-Sulfopropyl)-3,5-Dimethoxyaniline
INS/DEL	Insertion/Deletion
INS/INS	Insertion/Insertion
KOR	Kappa Opioid Receptors
LDL	Low Density Lipoprotein
M1	Muscarinic Receptor 1
M2	Muscarinic Receptor 2
M3	Muscarinic Receptor 3
M4	Muscarinic Receptor 4
M5	Muscarinic Receptor 5
NADP	Nicotinamide Adenine Dinucleotide Phosphate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
O2	Oxygen
OIWG	Olanzapine Induce Weight Gain
OR	Odds Ratio
PANSS	Positive and Negative Syndrome Scale
PBS	Phosphate-Buffered Saline
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol-Modified
POD	Peroxidase Enzyme
PRL	Prolactin
P-value	Probability Value
RFLP	Restriction Fragment Length Polymorphism
SD	Standard Deviation
SNP	Single Nucleotide Polymorphisms
SREBP-1C	Sterol Regulatory Element Binding Protein-1C
SPSS	Statistical Package for Social Sciences
SEM	Standard Error of The Mean
T cell	T – Lymphocyte Cell
TCHO	Total Cholesterol
TG	Triglyceride
TSF7L2	Transcription Factor 7 Like 2
TTAB	Tetradecy1 Trimethy1 Ammonium Bromide
UV	Ultraviolet
VLDL	Very Low-Density Lipoprotein
WNT	Wingless And Int-1

α_1	Alpha 1 Adrenergic Receptors
α_2	Alpha 2 Adrenergic Receptors
ICD	International Classification of Diseases
4-AAP	4-Amino Antipyrin
5HT1	5 – Hydroxytryptamine 1
5HT2A	5-Hydroxy Tryptamine 2A
5HT2C	5 – Hydroxytryptamine 2C

Abstract

Background

Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, makes it a disabling disorder for many patients and their families.

Olanzapine is commonly prescribed for management of schizophrenia and some patients developed resistance to it and other suffered from many adverse effects like weight gain, hyperglycemia, and hyperprolactinemia.

Aims:

This study was aimed to assess the role of D2 receptor A-241G (rs1799978) genetic polymorphism and 141C Ins/Del (rs1799732) genetic polymorphism on olanzapine response and safety profile respectively in schizophrenic patients in Karbala city.

Subjects and Methods:

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 psychiatry outpatient department and 50 apparently healthy without any disease comprising both genders aged 20 to 63 years, served as a control group were also enrolled in this study. Patient response to olanzapine was evaluated with aiding of the Positive and Negative Syndrome Scale (PANSS) and plasma level of Fasting Blood Sugar (FBS), Glycosylated Hemoglobin

(HbA1c), lipid profile, and prolactin were measured. The genotyping of D2 receptor A-241G (rs1799978) polymorphisms were detected using nested PCR method and the genotyping of D2 Receptor–141 C Insertion/Deletion (Ins/Del) (rs1799732) polymorphisms was detected using Restriction Fragment Length Polymorphism (RFLP) method.

Results:

The heterozygous (AG) and mutant (GG) alleles of D2 receptor A-241G (rs1799978) were significantly predominated in schizophrenic patients 14%, 8% respectively and absent in healthy volunteers. Schizophrenic patients were taken olanzapine and had the G allele of D2 receptor A-241G (rs1799978) exhibited a notably resistance olanzapine. The heterozygous (Ins/Del) and mutant (Del/Del) alleles of D2 receptor–141 C Ins/Del (rs1799732) were also significantly predominated in schizophrenic patients 12%,13% respectively 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 a notably higher susceptibility to metabolic adverse effects induced by olanzapine, such as weight gain, hyperglycemia, dyslipidemia, and hyperprolactinemia (P values less than 0.05).

Conclusion:

The genetic polymorphism of D2 receptor A-241G (rs1799978) was significantly associated with resistance to olanzapine and the genetic polymorphism of D2 receptor–141 C Ins/Del (rs1799732) was significantly associated with olanzapine induce metabolic adverse effects in Kerbalai schizophrenic patients.

Chapter One

Introduction

1. Introduction

1.1 Schizophrenia

Schizophrenia is a complex, chronic mental health disorder characterized by an array of symptoms, including delusions, hallucinations, disorganized speech or behavior, and impaired cognitive ability. The early onset of the disease, along with its chronic course, make it a disabling disorder for many patients and their families (Sullivan, Kounali et al. 2020). Disability often results from both negative symptoms (characterized by loss or deficits) and cognitive symptoms, such as impairments in attention, working memory, or executive function (McCutcheon, Marques et al. 2020). In addition, relapse may occur because of positive symptoms, such as suspiciousness, delusions, and hallucinations. The inherent heterogeneity of schizophrenia has resulted in a lack of consensus regarding the disorder's diagnostic criteria, etiology, and pathophysiology (Oliver, Joseph et al. 2013). The disruption of dopaminergic signaling has been identified as the root cause of these symptoms. schizophrenia is one of the world's top 10 most prevalent conditions that affects 1% of the overall population. Schizophrenia generally appears in late teens or early adulthood (Keepers, Fochtmann et al. 2020).

1.1.1. Epidemiology: Incidence and Prevalence

Schizophrenia is a crippling mental condition that affected 1% of people worldwide and Schizophrenia prevalence rates in Asian nations range from around 0.25% to 0.65% of the population and found that schizophrenia is more prevalent in Japan than in other Asian nations, with estimates ranging from 0.19 to 1.79%. Prevalence rates in China are thought to be approximately 0.45%. It is supposed that 70.8% of schizophrenia status occur in the 25–

54 years age group with a prevalence peak at around 40 years old (Baba, Guo et al. 2022).

German public's social study of those with schizophrenia and their causal attributions of schizophrenia; Brain illness makes up 70.0% of all cases, followed by heredity (60.2%), life events (72.3%), stress at work (57.7%), a broken family (39%), a lack of parental love (30.4%), a lack of willpower (36.4%), and an immoral way of life (20.9%) (Angermeyer and Matschinger 2005).

Schizophrenia affected between 0.24 and 4.7% of the population in the Arab world. Although epidemiology and prevalence studies regarding mental health disorders in Iraq were limited, the prevalence of psychiatric disorders rose from 12% in 2000 to 15% in 2020, with schizophrenia considered the most common disorder (Ahmed 2022). Iraqi males were considered the target group for this disease with an average age of 33 years old. The ratio of 95 Iraqi schizophrenic patients were Muslim, 4% christen and 1% were from other religions. About 51.5% were satisfied with their living, 39% were poor and 9.5% were rich in economic status (Al-Abbudi 2016).

1.1.2. Etiology of Schizophrenia

Schizophrenia is a complicated condition with a heterogeneous collection of symptoms. Although there is not only a family history of psychosis that is considered the majority of schizophrenia diagnoses, but genetics also play a significant influence in the disease's etiology. Schizophrenia may be exacerbated by issues with specific naturally occurring/brain chemicals, such as the neurotransmitters dopamine and glutamate also it cause by in Environmental Factors (Stressful Life Events, Urbanicity and Migration,

Obstetrical Complications, Seasonality of Birth and Infection , Inflammatory Responses and Medications) (American Psychiatric Association and Association 2013).

1.1.2.1. Environmental Factors

Many environmental factors could be triggered by the incidence of schizophrenia besides genes inherited from parents. Long-period exposure for certain factors may be an increased risk of schizophrenia (Janoutová, Janácková et al. 2016). These factors including:

1.1.2.1.1. Stressful Life Events

Many studies had mentioned an overabundance of stressful conditions for a few weeks could evoke the onset or relapse of schizophrenia. Some psychosocial statuses like bereavement, loss of job or home, divorce, the end of the relationship, and emotional abuse may lead to stress responses. Hypothalamic–Pituitary–Adrenocortical (HPA) axis is one of the primary stress response systems in the human body that lead to changes in neurochemical levels including dopamine, serotonin, and other neurotransmitters. Cortisol levels may be also elevated in response to stressful conditions and contributed to inducing psychosis (Mayo, Corey et al. 2017).

1.1.2.1.2. Urbanicity and Migration

Urbanicity was another environmental factor associated with raising the incidence of schizophrenia and non-affective psychosis. It was affected by population density, social fragmentation, and deprivation. These factors may induce monoamine dysfunction that is associated with a tendency for imprecise information processing potentially based on disturbed cortico-cortical plasticity (Heinz, Deserno et al. 2013).

1.1.2.1.3. Obstetrical Complications

Schizophrenia is also linked to problems during pregnancy and childbirth. Pregnancy complications (bleeding, diabetes, pre-eclampsia, and rhesus compatibility), abnormal fetal growth and development (low birth weight, congenital malformations, and reduced head circumference), and delivery complications (uterine atony, asphyxia, and emergency cesarean section) were well studied that enhanced incidence of schizophrenia via different mechanisms (Maj, van Os et al. 2021). Supplement of nutrients such as (Oxygen), O2 iodine, glucose, and iron to the fetus may be reduced and caused impaired CNS (Central Nervous System) development as well as intrauterine growth retardation; thus lack of metabolites and hypoxia developed overlong period cause basal ganglia damage (Davies, Segre et al. 2020). Another mechanism involved brain damage resulting from prematurity causing a high risk of intracranial hemorrhages, periventricular leukomalacia, interstitial respiratory distress syndrome, and infections (Radua, Ramella-Cravaro et al. 2018).

1.1.2.1.4. Seasonality of Birth

Most schizophrenic patients were more likely to be born in the winter or early spring months. The explanation of causes was not well developed and may be attributed to temperature, rainfall, humidity, and sunshine hours during pregnancy (Saleh, King et al. 2021).

1.1.2.1.5. Infection and Inflammatory Responses

Acute infections like acute encephalitis and autoimmune disorders like multiple sclerosis were common inflammatory disorders that enhanced the incidence of schizophrenia. These may be attributed to macrophages, B (B –

Lymphocyte Cell), and T cells (T – Lymphocyte Cell) invading the CNS in addition to extending the activation of microglial cells. Viral infections like herpes simplex virus-1 (HSV-1), HSV-2, and measles also had a role in evoking schizophrenia (Müller 2018).

1.1.2.2. Genetic Factors

Schizophrenia is regarded as one of the most heritable conditions that might promote its onset. There are probably several genetic variants that contribute to the onset of schizophrenia symptoms. These genes were involved in coding many functional proteins including dysbindin, neuregulin, D-amino acid oxidase, proline dehydrogenase, Catechol-O-methyltransferase, regulator of G protein signaling, serotonin (5–HT2A) receptor, and dopamine (D3) receptor located on chromosome 1q, 2q, 5q, 6q, 8q, 10q, 13q, 15q, and 22q (Comer, Jinadasa et al. 2020).

1.1.2.3. Medications

Drug-induced psychosis was well diagnosed as a factor that promoted episodes of schizophrenia. Cannabis, hallucinogens, and amphetamine had the highest rates of medication-evoked schizophrenia symptoms that were associated with increased subcortical production and excessive release of dopamine (Fiorentini, Cantù et al. 2021). Cannabis activated cannabinoid receptors type-1 (CB1) in the brain. This receptor was expressed on gamma–aminobutyric acid (GABA) ergic neurons that are associated with long-term loss of memory, dysregulation of excitatory and inhibitory synapses, and lower learning process (Shrivastava, Johnston et al. 2014). Opioids, alcohol, and sedatives had the lowest rates of medication-induced schizophrenia symptoms. Kappa opioid receptors (KOR) had a critical role in modulating

dopamine, serotonin, and glutamate release in the CNS and Dysregulation of the dynorphin (endogenous neurotransmitter peptide)/KOR system may be involved in developing some psychiatric disorders like schizophrenia (Clark and Abi-Dargham ,2019).

1.1.3. Pathophysiology of schizophrenia

The full explanation of schizophrenia pathophysiology was not well known, but neurotransmitter abnormalities like glutamate, dopamine, serotonin, and norepinephrine may be taken possession of important roles in developing schizophrenic symptoms. Abnormality of white matter in different areas of the brain mainly the right lentiform nucleus, left temporal gyrus, and right precuneus were also involved in schizoaffective disorders. Some studies found that declined volumes of hippocampal and deformation of the medial and lateral thalamic regions played the most important roles in evoked schizophrenia symptoms (Wy and Saadabadi, 2019). The imbalance of neurochemicals like aspartate, glycine, and GABA were also associated with schizophrenia (McCutcheon, Marques, et al. 2020).

In general, the excessive activation of D2 receptors in the mesolimbic pathway of the brain which connected the ventral tegmental area to limbic regions, may be contributed to the positive symptoms of schizophrenia. Low dopamine levels in the nigrostriatal pathway could be associated with the extrapyramidal system and cause motor symptoms. While low mesocortical dopamine levels may be responsible for causing the negative symptoms and cognitive impairments (McCutcheon, Abi-Dargham, et al. 2019).

1.1.4. Diagnosis of schizophrenia

Along with other psychiatric disorders, schizophrenia should be excluded, and its symptoms should not occur due to drug misuse, medication, or a physical problem. A variety of methods may be used to diagnose schizophrenia. Psychiatric diseases unlike other somatic diseases may be complicated by non-disease-related factors including, race, sex, socioeconomic status, context, theoretical views, type of interview, and religious and political beliefs of the patient that had been shown to affect the assessment of psychopathology (Oltmanns, Martin et al. 2011).

Schizophrenia has required a comprehensive diagnosis process that involved an interview, physical examination, laboratory testing, and screening test (Shefer, Henderson et al. 2014).

1.1.4.1. Interview

Interview-based assessments are the most effective process in the diagnosis of mental-related disorders. Schizophrenia is developed in many stages with various symptoms and behaviors. These stages depend on the onset of symptoms in the early period patient exhibited social withdrawal, anxiety, lack of motivation, and neglect of personal hygiene and activity of disorder when schizophrenic symptoms take full effects which are appeared after at least one month and based on the availability of at least two of five main schizophrenic symptoms (delusions, hallucinations, disorganized or incoherent speaking, disorganized or unusual movements and negative symptoms) (Healey, Combs et al. 2015).

Two types of schizophrenic symptoms should be assessed for investigation of schizophrenia. Positive symptoms include delusions, disordered thoughts

and speech, and tactile, auditory, visual, olfactory, and gustatory hallucinations. Positive symptoms generally respond well to medication. Negative symptoms including flat or blunted affect and emotion, poverty of speech (alogia), inability to experience pleasure (anhedonia), lack of desire to form relationships (asociality), and lack of motivation (avolition) (Correll and Schooler 2020). Negative symptoms contributed more to poor quality of life, functional disability, and the burden on others than positive symptoms. People with prominent negative symptoms often have a history of poor adjustment before the onset of illness, and response to medication is often limited (Weber, Scott et al. 2022).

1.1.4.2. Physical Examination

Physical examination may be done to exclude any associated complications and to support setting aside any other issues that may be contributing to the symptoms. It involved the appearance of the patient including heent examination (rapid eye movements, increased rate of blinking, sneezing, congestion, a sore throat, and poor oral hygiene) extremities examination (unusual movement), respiratory rate, pulse rate, blood pressure, body temperature, and musculoskeletal status (Srivastava and Nair 2022).

1.1.4.3. Laboratory Assessment

Blood, urine, and cerebrospinal fluid are tested to detect any chemical changes in the bodily fluid in order to exclude disorders that had symptoms similar to those of schizophrenia (Moody and Miller 2018).

1.1.4.4. Screening Test

Computerized tomography, magnetic resonance imaging, and other imaging are used to rule out problems like stroke, brain injuries, tumors, and other changes to patient brain structure. An electroencephalogram is also used to detect and record the electrical activity of the brain to rule out conditions like epilepsy (Liu, Li et al. 2020).

1.1.5. Types and clinical Features of Schizophrenia

There were many classifications of schizophrenia available according to symptoms, causes, international classification of diseases (ICD), or the American psychiatric association (APA). Schizophrenia was commonly classified according to the DSM-IV-TR into (Williams and First 2013)**:**

1.1.5.1. Paranoid Schizophrenia

Paranoid schizophrenia was a common type that represented positive symptoms of schizophrenia. It was characterized by delusions, periodic visual and auditory hallucinations, disorganized speech, problems concentrating, and substantial behavioral impairment (Lavin, Bucci et al. 2020).

1.1.5.2. Catatonic schizophrenia

Catatonic schizophrenia is a severe rarest type that is characterized by a noticeable motor behavior. The symptoms of this type involved either a lack of movement and communication, or hyperactivity, persistent agitation, and confusion. Some patients with this type exhibited mutism, ultimate acquiescence, amazement, and lack of nearly all willing activities that were interrupted by a part of hyperactivity and agitation (Rasmussen, Mazurek et al. 2016).

1.1.5.3. Residual schizophrenia

Residual schizophrenia is a sub-type of schizophrenia, indicated by persistent negative symptoms and lower levels of positive symptoms. In this type, the patient showed no signs of hallucination or delusions but still exhibited flat effects that are characterized by psychomotor problems, disorganized speech, anhedonia, asociality, and avolition (Saito, Sakurai et al. 2020).

1.1.5.4. Disorganized schizophrenia

Disorganized schizophrenia is also known as hebephrenic schizophrenia, in which thought disorder and flat affect are present together. It is characterized by disorganized behaviors and nonsensical speech. The hebephrenic patient is likely to have difficulty beginning a specific task or difficulty finishing a task (Kendler 2020).

1.1.5.5. Undifferentiated schizophrenia

Psychotic symptoms of schizophrenia in this type is presented but the criteria for paranoid, hebephrenic, or catatonic types had not been met (Ziso, Marsden et al. 2014).

1.1.6. Managements

Schizophrenia needs forever treatment, Although the symptoms may be subsided. The goal of therapy is comprised of regulating troubled behaviors, minimizing the intensity of psychosis and associated symptoms like agitation, aggression, negative signs, and affective symptoms, and setting and curing the factors that enhanced the incidence of the acute episode (Maroney 2020).

Psychosocial interventions are considered very essential therapy besides medication in the management of schizophrenia. Several psychosocial interventions can be beneficial in managing schizophrenia. These interventions encompass family therapy, assertive community treatment (ACT), supported employment, cognitive remediation, skills training, cognitive behavioral therapy (CBT), token economic interventions, as well as psychosocial approaches for substance use and weight management. By focusing on the entire family system, family therapy or education has the potential to minimize relapses and hospitalizations. (Barbui, Purgato et al. 2020).

Medications are the mainstay therapy for schizophrenia and the most commonly prescribed medications are antipsychotic drugs which act on the brain neurotransmitter mainly dopamine to control symptoms (Lally and MacCabe 2015).

1.1.6.1. Cognitive behavioral therapy

Cognitive behavioral therapy aims to equip individuals with schizophrenia with a range of coping skills to effectively handle challenging circumstances. It is a brief, targeted approach that focuses on problem-solving. Typically, this therapy entails one-hour sessions on a weekly basis for a duration of 12 to 16 weeks. CBT instructs individuals on adjusting their beliefs or behaviors that could contribute to negative emotions. The therapy consists of two primary elements: a cognitive aspect that assists individuals in altering their thinking about a situation, and a behavioral aspect that aids in modifying their reactions (Fusar-Poli, Radua et al. 2022).

In CBT sessions, individuals collaborate with therapists to understand the interplay between their thoughts, emotions, and actions. The objective is to alter undesirable feelings and problematic behaviors by acquiring strategies to adjust negative thoughts and approach them in a new way. The therapist guides the person in evaluating the validity of their thoughts and perceptions, disregarding any internal voices, and effectively managing symptoms (Turkington, Dudley et al. 2006).

1.1.6.2. Family Therapy

Most international clinical guidelines highly recommend family interventions for schizophrenia due to their well-documented effectiveness. While there isn't a singular method for family interventions, evidence-based family therapies generally encompass psychoeducation, stress reduction techniques, emotional processing, cognitive reappraisal, and structured problem-solving. These interventions involve employing a variety of psychotherapeutic strategies when working with the family members of individuals experiencing psychosis. The primary objective is to establish a cooperative bond between the family and the treatment team to facilitate the patient's journey towards recovery (Caqueo-Urízar, Rus-Calafell et al. 2015).

1.1.6.3. Assertive Community Treatment

ACT is a proven approach that provides comprehensive services, including treatment, rehabilitation, and community integration, to individuals who have been diagnosed with serious mental illness. ACT caters to individuals ranging from their late teens to older ages, who suffered from schizophrenia and face difficulties in functioning within their local community. The objective of ACT is to support patients in living according to their preferences and in the

location they desire, while ensuring they have secure housing in their preferred community rather than depending on the hospital. Additionally, it aims to alleviate the burden on the patient's family by promoting greater independence (Coldwell and Bender 2007).

1.1.6.4. Medication

Effective antipsychotic agents are those that align with the pathology of schizophrenia by either blocking D2 receptors, demonstrating greater selectivity to serotonin–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, Targowska-Duda et al. 2021).

Antipsychotic medications, known as major tranquilizers and neuroleptics, are prescribed for the treatment of various conditions such as schizophrenia, bipolar disorder-associated psychosis, depression, Alzheimer's disease, anxiety disorders, and Tourette syndrome. These medications possess the capacity to alleviate symptoms of psychosis, such as delusions and hallucinations, in a matter of hours or days. However, it may take up to four to six weeks for them to reach their maximum effectiveness. While these medications can assist in managing symptoms, they do not provide a cure for the underlying condition (Lally and MacCabe 2015).

The decision regarding which antipsychotic to utilize relies on evaluating the advantages, drawbacks, and expenses involved. Antipsychotic drugs are categorized into two primary groups: typical antipsychotic agents and atypical antipsychotic agents. When typical agents are administered in low to moderate doses, both classes exhibit comparable rates of patient drop-out and symptom relapse. Approximately 40-50% of individuals exhibit a favorable response,

30-40% experience a partial response, while 20% show treatment resistance (lack of satisfactory symptom improvement and trying two or three different antipsychotics for six weeks) (Lieberman, Tollefson et al, 2003).

1.1.6.4.1. Typical antipsychotic agents

Traditional or first-generation antipsychotics, such as chlorpromazine, fluphenazine, haloperidol, and perphenazine, are commonly referred to as typical antipsychotic agents. These medications are often more affordable, especially their generic versions, which can be an important factor to consider for long-term treatment. Due to their ability to block D2 receptors in the brain, as well as adrenergic (α) receptors, histamine (H1) receptors, and muscarinic (M) receptors, they had broad pharmacological effects, both desired and undesired. They can be classified into low-potency and high-potency categories. High-potency typical antipsychotics, such as fluphenazine and haloperidol. while, low-potency typical antipsychotics, like chlorpromazine. They are associated with an increased risk of neurological side effects, including the development of a potentially reversible or irreversible movement disorder called tardive dyskinesia. High-potency antipsychotics tend to cause more extrapyramidal side effects (EPS) while showing less sedation, orthostasis, and anticholinergic side effects such as dry mouth, urinary retention, and constipation. Conversely, low-potency typical antipsychotics are associated with fewer EPS but may cause more sedation, orthostasis, and anticholinergic side effects (Tamminga ,2022).

1.1.6.4.2. Atypical Antipsychotic Agents

Second-generation antipsychotics, also known as a typical 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. These medications work by antagonizing serotonin-2A and −2C receptors and/or exhibiting mesolimbic specificity towards dopamine neurons in the brain, specifically the nigrostriatal pathway. However, they may be associated with a range of adverse effects, including metabolic syndrome (such as weight gain, hyperglycemia, and diabetes), hyperprolactinemia, sedation, sexual dysfunction, cerebrovascular events, and anticholinergic effects. Commonly prescribed atypical antipsychotic agents include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole. Clozapine, the first approved atypical antipsychotic, is typically reserved for severely ill patients with schizophrenia or those at risk for suicidal behavior who have not responded to conventional or other atypical antipsychotics (Farah 2005).

1.1.6.5. Electroconvulsive Therapy

Electroconvulsive therapy is a process performed under general anesthesia and involves the application of small electric currents to the brain. This procedure appears to induce alterations in brain chemistry that can swiftly alleviate symptoms associated with specific mental health disorders. Particularly in cases of severe schizophrenia symptoms, it has demonstrated the ability to yield rapid and substantial improvements. When conventional medications and therapies have proven ineffective, it serves as a viable treatment option for schizophrenia (Galletly, Castle et al. 2016).

1.2. Olanzapine

Olanzapine, is prescribed for the management of schizophrenia and bipolar disorder symptoms in individuals aged 13 and above. Olanzapine like other an atypical antipsychotic agent, modulates specific neurotransmitter activity in the brain. This medication was a thienobenzodiazepine derivative initially developed as a chemical analogue of clozapine in order to overcome hematological disorders (Crapanzano, Amendola et al. 2022).

1.2.1. Pharmacodynamics

Olanzapine, an atypical antipsychotic, primarily acts on dopamine and serotonin receptors. It functions as an antagonist on various receptors, with varying levels of binding affinities. These affinities can be ranked as follows: M1 receptor > 5-HT2A receptor > M5 > H1 > M4 > D2 = 5-HT2C > M3 > M2 > α1 > D4 > D3 > α2. By acting as an antagonist, it inhibits the action of dopamine at the post-synaptic receptor in the mesolimbic pathway, specifically at the dopamine D2 receptors. Olanzapine binds loosely to these receptors and readily dissociates, thereby allowing normal dopamine neurotransmission to occur. This mechanism leads to a reduction in positive symptoms experienced by patients, such as hallucinations, delusions, and disorganized speech, thought, and behavior. In addition to its effect on D2 receptors, olanzapine also acts as an antagonist on 5-HT2A receptors in the frontal cortex. This action on serotonin helps alleviate negative symptoms, including anhedonia, flat affect, alogia, avolition, and poor attention as shown in figure (1 – 1). Notably, olanzapine exhibits a higher affinity for 5-HT2A receptors compared to D2 receptors (Grinchii and Dremencov 2020).

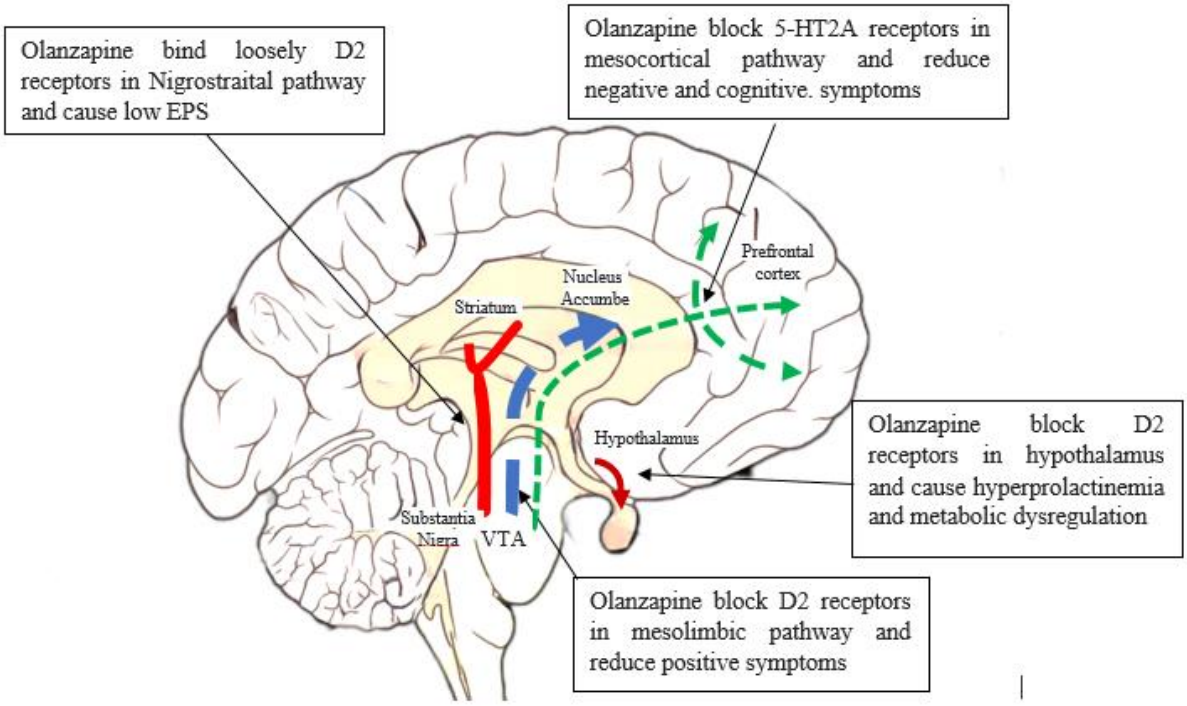

Figure (1 – 1): Pharmacological Actions of Olanzapine. (Grinchii and Dremencov 2020)

1.2.2. Pharmacokinetic

Olanzapine is offered in two common dosage forms with different strengths: oral tablets ranging from 2.5 to 20mg, and intramuscular injectable vials with a short-acting option of 10mg and extended-release suspensions of 210, 300, and 450mg. When olanzapine is taken daily, it takes approximately one week to achieve a steady-state plasma concentration. The oral formulation reaches peak concentration after 6 hours, while the intramuscular formulation takes 15-45 minutes. The average half-life of olanzapine is 30 hours. It is distributed widely throughout the body, with a volume of distribution of approximately 1000 liters. The drug binds extensively to plasma proteins

around 93%., primarily albumin and alpha-1 acid glycoprotein (Keepers, Fochtmann et al., 2020).

Olanzapine is primarily metabolized by the cytochrome P450 (CYP) system, mainly by isozyme 1A2 (CYP1A2) and to a lesser extent by CYP2D6. Due to the hepatic first-pass effect, more than 40% of the oral dose is typically eliminated. The clearance of olanzapine varies by sex, with women having approximately 25% lower clearance than men. Clearance also differs by race, as self-identified African Americans or Blacks exhibit 26% higher clearance. Glucuronidation is another metabolic pathway, with about 57% of olanzapine excreted primarily through the renal route and 30% eliminated through feces (Zubiaur, Soria-Chacartegui et al. 2021).

1.2.3. Medical uses

1.2.3.1. Schizophrenia

Olanzapine, an atypical antipsychotic, received FDA approval in 1996 for treating schizophrenia. It is categorized as a secondary treatment option due to potential metabolic dysregulation and weight gain risks. The drug demonstrates significant effectiveness in the initial phase of schizophrenia, shortening the duration of untreated psychosis. Olanzapine is widely prescribed and frequently utilized among antipsychotic medications with stablished efficacy in alleviating both positive and negative symptoms (Del Fabro, Delvecchio et al. 2019).

1.2.3.2. Bipolar disorder

Olanzapine, the initial atypical antipsychotic approved for acute mania treatment and the maintenance and relapse prevention of mania, displayed a moderate impact on bipolar depression. However, when combined with

fluoxetine, its effectiveness was significantly improved. It demonstrated remarkable efficacy in preventing relapses of both manic and depressive episodes, proving to be comparable to lithium or valproate. Additionally, when used alongside lithium or valproate, it exhibited even greater efficacy in preventing manic relapses in patients who had and only partially responded to lithium or valproate monotherapy (Narasimhan, and Bruce et al. 2007).

1.2.3.3. Other Uses

Olanzapine could potentially aid weight gain in adult outpatients with anorexia nervosa who are underweight, but it may not lead to an improvement in psychological symptoms (Han, Bian et al. 2022). It has demonstrated efficacy in managing hyperactivity, aggression, and repetitive behaviors associated with autism (Stepanova, Dowling et al. 2022). Olanzapine is commonly prescribed for off-label use in treating insomnia, which encompasses both difficulties with initiating sleep and maintaining sleep (Khaledi-Paveh, Maazinezhad et al. 2021). It is suggested as a component of antiemetic treatments for patients receiving high-risk vomiting-inducing chemotherapy (Zhang and Ying 2022).

١.٢,٤. Adverse Effects

1.2.4.1. Weight gain

Weight gain is a frequently observed side effect of olanzapine, primarily due to its ability to increase appetite, resulting in excessive eating known as hyperphagia. Thus, this medication should be used with caution in obese patients who have an intolerance to monitoring their eating behavior, and difficult to attract them to change lifestyle with regular daily exercise to overcome weight gain. Weight gain is the most common adverse effect of

antipsychotic gents abundancy in olanzapine that may be related to its activities on many receptors like D2 and D3, 5-HT2A and 5-HT2C, H1, and M3(Huang, Yu et al. 2018).

Olanzapine influences neuropeptides and hormones that are responsible for controlling appetite and energy metabolism, especially adipokines that are made in white adipose tissue like leptin and adiponectin. During various periods using olanzapine has been shown to increase the levels of leptin and decrease the levels of adiponectin. Olanzapine also has a direct effect on a hormone termed ghrelin, that stimulates food consumption and build up the adipose tissue by stimulating the arcuate nucleus in the hypothalamus (Lu, Wang et al. 2015).

The weight gain caused by olanzapine was overcome by concomitant using it with samidorphan which has a high affinity for human μ-, κ-, and δ-opioid receptors and block specifically μ-opioid receptors. Thus, the weight gain and metabolic irregularities associated with the antipsychotic medications have been alleviated (Correll, Newcomer et al. 2020).

Olanzapine-induced weight gain (OIWG) may be associated with genetic variation. many studies have been reported thirteen selective single-nucleotide polymorphisms isolated from nine genes that show a significantly related to OIWG. From these genes, the single-nucleotide polymorphisms related to α2A, D2, 5-HT2C, and M4 receptor genes have been approved to associated with weight gain and olanzapine exerts its therapeutic effects by binding to this receptors (Zhang, Lencz et al. 2016).

1.2.4.2. Dyslipidemia

Olanzapine is a one of the most common atypical antipsychotic agents induces dyslipidemia by increasing serum total cholesterol (TCHO), triglyceride (TG), and low-density lipoprotein (LDL) during one month of schizophrenia treatment. Olanzapine-induced dyslipidemia is a main risk in incidence of cardiovascular problems in schizophrenic patients (Li, Zhang et al. 2020).

The main roles of olanzapine induced dyslipidemia are not full known. Different factors have been reported associated with olanzapine induce dyslipidemia such as its antagonist to 5-HT1 and H1 receptors in the hypothalamus and promoted phosphorylation of adenosine monophosphate activated protein kinase (AMPK) in the CNS, result in enhanced eating behavior , dyslipidemia, and obesity (Manu, Dima et al. 2015). Subsequently, olanzapine may be caused insulin resistance and hinder the activity of lipoprotein lipase, resulting in increased levels of LDL cholesterol in the blood. Furthermore, insulin resistance triggers the activation of sterol regulatory element binding protein-1c (SREBP-1c), which promotes the production of very low-density lipoprotein (VLDL) in the liver, leading to elevated levels of plasma triglycerides. Additionally, olanzapine directly promotes lipogenesis in the liver by influencing the expression of AMPK, SREBP-1c, or peroxisome proliferation-activated receptor, thereby disrupting the transcription of genes responsible for regulating lipid metabolism(Oh, Park et al. 2011, Yan, Chen et al. 2013).

1.2.4.3. Hyperglycemia

Olanzapine possesses a significant capacity to reduce the sensitivity of insulin, resulting in impaired tolerance for glucose, particularly among a younger population. The exact mechanism behind olanzapine-induced hyperglycemia has not been completely elucidated, but it suggests that the transcription factor 7 like 2 (TCF7L2), an effector of the Wingless and Int-1 (WNT) signaling pathway, plays a crucial role in maintaining glucose balance. As result of OIWG and insulin resistance, overexpression of TCF7L2 is taken-placed in various body tissues like the liver, adipose tissue, and skeletal muscle. This overexpression altered glucose metabolism causing inhibition of hepatic gluconeogenesis, suppressing pancreatic β-cell proliferation, and promoting the lipid accumulation (Zhang, Xu et al. 2021).

Olanzapine may induce glucose dysregulation by blocking 5-HT1 receptors. Thus, the responsiveness of pancreatic beta cells could potentially reduce, resulting in decreasing insulin releasing and hyperglycemia (Kumar and Thomas 2011).

1.2.4.4. Hyperprolactinemia

Hyperprolactinemia is also the most underestimated adverse effects of antipsychotic medications like olanzapine. Olanzapine can increase prolactin levels by binding to D2 receptors with moderate affinity. Hyperprolactinemia is dose-dependent and may appear within three months of olanzapine using (Yang, Chen et al. 2018). There are several complications of hyperprolactinemia like hirsutism, amenorrhea, the absence of lactation, and disruption of normal ovarian cycles in women while, gynecomastia, erectile dysfunction, reduced sex drive, and impaired sperm production may develop

in men. Long-term hypogonadism is another complication of prolonged hyperprolactinemia, which can cause reduced bone density, osteoporosis, hip fractures, and increased incidence of cardiovascular problems (Montejo, Arango et al. 2017). Hyperprolactinemia may be caused by genetic variations of the D2 and 5-HT2A receptors especially following the use of olanzapine (Peuskens, Pani et al. 2014).

1.2.4.5. Others adverse effects

Traditional side effects of first-generation antipsychotic agents like akathisia, extrapyramidal symptoms, tardive dyskinesia, and neuroleptic malignant syndrome also occurred at a low rate with using of olanzapine. This may be related to low affinity and rapidly dissociation of olanzapine from the D2 receptors (Tollens, Gass et al. 2018).

Hypothermia, edema, and hematological abnormalities like neutropenia and thrombocytopenia have been reported with the use of olanzapine (Camilleri and Fiorini 2022).

1.2.5. Caution and Contraindication

Hepatic impairment is the important caution should be considered with using of olanzapine due to it changed liver enzymes like aminotransferase (Mauri, Paletta et al. 2018). Olanzapine can cause extrapyramidal symptoms, feeding disorders, and respiratory distress in newborns, if it used during the third trimester of pregnancy. Furthermore, Olanzapine is cautiously prescribed for patients who are obese or have diabetes (Larsen, Damkier et al. 2015).

Olanzapine should not be prescribed for patient dementia-related psychosis mainly elderly patient due to an increased mortality risk due to increased risk

of heart failure, sudden death due to cardiac causes, and pneumonia. Concomitant use of parenteral olanzapine (high dose) with benzodiazepines is not advised due to sedation and the risk of severe cardiorespiratory depression (Keepers, Fochtmann et al. 2020).

1.3. Dopamine Receptors

Dopamine receptors, found predominantly in the central nervous system of vertebrates, belong to a group of G protein-coupled receptors. Additionally, they are widely prevalent in peripheral tissues like blood vessels, kidneys, heart, and retina. They engage various effectors by means of G-protein coupling and other protein interactions. Dopamine serves as the principal naturally occurring neurotransmitter ligand for these receptors. Dopamine receptors play a role in various neurological functions, such as motivation and the perception of rewards, thinking and understanding, memory and acquiring new information, precise control of movements, and regulating neuroendocrine signals. Dopamine receptors are classified into five types, termed D1, D2, D3, D4, and D5, each one has specific roles. The encoding and the location of dopamine receptors are controlled by different genes like the 5q31-q34 gene which is encoding the D1 receptor. Where the D2 and D4 receptors are located on chromosome 11, the D3 receptor is presented on chromosome 3, and the D5 receptor is found on chromosome 4 (Klein, Battagello et al. 2019).

The responsiveness of antipsychotic agents and schizophrenia symptoms are determined by role of dopamine receptors and associated genes like cognitive impairments and malfunctioning of the pre-frontal cortex in the

brain are caused by genetic variations of D2, D3, and D4 receptors. Furthermore, the effectiveness of antipsychotic medication is affected by specific variations in single nucleotide polymorphisms (SNPs) of D2, D3, and D4 receptors (Rampino, Marakhovskaia et al. 2019).

1.3.1. The Effect of Dopamine D2 Receptors Genetic Variation on Olanzapine Therapeutic Response

The D2 receptor is the most common dopamine receptor discovered in humans, particularly overexpression in both the pituitary gland and the central nervous system. The chromosome 11q23 is the main location of D2 receptor and consists of six introns. The **Dopamine D2 Receptors** DRD2 gene had more than 200 genetic variations that were detected in the introns and the surrounding region. These variations have been linked to various conditions including addictions (alcohol, cocaine, nicotine, and opioids), mood disorders, schizophrenia, movement disorders, and drug response (Mi, Thomas et al. 2011).

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. 141C Insertion/Deletion located in the 5'-promoter region of the D2 gene, is powerful linked associated with schizophrenia. This genetic variation rs1799732 is exactly found in the gene promoter. The deletion variant in individuals tend to weight gain when taked with olanzapine compared to insertion variant. This SNP occurring in the promoter region of the D2 gene may lead to variations in the receptor's responsiveness to the effects of

antipsychotic drugs related to satiety and food consumption. the (rs1799732) polymorphisms which occurs approximately 9% in the Caucasian population, is related to increase dopamine receptor density in the striatum (Paderina, Boiko et al. 2022).

Cell membrane of lactotrophs contain D2 receptor and plays a role in decreasing the release of prolactin. The ability of olanzapine to bind to these receptors can be affected by genetic variation in the DRD2 respecter gene. Consequence this modification can impact the release of prolactin from the pituitary gland. The Ankyrin Repeat and Kinase Domain Containing 1 Gene Polymorphism (Taq1A) located downstream of DRD2 within a novel kinase gene. Taq1A exhibits two different forms, A1 and A2. individuals who carry the A1 allele and take olanzapine medication lead to have prolactin levels 40% elevated than individuals who do not possess this allele (López-Rodríguez, Román et al. 2011).

Mexican patients with DRD2 receptor A-241G genes for schizophrenia appear abundance of the G allele in individuals who were resistant to treatment (Escamilla, Camarena et al. 2018).

1.4. The Aim of the Study

١. To detect the distribution of the genetic variant of DRD2 gene (-141C Ins/Del, rs1799732), as well as its association with incidence of olanzapine adverse effects in sample of patients of Kerbala province.
٢. To detect the distribution of the genetic variant of the DRD2 gene (A-241G, rs1799978), as well as its association with efficacy of olanzapine in sample of patients of Kerbala province

Chapter Two

Subject, Materials, and Methods

2. Subject, Materials, and Methods

2.1. Subjects (Patients and Control)

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Tandon, Gaebel et al. 2013), 100 people with schizophrenia were included in this study. They comprised both male and female patients between the ages of 20 and 65. These patients were chosen from the Psychiatry Outpatient Department of Al-Hassan Al-Mojtaba hospital, where they went for their medical care and advice. A comparison group of 50 healthy people, aged 20 to 63 and included both males and females, was also enlisted**.**

2.1.1. Patients Criteria

2.1.1.1. Inclusion Criteria

Male and female patients with schizophrenia were receiving 10 mg /day olanzapine from 6 months up to years with no additional disorders.

2.1.1.2. Exclusion Criteria

١. The subjects receiving treatment or any other medication, such as bromocriptine, levodopa, or methyldopa, that interacts with olanzapine were excluded.
٢. Before taking olanzapine, patients with prior hyperglycemia/diabetes, hypotension, weight gain, hyperprolactinemia, **Dyslipidemia** or tardive dyskinesia are excluded.

2.1.2 Ethical and Scientific Approval

- The scientific and ethical committee at the college of pharmacy –Kerbala University discussed and approved the proposal of the research.
- The study received approval from the Ministry of Health of Iraq's Kerbala Health Department as well. The project was given the number 244 and was approved on December 26, 2022.
- Following the completion of a written consent form that contained a thorough explanation of the study's goals and a request to complete a specifically created questionnaire, all participants were enrolled in the study.

2.2 Materials

2.2.1 Instruments and their Origin

All instruments used in this study are listed in Table (2-1) accompanied by their manufacturing company.

Table (2-1): Instruments and the manufacturing companies

Instrument	Company/ Country
BS 240	Mindary – China
Centrifuge	Hettich – Germany
Digital camera	Canon – England
DIRUI	CM-180 – China
PCR machine (Thermocycler)	Verity – United state
Incubator	Binder – Germany
Micropipettes	Slamed – Japan
Vortex mixer	Human twist – Germany
Hood	Lab Tech – Korea
UV-trans illuminator	Syngene – England

2.2.2 Chemicals, Kits, and their Suppliers

All chemicals and kits used in this study with their producing company are listed in the table (2-2)

Table (2-2): Chemicals and kits and their producing companies.

Types	Materials	Company/ Country
Chemicals	Agarose	Bio Basic - Canada
	Ethanol	Hayman Kimia - UK
	Ethidium Bromide	Intron - Korea
	Nuclease free water	Bioneer - Korea
	TBE buffer	Bioneer - Korea
Biochemical Kits	Cholesterol Kit	Mindray - China
	Fasting serum glucose kit	Roche - Germany
	Glycosylated Hemoglobin kit	Minday - China
	HDL kit	Mindray – China
	Triglyceride kit	Mindray – China
Hormonal Kits	Prolactin Kit	DIRUI
Genetic Kits (Primers)	DNA extraction kit	Biotech – Korea
	DNA ladder marker	Bioneer – Korea
	PCR PreMix Kit	Bioneer – Korea
	$rs1799732$ $rs1799978$	Macrogen – Korea

2.3 Methods

2.3.1. Study Design

A case-control trial was conducted from October 2022 to April 2023, using 50 people who appeared to be healthy and free of any sickness as the control group and 100 Iraqi patients who had been diagnosed with schizophrenia.

2.3.2. Evaluation the Patient Response to Olanzapine

The Positive and Negative Syndrome Scale (PANSS), which has three parts: Positive (P), Negative (N), and cognitive or General Psychopathology (G) was used by the psychiatrist to assess the severity of the sickness and the patient's response to olanzapine. The General Psychopathology subscale has 16 items with a strong focus on cognition (G1 - G16), while the Positive and Negative subscales each have seven items (P1 - P7, N1 - N7). This information is shown in Table (2-3). Each component is given a score between 1 and 7according to severity, with 1 denoting absence, 2; minimum, 3; milds, 4; moderate, 5; moderate-severity, 6; severity, and 7; extremeness. A thorough definition and exact standards for each of the seven rating points are provided for each item on the PANSS. The minimum scores required by this scoring approach are 7 points for each of the Positive and Negative subscales and 16 points for the cognitive category, for a total minimum score of 30 points. Positive, Negative, and Cognition each have maximum scores of 49, 49, and 112 points, respectively, for a combined maximum score of 210 points (Shankar and Nate 2007).

Positive syndrome is characterized by symptoms like hallucinations, delusions, and disorganized thought. Cognitive, affective, and social

deficiencies, such as blunting of affect and passive disengagement, are characteristics of the negative syndrome. Many cognitive problems, including disorientation, poor concentration, lack of understanding, and deliberate social avoidance, make up general psychopathology.

Table (2 – 3): Positive and Negative Syndrome Scale (PANSS) (Shankar and Nate 2007)

Positive (P)		Negative (N)		Cognitive Psychopathology (G)	
P1	Delusions	**N1**	Blunted affect	**G1**	Somatic concern
P2	Conceptual disorganization	**N2**	Emotional withdrawal	**G2**	Anxiety
P3	Hallucinatory behavior	**N3**	Poor rapport	**G3**	Guilt feelings
P4	Excitement	**N4**	Passive/apathetic social withdrawal	**G4**	Tension
P5	Grandiosity	**N5**	Difficulty in abstract thinking	**G5**	Mannerism and posturing
P6	Suspiciousness/persecution	**N6**	Lack of spontaneity and flow of conversation	**G6**	Depression
P7	Hostility	**N7**	Stereotyped thinking	**G7**	Motor retardation
				G8	Uncooperativeness
				G9	Unusual thought content
				G10	Disorientation
				G11	Poor attention
				G12	lack of judgment and insight
				G13	Disturbing of volition
				G14	Poor impulse control
				G15	Preoccupation
				G16	Active social avoidance

2.3.3 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 (Ethylenediaminetetraacetic Acid) 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.

2.3.4. Determination of Body Mass Index

The body mass index (BMI) is calculated using a person's height and weight. One divides the body weight by the square of the body height to determine BMI. With weight in kilograms and height in meters, the outcome is represented as kilograms per square meter (kg/m2). A BMI of 18.5 to 24.9 indicates a normal weight, whereas a BMI of 25 to 30 indicates being overweight, and a BMI of greater than 30 indicates being obese (Rahman, Berenson et al. 2010).

2.3.5. Biochemical Assay Methods

2.3.5.1 Determination of Glycemic Indices

2.3.5.1.1. Estimation of Fasting Serum Glucose

The estimation process of fasting blood sugar (FBS) utilized the hexokinase enzyme, which enables the conversion of glucose into glucose-6-phosphate with the aid of ATP, which is a rate - limiting step. Once NADP (Nicotinamide Adenine Dinucleotide Phosphate) is present, glucose-6-phosphate dehydrogenase can convert glucose-6-phosphate into gluconate-6-phosphate, which is then used to assess the glucose level using UV light. In this procedure, just the glucose is oxidized. As glucose concentration is inversely associated with the rate of NADPH generation during the reaction, it is possible to detect this rate (González-González, González-Dávila et al. 2023).

2.3.5.1.2 Estimation of Glycosylated Hemoglobin

The BS240Pro device is used to automatically hemolyze a blood sample kept in an EDTA tube as part of the HbA1c calculation procedure. Tetradecyltrimethylammonium bromide (TTAB), a detergent that does not lyse leukocytes, is included in the hemolyzing reagent in this approach to eliminate interference from leukocytes. The beta-chain N terminal, which possesses antibody-recognizable sections identical to those of HbA1c, is where the assay measures all the glycated hemoglobin that is present there. A soluble antigen-antibody complex is created when glycohemoglobin and the anti-HbA1c antibody in the sample react. The HbA1c molecule only has one site for the HbA1c antibody, which leads to the creation of this complex. An insoluble antibody-polyhapten combination is created when the extra anti-HbA1c antibody combines with a polyhapten. Turbidimetric analysis can be used to gauge this complex (Sherwani, Khan et al. 2016).

2.3.5.2 Determination of Lipid Profile

2.3.5.2.1. Estimation of Total Cholesterol

The enzymatic colorimetric method on the BS240Pro was used to determine the amount of total cholesterol (TCHO) in the serum. This approach converts cholesterol esters into free cholesterol and fatty acids by using the cholesterol esterase enzyme (CE). The subsequent synthesis of cholest-4-en-3-one and hydrogen peroxide from the oxidation of cholesterol is made possible by the cholesterol oxidase enzyme (CHOD). The peroxidase enzyme (POD) then facilitates the oxidative coupling of phenol with 4-amino antipyrin (4-AAP) to produce a red quinone-imine dye when hydrogen peroxide is present.

$$\text{Cholesterol esters} + H_2O \xrightarrow{CE} \text{Cholesterol} + RCOOH$$

$$\text{Cholesterol} + O_2 \xrightarrow{CHOD} \text{Cholest-4-en-3-one} + H_2O_2$$

$$2\,H_2O_2 + \text{4-AAP} + \text{phenol} \xrightarrow{POD} \text{Quinone-imine dye} + 4\,H_2O$$

The measurement of cholesterol content, correlates inversely with the intensity of the dye produced, thus it caused rise in absorbance at 512 nm (Malik and Pundir 2002).

2.3.5.2.2. Estimation of Serum Triglyceride

An enzymatic quantitative colorimetric approach was utilized to quantify the concentration of TG in serum using the BS240Pro system. Serum triglyceride was measured enzymatically by a sequence of related reactions. Triglycerides were initially hydrolyzed by lipase into glycerol. Glycerol kinase and glycerol-3-phosphate oxidase then caused glycerol to be converted to H2O2. Through a peroxidase-catalyzed reaction that produced a colored chemical, the amount of H2O2 generated was quantified. The intensity of the color was directly correlated with the concentration of triglycerides, and the absorbance of this color was determined at 500 nm (Fossati and Prencipe 1982).

$$\text{triglycerides} + 3\,H_2O \xrightarrow{\text{Lipoprotein lipase}} \text{glycerol} + 3\,RCOOH$$

$$\text{glycerol} + ATP \xrightarrow{\text{Glycerol Kinase}} \text{glycerol-3-phosphate} + ADP$$

$$\text{glycerol-3-phosphate} + O_2 \xrightarrow{\text{Glycerol-3-Phosphate Oxidase}} \text{dihydroxyacetone phosphate} + H_2O_2$$

$$H_2O_2 + \text{4-aminophenazone} + \text{4-chlorophenol} \xrightarrow{\text{peroxidase}}$$

4-(p-benzoquinone-monoimino)-phenazone + 2 H2O + HCl.

2.3.5.2.3. Estimation of Serum High-Density Lipoprotein

Using an in vitro quantitative enzymatic colorimetric test, the BS 240 system was used to estimate the amount of HDL in serum. Low LDL, VLDL, and chylomicrons generated water-soluble compounds in the presence of magnesium ions and dextran sulfate that were unaffected by PEG-modified enzymes (Polyethylene Glycol-Modified). Cholesterase and cholesterol oxidase enzymes, together with PEG to target the amino groups, were used to evaluate HDL enzymatically. The quantitative breakdown of cholesterol esters into free cholesterol and fatty acids was carried out by cholesterol esterase. Cholesterol oxidase oxidized cholesterol in the presence of oxygen, generating 4 cholestenone and hydrogen peroxide in the process.

HDL-cholesterol esters + H_2O $\xrightarrow{\text{PEG-cholesterol esterase}}$ HDL-cholesterol + RCOOH

HDL-cholesterol + O_2 $\xrightarrow{\text{PEG-cholesterol oxidase}}$ Δ4-cholestenone + H_2O_2

2 H_2O_2 + 4-aminoantipyrine + HSDAa) + H+ + H_2O $\xrightarrow{\text{peroxidase}}$ purple blue pigment (Sodium N-(2-hydroxy-3-sulfopropyl)-3,5-dimethoxyaniline) + 5 H_2O

The amount of HDL cholesterol present is inversely correlated with the amount of blue quinonimine dye generated. It is determined by the rise in absorbance at 583 nm (Hafiane and Genest 2015).

2.3.5.2.4. Estimation of Serum Low-Density Lipoprotein and Very Low-Density lipoprotein

The Fried Ewald equation can be used to determine LDL based on the levels of TCHO, TG, and HDL:

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

The correlation between these variables was indicated by this arithmetic function. All readings should be given in milligrams per deciliter (mg/dL). TG/5 is a measure of estimated VLDL (Cohen, Cziraky et al. 2010).

2.3.5.3. Estimation of Prolactin

Sandwich immunodetection is used to measure prolactin levels. The procedure uses several different components, including the bovine serum albumin (BSA) as a stabilizer, the antibody anti-human PRL-fluorescence conjugate, the biotin-bovine serum albumin (BSA) conjugate-fluorescence conjugate, and sodium azide in phosphate-buffered saline (PBS) as a preservative in the detected buffer. This technique involves the formation of antigen-antibody complexes by the binding of the anti-human PRL antibody to the antigen present in the sample. These complexes subsequently move onto a matrix made of nitrocellulose, where they are picked up by a test strip's streptavidin and an additional immobilized anti-human PRL antibody. The number of antigen-antibody complexes generated in the sample is directly proportional to the detector antibody's fluorescence intensity, which indicates a higher concentration of PRL. An apparatus processed this fluorescence signal to calculate the concentration of PRL in the sample. (Alawad and Al-Omary 2019).

2.3.6. Genetic Analysis

2.3.6.1 Extraction of Genomic DNA from Blood Sample

The Genomic Total DNA extraction kit from biotech was used to produce pure DNA that was suited for immediate application and storage after being quickly and easily extracted from blood and other biological samples. The following steps made up the kit procedure:

- Fill 1.5 micro centrifuge tubes with 200 µl of whole blood.
- Fill the sample tube with 20 µl of proteinase K enzyme and pulse-mix by using a vortex.
- To generate a lysis solution, add 200 µl of BL buffer to the sample tube and thoroughly mix.
- Allow the mixture to rest for two minutes at room temperature.
- Mix the lysate several times while incubating it at 56 ºC for 10 minutes.
- Quickly centrifuge the sample tube to get rid of any liquid that may have gotten inside the lid.
- Add 200 µl of pure ethanol to the lysate, vortex to combine, and then quickly centrifuge once more.
- Applying the mixture carefully to the spin column, capping it, and centrifuging at 13,000 rpm for one minute are all necessary steps. Replace the collection tube and throw away the filtrate.
- Fill the spin column with 700 µl of WA buffer, centrifuge it for one minute at 13,000 rpm, and then remove the filtrate.
- Fill the spin column with 700 µl of WB buffer, centrifuge it for one minute at 13,000 rpm, then discard the filtrate and swap out the collecting tube. To dry the membrane, centrifuge for an additional minute.

- Use a fresh 1.5 ml tube as the spin-column replacement. Directly pour 80 µl of buffer CE onto the membrane, then let it sit at room temperature for 1 minute. To elute DNA, centrifuge at 13,000 rpm for 1 minute.

2.3.6.2. Polymerase Chain Reaction

2.3.6.2.1. Primer Preparation

The D2 receptor genes rs1799732 and rs1799978 were amplified by Polymerase Chain Reaction (PCR) using a particular primer. These primers were created using the primer-BLAST program and bought from Bioneer, Korea, in the form of a lyophilized product with various picomole concentrations. Each primer was dispersed in precise amounts of nuclease-free water to produce a stock solution with a concentration of 100 pmol/µl. Then, 10 µl of the stock solutions for each primer were combined with 90 µl of nuclease-free water to create the diluted work solution. When not in use, this work solution was then kept in a freezer at -20°C.

The PCR primer sequence for the D2 receptor gene -141C Ins/Del (rs1799732) and A-241G (rs 1799978) were illustrated in the table (2-3) (He, Yan et al. 2013).

Table (2-4) Primer sequence of D2 receptor -141C Ins/Del (rs1799732) and A-241G (rs 1799978)

Primer	Sequence	Product Size (bp)
(-141C Ins/Del rs 1799732)	P1: 5'-ACTGGCGAGCAGACGGTGAGGACCC-3' P2: 5'-TGCGCGCGTGAGGCTGCCGGTTCGG-3'	C/C: 144, 160 Del-c C/-: 303, 144, 160
(A-241G rs 1799978)	Forward1 5- ACTGGCGAGCAGACGGTGA -3 Reverse1 5- TGAAGCTGGACAGCTCTGC -3 Forwad2 5- CAGCCTGCAATCACAGCTTA -3 Reverse2 5- CAGCCTGCAATCACAGCTTG-3	252bp

(He, Yan et al. 2013)

2.3.6.2.2. Optimization of Polymerase Chain Reaction Conditions

The PCR reaction was optimized to determine the best concentration of DNA and primers, as well as the ideal annealing temperature and number of amplification cycles for the Restriction Fragment Length Polymorphism (RFLP) PCR reaction and nested PCR. The elements of the PCR reactions for each amplified fragment and the optimized PCR scripts were displayed in tables (2-4) and (2-5) respectively.

2.3.6.2.3. Running the Polymerase Chain Reaction

The PCR experiment involved using the reaction-specific PCR programs while combining the PCR components with a DNA solution as explained in the table (2-4).

Table (2-5): The components of PCR reaction for genotyping of D2 receptors rs1799732 (141c ins/del) and rs1779978 (241G) in PCR

Components	Volume (µl)
Forward primer	1.25
Reverse primer	1.25
DNA template	5
Deionized water	12.5
Premix	5
Total	**25**

Table (2-6): The Conditions of PCR for Genotyping of D2 Receptors rs1799732 and rs1779978.

Steps	Temperature/c	Time	Cycle
Denature temperature	95	4 min.	1
Initial denaturation	95	40 sec	35
Annealing	58	30 sec	
Extension	72	30 sec	
Final extension	72	5 min.	1

2.3.6.3. Agarose Gel Electrophoresis

The steps involved in agarose gel electrophoresis were as follows:

- The agarose gel was made by dissolving 1.5g of agarose powder in 100 ml of 1x TBE buffer (pH 8).
- On a hot plate, the solution was cooked until it reached the boiling point.
- 2 µl of ethidium bromide was added to the solution once it had cooled.
- To make wells for the loading of the PCR product, a comb was placed at one end of the tray.

- After being carefully poured into the tray, the agarose solution was left to harden for 30 minutes at room temperature.
- The comb was cautiously taken out of the tray.
- A TBE buffer was added to the tray, which was then put in an electrophoresis chamber.
- The wells were immediately loaded with PCR products.
- The voltage of the electrophoresis device was tuned to produce an electrical field of 5 v.cm-1 between the cathode and anode.
- An ultraviolet trans-illuminator running at 320-336 nm was utilized to find the bands after roughly 90 minutes.
- At the conclusion of the run, the gel was captured on camera.

2.4. Statistical Analysis

Statistical analysis will perform 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 percentage. The normal distribution of data was tested with the aid of Shapiro – wilk test. Numerical data will be analyzed by using an independent sample T-test and a one-way ANOVA-post-hoc-LSD test. Non-numerical data will be analyzed by using the Chi-square test. The multinomial logistic regression was used to assess the association of genetic variation with efficacy of olanzapine. The P values less than 0.05 will be considered statistically significant.

Chapter Three

Results

3. Results

3.1. Demographic Data

The demographic data including age, gender, and BMI 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 show in Table (3-1). Schizophrenic patients demonstrated significant weight gain, as evidenced by increased BMI compared to the healthy individuals ($P < 0.05$) as shown in Table (3-1) and Figures (3-1).

Table (3-1): Demographic data of both healthy and Schizophrenic Volunteers (Data Present as mean ± S.E and No (%))

Variables		Volunteer		*P* – value
		Healthy Mean (n=50)	Schizophrenic Mean (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**	24.52 ± 0.57	29.11 ± 0.64	<0.0001*
	Female	24.89 ± 0.69	30.01 ± 0.81	<0.0001*

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

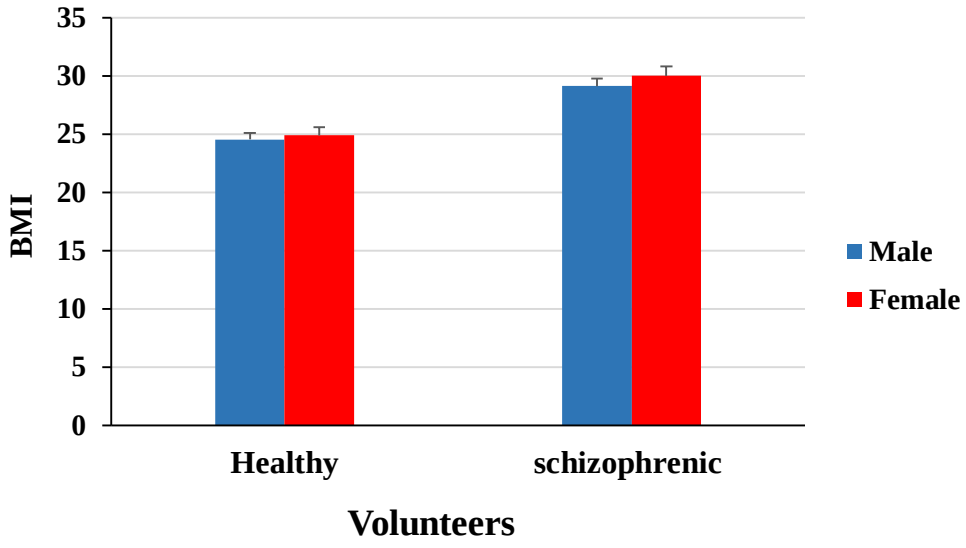

Figure (3-1): The BMI of the volunteers

3.2. Assessment of Metabolic Parameters

3.2.1. Glycemic Status

The FBS and HbA1c of schizophrenic patients were significantly increased as compared to the healthy individuals ($P < 0.05$) as shown in table (3-2) and figure (3-2) and (3-3).

Table (3-2): The Metabolic Parameters of both Healthy and Schizophrenic volunteers (data present as mean ± S.E)

Variables		Volunteer		*P* - value
		Healthy (n=50)	Schizophrenic (n=100)	
Glycaemic status	FBS (mg/dl)	103.2 ± 1.33	111.44 ± 2.02	0.007*
	HbA1c (%)	5.25 ± 0.07	5.85 ± 0.05	<0.0001*
Lipidemic status	TCHO (mg/dl)	140.34 ± 4.45	208.77 ± 3.3	<0.0001*
	TG (mg/dl)	128.18 ± 3.35	176.08 ± 5.33	<0.0001*
	HDL (mg/dl)	47.18 ± 1.28	35.22 ± 0.7	<0.0001*
	LDL (mg/dl)	67.52 ± 4.35	138.33 ± 2.9	<0.0001*
	VLDL (mg/dl)	25.64 ± 0.67	35.22 ± 1.07	<0.0001*
Prolactin level (mg/dl)	Male	19.44 ± 1.77	28.2 ± 1.12	<0.0001*
	Female	30.66 ± 1.67	42.11 ± 1.88	0.001*

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

Figure (3-2): The FBS of the volunteers

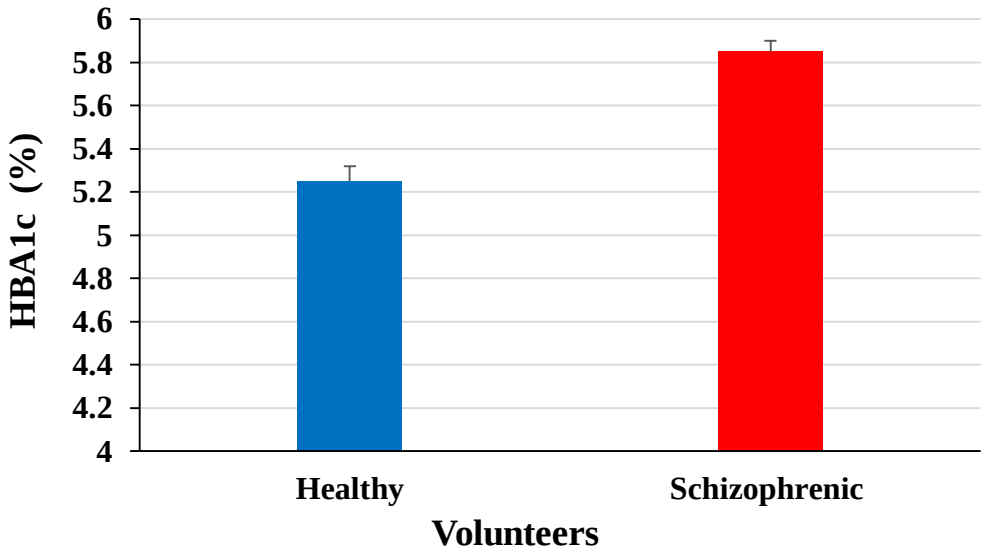

Figure (3-3): The HBA1c of the Volunteers

3.2.2. Lipidemic Status

The serum levels of bad lipid profile (TCHO, TG, LDL, and VLDL) in patients with schizophrenia were significantly elevated and the level of good lipid parameter (HDL) was significantly lowered in comparison with healthy individuals ($P < 0.05$) as shown in Table (3-2) and Figure (3-4).

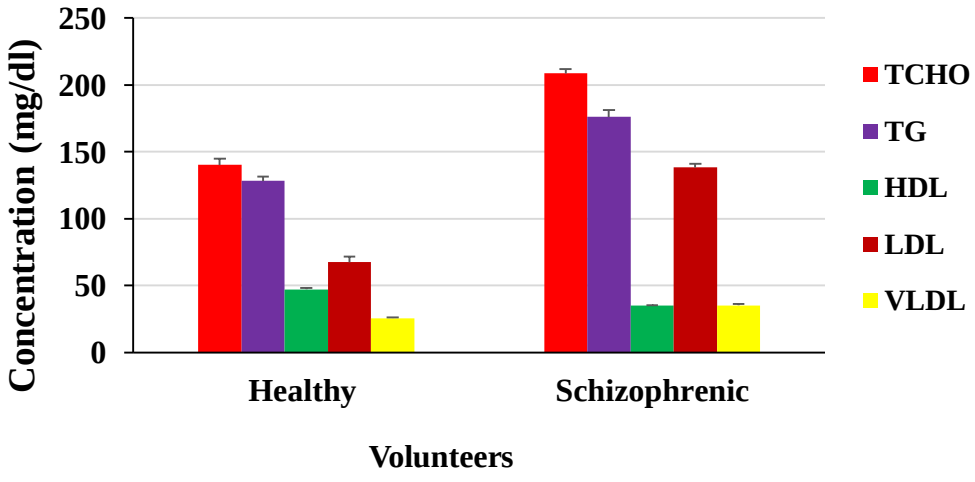

Figure (3-4): The lipid Profile of the Volunteers

3.2.3. Prolactin Level

The level of prolactin was significantly elevated in individuals with schizophrenia as compared with to the healthy volunteers ($P < 0.05$) as shown in table (3-2).

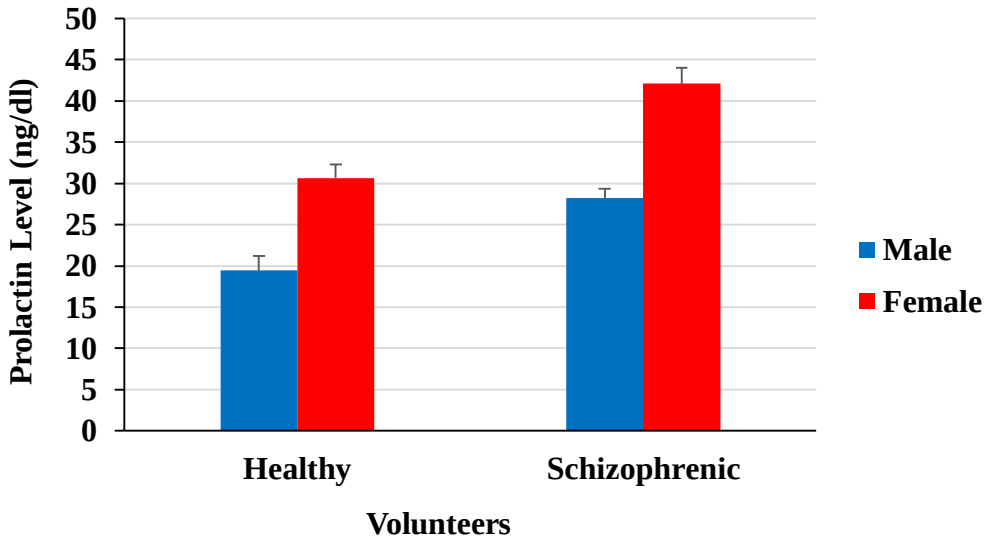

Figure (3-5): The Prolactin level of the Volunteers

3.3. Genetic Analysis

3.3.1. Prevalence of D2 Receptor Genes 141c ins/del (rs1799732)

The results of genotype D2 receptor –141 C ins/Del (rs1799732) genetic polymorphism showed a clear band with a molecular size 144, 160, and 303 bps as presented in figure (3-6). The wild allele (Ins/Ins) was predominated (100%) in healthy volunteers and about (75%) in schizophrenic patient, while the heterozygous type (Ins/Del) and mutant type (Del/Del) were only presented in schizophrenic individuals with ratio of 12% and 13% respectively as shown in figure (3-7). The frequencies of the D2 receptor alleles rs1799732 (141c

ins/del) were significantly different between the healthy and schizophrenic volunteers ($P < 0.05$) as show in table (3-3). There were significantly difference among both genders of healthy and schizophrenic individuals regarding three different alleles of rs1799732 (141c ins/del) ($P < 0.05$) as explained in tables (3-4) and (3-5) and figure (3-8).

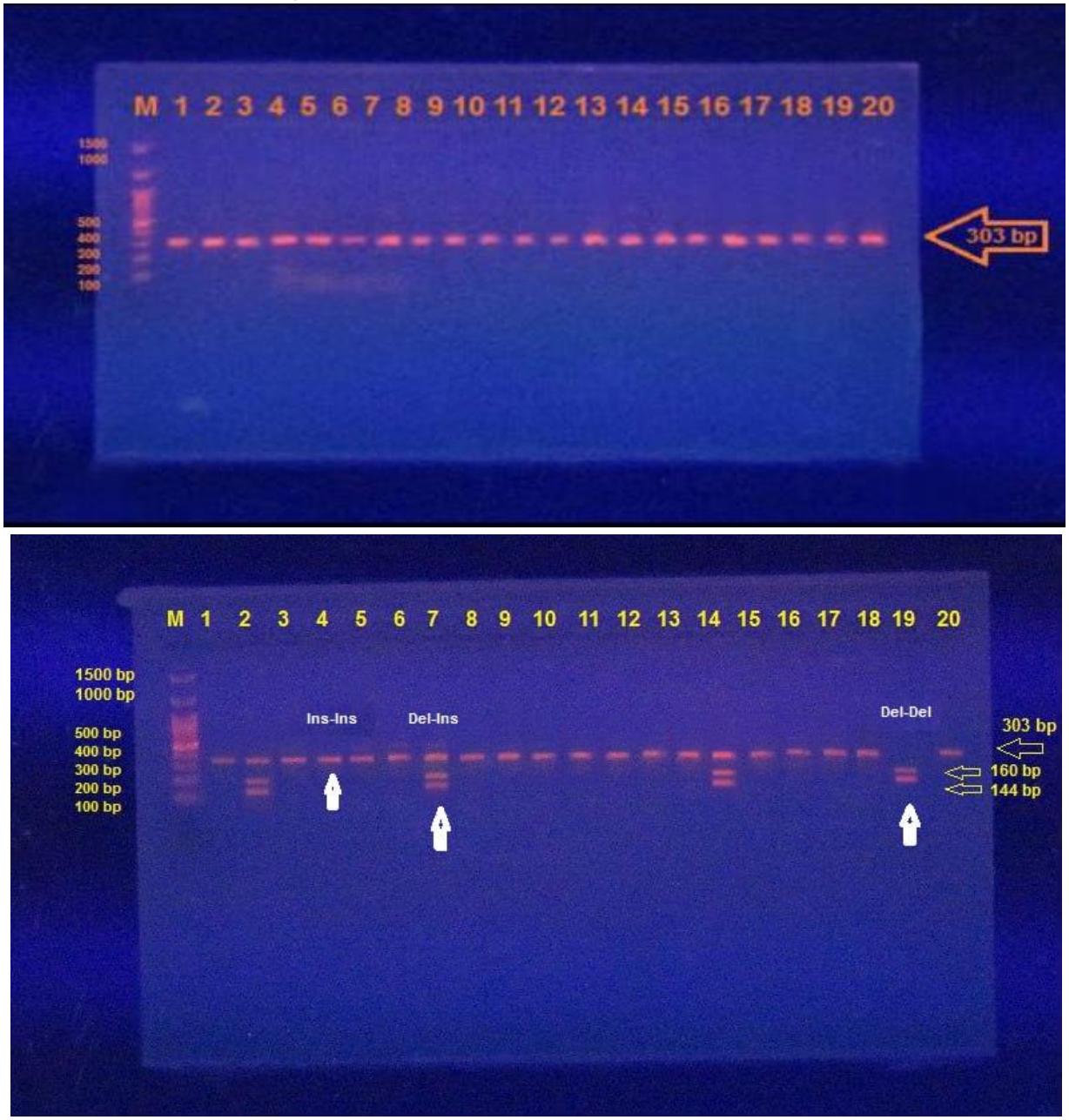

Figure (3-6): Genotyping of D2 Receptor Genes –141 C Ins/Del (rs1799732)

A: before restriction enzyme B: after restriction enzyme

Table (3-3): The Prevalence of D2 Receptor Alleles rs1799732 (141c ins/del) among Volunteers

Volunteers	Alleles of rs1799732 (141c ins/del)			*P* – Value
	Ins/Ins NO %	Ins/Del NO %	Del/Del NO %	
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.

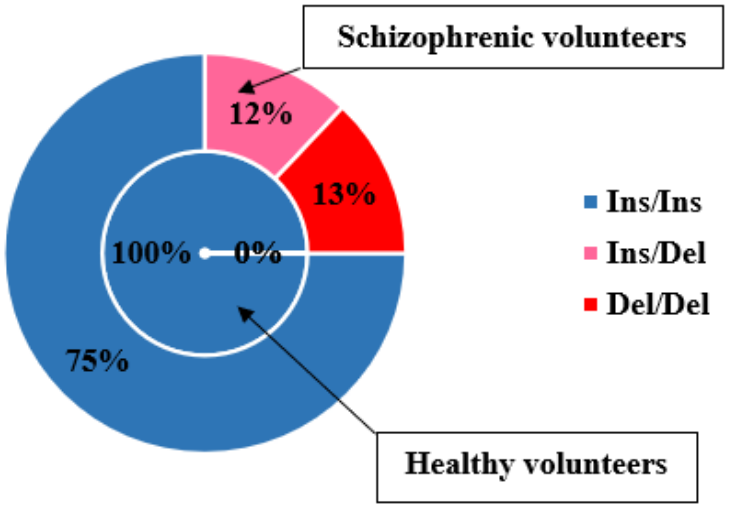

Figure (3-7): The Prevalence of D2 Receptor alleles rs1799732 (141c ins/del) among volunteers

Table (3-4): The Prevalence of D2 Receptor Alleles rs1799732 (141c ins/del) among Male volunteers

Male volunteers	Alleles of rs1799732 (141c ins/del)			*P* – Value
	Ins/Ins NO %	Ins/Del NO %	Del/Del NO %	
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 (3-5): The Prevalence of D2 Receptor alleles rs1799732 (141c ins/del) among female volunteers

Female volunteers	Alleles of rs1799732 (141c ins/del)			*P* - Value
	Ins/Ins NO %	Ins/Del NO %	Del/Del NO %	
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.

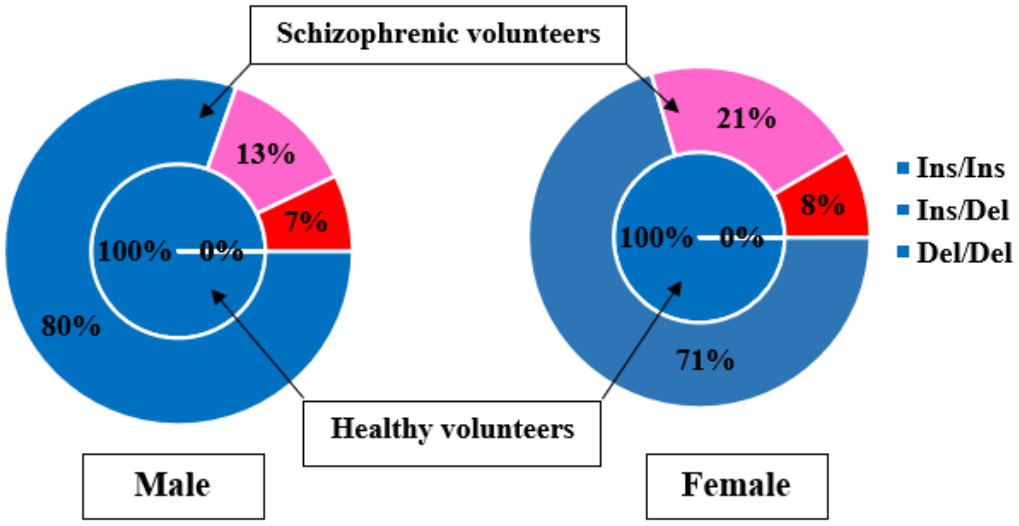

Figure (3-8): The Prevalence of D2 Receptor alleles rs1799732 (141c ins/del) among both male and female volunteers

3.3.2. Prevalence of D2 receptor genes A-241G (rs1799978)

The results of genotype D2 receptor A-241G (rs1799978) genetic polymorphism showed a clear band with a molecular size 252 bps as presented in figure (3-9). The wild allele (AA) was predominated (100%) in healthy volunteers and about (78%) in schizophrenic patient, while the heterozygous

type (AG) and mutant type (GG) were only presented in schizophrenic individuals with ratio of 14% and 8% respectively as shown in figure (3-10). The frequencies of the D2 receptor alleles rs1799978 (A-241G) were significantly different between the healthy and schizophrenic volunteers ($P < 0.05$) as show in table (3-6). There were significantly difference among male gender of healthy and schizophrenic individuals and There were not significantly difference among female gender of healthy and schizophrenic individuals regarding three different alleles of rs1799978 (A-241G) ($P > 0.05$) as explained in tables (3-٧) and (3-8) and figure (3-11).

Figure (3- 9): Genotyping of D2 receptor genes A-241G (rs1799978)

Table (3-6): The Prevalence of D2 receptor alleles A-241G (rs1799978) among volunteers

Volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA NO %	AG NO %	GG NO %	
Healthy	50 (100%)	0 (0%)	0 (0%)	0.002*
Schizophrenic	78 (75%)	14 (14%)	8 (8%)	

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

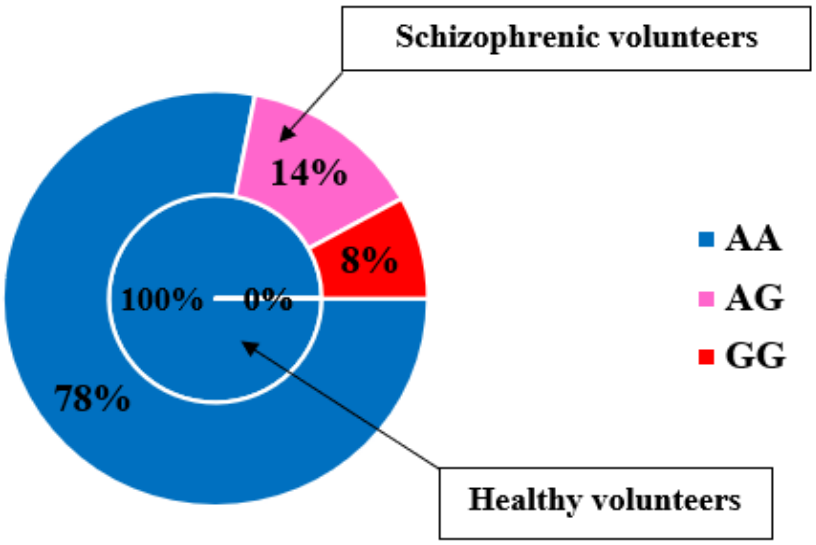

Figure (3-10): The Prevalence of D2 receptor alleles A-241G (rs1799978) among volunteers

Table (3-7): The Prevalence of D2 receptor alleles A-241G (rs1799978) among male volunteers

Male volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA NO %	AG NO %	GG NO %	
Healthy	32 (100%)	0 (0%)	0 (0%)	0.037*
Schizophrenic	45 (81.8%)	4 (7.3%)	6 (10.9%)	

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

Table (3-8): The Prevalence of D2 Receptor alleles rs1799978 (A-241G) among female volunteers

Female volunteers	Alleles of rs1799978 (A-241G)			*P* – Value
	AA NO %	AG NO %	GG NO %	
Healthy	18 (100%)	0 (0%)	0 (0%)	0.052
Schizophrenic	33 (73.4%)	10 (22.2%)	2 (4.4%)	

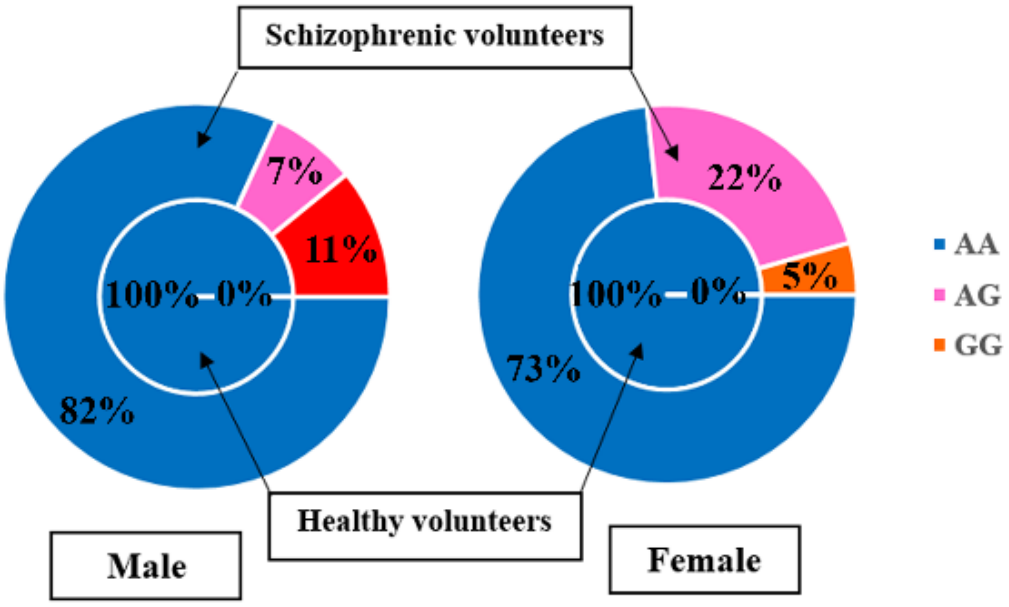

Figure (3-11): The Prevalence of D2 Receptor Alleles A-241G (rs1799978) among both Male and Female Volunteers

3.3.3. Effects of D2 Receptor Alleles A-241G (rs1799978) on PANSS

The schizophrenic symptoms were represented by PANSS score which was significantly high in schizophrenic patients who taken olanzapine and had either heterozygous (AG) allele or mutant (GG) allele of A-241G (rs1799978) as compared to those with wild (AA) allele (P<0.05) as shown in table (3-9). There were significantly difference among schizophrenic volunteers who carried heterozygous (AG) allele and mutant (GG) allele of A-241G (rs1799978) regarding the PANSS score (P<0.05) as shown in table (3-9) and figure (3-12). There were significantly associated between response of schizophrenic patient according to PANSS and G allele of A-241G (rs1799978) (P<0.05) as explained in table (3-10).

Table (3-9): The PANSS Score of Schizophrenic and Healthy Volunteers (data present as mean ± S.E)

Variables	Volunteer				*P* -value
	Healthy	Schizophrenic			
		AA mean	AG mean	GG mean	
PANSS	30.24 ± 0.32	70.54 ± 2.46	146.93 ± 4.91	197.13 ± 4.07	<0.0001*

a: Significant effect (P < 0.05) among all study groups.

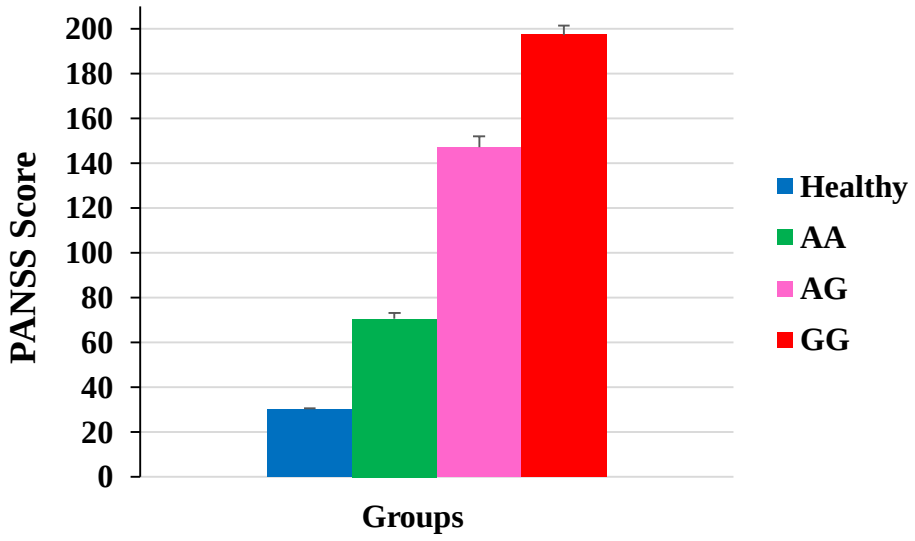

Figure (3-12): The PANSS score of schizophrenic and healthy volunteers.

Table (3-10): The Multinomial Logistic Regression of D2 Receptor alleles A-241G (rs1799978) and PANSS score.

Variable	Allele of A-241G	OR (95% CI)	*P* -value
PANSS	AA	1*	
	AG	8.022 (7.098 – 9.067)	<0.0001[a]
	GG	7.928 (7.006 – 9.237)	<0.0001[a]

a: significant effect (p<0.05), OR: Odds Ratio, CI: Confidence interval, *: reference group

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

3.3.4.1. Body Weight

Both gender of schizophrenic patients who received olanzapine and had either heterozygous (Ins/Del) or mutation (Del/Del) type of 141c ins/del (rs1799732) were significantly increased in BMI as compared to those with wild (Ins/Ins) allele and healthy volunteers (P <0.05) as presented in Table (3-11) and Figure (3-13). There were no significant difference when the both gender of schizophrenic patient with heterozygous (Ins/Del) alleles compared to those with Del/Del alleles regarding BMI (P >0.05) as shown in the Table (3-11). There were significantly associated between weight gain of schizophrenic patient and deletion allele of 141c ins/del (rs1799732) (P<0.05) as explained in table (3-12).

Table (3-11): 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 mean	Ins/Del mean	Del/Del mean	
BMI (kg/m^2)	Male	24.52 ± 0.57	24.26 ± 0.58	29.47 ± 0.59	30.44 ± 0.53	<0.0001 [a, b]
	Female	24.89 ± 0.69	25.19 ± 0.72	31.3 ± 0.94	34.38 ± 0.62	<0.0001 [a, b]

a: Significant effect (P < 0.05) when Ins/Del and Del/Del groups compared to Ins/Ins and healthy groups.

b: No Significant effect (P > 0.05) when Ins/Del group compared Del/Del group.

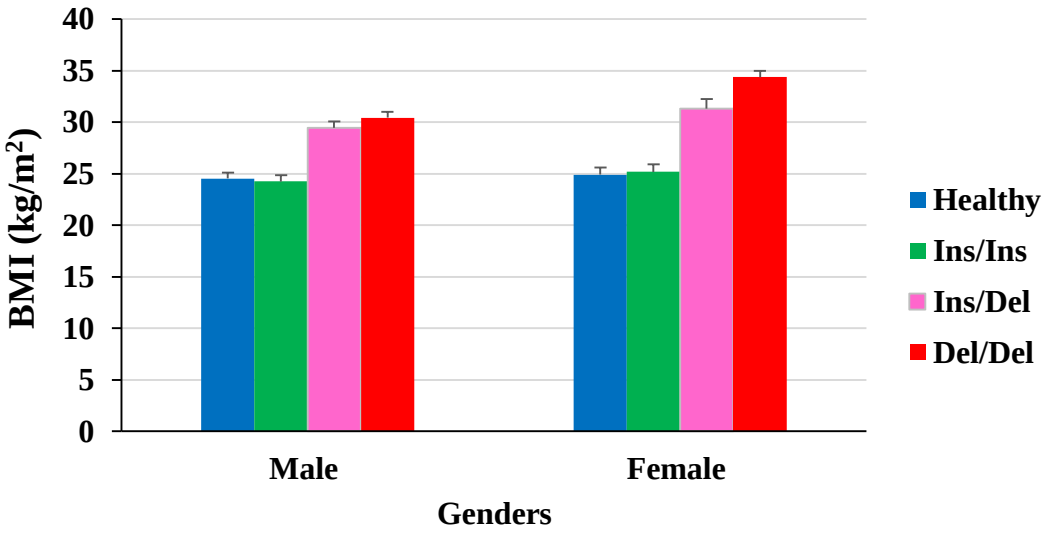

Figure (3-13); The BMI of Heathy and Schizophrenic Patients of different alleles of 141c ins/del (rs1799732).

Table (3-12): The multinomial logistic Regression of D2 Receptor alleles 141c ins/del (rs1799732) and BMI.

Variable		Allele of 141c ins/del	OR (95% CI)	*P* –value
BMI	Gender	Healthy	1*	
	Male	Ins/Ins	0.981 (0.867 – 1.110)	0.758
	Female		1.025 (0.867 – 1.213)	0.770
	Male	Ins/Del	1.492 (1.096 – 2.030)	0.011[a]
	Female		1.815 (1.131 – 2.913)	0.014[a]
	Male	Del/Del	1.617 (1.133 – 2.307)	0.008[a]
	Female		3.018 (1.348 – 6.760)	0.007[a]

a: significant effect (p<0.05), OR: Odds Ratio, CI: Confidence interval, *: reference group

3.3.4.2. Glycemic status

The FBS and HbA1c of schizophrenic patient with olanzapine and had either heterozygous (Ins/Del) or mutation (Del/Del) type of 141c ins/del (rs1799732) were significantly elevated as compared to those with the wild (Ins/Ins) type and healthy volunteers (*P* <0.05) as shown in table (3-13) and

figure (3-14) and (3-15). There was no significant difference when the schizophrenic patients with heterozygous (Ins/Del) allele compared to those with mutant (Del/Del) allele regarding FBS and HbA1c (P >0.05) as presented in the Table (3-13) and Figure (3-14) and (3-15). There were significantly associated between elevated FBS and HbA1c of schizophrenic patient and deletion allele of 141c ins/del (rs1799732) (P<0.05) as explained in Table (3-14).

Table (3-13): 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 mean	Ins/Del mean	Del/Del mean	
Glycemic status	FBS (mg/dl)	103.2 ± 1.33	103.49 ± 2.22	141.42 ± 1.41	144.92 ± 1.22	<0.0001 [a, b]
	HbA1c (%)	5.25 ± 0.07	5.37 ± 0.06	6.16 ± 0.19	6.35 ± 0.3	<0.0001 [a, b]

a: Significant effect (P < 0.05) when Ins/Del and Del/Del groups compared to Ins/Ins and healthy groups.

b: No Significant effect (P > 0.05) when Ins/Del group compared Del/Del group.

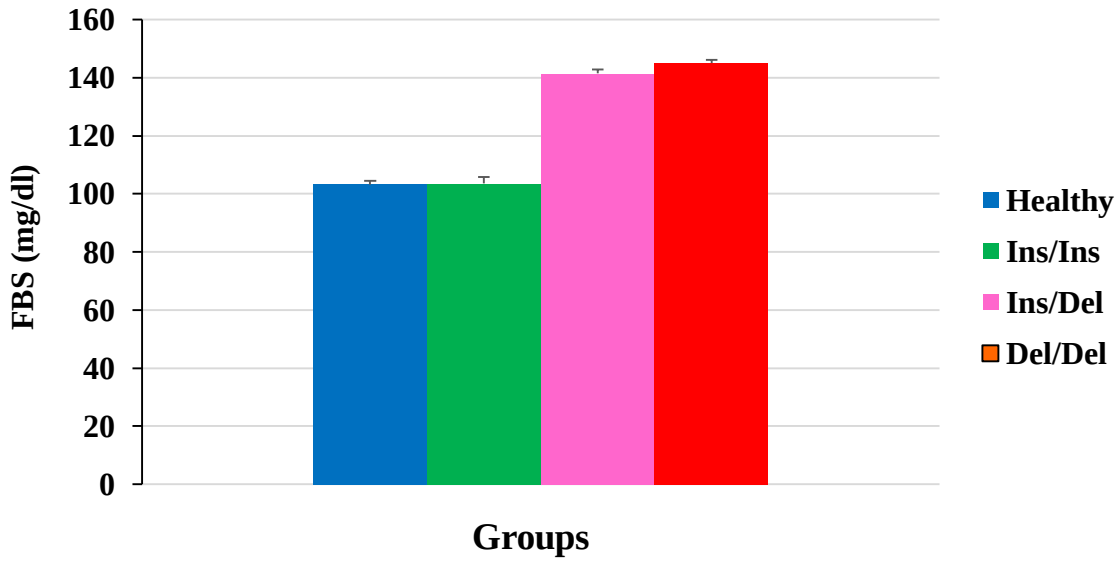

Figure (3-14); The FBS of heathy and schizophrenic patients of different alleles of 141c ins/del (rs1799732).

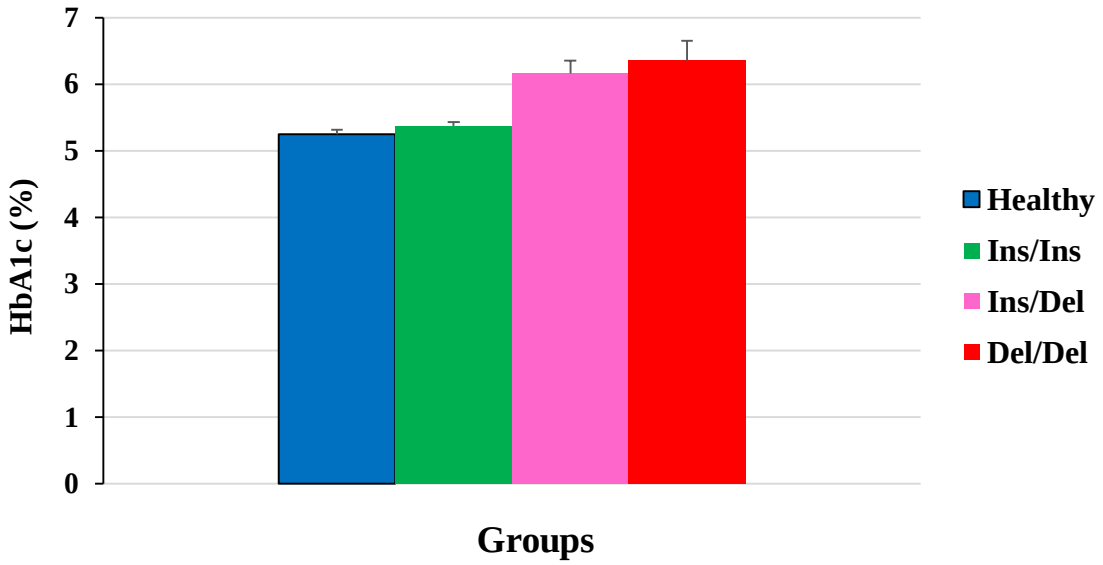

Figure (3-15); The HBA1c of heathy and schizophrenic patients of different alleles of 141c ins/del (rs1799732).

Table (3-14): The multinomial logistic regression of D2 receptor alleles 141c ins/del (rs1799732) and Glycemic status.

Variable	Allele of 141c ins/del	OR (95% CI)	*P* –value
Glycemic parameters	**Healthy**	1*	
FBS	**Ins/Ins**	0.997 (0.975 – 1.019)	0.794
HbA1c		1.489 (0.770 – 2.880)	0.237
FBS	**Ins/Del**	1.067 (1.034 – 1.101)	<0.0001[a]
HbA1c		10.001 (3.228 – 30.418)	<0.0001[a]
FBS	**Del/Del**	1.070 (1.037 – 1.105)	<0.0001[a]
HbA1c		13.670 (4.405 – 42.426)	<0.0001[a]

a: significant effect (p<0.05), OR: Odds Ratio, CI: Confidence interval, *: reference group

3.3.4.3. Lipidemic status

The plasma level of TCHO, TG, LDL, and VLDL in schizophrenic volunteers with either heterozygous (Ins/Del) allele or mutant (Del/Del) allele

were significantly elevated, and the plasma level of HDL was significantly reduced in schizophrenic volunteers with either heterozygous (Ins/Del) allele or mutant (Del/Del) allele as compared to those with wild (Ins/Ins) allele and healthy volunteers (P <0.05). There was no significant difference between schizophrenic volunteers carried heterozygous (Ins/Del) allele and those carried mutant (Del/Del) allele regarding plasma level of lipid profile (P >0.05) as shown in table (3-15) and figure (3-16). There were significantly associated between elevated plasma lipid profile of schizophrenic patient and deletion allele of 141c ins/del (rs1799732) (P<0.05) as explained in table (3-16).

Table (3-15): The Effects of D2 receptor alleles 141c ins/del (rs1799732) on lipidemic status of schizophrenic volunteers (data present as mean ± S.E)

Variables		Volunteer				*P* – value
		Healthy	Schizophrenic			
			Ins/Ins	Ins/Del	Del/Del	
Lipidemic status	TCHO (mg/dl)	140.34 ± 4.45	150.91 ± 4.61	234 ± 5.54	243.15 ± 6.48	<0.0001 [a, b]
	TG (mg/dl)	128.18 ± 3.35	138.45 ± 4.82	197.33 ± 6.34	208.38 ± 5.55	<0.0001 [a, b]
	HDL (mg/dl)	47.18 ± 1.28	44.53 ± 1.16	26.75 ± 1.41	28.46 ± 1.48	<0.0001 [a, b]
	LDL (mg/dl)	67.52 ± 4.35	78.68 ± 4.82	167.78 ± 6.14	173.02 ± 5.3	<0.0001 [a, b]
	VLDL (mg/dl)	25.64 ± 0.67	27.69 ± 0.96	39.47 ± 1.07	41.68 ±0.99	<0.0001 [a, b]

a: Significant effect (P < 0.05) when Ins/Del and Del/Del groups compared to Ins/Ins and healthy groups.

b: No Significant effect (P > 0.05) when Ins/Del group compared Del/Del group.

Table (3-16): The Multinomial logistic regression of D2 receptor alleles 141c ins/del (rs1799732) and lipidemic status.

Variable	Allele of 141c ins/del	OR (95% CI)	*P* –value
Lipid profile	**Healthy**	1*	
TCHO	**Ins/Ins**	1.008 (0.998 – 1.054)	0.116
TG		1.007 (0.998 – 1.017)	0.141
HDL		0.971 (0.934 – 1.008)	0.129
LDL		1.008 (0.998 – 1.018)	0.105
VLDL		1.038 (0.988 – 1.090)	0.141
TCHO	**Ins/Del**	1.090 (1.050 – 1.132)	<0.0001[a]
TG		1.035 (1.019 – 1.051)	<0.0001[a]
HDL		0.718 (0.626 – 0.824)	<0.0001[a]
LDL		1.085 (1.049 – 1.123)	<0.0001[a]
VLDL		1.185 (1.096 – 1.282)	<0.0001[a]
TCHO	**Del/Del**	1.102 (1.059 – 1.147)	<0.0001[a]
TG		1.038 (1.022 – 1.054)	<0.0001[a]
HDL		0.749 (0.664 – 0.846)	<0.0001[a]
LDL		1.090 (1.052 – 1.129)	<0.0001[a]
VLDL		1.204 (1.113 – 1.303)	<0.0001[a]

a: significant effect ($p<0.05$), OR: Odds Ratio, CI: Confidence interval, *: reference group

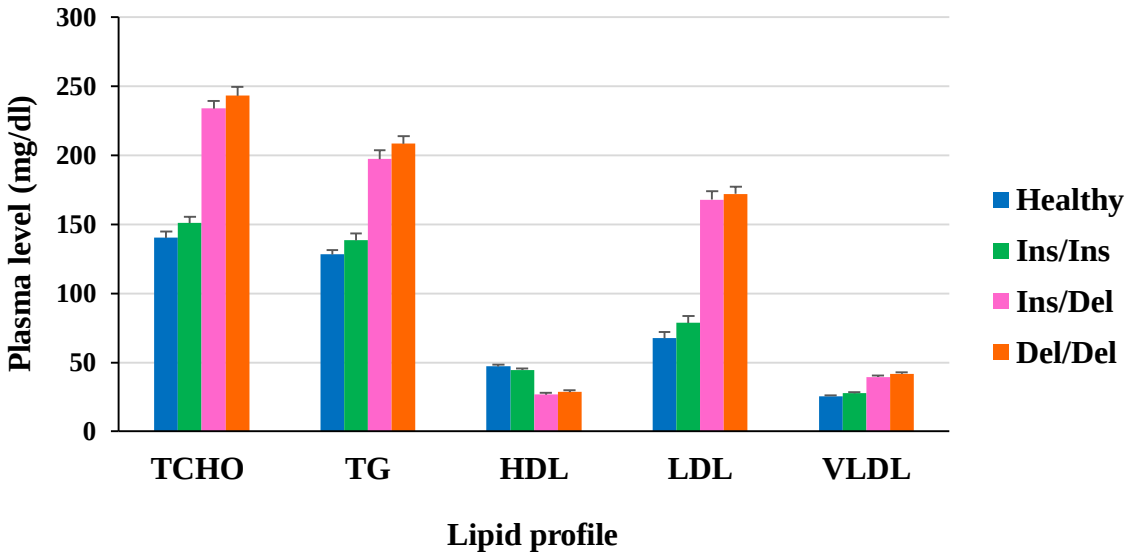

Figure (3-16); The lipid profile of heathy and schizophrenic patients of different alleles of 141c ins/del (rs1799732).

3.3.4.4. Prolactin level

The prolactin level of both genders schizophrenic volunteers who received olanzapine and carried either the heterozygous (Ins/Del) allele or mutant (Del/Del) allele of 141c ins/del (rs1799732) was significantly increased as compared to those of wild (Ins/Ins) allele and healthy volunteers (P <0.05) as presented in table (3-17) and figure (3-17). There was no significant difference between schizophrenic volunteers carried heterozygous (Ins/Del) allele and those carried mutant (Del/Del) allele regarding plasma prolactin level (P >0.05) as shown in table (3-17) and figure (3-17). There were significantly associated between elevated plasma prolactin level of schizophrenic patient and deletion allele of 141c ins/del (rs1799732) (P<0.05) as explained in table (3-18).

Table (3-17): The Effects of D2 receptor alleles 141c ins/del (rs1799732) on prolactin level of schizophrenic volunteers (data present as mean ± S.E)

Variables		Volunteer				*P* – value
		Healthy	Schizophrenic			
			Ins/Ins mean	Ins/Del mean	Del/Del mean	
Prolactin level (ng/dl)	Male	19.44 ± 1.77	21.56 ± 1.11	31.77 ± 1.27	34.9 ± 1.25	<0.0001 [a, b]
	Female	30.66 ± 1.67	31.11 ± 1.42	39.3 ± 1.76	44.3 ± 1.78	0.004 [a, b]

a: Significant effect (P < 0.05) when Ins/Del and Del/Del groups compared to Ins/Ins and healthy groups.

b: No Significant effect (P > 0.05) when Ins/Del group compared Del/Del group.

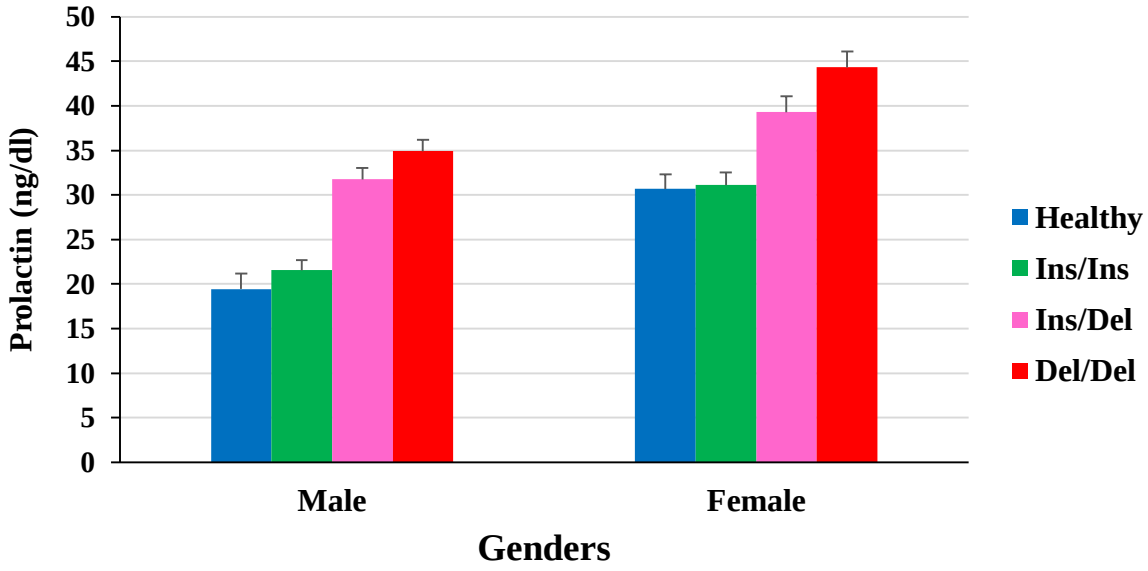

Figure (3-17); The Prolactin level of heathy and schizophrenic patients of different alleles of 141c ins/del (rs1799732).

Table (3-18): The multinomial logistic regression of D2 receptor alleles 141c ins/del (rs1799732) and prolactin level.

Variable		Allele of 141c ins/del	OR (95% CI)	*P* –value
Prolactin level	**Gender**	**Healthy**	1*	
	Male	**Ins/Ins**	1.030 (0.976 – 1.088)	0.282
	Female		1.008 (0.934 – 1.087)	0.845
	Male	**Ins/Del**	1.175 (1.049 – 1.317)	0.005[a]
	Female		1.161 (1.001 – 1.346)	0.049[a]
	Male	**Del/Del**	1.216 (1.070 – 1.383)	0.003[a]
	Female		1.375 (1.042 – 1.813)	0.024[a]

a: significant effect ($p<0.05$), OR: Odds Ratio, CI: Confidence interval, *: reference group

Chapter Four
Discussions

4. Discussion:

Although, olanzapine is the most common atypical antipsychotic agent used in management of many diseases like schizophrenia, bipolar disorder, anorexia nervosa, and autism. Its resistance, which was brought on by some psychiatric disorders such the negative symptoms of schizophrenia, may cause restrictions on use or the need to switch to another antipsychotic drug or add antidepressants, both of which may exacerbate unpleasant side effects (Leucht, Corves et al. 2009, Lang, Zang et al. 2023). It also can induce many adverse effects that may lead to restricted use or discontinue from management of chronic psychiatric disorder and the exact mechanism of schizophrenia developed resistance to olanzapine and olanzapine-induced some of these adverse effects were remains unknown (Stroup and Gray 2018).

4.1. Demographic Data

Although the age and gender of schizophrenic patients and healthy volunteers were not significant difference, most of the schizophrenic patients taken olanzapine suffered from obesity. In clinical trials testing the effectiveness of antipsychotic medications, it was discovered that 30% of schizophrenia patients using olanzapine gained more weight than 7% of their baseline. Except for clozapine, olanzapine has been reported to cause much more weight gain than other atypical antipsychotic medications (Meftah, Deckler et al. 2020). It may more strongly and frequently cause weight gain through the induction of food cravings and binge eating. These may involve blocking many receptors including D2, 5-HT2C, and H1 receptors (Kluge, Schuld et al. 2007). Body weight increases quickly when olanzapine is first started, and patients continue to acquire weight over time. This is a significant clinical issue that must be addressed since it can result in worse treatment

compliance, higher cardiovascular and cerebrovascular morbidity and death, and decreased quality of life (Dayabandara, Hanwella et al. 2017).

4.2. Assessment of Metabolic Parameters:

4.2.1. Glycemic Status

In this study, schizophrenic patients taking olanzapine suffered from prediabetic status in compared to healthy volunteers. Olanzapine has been found to have direct diabetogenic effects, decreased glucose homeostasis, and weight gain. Thus, long term use of olanzapine could result in hyperglycemia, and diabetes due to insulin resistance (Ikegami, Ikeda et al. 2013). One of possible mechanisms of olanzapine induced hyperglycemia, it activated Adenosine 5 -Monophosphate-activated Protein Kinase (AMPK) in the ventral hypothalamus result in an increase in endogenous glucose synthesis (Kim, Huang et al. 2007). Another study mentioned that atypical cases of olanzapine-induced hyperglycemia include those that happen within 6 months of starting treatment and persist even after the level of HbA1c reaches >10%, a ratio that typically indicates an irreversible level in patients with type I or type II diabetes. Additionally, a small percentage of patients taking olanzapine may experience the rapid development of diabetic ketoacidosis (within 6 months after treatment) in schizophrenic patients who have no symptoms of diabetes before the medication directly affects the function of pancreatic cells, the only source of insulin (Polcwiartek, Vang et al. 2016).

4.2.2. Lipidemic Status

This study showed that schizophrenic patients taking olanzapine were significantly suffered from dyslipidemia in comparison to healthy volunteers. Compared to other atypical antipsychotics, olanzapine showed a higher

propensity to cause severe dyslipidemia, which is marked by an increase in TCHO, LDL, and TG levels (Zhou, Nagashima et al. 2023). Numerous studies that looked at the impact of olanzapine medication duration on lipid profiles in schizophrenia patients found that 4 weeks of olanzapine treatment led to aberrant serum lipid levels. Olanzapine blocks the 5-HT and H1 receptors in the hypothalamus and increases the phosphorylation of AMPK in the central nervous system. In turn, this leads to increased food consumption, dyslipidemia, and obesity. Olanzapine slows the breakdown of LDL and raises plasma LDL-C levels by inhibiting the action of lipoprotein lipase (Li, Zhang et al. 2020). Additionally, olanzapine-insulin resistance raises sterol regulatory element binding protein-1c (SREBP-1c), which boosts the liver's ability to produce excessive LDL, raising plasma TG levels (Postic and Girard 2008). Olanzapine also increased lipogenesis directly in the liver by altering the expression of AMPK, SREBP-1c, or peroxisome proliferation-activated receptor in the liver and by disrupting the transcription of genes regulating lipid metabolism (Jassim, Skrede et al. 2012).

4.2.3. Prolactin level

In this study, schizophrenic patients taking olanzapine suffered from hyperprolactinemia in comparison to healthy volunteers. Clinical observations have demonstrated that olanzapine raises PRL concentrations in a dose-dependent way, and hyperprolactinemia is a significant adverse impact of antipsychotics on the endocrine system that results in sexual dysfunction and galactorrhea (Yang, Chen et al. 2018). Human hyperprolactinemia may be linked to a high prevalence of obesity, and olanzapine-induced hyperprolactinemia may theoretically be able to control female weight growth (Tek, Kucukgoncu et al. 2016). Although D2 receptor inhibition in the

mesolimbic and mesocortical areas appears essential to antipsychotic efficacy, D2 receptor blockade can have negative effects in other brain regions. This is true for all antipsychotic medications. Blocking D2 receptors in the striatum induces Parkinsonism, but blocking D2 receptors on lactotroph cells results in hyperprolactinemia because it eliminates the primary inhibitory influence on prolactin release (Haddad and Wieck 2004).

4.3. Genetic Analysis

4.3.1. Prevalence of D2 Receptor Genes 141c ins/del (rs1799732)

This study explained the present heterozygous (Ins/Del) and mutant (Del/Del) alleles of D2 receptor alleles 141c ins/del (rs1799732) among both gender of Iraqi schizophrenic patients and not presented in healthy volunteers. Some studies mentioned The functional polymorphism 141C Ins/Del in the 5′-promoter region of D2 receptor may influence schizophrenia susceptibility (Arinami, Gao et al. 1997). Another study revealed that the D2 receptor alleles 141c ins/del (rs1799732) is functional and associated with risk of schizophrenia development and discovered a link between schizophrenia and the allele -141CIns. The elevated D2 receptor brain density in people with schizophrenia may be caused by an increased frequency of the -141CIns allele. According to this research, the -141C Ins allele may be linked to dopamine hyperactivity, which causes psychotic symptoms, supporting the dopamine theory for schizophrenia (Cordeiro, Siqueira-Roberto et al. 2009). Various ethnic groups had various D2 receptor locus associations with schizophrenia. Due to differences in the distribution of D2 receptor allele frequencies among East Asians, Caucasians, Latinos, Indians, and Sri Lankans, divergence may have been influenced by genetic backgrounds. Evidently, schizophrenia risk is significantly increased by genetic

vulnerability (Yao, Pan et al. 2015). Antipsychotic and addiction medications have been shown to be affected by the D2 receptor -141C Ins/Del polymorphism. The promoter region of the D2 receptor gene contains the -141C Ins/Del polymorphism, which is present in about 22% of the Japanese population. Chinese and Caucasian groups (9%) have a lower prevalence of this gene (Mi, Thomas et al. 2011).

4.3.2. Prevalence of D2 Receptor Genes A-241G (rs1799978)

This study explained the present heterozygous (AG) and mutant (GG) alleles of D2 receptor alleles A-241G (rs1799978) among both gender of Iraqi schizophrenic patients and not presented in healthy volunteers. The similar outcome was shown in Thai children and adolescents with autism, and this genetic variant displayed non-stable clinical symptom (Nuntamool, Ngamsamut et al, 2017). A Canadian study found that aggressive kids were more likely to have two copies of the G gene at A-241G (Zai, Ehtesham et al, 2012). Lee et al. identified and studied this SNP in the 5-UTR' region of D2 receptor gene of Korean population for its potential association with schizophrenia and bipolar disorders. It has been discovered that there may be a link between this SNP and specific forms of schizophrenia (Lee, Joo et al. 2011). Another investigation found that the D2 receptor allele A-241G (rs1799978) gene is encodes a high level of D2 receptor, which may result in inadequate risperidone blocking of these receptors and unstable clinical symptoms (Arinami, Gao et al, 1997).

4.4. Effects of D2 Receptor alleles A-241G (rs1799978) on PANSS

In this study, the schizophrenic symptoms according PANSS score in patients with either heterozygous (AG) and mutant (GG) alleles of D2

receptor alleles A-241G (rs1799978) and taken olanzapine were not significantly improved in comparison to those with wild (AA) allele Numerous clinical research found that in the Han Chinese and Japanese populations, carriers of the AA allele of A-241G had greater PANSS score improvements and responses to antipsychotic medications than carriers of the AG and GG alleles (Ma, Zhang et al. 2019). In relation to SNP A-241G, Ikeda et al. found relationships between the A allele and response and the G allele and absence of response (Ikeda, Yamanouchi et al. 2008). Patients with schizophrenia who carried the G allele of the DRD2 gene at position 241 (rs1799978) showed a moderate amount of evidence for a slower and worse response to olanzapine, increased weight gain, and acceptability of higher prescription doses. In these patients, drug switching might be considered (Zubiaur, Soria-Chacartegui et al. 2021). In contrast, a different study discovered that the D2 receptor allele A-241G (rs1799978) genetic polymorphism was substantially related with olanzapine sensitivity, and G allele carriers demonstrated greater response to olanzapine compared to patients with wild AA (Yan, Song et al. 2020).

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

4.5.1. Body Weight

In this study, both gender of schizophrenic patients who received olanzapine and had heterozygous (Ins/Del) or mutant (Del/Del) type of 141c ins/del (rs1799732) were significantly suffered from weight gain characterized by elevated BMI in comparison to those with the wild allele (Ins/Ins). Lencz et al., 2010 mentioned that the deletion allele of D_2 receptor

gene 141c ins/del (rs1799732) were significantly gained more body weight over time as compared to those with insertion allele (Lencz, Robinson et al. 2010). The deletion allele of D_2 receptor gene 141c ins/del (rs1799732) was associated with overweight and obesity in schizophrenic females from Northwest Iran. This may be induced hedonic hunger (Aliasghari, Nazm et al. 2021). This polymorphism may be responsible for increasing the density of D_2 receptor in the striatum, thus olanzapine was interacted with more D_2 receptor (Arranz and De Leon 2007).

4.5.2. Glycemic status

This study revealed that the glycemic status of olanzapine taken schizophrenic patients with wild (Ins/Ins) alleles of 141c ins/del (rs1799732) was not significantly differed from that of the healthy volunteers. In contrast, the level FBS and HbA1c in olanzapine taken schizophrenic patients with either heterozygous (Ins/Del) or mutation (Del/Del) allele of 141c ins/del (rs1799732) were significantly elevated in comparison to those with the wild allele (Ins/Ins) and healthy volunteers. These results computable with other studies revealed that schizophrenic patients carried the deletion allele of 141c ins/del (rs1799732) more disposed to have metabolic syndrome induced by atypical antipsychotic like elevation of FBS. In addition to weight gain, this effect may be related to role of D2 receptors in pancreatic cells that modulated the releasing of insulin and glucagon (Aliasghari, Nazm et al. 2021, Aslanoglou, Bertera et al. 2021, Zubiaur, Soria-Chacartegui 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).

4.5.3. Lipidemic status

In this study, schizophrenic patients who 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 mention by Paderina, et al, that revealed about 64 – 80% of schizophrenic patients who treated with atypical antipsychotic and had genetic polymorphism of 141c ins/del (rs1799732) were suffered from hyperlipidemia and metabolic syndrome (Paderina, Boiko et al. 2022). Olanzapine had the ability to induce hyperlipidemia not associated with obesity that may disappear within few weeks from discontinuation of olanzapine. This effect may be not fully understood (de Leon and Diaz 2007). Some study mention that β-lactotensin and neurotensin could be rapidly declined the serum cholesterol level by stimulating mainly D2 receptors, thus, olanzapine competed with these peptides by blocking D2 receptors which may be overexpression in schizophrenic patients with deletion allele of 141c ins/del (rs1799732) (Yamauchi, Ohinata et al. 2003).

4.5.4. Prolactin level

This study demonstrated that prolactin level was significantly elevated in schizophrenic patients who carried either heterozygous or mutant allele of 141c ins/del (rs1799732) as compared to those with wild allele. Zhang et al., (2011) mentioned that atypical antipsychotic induced hyperprolactinemia a significantly association with genetic polymorphism of the D2 receptor −141C Ins/Del (Zhang, Zhang et al. 2011). Olanzapine-induced

hyperprolactinemia is attributed to blocking of D2 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, Soria-Chacartegui et al. 2021). In another study, Risperidone-induced hyperprolactinemia was identified in 87.2% of the patients, and a substantial relationship of the 141 C deletion and the likelihood of increased prolactin levels was discovered (Charan, Shewade et al, 2016).

Conclusions & Recommendations

Conclusions

From the present study the followings can be concluded:

١. The heterozygous alleles (Ins/Del) and mutant alleles (Del/Del) of D2 receptor genes –141 C Ins/Del (rs1799732) were might present in schizophrenic individuals and absent in health volunteers.

٢. The heterozygous alleles (AG) and mutant alleles (GG) of D2 receptor genes A-241G (rs1799978) were might present in schizophrenic individuals and absent in health volunteers.

٣. The genetic polymorphism of D2 receptor A-241G (rs1799978) was significantly associated with resistance to olanzapine in Kerbalai schizophrenic patients.

٤. The genetic polymorphism of D2 receptor –141 C Ins/Del (rs1799732) was significantly associated with olanzapine may aggravation induce metabolic adverse effects in Iraqi schizophrenic patients.

Recommendations

١. Further studies will be necessary to evaluate the impact of other genetic variants associated with safety and responsibility of olanzapine response like other dopamine receptors Taq1A, D3 and serotonin receptors such as 5HT2A, 5HT2C.

٢. A larger scale study including more schizophrenic patients from different Iraqi cities is required.

٣. In the clinical setting, it is recommended that genetic tests should be developed to predict the safety and a person's response to olanzapine.

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Appendix

جمهورية العراق

محافظة كربلاء المقدسة
دائرة صحة كربلاء المقدسة
مركز التدريب والتنمية البشرية
شعبة ادارة المعرفة / وحدة ادارة البحوث

Holy Karbala governorate
Karbala Health Department
General manager's office
Training and Human Development
Center

العدد: ٢١٧٩
التاريخ / ٢٠٢٢ / ١٢ / ٢٦

إلى /جامعة كربلاء المقدسة / كلية الصيدلة
الموضوع /تسهيل مهمة

دائرة صحة كربلاء المقدسة
قسم التدريب
والتنمية البشرية

تحية طيبة....

كتابكم المرقم د.ع/١٦٧٦/٦في ٢٠٢٢/١٠/١٨
نود إعلامكم بأنه لا مانع لدينا من تسهيل مهمة طالبة ماجستير(زهراء جواد محمد علي)
لإنجاز بحثها الموسوم:

Association Between DRD2 Genetic Variation and Olanzapine)
(Treatment Response and safety in Iraqi population

في مؤسستنا الصحية وبأشراف الدكتور (احمد القرغولي) على ان لا تتحمل دائرتنا اي نفقات مادية مع الاحترام ،

الدكتورة
تقوى خضر عبد الكريم
مدير مركز التدريب والتنمية البشرية
٢٠٢٢/ ١٢/ ٢٦

نسخة منه الى
مستشفى الامام الحسن المجتبى (عليه السلام) التعليمي اجراء اللازم مع الاحترام ،

Ministry of Higher Education
and Scientific Research
University of Karbala
College of Pharmacy
Department of Postgraduate Studies

جمهورية العراق
وزارة التعليم العالي والبحث العلمي
جامعة كربلاء
كلية الصيدلة
شعبة الدراسات العليا

Issue No.:
Date:

العدد: د.ع/ 6 / 1676
التاريخ: 18 / 10 / 2022

الى/ دائرة صحة كربلاء / المستشفى التركي
م/تسهيل مهمة

تحية طيبة ..

يرجى تفضلكم بالموافقة على تسهيل مهمة طالبة الدراسات العليا / ماجستير/ الادوية والسموم في كليتنا (زهراء جواد محمد علي) لغرض اكمال اجراءات بحث الماجستير الموسوم:

Association Between DRD2 Genetic Variation and Olanzapine Treatment Response and safety in Iraqi Population

شاكرين تعاونكم معنا مع التقدير....

أ.د. احمد صالح الخزعلي
عميد كلية الصيدلة
2022 / 10 /

الدكتور
صالح علي عبد الرسول

سفة منه الى:
مكتب السيد العميد ، للتفضل بالاطلاع .
مكتب معاون العميد للشؤون العلمية .
شعبة الدراسات العليا للحفظ مع الاوليات .
الصادرة .

Email: Pharmacy@uokerbala.edu.com
العراق- محافظة كربلاء- مكتب بريد كربلاء- ص ب 1125


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لمستقبلات D2-141 C Ins/Del (rs1799732) باستخدام طريقة تعدد شكل طول جزء الحصر (RFLP).

النتائج : أظهرت النتائج بأن الأليلات المتباينة (AG) والمتماثلة (GG) لمستقبلات الدوبامين A-٢٤١G (rs١٧٩٩٩٧٨) سائدة بشكل كبير في مرضى الانفصام الشخصي وغير موجود لدى المتطوعين الأصحاء. اظهر مرضى الانفصام الذين يحملون الأليل المتنحي لمستقبلات الدوبامين A-٢٤١G (rs١٧٩٩٩٧٨) مقاومة ملحوظة للأولانزابين. وكانت الأليلات غير المتجانسة (Ins / Del) والأليلات المتحولة (Del / Del) لمستقبلات الدوبامين ١٤١ C Ins / Del (rs1799732) - أيضا سائدة بشكل كبير في مرضى الانفصام وغير موجود لدى المتطوعين الأصحاء. وتم ملاحظة ظهور الاعراض الجانبية الايضية لعقار الأولانزابين لدى مرضى الاتفصام الذين يحملون الأليل المتنحي لمستقبلات الدوبامين ١٤١ C Ins/Del (rs1799732)- مثل زيادة الوزن، وارتفاع السكر في الدم، وعسر شحميات الدم، وافرط بروالاكتين الدم.

الاستنتاج : إشارة الدراسة الى ارتبط تعدد الأشكال الجينية لمستقبلات الدوبامين A-241G (rs1799978) بشكل كبير مع مقاومة الأولانزابين، وارتبط تعدد الأشكال الجينية لمستقبلات الدوبامين ١٤١ C Ins/Del (rs1799732)- بشكل كبير مع ظهور الاعراض الجانبية الايضية لأولانزابين في مرضى الكربلائين الذين يعانون من الانفصام الشخصية.

الخلاصة

الخلفية : ان انفصام الشخصية هو اضطراب صحي عقلي معقد ومزمن يتميز بمجموعة من الأعراض، بما في ذلك الأوهام والهلوسة والكلام أو السلوك غير المنظم وضعف القدرة الإدراكية. إن البداية المبكرة للمرض، إلى جانب مساره المزمن، تجعله اضطرابًا معيقًا للعديد من المرضى وعائلاتهم. على الرغم من محدودية دراسات الأوبئة وانتشار اضطرابات الصحة النفسية في العراق، إلا أن معدل انتشار الاضطرابات النفسية ارتفع من ١٢% عام ٢٠٠٠ إلى ١٥% عام ٢٠٢٠، ويعتبر الفصام أكثر الاضطرابات شيوعًا.

إن أولانزابين علاج مضاد للذهان عادة ما يوصف لعلاج مرض انفصام الشخصية وقد طور بعض المرضى مقاومة له بينما عانى آخرون من العديد من الآثار الضارة مثل زيادة الوزن وارتفاع السكر في الدم وازيادة نسبة البرولاكتين الدم مما قد يزيد من خطر الإصابة بأمراض أخرى مثل داء السكري وأمراض القلب والأوعية الدموية. قد يكون تعدد الأشكال الجيني لمستقبل D2 مسؤولاً عن مقاومة عقار الأولانزابين وحدوث مثل هذه التأثيرات الضارة.

الهدف من الدراسة : هدفت هذه الدراسة إلى تقييم دور تعدد الأشكال الجينية في مستقبل D2 A-٢٤١G (rs١٧٩٩٩٧٨) والاستجابة لأولانزابين ودور تعدد الأشكال الجينية في مستقبل D2-١٤١C Ins/Del (rs١٧٩٩٧٣٢) والآثار الضارة الجانبية التي يحدثها الأولانزابين في مرضى العراقيين الذين يعانون من انفصام الشخصية.

المرضى والطرق : تم إجراء دراسة ضبط الحالة في الفترة من أكتوبر ٢٠٢٢ إلى أبريل ٢٠٢٣ في مستشفى الحسن المجتبى بمشاركة ١٠٠ مريض مصاب بالانفصام الشخصي من كلا الجنسين، تتراوح أعمارهم بين ٢٠ الى ٦٥ عامًا من قسم العيادات الخارجية للطب النفسي، كما تم مشاركة ٥٠ مريضًا يتمتعون بصحة جيدة دون أي مرض يشمل كلا الجنسين الذين تتراوح أعمارهم بين ٢٠ إلى ٦٣ عامًا، كمجموعة ضابطة في هذه الدراسة. تم تقييم استجابة المريض للأولانزابين بمساعدة PANSS واستخدام البلازما لقياس مستوى سكر الصائم، اختبار الهيموغلوبين السكري HbA1C، وملف الدهون، والبرولاكتين. تم معرفة الانماط الجينية لمستقبلات D2 A-241G (rs1799978) باستخدام طريقة تفاعل البوليمراز المتسلسل المنعقد (Nested PCR) وتم معرفة الانماط الجينية

جمهورية العراق

وزارة التعليم العالي والبحث العلمي
جامعة كربلاء
كلية الصيدلة

العلاقة بين التباين الوراثي لمستقبلات الدوبامين والاستجابة للعلاج بالأولانزابين امانه وسلامته في سكان محافظة كربلاء

رسالة مقدمة الى

كلية الصيدلة في جامعة كربلاء كجزء من متطلبات نيل درجة الماجستير في الادوية و السموم

من قبل

زهراء جواد محمد علي الموسوي

(بكالوريوس صيدلة/ جامعة الكوفة ٢٠٠٤)

بإشراف

أ.م.د. أثير ماجد رشيد الجحيشي

دكتوراه أدوية

٢٠٢٣ ميلادي

١٤٤٥

هجري