PREVALENCE OF THE METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS RECEIVING SECOND GENERATION ANTIPSYCHOTIC AGENTS – A CROSS SECTIONAL STUDY

REG. NO: BO0108002

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In partial fulfillment
of the requirements for the degree of

M.D.

In

PHARMACOLOGY

DEPARTMENT OF PHARMACOLOGY AND PHARMACOTHERAPEUTICS,
J. N. MEDICAL COLLEGE, BELGAUM-590010,
KARNATAKA.

MAY 2011

KLE UNIVERSITY, BELGAUM, KARNATAKA

Endorsement By The HEAD OF DEPARTMENT, Principal / Head Of The Institution

This is to certify that the dissertation entitled **"PREVALENCE OF THE METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS RECEIVING SECOND GENERATION ANTIPSYCHOTIC AGENTS – A CROSS SECTIONAL STUDY"** is a bonafide research work done by **REG.NO:BO0108002.**

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ABBREVIATIONS

α: Alpha

ß : Beta

5HT: 5 hydroxytryptamine (serotonin)

AHA/NHLBI: American Heart Association/National Heart Lung and Blood Institute

AMPA: Alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid

Apo : Apolipoprotein

BMI: Body mass index

BP: Blood pressure

CATIE: Clinical Antipsychotic Trials of Intervention Effectiveness

CETP: Choletsteryl ester transfer protein

CNS: Central nervous system

CRP: C-reactive protein

CVD: Cardiovascular disease

DLPFC: Dorsolateral prefrontal cortex

EGIR: European Group for the Study of Insulin Resistance

eNOS: endothelial nitric oxide synthase

ERK: Extracellular regulated kinase

ET-1: Endothelin-1

FFA: Free fatty acid

FGA: First generation antipsychotic

GABA: Gamma amino butyric acid

GLUT4: Glucose transporter 4

HDL: High density lipoprotein

HVA: Homovanillic acid

IDF: International Diabetes Foundation

IDL: Intermediate density lipoprotein

IL-6: Interleukin 6

IRS: Insulin receptor substrate

LCAT: Lecithin cholesterol acyl transferase

LDL: Low density lipoprotein

LDLR: LDL receptor

Lp(a): Lipoprotein a

LPL: Lipoprotein lipase

LSD: Lysergic acid diethylamide

MAP kinase: Mitogen activated protein kinase

MCP-1: Macrophage chemoattractant protein -1

mg/dl: milligram per deciliter

mmHg: millimeters of mercury

NCEP -ATPIII – National Cholesterol Education Programme Adult Treatment Panel III

nm: nanometer

NMDA: N-methyl-D-aspartate

NO: Nitric oxide

PDK1: Phosphoinositide – dependent protein kinase 1

PI3-K: Phosphoinositide 3 kinase

PNS: Peripheral nervous system

T2D: Type 2 diabetes

TG: Triglyceride

TNF α: Tumour necrosis factor α

VLDL: Very low density lipoprotein

WHO: World Health Organization

ABSTRACT

Objective: The present study was taken up to assess the prevalence of the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents and also to determine the most sensitive and specific screening methods for detecting metabolic syndrome in these patients.

Materials and Methods: The present study was undertaken at the Department of Psychiatry, KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum. 80 patients diagnosed to be suffering from schizophrenia and receiving a single second generation antipsychotic (olanzapine, risperidone or quetiapine) for 3 months or more were enrolled in the study after obtaining written informed consent.

Patients were requested to come the next day in the fasting state for the purpose of physical examination and blood collection. Patients were screened for metabolic syndrome using AHA/ NHLBI modified NCEP ATP III criteria.

Results: Prevalence of the metabolic syndrome was found to be 35%. The prevalence in female patients was found to be higher (37.2%) than in males (32.43%). Prevalence was found to be higher (62.5%) in older patients aged 45 years and above. Prevalence of insulin resistance was found to be 55%. The method with highest sensitivity for screening of the metabolic syndrome was serum HDL cholesterol with a sensitivity of 89.28%. Fasting blood glucose estimation and measurement of waist circumference were found to have highest and equal specificity of 90.38% for screening of metabolic syndrome.

Conclusion: There is a high prevalence of the metabolic syndrome in schizophrenic patients treated with second generation antipsychotic agents. Increasing awareness of this association among clinicians will help to prevent, detect and treat this condition which is associated with considerable morbidity and mortality.

Keywords: metabolic syndrome, schizophrenia, olanzapine, risperidone, quetiapine

TABLE OF CONTENTS

LIST OF TABLES

INTRODUCTION

Mental health is defined as the successful performance of mental functions, in terms of thought, mood and behaviour that results in productive activities, fulfilling relationships with others and the ability to adapt to change and cope with adversity.[1]

Mental disorders are not the exclusive preserve of any special group; they are truly universal. Mental and behavioural disorders are found in people of all regions, all countries and all societies. According to an analysis done by the World Health Organization (WHO) an estimated 450 million people across the world suffer from neuropsychiatric conditions. [2]

Surveys of mental morbidity carried out in various parts of India suggest a morbidity rate of not less than 18-20 per 1000 and the types of illness and prevalence are very much the same as in other parts of the world.[2]

Schizophrenia is the heartland of psychiatry and the core of its clinical practice. Every layman's concept of madness is based on the oddities and abnormalities of those who suffer from this enigmatic illness. It probably causes more suffering and distress and blights more lives than any other cancer and certainly represents a major burden for care-givers, health services and society as a whole.[3]

Antipsychotic medications are the mainstay of treatment for psychotic illnesses and are also widely used in many other psychiatric conditions. Introduced about 50 years ago, these medications have helped millions of people manage their symptoms. For people who respond well, antipsychotics can mean the difference between leading an engaged, fulfilling community life and being severely disabled. [4]

The first-generation antipsychotics (FGAs) are still widely available and are effective at treating positive symptoms of psychosis, such as hallucinations and

delusions. FGAs do not, however, adequately alleviate many other common and important aspects of psychotic illness, such as negative symptoms (e.g., withdrawal, apathy, poverty of speech), cognitive impairment and affective symptoms. In addition, all FGAs can produce significant extrapyramidal side effects at clinically effective doses. These side effects, which include dystonic reactions, drug-induced parkinsonism, akathisia and tardive dyskinesia, can make treatment intolerable for some people, leading to subjective distress, diminished function, stigma and nonadherence.[4]

The introduction of second-generation antipsychotics (SGAs) or "atypical" antipsychotic drugs promised enhanced efficacy and safety. The newer agents appear more efficacious than conventional drugs in reducing negative symptoms (e.g. lack of emotion, interest, and expression). The safety advantages of the atypical drugs have been questioned because of their propensity to induce weight gain and alter glucose and lipid metabolism. [5]

Second generation antipsychotics which have formed the cornerstone of treatment in psychiatry today and which revolutionized this field, now stand on the brink of accusations of having given rise to a new epidemic in psychiatry – the metabolic syndrome. [6]

The concept of metabolic syndrome or syndrome X as elucidated by Reaven in 1988 is a reality today. Originally proposed as a link between insulin resistance and hypertension in the causation of cardiovascular disease (CVD), it has now been extended to psychiatry and is seen as an adverse effect of psychotropic drugs especially second generation antipsychotics. Recent comprehensive reviews have well established that metabolic syndrome is indeed the concern of the future.[6]

People with severe mental illness, especially schizophrenia, suffer from increased morbidity and mortality compared with the general population, having a life expectancy that is approximately 20% shorter. In a meta-analysis of 18 international studies, 60% of excess mortality in schizophrenia was attributable to physical illness, with cardiovascular disease being the major contributor. People with schizophrenia are reported to be twice more likely to die from cardiovascular disease than those in the general population, with coronary heart disease being the leading cause of death.[7]

Several levels of evidence, from data linkage analyses to clinical trials, demonstrate that treatment-related metabolic disturbances are commonplace in this patient group and that the use of certain second-generation antipsychotics (SGAs) may compound the risk of developing the metabolic syndrome and CVD. Appropriate identification and management of these risk factors are very important in reducing the risk and thereby improving the physical health of these patients.[7]

The present study was taken up to assess the prevalence of the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents.

OBJECTIVES

1. To assess the prevalence of the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents

2. To determine the most sensitive and specific screening methods for detecting metabolic syndrome in these patients.

REVIEW OF LITERATURE

A. Schizophrenia

Schizophrenia is a clinical syndrome of variable but profoundly disruptive psychopathology that involves cognition, emotion, perception and other aspects of behaviour. The expression of these manifestations varies across patients and over time, but the effect of the illness is always severe and is usually long lasting.[8]

1. Historical aspects:

Symptoms relating to schizophrenia have been noted since the age of antiquity. A popular belief was that strange behaviour was a result of possession by the devil or assaults from the gods for immoral behaviour (a kind of devine punishment). [9]

Hindu descriptions date back to approximately 1400 BC and can be found in the Atharva Veda, one of the 4 Vedas, which are primary texts of Hinduism.[9]

Beginning in the 1700s, increased emphasis was placed on detailed and accurate descriptions of abnormal mental processes and states. Jean Etienne Esquirol, a student of Philippe Pinel – a French physician, defined hallucinations in a way that is similar to current terminology. They were described as an "intimate conviction of a sensation actually perceived, while no external object capable of exciting that sensation is accessible to the senses." [9]

The 19th century saw an explosion of information about the body and mind. In 1871 Hecker referred to a 'Hebephrenia' or a silly, undisciplined mind after Hebe, goddess of youth and frivolity .Soon after, in 1874, Kahlbaum referred to both catatonic and paranoid disorders of the mind, the term catatonia describing a

movement disorder characterized by a mannequin-like muscle stiffness associated with unusual postures and a pervading fear. [9]

Then in 1878 Emil Kraepelin, perhaps auspiciously, combined these various 'disorders' into a single disease entity which he termed dementia praecox or 'dementia of early onset' reflecting a decline of cognitive processes which he divided into four subtypes - simple, marked by slow social decline concomitant with apathy and social withdrawal; paranoid, with its attendant fear and 'persecutory' delusions; hebephrenic and catatonic, characterized by a poverty of movement and expression. Kraepelin named the disorder 'dementia praecox' (early dementia) to distinguish it from other forms of dementia (such as Alzheimer's disease) which typically occur late in life. He used this term because his studies focused on young adults with dementia. [9]

It was Bleuler who first coined the divisive term 'schizophrenia' in 1911. Bleuler defined schizophrenia with his four "A's", referring to the blunted Affect (diminished emotional response to stimuli); loosening of Associations (by which he meant a disordered pattern of thought, inferring a cognitive deficit), Ambivalence (an apparent inability to make decisions, again suggesting a deficit of the integration and processing of incident and retrieved information) and Autism (a loss of awareness of external events, and a preoccupation with the self and one's own thoughts). Bleuler was also the first to describe the symptoms as positive or negative. [9]

The word "schizophrenia" comes from the Greek roots schizo (split) and phrene (mind) to describe the fragmented thinking of people with the disorder. His term was not meant to convey the idea of split or multiple personality. [9]

In 1959 Kurt Schneider termed the core features "first-rank" symptoms. These symptoms included:

a) Hearing one's thoughts spoken aloud

b) Auditory hallucinations commenting on one's own behaviour

c) Thought withdrawal, insertion and broadcasting

d) Somatic hallucinations or the experience of one's thoughts as being controlled or influenced by outside.[9]

2. Pathophysiology of schizophrenia

a. Dopamine hypothesis:

Dopamine hypothesis of schizophrenia was the first neurotransmitter based concept to be developed. It is highly relevant to the understanding of the major dimensions of schizophrenia such as positive and negative symptoms and cognitive impairment. It is also essential to the understanding of the mechanism of action of most and probably all antipsychotic drugs. Several lines of evidence which suggest that excessive limbic dopaminergic activity plays a role in psychosis are:

- Many antipsychotic drugs strongly block postsynaptic dopamine (D_2) receptors in the central nervous system (CNS) especially in the mesolimbic and striatal frontal system.
- Drugs that increase dopaminergic activity such as levodopa, amphetamine and apomorphine either aggravate schizophrenia or produce psychosis de-novo in some patients.
- Some but not all potmortem studies of schizophrenic subjects have reported increased dopamine levels and D_2 receptor density in the nucleus accumbens, caudate nucleus and putamen. [10]

b. Serotonin hypothesis:

The discovery that hallucinogens such as lysergic acid diethylamide (LSD) and mescaline are serotonin agonists led to the search for endogenous hallucinogens in the urine, blood and brains of patients with schizophrenia. This proved fruitless, but the identification of many serotonin receptor subtypes led to the pivotal discovery that $5HT_{2A}$ receptor stimulation was the basis for hallucinatory effects of these agents. [10] Serotonin activity has been implicated in the suicidal and impulsive behaviour seen in schizophrenics. Serotonin received much attention since serotonin dopamine antagonists like clozapine and risperidone have potent serotonin related activities. $5HT_2$ receptor antagonism has been emphasized in reducing psychotic symptoms.[1]

c. Glutamate hypothesis:

It is centered on the clinical observation that N-methyl-D-aspartate (NMDA) receptor antagonists such as phencyclidine and ketamine produce a syndrome that is indistinguishable from schizophrenia. Brain regions implicated in schizophrenia include the prefrontal cortex, hippocampus and thalamus. Major connections between these brain regions are glutamatergic. Glutamate is the major excitatory neurotransmitter in the brain and is known to activate both ionotropic and metabotropic glutamate receptors. The most consistently replicated findings are a decrease in the α-amino-3-hydroxy-5-methylisoxazole-4- propionic acid (AMPA) receptor mRNA and protein expression in the hippocampus and downregulation of the NMDA NR1 receptor in the temporal cortex, hippocampus and thalamus.[11]

d. Cholinergic hypothesis:

Decreased levels of nicotinic and muscarinic cholinergic receptors are reported in the hippocampus, frontal cortex, thalamus and striatum in schizophrenia.

Cholinergic transmission is known to be integral to cognition and memory, functions which are disrupted in schizophrenia. Decrease in muscarinic $M_1$and M_4 receptors has been reported in the prefrontal cortex and striatum in schizophrenia. There is also evidence of reduced expression of nicotinic receptor subunits α_4 and $\alpha_{4ß2}$ in the frontal cortex and hippocampus respectively in schizophrenia.[11]

e. Gamma amino butyric acid (GABA) deficits:

Deficits in GABAergic interneurons in dorsolateral prefrontal cortex (DLPFC) are among the best replicated neuropathological findings in schizophrenia. Because of the importance of GABAergic inhibition in critical circuits of normal brain function – including working memory – deficits in GABAergic neurons are likely to make contributions to cognitive and other clinical dimensions of schizophrenia. [12]

f. Genetic associations:

A handful of genes are now beginning to emerge as likely to be implicated in schizophrenia including neuregulin – 1 (NRG-1), Disrupted in schizophrenia – 1 (DISC-1), Regulator of G protein signaling 4 (RGS-4), Catechol – O – methyl transferase (COMT) and Dysbindin (DTNBP1). [12]

The etiology of schizophrenia involves a complex interplay among risk genes and protective genes in the setting of particular factors during early development like exposure to infection, trauma and hypoxia. Gene environment interactions will ultimately determine whether a given individual will develop psychosis.[12]

3. Co- morbid conditions in schizophrenia:

It is now widely acknowledged that schizophrenia contributes substantially to the global burden of disease. It is also well known that schizophrenia is associated with elevated suicide rates. Less widely appreciated is the fact that people with

schizophrenia are at an increased risk for premature deaths associated with comorbid somatic conditions.[13]

Compared with the general population life expectancy in patients with schizophrenia is shorter by as much as 20% attributable to higher rates of suicide, accidental deaths and natural causes such as CVD, infectious disease and endocrine disorders.[14]

Approximately 70% of people who have schizophrenia suffer from at least one medical co-morbidity and 33% suffer from three or more comorbid health disorders. Common medical comorbidities include hypertension, chronic obstructive pulmonary disease and diabetes all of which contribute to the risk of cardiovascular disease and associated mortality. Early mortality is more than fivefold higher in people who have schizophrenia than in the general population. In fact schizophrenia is considered a life shortening illness. [15]

Somatic illness is increased in schizophrenia for a variety of reasons. People with who have schizophrenia have sedentary lifestyles & engage in very little physical activity for various reasons including sedating effects of medications and poor economic backgrounds. [15]

Comorbid substance abuse disorders have emerged as one of the greatest obstacles to the effective treatment of persons with schizophrenia. Estimates of the prevalence of such comorbidity vary, but as many as half of persons with schizophrenia may suffer from a cormorbid drug or alcohol disorder. Substances of abuse include alcohol, cocaine, heroin and marijuana. Substance abuse is also known to increase the risk of several medical disorders including coronary heart disease.[16]

McCreadie studied the risk of coronary heart disease and stroke in addition to lifestyle factors in 102 patients with schizophrenia. 70% of male patients and 86% of female patients were either overweight or obese. The mean 10 year risk of coronary heart disease was 9.6% as compared to 6.4% in the general population as was the risk of stroke.[17]

Ryan et al examined the prevalence of impaired fasting glucose in 26 first episode patients with schizophrenia who were drug naive compared to age matched healthy controls. More than 15% of patients showed impaired fasting plasma glucose in addition to high insulin and cortisol levels. It was observed that waist to hip ratio positively correlated with plasma triglycerides and negatively correlated with HDL cholesterol.[18]

It has also been hypothesized that schizophrenia and other psychiatric disorders might carry an inherent risk of elevated lipid levels, diabetes mellitus and coronary heart disease.[19]

B. The Metabolic syndrome

The metabolic syndrome is a constellation of interrelated risk factors of metabolic origin—*metabolic risk factors*—that appear to directly promote the development of atherosclerotic cardiovascular disease. [20]

The metabolic syndrome refers to the co-occurrence of several known cardiovascular risk factors, including insulin resistance, obesity, atherogenic dyslipidemia and hypertension.[21]

The conceptual evolution of the metabolic syndrome has been summarized in Table 1. [22]

Table 1: Conceptual evolution of the metabolic syndrome

Concept	Scientists	Year
Hypertension-hyperglycemia-hyperuricaemia syndrome	Kylin	1923
Plurimetabolic syndrome	Avogaro & Crepaldi	1967
Metabolic syndrome	Hanefeld & Leonhardt	1981
Syndrome X	G.M.Reaven	1988
Deadly quartet	Kaplan	1989
Insulin resistance syndrome	DeFronzo & Ferrannini	1991

1. Importance of identifying patients with the metabolic syndrome:

1. It identifies patients who are at high risk of developing atherosclerotic CVD and type 2 diabetes (T2D).
2. By considering the relationships between the components of metabolic syndrome, we may be able to better understand the pathophysiology that links them with each other and with the increased risk of CVD.
3. It facilitates epidemiological and clinical studies of pharmacological, lifestyle and preventive treatment approaches.[21]

2. Definitions of the metabolic syndrome:

In the past few years, several expert groups have attempted to set forth simple diagnostic criteria to be used in clinical practice to identify patients who manifest the multiple components of the metabolic syndrome. These criteria have varied somewhat in specific elements, but in general they include a combination of both underlying and metabolic risk factors. [20]

The expression, 'make it as simple as possible, but not simpler' has been attributed to Albert Einstein. Following this principle, the current definitions of metabolic syndrome may be distilled into four central features: insulin resistance, visceral obesity, atherogenic dyslipidemia and endothelial dysfunction. These four central features would make up the simplest comprehensive definition for the metabolic syndrome, which cannot be simplified further. [21]

The commonly used criteria for identifying patients with metabolic syndrome are summarized in Table 2. [20]

Table 2: Criteria for identifying the metabolic syndrome

	NCEP ATP III (2005 revision) – National Cholesterol Education Programme – Adult Treatment Panel III – Modified by AHA/NHLBI	**WHO (1998) – World Health Organization**	**EGIR (1999) – European Group for the Study of Insulin Resistance**	**IDF (2005) International Diabetes Foundation**
Absolutely required	None	Insulin resistance (Impaired glucose tolerance, impaired fasting glucose, T2D or other evidence of insulin resistance)	Hyperinsulinemia (plasma insulin >75th percentile)	Increased waist circumference (population specific)
Criteria	Any three of the five criteria below	Insulin resistance or diabetes plus two of the five criteria below	Hyperinsulinemia plus two of the four criteria below	Obesity, plus two of the four criteria below
Obesity	Waist circumference ≥90 cm(M), ≥ 80cm(F) – For Asians	Waist/hip ratio: >0.90 (M), >0.85 (F);or BMI >30kg/m^2	Waist circumference ≥94cm (M), ≥ 80 cm (F)	Central obesity already required

Hyperglycemia	Fasting glucose ≥100mg/dl	Insulin resistance already required	Insulin resistance already required	Fasting glucose ≥100mg/dl
Dyslipidemia	TG ≥150mg/dl	TG ≥150mg/dl or HDL-C<35mg/dl (M), <39mg/dl (F)	TG ≥177mg/dl or HDL-C<39mg/dl	TG ≥150mg/dl
Dyslipidemia (second, separate criteria)	HDL cholesterol: < 40mg/dl (M); <50mg/dl (F)			HDL cholesterol: < 40mg/dl (M); <50mg/dl (F)
Hypertension	≥130 mmHg systolic BP or ≥85mmHg diastolic BP	BP: ≥140/90 mmHg	BP: ≥140/90 mmHg	≥130 mmHg systolic BP or ≥85mmHg diastolic BP
Other criteria		Microalbuminuria		

Abbreviations:

BP: Blood pressure

HDL-C: High density lipoprotein cholesterol

M – Males; F-Females

TG: Triglycerides

3 NCEP ATPIII Criteria

In 2001, the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) devised a definition for the metabolic syndrome which was updated by the American Heart Association and the National Heart, Lung and Blood Institute (AHA/NHLBI) in 2005. The AHA/NHLBI modifications include a

lowering of waist circumference cutpoints in ethnic groups or individuals at risk of insulin resistance and a reduction in threshold for fasting glucose from110mg/dl to 100mg/dl. [20]

The comparison between the original criteria proposed by the NCEP-ATP III and the present criteria as modified by AHA/NHLBI is depicted in Table 3. [20]

Table 3:– Comparison between original and present criteria of NCEP-ATP III for identifying patients with metabolic syndrome.

Criteria – Any three of five criteria must be present to make a diagnosis of metabolic syndrome	**2001 version**	**2005 version** **Modified by AHA/NHLBI**
Obesity	Waist circumference ≥102 cm in men ; ≥ 88 cm in women	Waist circumference (For Asian population) ≥ 90cm in men ; ≥ 80cm in women
Hyperglycaemia (Fasting blood glucose)	>110mg/dl	≥100mg/dl
Dyslipidemia	TG ≥150mg/dl	TG ≥150mg/dl
Dyslipidemia (second, separate criteria)	HDL cholesterol< 40mg/dl in men; <50mg/dl in women	HDL cholesterol< 40mg/dl in men; <50mg/dl in women
Hypertension	≥130/85mmHg	≥130 mmHg systolic BP or ≥ 85mmHg diastolic BP

The NCEP ATP III definition is one of the most widely used criteria for identifying metabolic syndrome because:

1. It incorporates the key features of hyperglycemia/insulin resistance, visceral obesity, atherogenic dyslipidemia and hypertension.

2. It uses measurements and laboratory results that are readily available to physicians, facilitating its clinical and epidemiological application.
3. It is also simple and easy to remember.
4. Importantly, it does not require that any specific criterion be met; only that at least three of five criteria are met. [21]

4. Physiological aspects relevant to metabolic syndrome:

a. Lipid metabolism:

Fat absorbed from the diet and lipids synthesized by the liver and adipose tissue must be transported between the various tissues and organs for utilization and storage. Since lipids are insoluble in water, the problem of how to transport them in the aqueous blood plasma is solved by associating nonpolar lipids like triglycerides (TG) and cholesteryl esters with amphipathic lipids like phospholipids and cholesterol and proteins to make water miscible lipoproteins. [23]

b. Structure of lipoprotein:

Lipoproteins have a nonpolar lipid core consisting of hydrophobic lipids like triglycerides and cholesteryl esters and a surface layer of amphipathic phospholipid and cholesterol molecules and a protein moiety. The protein moiety of a lipoprotein is known as apolipoprotein or apoprotein. [23]

The important characteristics of lipoproteins have been summarized in Table 4.[24]

Table 4: Characteristics of lipoproteins

Lipoprotein	Apolipoprotein content	Major lipids	Size(nm diameter)	Density (g/ml)
Chylomicrons	B-48,E, A-I, A-II,A-IV,C-I,C-II, C-III	Triglycerides from diet	80-500	<0.95
Chylomicron remnants	B-48, E	Triglycerides, phospholipids, cholesterol	45-150	<1.006
Very low density lipoproteins (VLDL)	B-100, E, C-II, C-III	Triglycerides from liver	30-80	0.95-1.006
Intermediate density lipoproteins (IDL)	B-100, E	Cholesteryl esters, triglycerides	25-35	1.006-1.019
Low density lipoproteins (LDL)	B-100	Cholesteryl esters,	18-25	1.019-1.063
High density lipoproteins (HDL)	A –I, A-II, AV	Cholesteryl esters, phospholipids	5-12	1.063-1.210
Lipoprotein (a)-Lp(a)	B-100, apo(a)	Cholesteryl esters	-30	1.055-1.085

Apoliporoteins (Apo) and their functions have been summarized in Table 5. [24]

Table5: Apolipoproteins and their functions

Apolipoprotein	Functions
Apo B100	Structural component for lipoproteins – VLDL, IDL & LDL, ligand for LDL receptor
Apo B48	Chylomicron secretion from intestine
Apo E	Ligand for binding of triglyceride rich particles to LDL receptor
Apo AI	Structural component of HDL, activates lecithin acyl cholesterol transferase (LCAT)

Apo AII	Genetically and biochemically associated with familial combined hyperlipidemia
Apo AIV	Potential role in regulating food intake
Apo V	Required for normal lipolysis of triglyceride rich lipoproteins
Apo CII	Activator of lipoprotein lipase
Apo CIII	Inhibitor of lipoprotein lipase
Apo (a)	Covalent bond with apo B100 forms Lp(a)and renders particle resistant uptake by LDL receptor

c. Exogenous lipid metabolism:

Dietary fats are broken down in the gut to free cholesterol and fatty acids, which are transported across cell membranes into the enterocyte. Here, they are re-esterified into cholesteryl ester and triglycerides and then packaged onto apo B48. These particles gain access to the plasma through the thoracic duct and acquire other apolipoproteins in part by transfer from HDL and these mature chylomicrons circulate to peripheral tissues. Lipoprotein lipase (LPL), bound to the capillary endothelium in tissues such as adipose tissue and muscle, is activated by apo CII on chylomicrons and fatty acids hydrolyzed from triglycerides by LPL are released and transported into adipose tissue for storage or muscle for energy. [24]

Progressive hydrolysis of triglyceride converts chylomicrons into chylomicron remnants, which are relatively enriched in cholesteryl esters. Chylomicron remnants are removed in the liver. Chylomicrons are large, and it is unlikely that they contribute to atherosclerosis. Chylomicron remnants are enriched in cholesteryl esters, the major lipid component of the atherosclerotic lesion, and small enough to enter the subendothelial space, where they are taken up by macrophages. [24]

d. Endogenous lipid metabolism:

Fats deposited in the liver are further metabolized into component lipid species, re-esterified as cholesteryl ester and triglycerides, and either stored in hepatocytes or exported as lipoproteins. The liver produces the triglyceride-rich lipoprotein VLDL. Their production is stimulated by increased delivery of free fatty acids (FFAs) into the hepatocytes either from high intake of dietary fat or from mobilization of fatty acids from adipose tissue with fasting or uncontrolled diabetes mellitus. [24]

Nascent VLDL containing one apo B100 molecule per particle is secreted into the plasma, where it acquires apo E, apo CII, and apo CIII. In a process analogous to that occurring with chylomicrons, apo CII on VLDL activates LPL, and fatty acids hydrolyzed from triglycerides by LPL are released in capillary beds and transported into tissues. With continued hydrolysis and the loss of both phospholipids and apolipoproteins to HDL, VLDL is converted to IDL, a cholesteryl ester–rich particle with an apolipoprotein complement of only apo B and apo E. IDL can be taken up by either the LDL receptor related protein (LRP) or the LDL receptor in the liver. In the presence of a normal apo E molecule, IDLs are converted to LDL, with one molecule of apo B100 per particle and cholesteryl ester with essentially no triglycerides. [24]

e. Reverse cholesterol transport and high density lipoprotein metabolism:

Lipid metabolism is extremely dynamic. At the same time lipoproteins are processed to modify their nonpolar lipids, particles are interacting with each other, exchanging surface materials, apolipoproteins and nonpolar lipids. HDL is an important reservoir for components cast off during the metabolism of other lipoproteins as well as lipids discarded by cells. Nascent HDL is generated by the

liver and intestine as a phospholipid disc containing apo AI and apo AII. It accepts unesterified (free) cholesterol and phospholipids shed from cells. This unesterified cholesterol is converted to cholesteryl ester by the action of lecithin cholesterol acyl transferase (LCAT) and stored in the center of the disc, allowing it to become a spherical particle. The particle is further modified as a consequence of the action of LPL on triglycerides in apo B–containing lipoproteins. As the core triglycerides of VLDL are metabolized, the particle collapses, leaving redundant surface lipids (phospholipid in the form of lecithin and unesterified cholesterol) and excess apolipoproteins such as apo CII, apo CIII and apo E that are transferred to HDL. [24]

Reverse cholesterol transport is the beneficial process by which cholesterol present in peripheral cells such as foam cells in a growing atherosclerotic lesion is transported back to the liver for excretion. There are at least two well-defined pathways mediating this transfer. First, after accepting cholesterol from peripheral cells and esterifying it through the action of LCAT, HDL can interact directly with the liver by binding to scavenger receptor B1 (SR-B1) and transferring cholesteryl ester to the hepatocyte. Second, HDL can transfer cholesteryl ester to apo B100–containing lipoproteins such as VLDL through the action of cholesteryl ester transfer protein (CETP). This cholesteryl ester can ultimately be transported to the liver after conversion of VLDL to IDL to LDL and uptake by the LDL receptor (LDLR). [24]

f. Insulin signaling:

Insulin is produced by the pancreas in response to hyperglycemia and stimulates glucose use differently in various tissues. Physiological insulin signaling occurs following the binding of insulin to the insulin receptor, a ligand-activated tyrosine kinase. Binding of insulin results in tyrosine phosphorylation of downstream substrates and activation of two parallel pathways: the phosphoinositide 3-kinase

(PI3K) pathway and the mitogen activated protein (MAP) kinase pathway. Tyrosine phosphorylation of insulin receptor substrates (IRS) activates PI3K, leading to activation of the 3-phosphoinositide-dependent protein kinase 1 (PDK1) kinase and Akt kinase. The PI3K-Akt pathway is responsible for many of the downstream metabolic effects of insulin. In vascular endothelial cells, Akt kinase phosphorylates and activates endothelial nitric oxide synthase (eNOS). In skeletal muscle and adipose tissue, Akt kinase stimulates translocation of the insulin responsive glucose transporter (GLUT4) to the cell surface, leading to increased glucose uptake. [21]

In parallel, tyrosine phosphorylation of the Shc protein activates the GTP exchange factor Sos. This results in activation of the MAP kinase pathway involving Ras, Raf, MAP kinase and extracellular regulated kinase (ERK). The MAP kinase pathway mediates endothelin-1 (ET-1) production, leading to vasoconstriction; expression of the vascular cell adhesion molecules VCAM-1 and E-selectin, leading to more leukocyte-endothelial interactions; and growth and mitogenesis effects on vascular smooth muscle cells. [21]

g. Effects of insulin on carbohydrate and lipid metabolism:

Carbohydrate metabolism:

- Insulin inactivates liver phosphorylase the principal enzyme involved in conversion of hepatic glycogen to glucose.
- Insulin enhances uptake of glucose from the blood by the liver cells by increasing the activity of glucokinase which causes phosphorylation of glucose which has been taken up by the liver cells.
- Insulin also increases the activity of glycogen synthase the enzyme involved in the synthesis of glycogen from glucose. [25]

Lipid metabolism:

- Insulin activates lipoprotein lipase in the capillary walls of the adipose tissue which splits triglycerides into fatty acids, a requirement for them to be absorbed into the adipose cells where they are again converted into triglycerides and stored.
- Insulin inhibits the action of hormone sensitive lipase, the enzyme which causes hydrolysis of triglycerides which have already been stored in the adipose cells.[25]

5. Pathophysiology of the Metabolic Syndrome:

a. Insulin resistance:

It indicates the presence of an impaired biological response to either exogenously administered or endogenously secreted insulin. It is manifested by decreased insulin stimulated glucose transport and metabolism in adipocytes and by impaired suppression of hepatic glucose output.[26] The degree to which glucose homeostasis deteriorates in insulin resistant individuals will vary as a function of both the magnitude of the loss of in vivo insulin action and the capacity of the beta cell to compensate for this defect. The majority of individuals with impaired glucose tolerance or non insulin dependent diabetes mellitus are insulin resistant as compared to appropriately matched individuals with normal glucose tolerance.[27]

In insulin resistance, the PI3K-Akt pathway is affected, whereas the MAP kinase pathway is not. This leads to a change in the balance between these two parallel pathways. Inhibition of the PI3K-Akt pathway leads to a reduction in endothelial nitric oxide (NO) production, resulting in endothelial dysfunction, and a reduction in GLUT4 translocation, leading to decreased skeletal muscle and fat

glucose uptake. By contrast, the MAP kinase pathway is unaffected, so there is continued endothelin (ET-1) production, expression of vascular cell adhesion molecules and mitogenic stimulus to vascular smooth muscle cells. In these ways, insulin resistance leads to vascular abnormalities that predispose to atherosclerosis.[21]

b. Visceral adiposity:

Central or intra-abdominal obesity is more strongly linked than total adiposity to insulin resistance and a number of important metabolic variables like plasma glucose, insulin, total plasma cholesterol, triglycerides and HDL cholesterol. [26] Many metabolic investigations have shown that excess visceral adiposity is a key feature of a phenomenon referred to as ectopic fat deposition, which has been associated with a plethora of metabolic dysfunctions. [28]

A number of hypotheses have been proposed to explain the relationship between intra-abdominal fat and abnormal metabolism:

- Visceral adipocytes are hyperlipolytic and have distinct secretion profile of cytokines referred to as adipokines. Macrophages are present within the adipose tissue and their density is increased in hypertrophic obesity, which is associated with a reduced production of anti-inflammatory adipokine, adiponectin. [28]
- Cross talk between adipocytes and macrophages results in amplification of a detrimental metabolic/inflammatory response by increasing synthesis of tumour necrosis factor (TNF-α), which in turn activates interleukin 6 (IL-6) and macrophage chemo attractant protein–1 (MCP-1) which allows recruitment of more macrophages. IL-6 is a key driver of production of C

reactive protein (CRP) in the liver. It has been found that higher the CRP levels more severe is the metabolic syndrome.[28]

- Abdominal adipose store is resistant to the antilipolytic effect of insulin which leads to increased lipase activity and a greater flux of fatty acids into the circulation with the portal circulation receiving the greatest fatty acid load. [26]
- High levels of 11beta-hydroxysteroid dehydrogenase type1 in the mesenteric fat could result in enhanced conversion of inactive cortisone to active cortisol resulting in increased local cortisol production.[26]

c. Atherogenic dyslipidemia

The key features of atherogenic dyslipidemia are high plasma TG levels, low HDL cholesterol levels and an increase in small dense LDL. Insulin resistance and visceral obesity are associated with atherogenic dyslipidemia. Insulin resistance leads to atherogenic dyslipidemia in several ways.

- Insulin normally suppresses lipolysis in adipocytes, so impaired insulin signaling increases lipolysis, resulting in increased FFA levels. In the liver, FFAs serve as a substrate for synthesis of TGs. FFAs also stabilize the production of apoB, the major lipoprotein of VLDL particles, resulting in more VLDL production.
- Insulin normally degrades apoB through PI3K-dependent pathways, so insulin resistance directly increases VLDL production.
- Insulin regulates the activity of lipoprotein lipase, the rate-limiting and major mediator of VLDL clearance. [21]

Thus, hypertriglyceridemia in insulin resistance is the result of both an increase in VLDL production and a decrease in VLDL clearance. VLDL is metabolized to remnant lipoproteins and small dense LDL, both of which can promote atheroma formation. The TGs in VLDL are transferred to HDL by CETP in exchange for cholesteryl esters, resulting in TG-enriched HDL and cholesteryl ester-enriched VLDL particles. The TG-enriched HDL is a better substrate for hepatic lipase, so it is cleared rapidly from the circulation, leaving fewer HDL particles to participate in reverse cholesterol transport from the vasculature. [21]

d. Endothelial dysfunction

Endothelial dysfunction is the final common pathway between many cardiovascular risk factors and the development of atherosclerosis. Endothelial dysfunction, broadly defined, occurs when the endothelium fails to serve its normal physiological and protective mechanisms. It may occur when the normal responses of the endothelium are affected, for example by oxidative stress, hyperglycemia, advanced glycation products, FFAs, inflammatory cytokines or adipokines. A common feature of endothelial dysfunction is the reduced bioavailability of NO in the vasculature. [21]

Insulin resistance causes endothelial dysfunction by decreasing Akt kinase activity, resulting in diminished nitric oxide synthase phosphorylation and activity. In addition, insulin-mediated ET-1 expression and vascular smooth muscle mitogenic effects are not affected by insulin resistance, further contributing to endothelial dysfunction. [21]

Visceral adiposity causes endothelial dysfunction through the effects of resistin, IL-6 and TNFα on eNOS phosphorylation. In addition to blocking IRS-1

activation, TNFα directly activates NADPH oxidase, increasing superoxide generation; TNFα also stimulates lipolysis, resulting in FFA release. By contrast, adiponectin, which stimulates eNOS phosphorylation, is diminished in metabolic syndrome. In visceral fat, leptin resistance also increases the generation of reactive oxygen species. FFAs contribute to endothelial dysfunction by a combination of diminished PI3K-Akt signaling, increased reactive oxygen species and increased ET-1 production. [21]

6. Metabolic syndrome and Schizophrenia:

For the increased risk of metabolic syndrome and other metabolic abnormalities in patients with schizophrenia, three complementary and partially overlapping causes are put forward in the literature: lifestyle factors, aspects of the psychotic disorder and antipsychotic medication. People with schizophrenia on average have a lifestyle which increases their risk for the development of metabolic syndrome: sedentary lifestyle, lack of regular physical activity, substance abuse and high rates of smoking. Part of these lifestyle factors are influenced by the aspects of the illness such as negative symptoms and vulnerability to stress.[29]

In an extensive meta-analysis, Newcomer points to studies performed in drug naïve schizophrenic patients compared with age and sex matched cohorts from the general population, whose outcome suggests a link between schizophrenia and diabetes mellitus, dyslipidemia and other metabolic disturbances. [30]

Second generation antipsychotics, the mainstay of schizophrenia treatment, have metabolic effects that are of particular concern. Some of these drugs have been associated with weight gain, obesity, diabetes mellitus and dyslipidemia. Alarm about the association between antipsychotics and these CVD risk factors is growing as

evidence accumulates. The potential harmful impact of these medications on a patient's physical health may cause nonadherence and treatment discontinuation. [19]

Further research is needed in order to determine whether this increased risk is a result of the symptoms of the disease, an underlying genetic factor or the antipsychotic drugs.[19]

C. Drugs used in the treatment of schizophrenia:

1. Historical aspects:

a. First generation antipsychotics (FGAs) or Typical antipsychotics:

In the late 1930s a phenothiazine derivative promethazine was found to have antihistaminic and sedative effects. The drug was introduced into clinical anaesthesia as a potentiating and autonomic stabilizing agent. This work prompted a search for phenothiazine derivatives with similar effects. [31]

The first phenothiazines were the first effective antipsychotic drugs. Drugs from this class were originally used as antihelminthics in veterinary medicine. In 1950, Paul Charpentier, at the Rhone-Poulenc laboratories in Paris, synthesized chlorpromazine.[8] Henri Laborit a surgeon, described the ability of this compound to potentiate anaesthetics and produce "artificial hibernation." [31]

In 1952 Delay and Deniker became convinced that chlorpromazine achieved more than symptomatic relief of agitation or anxiety and that it had an ameliorative effect upon psychotic processes in diverse disorders, including mania and schizophrenia. [31]

In 1953, reports surfaced indicating that chlorpromazine can cause parkinsonian symptoms. Later that year, clinicians noted that chlorpromazine could

also result in forms of persistent dyskinesia, a syndrome that would later be called tardive dyskinesia. [8]

The introduction of chlorpromazine was followed by the introduction of other phenothiazines, including perphenazine and fluphenazine. In 1958, the first effective butyrophenone, haloperidol was introduced by Paul Janssen from Belgium. The first thioxanthene antipsychotics were introduced the same year by P.V.Peterson and his coworkers.[8]

b. Second generation Antipsychotics (SGAs) or Atypical Anyipsychotics:

After more than forty years of dopamine receptor antagonists with often unavoidable extrapyramidal side effects, a new generation of antipsychotic drugs has become available. These are first and foremost the serotonin dopamine antagonists (SDAs) named after their alleged mechanism of action, now followed by newer dopamine type 2 (D_2) receptor antagonists. [8]

Clozapine was discovered in 1958 in Bern, Switzerland. The drug appeared to be an effective antipsychotic agent that did not cause extrapyramidal side effects. The enthusiasm about clozapine was dampened when it was discovered that the drug was associated with significant haemotological toxicity particularly granulocytopenia. [8]

Clozapine was approved for use in the United states in 1990 for schizophrenia patients who are resistant to treatment with other antipsychotic drugs or who are unable to tolerate conventional drugs because of extrapyramidal side effects. [8]

Risperidone was the first antipsychotic agent to gain FDA approval after clozapine. It was discovered, patented and marketed by Janssen Pharmaceuticals. [8]

Eli lilly and Company discovered olanzapine in Great Britain in 1982. It is derived from clozapine as an agent without strong D_2 receptor blockade. In 1986,

renewed interest in the compound emerged. Olanzapine became available in the American and European markets in the fall of 1986. [8]

Quetiapine was developed by Zeneca Laboratories. Its new drug application was filed with the FDA in 1996 and approved in 1998.[8]

2. Classification of first generation antipsychotics (FGAs) [11]

(i) Phenothiazines:

a. Aliphatic side chain: Chlorpromazine, Triflupromazine

b. Piperidine side chain: Thioridazine, Mesoridadazine

c. Piperazine side chain: Trifluoperazine, Perphenazine, Fluphenazine

(ii) Thioxanthenes: Chloprothixene, Thiothixene, Flupenthixol

(iii) Dinbenzoxazepine: Loxapine

(iv) Butyrophenones: Haloperidol, Droperidol

(v) Diphenylbutylpiperidines: Pimozide, Penfluridol

3. Classification of second generation antipsychotics (SGAs)[22]

(i) Serotonin Dopamine Antagonists: Risperidone, Ziprasidone, Sertindole.

(ii)Multi acting Receptor Targeted Antipsychotics: Clozapine, Olanzapine, Quetiapine

(iii) Partial Dopamine Agonist: Aripiprazole

(iv) D_2/D_3 Antagonists: Sulpiride, Amisulpride

4. Neurotransmitters related to antipsychotic action:

a. Dopamine:

Dopamine is particularly important in relation to neuropharmacology, because it is involved in several common disorders of brain function, notably Parkinson's disease, schizophrenia and attention deficit disorder, as well as in drug dependence and certain endocrine disorders. [32]

Dopamine, a catecholamine neurotransmitter is synthesized in the terminals of dopaminergic neurons from tyrosine. It is metabolised by monoamine oxidase and catechol-O-methyl transferase, the main products being dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). [32]

Dopamine is most abundant in the corpus striatum, a part of the extrapyramidal motor system concerned with the coordination of movement and high concentrations also occur in certain parts of the limbic system and hypothalamus. [32]

Dopaminergic pathways: Important for understanding schizophrenia and the mechanism of action of antipsychotic drugs. [10]

- Mesolimbic – mesocortical pathway: Projects from cell bodies near substantia nigra to the limbic system and neocortex. This pathway is most closely related to behaviour and psychosis.
- Nigrostriatal pathway: Consists of neurons that project from the substantia nigra to the dorsal striatum, which includes the caudate and putamen. It is involoved in the co-ordination of voluntary movement. Blockade of D_2 receptors in this pathway is responsible for extrapyramidal symptoms.
- Tuberoinfundibular pathway: Arises in the arcuate nuclei and periventricular neurons and releases dopamine into the pituitary portal

circulation, which in turn inhibits prolactin secretion from the anterior pituitary.

- Medullary-periventricular pathway: Consists of neurons in the motor nucleus of the vagus whose projections are not well defined. This system may be involved in eating behaviour.
- Incertohypothalamic pathway: Forms connections from the medial zona incerta to the hypothalamus and the amygdala. It appears to regulate the anticipatory motivational phase of copulatory behaviour in rats.[10]

Dopamine receptors:

Two types of receptors, D_1 and D_2, were originally distinguished on pharmacological and biochemical grounds. The original D_1 family now includes D_1 and D_5 receptors while D_2 family consists of D_2, D_3 and D_4 receptors.All belong to the family of G-protein-coupled transmembrane receptors. [32]

D_1 and D_5 receptors stimulate formation of cyclic AMP and phosphatidyl inositol hydrolysis. D_2, D_3 and D_4 receptors decrease cyclic AMP formation and modulate potassium and calcium currents. [32]

Distribution of dopamine receptors in the CNS: [31]

D_1 - striatum, neocortex

D_2 - striatum, substantia nigra pars compacta, pituitary

D_3 - olfactory tubercle, nucleus accumbens, hypothalamus

D_4 - frontal cortex, medulla, midbrain

D_5 - hippocampus, hypothalamus

b. Serotonin (5 – Hydroxytryptamine):

The precursor of serotonin is tryptophan an amino acid derived from dietary protein. Tryptophan is actively taken up into neurons, converted by tryptophan hydroxylase to 5- hydroxytrytophan and decarboxylated by a non specific amino acid decarboxylase to 5-hydroxytryptamine. [32]

Serotonin containing neurons are concentrated in the midline raphe nuclei in the pons and medulla, projecting diffusely to the cortex, limbic system, hypothalamus and spinal cord. [32]

The main serotonin receptor subtypes, their location and functions are summarized in Table 6. [32]

Table 6: Main serotonin (5HT) receptor subtypes

Receptor	Location	Main effects
1A	CNS	Neuronal inhibition, Behavioural effects: sleep, feeding, thermoregulation, anxiety
1B	CNS, Vascular smooth muscle	Presynaptic inhibition, Behavioural effects, Pulmonary vasoconstriction
1D	CNS blood vessels	Cerebral vasoconstriction, Locomotion
2A	CNS, Peripheral nervous system (PNS), Smooth muscle, Platelets	Neuronal excitation, Behavioural effects, Contraction of gut and bronchial smooth muscle, Platelet aggregation, Vasoconstriction/Vasodilatation
2B	Gastric fundus	Contraction
2C	Choroid plexus	Cerebrospinal fluid secretion
3	PNS, CNS	Neuronal excitation, Emesis, Behavioural effects: anxiety
4	PNS (Gastrointestinal tract), CNS	Neuronal excitation, GI motility
5	CNS	Not known
6	CNS	Not known
7	CNS, Gastrointestinal tract and Blood vessels	Not known

Physiological and behavioural functions related to serotonin pathways: [32]

- Various behavioural responses (eg:hallucinations).
- Feeding behaviour.
- Control of mood and emotion.
- Control of sleep/wakefulness.
- Control of sensory perception including nociception.
- Control of body temperature.
- Vomiting.

5. Mechanism of action of antipsychotic drugs:

The dopamine hypothesis states that antipsychotics reduce psychotic symptoms by decreasing dopamine activity. It was originally proposed by Arvid Carlsson from Sweden. The dopamine hypothesis has focused considerable attention on the mesolimbic and mesocortical systems as possible sites where antipsychotic effects are mediated. The first generation antipsychotic agents block D_2 receptors and their binding affinity is very strongly correlated with clinical antipsychotic and extrapyramidal potency. In vivo imaging studies of D_2 receptor occupancy indicate that for antipsychotic efficacy the first generation antipsychotics must be given in sufficient doses to achieve 60% occupancy of striatal D_2 receptors. Extrapyramidal syndromes are produced when occupancy of striatal D_2 receptors reaches 80% or higher.[11]

Most of the second generation antipsychotics have a higher affinity for the $5HT_{2A}$ receptor than for the D_2 receptor, suggesting an important role for the serotonin system in the etiology of schizophrenia and the action of these drugs. They also have a greater specificity for the mesolimbic compared to the striatal dopamine

system. These new agents have shown selectivity for the limbic system in electrophysiological studies and in animal tests. In contrast, traditional antipsychotics agents affect both the limbic and striatal dopamine neurons, which results in extrapyramidal effects at therapeutic doses. [11]

The adverse effects of antipsychotic drugs on the CNS, endocrine system and autonomic nervous system are summarized in Tables 7 and 8. [31, 10]

Table7: Neurological Side Effects of Antipsychotic Drugs:

Reaction	**Features**
Acute dystonia	Spasm of muscles of tongue, face, neck, back
Akathisia	Motor restlessness; not anxiety or agitation
Parkinsonism	Bradykinesia, rigidity, tremors, mask facies, shuffling gait.
Neuroleptic malignant syndrome	Catatonia, stupor, fever, unstable blood pressure, myoglobinemia
Perioral tremor (rabbit tremor)	Perioral tremor (may be a late variant of parkinsonism)
Tardive dyskinesia	Oral-facial dyskinesia; widespread choreoathetosis or dystonia

Table 8: Other adverse effects of antipsychotic drugs:

System affected	**Manifestations**	**Mechanism**
Autonomic nervous system	Loss of accommodation, dry mouth, difficulty urinating, constipation	Muscarinic cholinoceptor blockade
	Orthostatic hypotension, impotence, failure to ejaculate	α - Adrenoceptor blockade
Endocrine system	Amenorrhoea, galactorrhoea, infertility, impotence	Dopamine- receptor blockade resulting in hyperprolactinemia

6. Metabolic adverse effects of antipsychotics:

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a multisite clinical study sponsored by the National Institute of Mental Health, assessed the efficacy and safety/tolerability of olanzapine, quetiapine, risperidone and ziprasidone compared with the conventional antipsychotic perphenazine in 1,460 patients diagnosed with chronic schizophrenia. [5]

Average weight gain was greater with olanzapine than with any of the other drugs. Percentage of patients who gained more than 7% of their baseline bodyweight was greatest in the olanzapine group. Treatment with olanzapine was associated with significantly elevated levels of cholesterol and triglycerides and glycosylated haemoglobin. Risperidone reduced cholesterol levels but produced small significant increases in triglycerides and glycosylated haemoglobin. Quetiapine was associated with a disturbance in all metabolic parameters but less than that of olanzapine and greater than that of risperidone. Ziprasidone produced reduction of cholesterol, triglyceride and glycosylated haemoglobin. [5]

A prospective open - labeled nonrandomized study compared the effects of 6 antipsychotics on the development of the metabolic syndrome in 238 schizophrenic patients. Aripiprazole was the only antipsychotic that was associated with no weight gain, improved glucose tolerance and reduced incidence of metabolic syndrome. Clozapine and olanzapine were associated with the greatest risk of weight gain and glucose alterations. Risperidone, quetiapine and amisulpride demonstrated an intermediate risk profile of weight gain, glucose metabolism abnormalities and metabolic syndrome. [33]

The metabolic and endocrine risk profile of various SGAs has been summarized in Table 9. [33]

Table 9: Metabolic and endocrine risk profile of SGAs

	Weight gain risk	**Diabetes risk**	**Dyslipidemia risk**	**Hyperprolactinemia risk**
Clozapine	+++	++	++	+/-
Olanzapine	+++	++	++	+
Risperidone	++	+	+/-	++
Quetiapine	++	+/-	+/-	+
Aripiprazole	+/-	Insufficient data	Insufficient data	+/-
Ziprasidone	+/-	Insufficient data	Insufficient data	+/-
Amisulpride	+/-	Insufficient data	Insufficient data	+++

+: increased effect; -: no effect

7. Mechanisms of metabolic abnormalities induced by SGAs:

The mechanism of antipsychotic induced weight gain involves occupancy of serotonergic, histaminergic, muscarinic and other receptors more or less directly involved in the modulation of food intake and energy expenditure. This has been suggested as the primary mechanism of antipsychotic induced weight gain. The different pharmacodynamic profile of antipsychotics on these receptors has been invoked as the key factor for the different weight gain liabilities of antipsychotic drugs. Prolactin elevation, changes in insulin sensitivity and decreased activity caused by sedation are other possible mechanisms of weight gain. [33]

It has been suggested that clozapine and olanzapine have direct effects on glucose regulation by inducing insulin resistance, directly or via changes in body weight and fat deposition or limiting the capacity of the beta cells to secrete an appropriate amount of insulin. Low concentrations of clozapine and olanzapine can markedly and selectively impair cholinergic-stimulated insulin secretion by blocking muscarinic M_2 receptors. [33]

It has been proposed that hyperlipidemia results from an increase in insulin resistance from antipsychotic treatment. Insulin resistance enhances lipolysis, increasing FFAs along with production of triglycerides. The resulting changes in lipid metabolism may lead to production of smaller, denser HDL particles that have an increased clearance through the kidney. [15]

For physical health monitoring of schizophrenic being treated with SGAs guidelines have been proposed by the American Psychiatric Association, American Diabetes Association and the Conference at Mount Sinai which have been summarized in Table 10. [4, 34, 35]

Table 10: Guidelines for monitoring metabolic parameters during antipsychotic therapy:

Measure and publishing agency	Baseline	Maintainance
Bodyweight/Body mass index		
American Psychiatric Association	X	Every visit for first 6 months; quarterly thereafter
American Diabetes Association	X	4, 8, 12 weeks; quarterly thereafter
Mount Sinai Guidelines	X	Every visit for first 6 months; at least quarterly thereafter

Waist circumference		
American Psychiatric Association	-	-
American Diabetes Association	X	Annually
Mount Sinai Guidelines	X	Every visit for first 6 months; at least quarterly thereafter
Blood pressure		
American Psychiatric Association	X	As clinically indicated, particularly as doses are titrated
American Diabetes Association	X	12 weeks; then annually
Mount Sinai Guidelines	-	-
Lipid panel		
American Psychiatric Association	X	At least every 5 years
American Diabetes Association	X	12 weeks; then every 5 years
Mount Sinai Guidelines	X	At least every 2 years when LDL is normal; every 6 months when LDL is > 130mg/dl
Fasting plasma glucose		
American Psychiatric Association	X	4 months after medication initiation or change; then yearly
American Diabetes Association	X	12 weeks after medication initiation or change; then yearly
Mount Sinai Guidelines	X	For patients with risk factors for diabetes: 4 months after starting then, yearly

D. Management of metabolic syndrome:

It has been documented that a reduction of 10% in cholesterol levels results in a 30% reduction of CVD risk, a lowering of blood pressure of 4% to 6% decreases CVD risk by 15% and smoking cessation would result in a 50% to 70% lowering of CVD prevalence.[33]

Appropriate dieting, lowering blood pressure, increased physical activity and cessation of smoking should be important components in multidisciplinary programmes for people with schizophrenia to prevent or treat the metabolic syndrome or single metabolic aberrations that frequently occur in these patients. [33]

All patients receiving an antipsychotic that is associated with significant weight gain potential and their care – givers should be informed the risk of weight gain and health risks associated with excessive weight. This requirement is especially important for patients who are overweight or obese at the start of therapy or who have a family history of obesity or diabetes. [33]

If a patient develops metabolic abnormalities or weight gain corresponding to 1 body mass index (BMI) unit or greater than 5% increase of baseline bodyweight, following initiation of antipsychotic therapy, consideration should be given to switching the patient to another antipsychotic with a less dismetabolic potential. [33]

1. Weight reduction:

Treatment for obesity requires lifestyle and behavioural changes and may include possible pharmacological interventions. Patients should be encouraged to engage in exercise and make better food choices, including smaller portions and healthier selections. Multiple adjunctive medications have been evaluated to treat weight gain associated with antipsychotic therapy including sibutramine, topiramate,

reboxetine, metformin, etc. Most studies were small and of short duration. Thus, no current recommendations are available to guide adjunctive treatment for weight loss.[15]

2. Diabetes mellitus:

Initial interventions for glycemic control in people who have diabetes generally include diet and exercise. If lifestyle modifications do not reduce the glycosylated haemoglobin (HbA1C) level below 7% in 3 months, pharmacological interventions are recommended. Current recommendations for tight control include an HbA1C below 7%, blood pressure below 130/80mmHg, LDL level below 100mg/dl, triglycerides level below 150mg/dl and HDL level above 40mg/dl. Several classes of drugs like sulfonylureas, biguanides, thiazolidinediones and alpha glucosidase inhibitors are available. [15]

Prevention of cardiovascular complications is also recommended as a part of the diabetes treatment. Patients with diabetes should receive aspirin, should maintain good blood pressure control and should try to quit smoking. Routine use of angiotensin converting enzyme inhibitors ar angiotensin receptor blockers reduces incidence of renal complications. Statins are recommended in people who have diabetes regardless of their baseline lipid values. [15]

3. Hyperlipidemia:

Current treatments of hyperlipidemia are guided by recommendations from the NCEP-ATP III guidelines as described in Table 11. [36]

Table 11: LDL goals and cut points for therapeutic lifestyle changes and drug therapy for different risk categories:

Risk Category	LDL Goal (mg/dl)	LDL level at which to initiate lifestyle changes (mg/dl)	LDL level at which to consider drug therapy (mg/dl)
CHD or CHD risk equivalents (10 year risk>20%[a])	<100 (optional: <70 for very high risk patients)	≥100	≥100
Two or more risk factors[b] (10 year risk – 10%-20% [a])	<130 (optional <100)	≥130	≥130 (100-129: LDL – lowering drug optional)
Two or more risk factors (10 year risk <10%)	<130	≥130	≥160
0-1 risk factors	<160	≥160	≥190 (160-189: LDL – lowering drug optional)

Abbreviation: CHD: Coronary heart disease

a: Ten year risk assessment calculated using Framingham scoring.

b: Risk factors include cigarette smoking; hypertension; low HDL cholesterol; family history of premature CHD; age (men ≥ 45 years, women ≥ 55 years).

4. Hypertension:

Current recommendations for the treatment of hypertension follow the guidelines from the Joint National Committee on Prevention, Detection, Evaluation and Treatment of high blood pressure which have been described in table 12. [37]

Table 12: Classification and management of hypertension in adults - JNC 7 report

Blood pressure classification	**Systolic BP (mm Hg [a])**		**Diastolic BP (mm Hg [a])**	**Lifestyle modification**	**Drug therapy -Without compelling indications**	**Drug therapy - With compelling indications [d]**
Normal	< 120	And	< 80	Encourage		
Prehypertension	120-139	Or	80-89	Yes	No antihypertensive drug indicated	Drug(s) for the compelling indications [b]
Stage 1 hypertension	140-159	Or	90-99	Yes	TTD for most; may consider ACEI, ARB, Beta blocker, CCB or combination	Drug(s) for the compelling indications. Other antihypertensive drugs as needed.
Stage 1 hypertension	≥ 160	Or	≥ 100	Yes	Two-drug combination for most (usually TTD and ACEI or ARB or beta blocker or CCB) [c]	Drug(s) for the compelling indications. Other antihypertensive drugs as needed.

Abbreviations:

ACEI: Angiotensin converting enzyme inhibitors; ARB: Angiotensin receptor blockers; CCB: Calcium channel blockers; TTD: Thiazide type diuretic

a: Treatment determined by high blood pressure classification.

b: Treat patients with chronic kidney disease to blood pressure goal of <130/80mmHg.

c: Initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

d: Disease states with medication indications: chronic kidney disease; diabetes; heart failure; high coronary disease risk; postmyocardial infarction; recurrent stroke prevention.

E. Drugs used in the present study:

1. Risperidone:

a. Chemistry: Risperidone is a benzisoxizole derivative. [11]

b. Pharmacodynamics: Risperidone's presumed mechanism of action is associated with its potent central antagonism of both serotonin 5-HT $_{2A}$ and dopamine D_2 receptors. It also demonstrates high affinity for adrenergic α_1 and α_2 receptors and histaminergic H_1 receptors. It has moderate affinity for serotonin 5HT $_{1C}$, $5HT_{1D}$ & 5HT $_{2A}$ receptors and weak affinity for dopamine D_1 receptors.

Risperidone blocks 65% of D_2 receptors at an average dose of 2mg per day. At an average dose of 6mg per day, 80% of D_2 receptors are blocked and extrapyramidal side effects may occur. [11]

c. Phamacokinetics: Risperidone has a bioavailability of 70% after oral administration. It is metabolized in the liver to 9-hydroxyrisperidone which has the same pharmacological profile as the parent compound. After ingestion peak plasma levels of the parent compound occur within 1 hour and within 3 hours for 9-hydroxyrisperidone. Steady state is expected to be reached by 5 days. Combined half life of risperidone and it's metabolites has a mean of 20hours. Seventy percent of risperidone is excreted in the urine. [11]

d. Uses of risperidone:

- Schizophrenia and psychosis: Risperidone is effective in treating psychosis associated with schizophrenia and other forms of psychosis both in the acute phase as well as for maintainance treatment.
- Bipolar mania: Risperidone is effective in the treatment of mania and more efficacious when used in combination with a mood stabilizer.
- Autism: Risperidone is effective in treating irritability associated with autism in children and adolescents.
- Other indications: Risperidone has been used off label for a number of conditions like posttraumatic stress disorder, adjunctive treatment in treatment –refractory obsessive compulsive disorder, Tourette's syndrome in children and acquired immunodeficiency syndrome (AIDS) – related dementia and psychosis. [11]

e. Adverse effects:

- Orthostatic hypotension and syncope: Risperidone has antagonistic activity at α receptors, which contributes to it's risk of orthostatic hypotension, dizziness and syncope. It should be used with caution in individuals with known cardiovascular disease.
- Extrapyramidal side effects: Double blind trials indicate that risperidone treatment is associated with a dose dependent increase in extrapyramidal side effects like dystonic reactions and akathisia. These effects usually occur at doses of ≥6mg. Many patients require only 2 to 4mg of risperidone.
- Hyperprolactinemia: Risperidone treatment increases prolactin levels which is sometimes but not always associated with inhibited reproductive function and

symptoms such as galactorrhoea, amenorrhoea, gynaecomastia, erectile dysfunction and anorgasmia.

- Weight changes: In the CATIE trial 14% of subjects taking risperidone gained more than 7% of their baseline body weight.
- Hyperglycemia: Results from the CATIE study indicate that risperidone produced changes in glucose level comparable to quetiapine, with an increase lower than that with olanzapine and higher than that with ziprasidone treatment.
- Hyperlipidemia: In the CATIE study risperidone demonstrated small but significant increase triglycerides but, decreased cholesterol levels.

f. Dose: Adult antipsychotic oral dose- 2-8 mg [31]

2. Olanzapine:

a. Chemistry: Olanzapine is a thienobenzodiazepine. It can be considered a derivative of of clozapine with substitution of thieno ring for clozapine's carbonyl ring. [11]

b. Pharmacodynamics: Olanzapine is a high affinity antagonist at 5-HT $_{2A/2C}$, 5-HT$_6$, D $_{1-4}$, H_1 & α_1 receptors. It is a moderate affinity antagonist at muscarinic M $_{1-5}$ and $5HT_3$ receptors. A dose of 10 to 20mg results in 68-84% D_2 occupancy. It's 5-HT$_2$ activity is approximately eight times as strong as its dopamine receptor blockade.

c. Pharmacokinetics: Olanzapine is well absorbed after oral administration reaching a peak plasma concentration in 6hours. It has a mean half life of 31 hours (range of 21 to 54 hours).Steady state plasma concentration is achieved in 7days. The drug is 93%

protein bound to plasma proteins. Primary metabolic pathways are glucoronidation and P450 mediated oxidation. [11]

d. Uses of olanzapine:

- Schizophrenia- Used for both acute treatment and for maintainance.
- Bipolar disorder: Olanzapine is effective as monotherapy for the treatment of mania and mixed states. It is also effective for the same conditions when combined with lithium or valproate.
- Other possible conditions: In double blind studies olanzapine has been found to be effective in patients with schizoaffective disorder, Tourette's syndrome, as an adjunct to selective serotonin reuptake inhibitors for post traumatic stress disorder and for psychosis in dementia. [11]

e. Adverse effects:

- Weight gain: In the CATIE study it was found that 30% of subjects taking olanzapine had a significant weight gain of more than 7%. Studies during long term therapy with olanzapine found that 56% of patients gained greater than 7% of baseline weight.
- Hyperlipidemia: Patients treated with olanzapine may experience serious increases in total cholesterol, LDL cholesterol and triglycerides. Triglycerides are most likely to be elevated. In the CATIE study the mean increase in triglycerides in patients taking olanzapine was 40.5mg/dl, greater than with any other drug.
- Hyperglycemia: A number of studies including CATIE found greater elevations in blood glucose on olanzapine than on other antipsychotics. There is also substantial evidence that olanzapine treatment is associated with an

increased risk for the development of type 2 diabetes mellitus. There is also evidence that olanzapine can result in elevations in blood glucose that are life threatening.

- Effects on the cardiovascular system: Olanzapine is associated with orthostatic hypotension, tachycardia and possibly syncope.
- Gastrointestinal adverse effects: The anticholinergic effects of olanzapine can lead to constipation in some patients.
- Adverse effects on CNS: Olanzapine is somewhat sedating and may affect motor skills. [11]

f. Dose: Adult antipsychotic oral dose- 5-10 mg [31]

3. Quetiapine:

a. Chemistry: Quetiapine is a dibenzothiazepine with more potent 5-HT_2 than D_2 receptor blocking properties. [11]

b. Pharmacodynamics: Quetiapine is a multitransmitter antipsychotic agent. It has a high affinity for $5HT_2$, H_1, α_1 and α_2 receptors. It has a moderate affinity for $5HT_{1A}$ and D_2 receptors amd a low affinity for D_1 receptors. It has a very low affinity for M_1 and D_4 receptors. [11]

c. Pharmacokinetics: Quetiapine reaches a maximum plasma concentration 1.5 hours after oral intake. The plasma half life is 6 hours. Steady state levels are reached in 48 hours. Quetiapine is extensively metabolized by the liver. Ninety five percent of quetiapine is recovered as metabolites in urine and faeces. [11]

d. Uses of quetiapine:

- Schizophrenia: Quetiapine is used for both acute treatment and maintainance treatment.

- Bipolar disorder: Quetiapine has an indication for acute treatment of bipolar mania, either as monotherapy or as adjunctive treatment with lithium or valproate.
- Other indications: Quetiapine is used to treat major depressive disorder, obsessive compulsive disorder, borderline personality disorder and psychosis in Parkinson's disease.

e. Adverse effects:

- Weight changes: Quetiapine is associated with significant increases in weight, likely related in part to it's high affinity for histaminergic H_1 receptors. In the CATIE trial 16% of patients treated with quetiapine gained over 7% of their body weight.
- Hyperlipidemia: In the CATIE study quetiapine treated patients experienced mean increases in cholesterol and triglycerides of 6.6 and 21.2 mg/dl respectively, increases second only to olanzapine and significantly higher than that seen with risperidone.
- Hyperglycemia: Quetiapine is associated with increase in plasma glucose and increased risk of diabetes, but the degree of glucose increase is less dramatic than that of lipid and triglyceride increases. In the CATIE trial increase in blood glucose with quetiapine was not significantly larger than that seen with risperidone.
- Orthostatic hypotension and syncope: Quetiapine is a strong antagonist at the α_1 adrenergic receptor, contributing to it's risk of orthostatic hypotension, syncope, dizziness and tachycardia.

- Somnolence and sedation: Quetiapine can cause significant sedation and somnolence, especially during initial dose titration. The sedation and somnolence are likely secondary to quetiapine's high affinity for histaminergic H_1 receptors.

f. Dose: Adult antipsychotic oral dose- 300-500mg [31]

METHODOLOGY

A. Source of data: Department of Psychiatry, KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum. Study was approved by Institutional Human Ethics Committee.

B. Method of collection of data:

C. Study design:

One year cross sectional study

D. Sample size:

Sample size was calculated using the formula $n = 4pq/d^2$, where n is the required sample size, p is the prevalence of the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents which was found to be 28%[38], q = 100-p = 72%.Considering absolute error, d as 10% required sample size, n was calculated and found to be 80.

E. Procedure:

Inpatients as well as outpatients visiting the department of psychiatry, diagnosed to be suffering from schizophrenia using diagnostic criteria from the revised fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) and receiving a single second generation antipsychotic agent (olanzapine, risperidone or quetiapine) for a period of 3 months or more were enrolled in the study after obtaining written informed consent. Particulars and history were obtained using study proforma. Patients were requested to come the next day in fasting state (overnight fast of 12 – 14hours) for the purpose of blood collection for lipid studies and fasting blood glucose. Patients were screened for the metabolic syndrome using

NCEP- ATP III criteria (National Cholesterol Education Program, Adult Treatment Panel III) modified by AHA/NHLBI in 2005 which are as follows:

a. Central obesity: Waist circumference ≥ 90cm and ≥ 80cm respectively

in males and females.

b. Hypertriglyceridemia: Triglycerides ≥ 150 mg/dl

c. Low HDL cholesterol: < 40 mg/dl and < 50mg/dl respectively in males and females.

d. Hypertension: Blood pressure ≥ 130mmHg systolic or ≥ 85mmHg diastolic.

e. Fasting plasma glucose ≥ 100mg/dl.

For a diagnosis of metabolic syndrome three or more of these criteria must be present.[20]

F. Inclusion criteria:

Patients of either sex aged between 18 and 65 years suffering from schizophrenia and receiving a single second generation antipsychotic agent (olanzapine, risperidone or quetiapine) for 3 months or more were included in the study.

G. Exclusion criteria:

a. Patients receiving more than one antipsychotic medication.

b. Patients with a known diagnosis of type 1 or type 2 diabetes mellitus.

c. Patients with a known diagnosis of hypertension.

d. Patients suffering from anorexia nervosa, bulimia nervosa or neoplastic disease.

e. Patients with a history of alcohol dependence.

f. Patients suffering from any major endocrine disorder.

g. Patient on treatment for any major medical or surgical illness.

h. Pregnant and lactating women.

i. Non complying patients.

H. Methods used for screening of metabolic syndrome:

1. Measurement of waist circumference: [21]

To measure the waist circumference the top of the right iliac crest is located. A measuring tape is placed in a horizontal plane around the abdomen at the level of the iliac crest. Before reading the tape measure, it is ensured that the tape is snug but does not compress the skin and is parallel to the floor. Measurement is made at the end of a normal expiration.

2. Measurement of blood pressure: [39]

Blood pressure was measured using a sphygmomanometer with patient in supine and erect posture. Mean of the two readings was considered.

3. Estimation of Triglycerides: [40]

Enzymatic – Colorimetric Test: (GPO/PAP method)

a. Principle:

Lipoprotein lipase hydrolyses triglycerides to glycerol and free fatty acids. The glycerol formed with ATP in the presence of glycerol kinase forms glycerol 3 phosphate which is oxidized by the enzyme glycerol phosphate oxidase to form hydrogen peroxide. The hydrogen peroxide further reacts with phenolic compound and 4-aminoantupyrine by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly propotional to the amount of triglycerides present in the sample.

Lipoprotein lipase

Triglycerides ----------→ Glycerol + Free fatty acids

Glycerol kinase

Glycerol + ATP ----------→ Glycerol 3 phosphate + ADP

Glycerol 3 phosphate oxidase

Glycerol 3 phosphate + O_2----------→ Dihydoxyacetone phosphate + H_2O_2

Peroxidase

H_2O_2 + 4 Aminoantipyrine + Phenol ----------→ Red Quinoneimine dye + H_2O

b. Contents of triglyceride estimation kit:

L1: Enzyme reagent 1

L2: Enzyme reagent 2

S: Triglycerides Standard (200mg/dl)

Working reagent: Pour the contents of bottle containing L2 (Enzyme Reagent 2) into bottle containing L1 (Enzyme reagent 1).

c. Sample material: Serum or EDTA plasma

d. Procedure:

Wavelength/filter: 505nm/Green

Temperature: 37^0 C / Room temperature

Lightpath: 1cm

Pipette into clean dry test tubes labeled as Blank (B), Standard (S) and Test (T):

Addition sequence	**B(ml)**	**S(ml)**	**T(ml)**
Working reagent	1.0	1.0	1.0
Distilled water	0.01	-	-
Triglycerides Standard (S)	-	0.01	
Sample	-	-	0.01

Mix well and incubate at 37^0C for 5 minutes or at room temperature 25^0C) for 15 minutes. Measure the absorbance of the standard (Abs.S) and test sample (Abs.T) against the blank, within 60 minutes.

e. Calculations:

$$\text{Triglycerides in mg/dl} = \frac{\text{Abs.T}}{\text{Abs.S}} \times 200$$

4. Estimation of total Cholesterol: [40]

CHOD-PAP method:

a. Principle: Cholesterol esterase hydrolyses esterified cholesterols to free cholesterol. The free cholesterol is oxidized to form hydrogen peroxide which further reacts with phenol and 4-aminoantipyrine by the catalytic action of peroxidase to form a red coloured quinoneimine dye complex. Intensity of the colour formed is directly proportional to the amount of cholesterol present in the sample.

Cholesterol Esterase

Choleterol esters + H_2O ----------→ Cholesterol + Fatty acids

Cholesterol oxidase

Cholesterol + O_2 ----------→ Cholestenone + H_2O_2

Peroxidase

H_2O_2 + 4Aminoantipyrine + Phenol ----------→ Red Quinoneimine dye + H_2O

b. Contents:

L1: Cholesterol Reagent

S: Cholesterol Standard (200mg/dl)

c. Sample material: Serum or EDTA plasma

d. Procedure:

Wavelength / Filter: 505nm/Green

Temperature: 37^0C / Room temperature

Lightpath: 1cm

Pipette into dry clean dry test tubes labeled as Blank (B), Standard (S) and Test (T)

Addition sequence	**B(ml)**	**S(ml)**	**T(ml)**
Cholesterol reagent (L1)	1.0	1.0	1.0
Distilled water	0.01	-	-
Cholesterol Standard (S)	-	0.01	
Sample	-	-	0.01

Mix well and incubate at 37^0C for 5 min or at room temperature for 15min. Measure the absorbance of the standard (Abs.S) and Test (Abs.T) against the blank within 60min.

e. Calculation:

$$\text{Cholesterol in mg/dl} = \frac{\text{Abs.T}}{\text{Abs.S}} \times 200$$

5. Estimation of HDL cholesterol: [40]

PEG precipitation method:

a. Principle:

When the serum is reacted with the polyethylene Glycol contained in the precipitating reagent, all the VLDL and LDL are precipitated. The HDL remains in the supernatant and is then assayed as a sample for cholesterol using the Cholesterol (CHOD/PAP) reagent.

b. Contents:

L1: Precipitating reagent.

S: HDL cholesterol standard (25mg/dl)

c. Sample material: Serum or EDTA plasma

d. Procedure:

Precipitation of VLDL & LDL:

Pipette into a clean dry test tube:

Precipitating reagent	0.1ml
Sample	0.1ml

Mix well and incubate at room temperature for 5 minutes. Centrifuge at 2500-3000 rpm to obtain a clear supernatant.

Procedure for the cholesterol assay:

Wavelength/Filter: 505nm/Green

Temperature: 37^0C

Lightpath: 1cm

Pipette into clean dry test tubes labeled as Blank (B), Standard (S) and Test (T).

Addition sequence	**B(ml)**	**S(ml)**	**T(ml)**
Working reagent	1.0	1.0	1.0
Distilled water	0.05	-	-
HDL Standard (S)	-	0.05	
Supernatant	-	-	0.05

Mix well and incubate at 37^0C for 5 min or at room temperature for 15min. Measure the absorbance of the standard (AbsS) and test sample (AbsT) against the blank within 60minutes.

e. Calculation:

$$\text{HDL Cholesterol in mg/dl} = \frac{\text{AbsT}}{\text{AbsS}} \times 25 \times 2$$

(Where 2 is the dilution factor due to the deproteinization step)

Calculation of LDL cholesterol (mg/dl):

(Freidewald Formula)

LDL cholesterol = Total cholesterol – [(Triglycerides /5) + (HDL cholesterol)]

6. Estimation of blood glucose: [40]

Glucose oxidase / Peroxidase method (GOD-POD method):

a. Principle: Glucose oxidase oxidizes the specific substrate, ß – D – glucose, to gluconic acid and hydrogen peroxide is generated. Hydrogen peroxide thus produced is acted upon by peroxidase and oxygen is liberated. The liberated oxygen is transferred to chromogen system consisting of 4-aminoantipyrine and phenolic compound to produce red quinoneimine dye. The intensity of colour is directly proportional to the concentration of glucose and is measured photometrically at 505nm (500-540nm or with green filter).

$$\text{Glucose} + O_2 + H_2O \xrightarrow{\text{Glucose Oxidase}} \text{Gluconate} + H_2O_2$$

$$H_2O_2 + \text{Phenolic compound} + 4 - \text{Aminoantipyrine} \xrightarrow{\text{Peroxidase}} \text{Coloured complex} + H_2O$$

b. Contents of glucose estimation kit:

- 1 Glucose (Enzyme/Chromogen)
- 2 Glucose (Phenol)

- Standard (100mg/dl)
- Reconstitution bottle

Preparation of working reagent:

Transfer the contents of bottle containing 1 glucose (enzyme/chromogen) into the bottle provided for reconstitution. To this add 100ml of contents of bottle labelled as 2 glucose (phenol). Mix well to dissolve.

c. Sample: EDTA plasma.

d. Procedure:

Type of Reaction: End point

Wavelength: 505nm (500-540nm)

Flowcell temperature: 37^0C

Incubation: 5min at 37^0C

Standard Concentration: 100mg/dl

Sample volume: 10 Microlitres (0.01ml)

Working reagent volume: 1.0ml

Lightpath: 1cm

Pipette into test tubes	**Blank**	**Standard**	**Test**
Working reagent (ml)	1.0	1.0	1.0
Standard (ml)	-	0.01	-
Sample (ml)	-	-	0.01

Mix well and incubate for 5 minutes at 37^0C. Mix and read absorbance of standard and test at 505nm (500 – 540nm) or with green filter against reagent blank.

e. Test results:

$$\text{Glucose concentration (mg/dl)} = \frac{\text{Absorbance of Test}}{\text{Absorbance of standard}} \times 100$$

I. Statistical Analysis:

Prevalence of metabolic syndrome was calculated by using rates and ratios and was obtained as percentage of the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents. Effect of variables like age and sex on the metabolic syndrome was analyzed using Chi-Square test with p value ≤ 0.05 being considered significant. Screening tests were evaluated using standard criteria.

RESULTS

A. Prevalence of metabolic syndrome = $\frac{\text{No. of patients with metabolic syndrome}}{\text{Total no. of patients in study sample}} \times 100$

Prevalence of metabolic syndrome = 28/80 × 100

= 35%

B. Prevalence of metabolic syndrome in females = $\frac{\text{No.of females with metabolic syndrome}}{\text{Total no.of females in study sample}} \times 100$

Prevalence of metabolic syndrome in females = 16/43 x 100 = 37.2%

C. Prevalence of metabolic syndrome in males = $\frac{\text{No. of males with metabolic syndrome}}{\text{Total no.of males in study sample}} \times 100$

Prevalence of metabolic syndrome in males = 12/37x100 = 32.43%

D. Table 13: Association between gender and metabolic syndrome using Chi-Square test

P value ≤ 0.05 was considered as significant.

Metabolic syndrome	Females	Males	Total
Absent	27	25	52
Present	16	12	28
Total	43	37	80

The p value by chi-square test is 0.655 (NS) – Not significant.

E. Table 14: Association between age and metabolic syndrome using Chi-Square test

Metabolic syndrome	15-24 years	25-34 years	35-44 years	Above 45 years	Total
Absent	23	14	9	6	52
Present	4	8	6	10	28
Total	27	22	15	16	80

The p value by chi-square test is 0.016 (S) – significant

F. Table 15: Association between age and metabolic syndrome (Corresponding percentages)

Metabolic syndrome	Percentages			
Absent	85.19 %	63.64 %	60.00 %	37.50 %
Present	14.81 %	36.36 %	40.00 %	62.50 %

G. Prevalence of the metabolic syndrome with individual drugs:

1. Prevalence of metabolic syndrome with olanzapine = $\frac{\text{No. of patients on olanzapine with metabolic syndrome}}{\text{Total no. of patients on olanzapine}} \times 100$

Prevalence of metabolic syndrome with olanzapine = 11/44 x 100=25%

2. Prevalence of metabolic syndrome with risperidone = $\frac{\text{No. of patients on risperidone with metabolic syndrome}}{\text{Total no. of patients on risperidone}} \times 100$

Prevalence of metabolic syndrome with risperidone = 12/30 x 100=40%

3.Prevalence of metabolic syndrome with quetiapine = $\frac{\text{No. of patients on quetiapine with metabolic syndrome}}{\text{Total no. of patients on quetiapine}} \times 100$

Prevalence of metabolic syndrome with quetiapine = 5/6 x 100=83.33%

H. Prevalence of the individual components of the metabolic syndrome:

Prevalence of impaired fasting blood glucose: 23.75%

Prevalence of elevated waist circumference: 28.75%

Prevalence of hypertriglyceridemia: 38.75%

Prevalence of low HDL cholesterol: 77.5%

Prevalence of hypertension: 37.5%

I. Prevalence of insulin resistance:

$$\text{Prevalence of insulin resistance} = \frac{\text{No. of patients with insulin resistance}}{\text{Total no. of patients in study sample}} \times 100$$

Prevalence of insulin resistance = 44/80x100 = 55%

Insulin resistance was calculated using serum triglycerides to serum HDL cholesterol ratio.

Insulin resistance is defined as a ratio of serum triglycerides to serum HDL cholesterol ≥3

J. Evaluation of screening methods:

1. Table 16: Evaluation of Serum Triglycerides estimation as a screening method:

Screening test results	**Metabolic Syndrome**		**Total**
	Present	**Absent**	
Positive	18 (a)	13 (b)	31 (a+b)
Negative	10 (c)	39 (d)	49 (c+d)
	28 (a+c)	52 (b+d)	80 (a+b+c+d)

Sensitivity (true positive) = a / (a+c) x 100 = 18/28 x 100 = 64.28%

Specificity (true negative) = d / (b+d) x 100 = 39/52 x 100 = 75%

Positive predictive value = a / (a+b) x 100 = 18/31 x 100 = 58.06%

Negative predictive value = d / (c+d) x 100 = 39/49 x 100 = 79.59%

2. Table 17: Evaluation of Serum HDL cholesterol estimation as a screening method:

Screening test results	Metabolic Syndrome		Total
	Present	Absent	
Positive	25 (a)	37 (b)	62 (a+b)
Negative	3 (c)	15 (d)	18 (c+d)
	28 (a+c)	52 (b+d)	80 (a+b+c+d)

Sensitivity (true positive) = a / (a+c) x 100 = 25/28 x 100 = 89.28%

Specificity (true negative) = d / (b+d) x 100 = 15/52 x 100 = 28.84%

Positive predictive value = a / (a+b) x 100 = 25/62 x 100 = 40.32%

Negative predictive value = d / (c+d) x 100 = 15/18 x 100 = 83.33%

3. Table 18: Evaluation of Serum fasting blood glucose estimation as a screening method:

Screening test results	Metabolic Syndrome		Total
	Present	Absent	
Positive	14 (a)	5 (b)	19 (a+b)
Negative	14 (c)	47 (d)	61 (c+d)
	28 (a+c)	52 (b+d)	80 (a+b+c+d)

Sensitivity (true positive) = a / (a+c) x 100 = 14/28 x 100 = 50%

Specificity (true negative) = d / (b+d) x 100 = 47/52 x 100 = 90.38%

Positive predictive value = a / (a+b) x 100 = 14/19 x 100 = 73.68%

Negative predictive value = d / (c+d) x 100 = 47/61 x 100 = 77.04%

4. Table 19: Evaluation of blood pressure measurement (hypertension) as a screening method:

Screening test results	Metabolic Syndrome		Total
	Present	Absent	
Positive	18 (a)	12 (b)	30 (a+b)
Negative	10 (c)	40 (d)	50 (c+d)
	28 (a+c)	52 (b+d)	80 (a+b+c+d)

Sensitivity (true positive) = a / (a+c) x 100 = 18/28 x 100 = 64.28%

Specificity (true negative) = d / (b+d) x 100 = 40/52 x 100 = 76.92%

Positive predictive value = a / (a+b) x 100 = 18/30 x 100 = 60%

Negative predictive value = d / (c+d) x 100 = 40/50 x 100 = 80%

5. Table 20: Evaluation of measurement of waist circumference as a screening method:

Screening test results	Metabolic Syndrome		Total
	Present	Absent	
Positive	18 (a)	5 (b)	23 (a+b)
Negative	10 (c)	47 (d)	57 (c+d)
	28 (a+c)	52 (b+d)	80 (a+b+c+d)

Sensitivity (true positive) = a / (a+c) x 100 = 18/28 x 100 = 64.28%

Specificity (true negative) = d / (b+d) x 100 = 47/52 x 100 = 90.38%

Positive predictive value = a / (a+b) x 100 = 18/23 x 100 = 78.26%

Negative predictive value = d / (c+d) x 100 = 47/57 x 100 = 82%

DISCUSSION

In the present study a total of 80 patients suffering from schizophrenia and treated with a single second generation antipsychotic (olanzapine, quetiapine or risperidone) for 3 months or more were screened for metabolic syndrome using AHA/NHLBI modified NCEP ATP III criteria.

Prevalence of the metabolic syndrome was found to be 35% which was comparable to previous studies as depicted in the following table:

Table 21: Prevalence of metabolic syndrome from various studies:

Study	**Country**	**Prevalence**
Heiskanen et al [41]	Finland	37%
Almeras et al [42]	Canada	33%
DeHert et al[43]	Belgium	32.3%
Straker et al [38]	USA	28%
Sadichha et al[6]	India	10%
Meyer et al [44]	USA	51.2%
Lamberti et al[45]	USA	53.8%

In the present study prevalence of metabolic syndrome (35%) in schizophrenic patients was found to be higher than in the general population (18.3%) as per the results of a study conducted by Deepa et al on the general population of Chennai.[46] Higher prevalence of metabolic syndrome in schizophrenics could be due to lifestyle factors, aspects of the psychotic disorder and antipsychotic medication.

In the present study prevalence of the metabolic syndrome in females and males was 37.2% and 32.43% respectively though the difference in prevalence was

not statistically significant. The prevalence of metabolic syndrome in females has also been found to be higher in studies conducted by DeHert et al [43] (females – 35.8%; males – 30.5%) and Meyer et al (females-100%; males – 52.7%).[44]

In the present study prevalence of the metabolic syndrome was significantly higher (62.5%) in patients aged 45 years and above as compared to patients of the younger age group in which the prevalence was ranging between 14-40%.

Prevalence of metabolic syndrome with quetiapine, risperidone and olanzapine was 83.33%, 40% and 25% respectively. The individual prevalences cannot be given much significance since the patients were not formally divided into groups considering the cross sectional nature of this study and small sample size.

In the present study impaired fasting blood glucose was found in 23.75% of patients which is higher than in the general population (14.7%) as per the results of the study conducted by Deepa et al on the general population of Chennai.[46] It is also higher than the figure quoted by Sahoo et al who found a prevalence of 15.2% in their group of schizophrenic patients treated with SGAs.[6] A recent systematic review and meta-analysis concluded that all SGAs (excluding aripiprazole, ziprasidone and amisulpride for which there was insufficient data to be included in the analysis) were associated with a 30% increased risk of diabetes as compared to FGAs in people with schizophrenia.[47]

In the present study elevated waist circumference was found in 28.75% of patients which is higher than in the general population in which it was found to be 18.5%.[46] It is significantly higher than the prevalence found in the study done by Sahoo et al in it which was 5.1%.[6] According to a consensus statement issued by the American Diabetes Association along with the American Psychiatric Association and

the North American Association of Clinical Endocrinologists olanzapine and clozapine treatment are associated with the greatest weight gain potential. Risperidone and quetiapine produce intermediate weight gain.[4]

In the present study prevalence of hypertriglyceridemia and low HDL cholesterol was found to be 38.75% and 77.5% respectively. Prevalence of hypertriglyceridemia was comparable to the prevalence quoted by Sahoo et al [6] which was 39.4% but, higher than in the general population which was 25.2%.[46] Prevalence of low HDL cholesterol in the present study (77.5%) was significantly higher than that found by Sahoo et al which was 23.2% and also higher than in the general population which was found to be 63.5%. Melkersson and Dahl have concluded that relative risk for hyperlipidemia is highest for clozapine and olanzapine, moderate for quetiapine and low for risperidone and ziprasidone. [48]

In the present study prevalence of hypertension was 37.5% which was comparable to the results of Sahoo et al [6] who found a prevalence of 36.4% and higher than that of the general population in which it was found to be 31.2%.[46] Very few data support clinically important changes in blood pressure during clinical and observational trials of antipsychotic medications, but study follow – up may not be long enough to capture changes over the long term.[15]

In the present study insulin resistance was detected in 55% of patients. Insulin resistance was calculated using the serum triglycerides to serum HDL ratio. A patient having a ratio of ≥3 was diagnosed to be suffering from insulin resistance.[49] All patients suffering from the metabolic syndrome were found to be insulin resistant by this parameter. It was observed that the number of patients with insulin resistance was 44 as compared to the number of patients with the metabolic syndrome which was 28. In other words, more patients were found to have insulin resistance than metabolic

syndrome. We may therefore hypothesise that, insulin resistance is a precursor of metabolic syndrome. Detection of insulin resistance may predict future predisposition to the development of metabolic syndrome.

The reason that TG: HDL ratio is sensitive to insulin resistance derives from the fact that increased TG levels interfere with an important regulatory function governing the production of apolipoprotein B100 (ApoB100), a core lipoprotein in very low,intermediate and low density lipoprotein particles (39). The overproduction of ApoB100 results in more of these TG-rich particles, with resultant hypertriglyceridemia. In addition, the greater presence of these light TG-rich lipoproteins causes the transfer of TG to high density lipoprotein (HDL) at the expense of HDL cholesterol content. After passage through the liver, where TG is cleaved by enzymatic processes, the remaining HDL particle is smaller than normal and more readily cleared in the kidney, resulting in the characteristic low serum HDL levels seen with insulin-resistant states (39). The TG : HDL ratio thus reflects the combined effects of low HDL and elevated TG seen in insulin-resistant patients.[50]

Among the five criteria used for screening of metabolic syndrome low HDL cholesterol had the highest sensitivity correctly identifying 25 (89.28%) of 28 patients with the metabolic syndrome. Elevated fasting blood glucose and elevated waist circumference were found to have highest and equal specificity with normal values appropriately categorizing 47 (90.38%) of 52 patients without the metabolic syndrome.

Schizophrenic patients are at risk of metabolic syndrome and related metabolic problems, which should not be ignored by clinicians. In particular, in the presence of risk factors such as older age, female gender, long duration of both illness and

treatment, and family history of obesity, clinicians should evaluate the metabolic condition of patients. Recommendations to physicians are:

1. Provide suggestions to increase the level of physical activity and improve patient diet (in collaboration to dieticians).
2. Regularly evaluate blood pressure, waist circumference, and blood biochemical analyses and refer patients to appropriate departments for consultation.
3. Reconsider the use of antipsychotics associated with the risk of metabolic problems.

CONCLUSION

It can be concluded that there is a high prevalence of the metabolic syndrome in schizophrenic patients treated with second generation antipsychotic agents. Increasing awareness of this association among clinicians will help to prevent, detect and treat this condition which is associated with considerable morbidity and mortality.

SUMMARY

In the present study a total of 80 patients suffering from schizophrenia and treated with a single second generation antipsychotic (olanzapine, quetiapine or risperidone) for 3 months or more were screened for metabolic syndrome using AHA/NHLBI modified NCEP -ATP III criteria.

Prevalence of the metabolic syndrome was found to be 35% which was higher than that of the general population. Prevalence of insulin resistance was 55% with all patients suffering from the metabolic syndrome being found to be insulin resistant. It was observed that the number of patients with insulin resistance was 44 as compared to the number of patients with the metabolic syndrome which was 28. Among the five criteria used for screening of the metabolic syndrome low HDL cholesterol had the highest sensitivity. Elevated fasting blood glucose and elevated waist circumference were found to have highest and equal specificity.

There is a high prevalence of the metabolic syndrome in schizophrenic patients treated with second generation antipsychotic agents. Increasing awareness of this association among clinicians will help to prevent, detect and treat this condition which is associated with considerable morbidity and mortality.

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PROFORMA

I. Patient Identification

Name: Age/Sex: I.P.No/O.P.No:

Address: DOA:

DOD/DOE:

Occupation: Religion:

II. History:

Diagnosis:

Duration of illness:

Drug: Dose:

Duration of treatment:

Other treatment:

History of other illnesses:

Diabetes: Hypertension:

Ischaemic heart disease: Stroke:

Cancer: Anorexia nervosa:

Bulimia:

Personal history:

Alcohol dependence:

III. General Physical Examination:

Weight (kg): Waist circumference (cm):

Pallor:

Icterus:

Lymph nodes:

Temperature:

Pulse:

Blood pressure: Supine posture: Erect posture: Mean:

Respiratory rate:

IV. Investigations:

Fasting blood glucose:

Serum triglycerides:

Serum HDL cholesterol:

CONSENT FOR PARTICIPATION IN RESEARCH STUDY

PREVALENCE OF THE METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS RECEIVING SECOND GENERATION ANTIPSYCHOTIC AGENTS – A CROSS SECTIONAL STUDY

Principal Investigator: Dr. _____

Guide: Dr. _____

We are requesting you to be a participant in the above said research at KLES Dr. Prabhakar Kore Hospital and MRC,Belgaum being conducted by Dr. _____, postgraduate student in the department of Pharmacology at J.N.Medical College, Belgaum.

Your participation in this study is voluntary, whether or not to participate will not affect your current or future relationship with the KLES Dr. Prabhakar Kore Hospital and MRC, Belgaum.

Procedure involved:

If you agree to participate in this research you will be asked the relevant history and will be subjected to clinical examination. You will be requested to come in the fasting state the next day and blood will be collected from your arm and will be subjected to biochemical investigations like fasting blood glucose, serum triglycerides and serum HDL cholesterol.

Risks and benefits:

There are no risks involved in this procedure. If any complications arise during the procedure the patients will be treated with the best of our knowledge. There will be no compensation or payment for such medical treatment.

If you attain any complication during the period you may contact Dr._____, Phone No. _____and Dr. _____ Professor, Department of Pharmacology, Phone no._____.

During the course of the study you will be informed of any significant new findings such as changes in the risks and benefits resulting from participation in the research.

Privacy and confidentiality:

The only people who will know that you are a research participant are members of the research team. No information provided by you or about you during the research will be disclosed to others without your written consent. When the results of the research are published or discussed in conferences no information will be disclosed that would disclose your identity. Any information obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission.

Voluntary participation:

Your participation in this study will help us reduce morbidity and mortality due to the metabolic syndrome in schizophrenic patients receiving second generation antipsychotic agents. You are free to discontinue participation in the study at any time for any reasons and will not receive any reimbursement for participation in the research.

If you have any questions about your rights as a research participant you may contact Dr. _____, Principal and Chairman of JNMC Institutional Ethical Committee for Human Subjects Research, Phone No. _____ at J.N.

Medical College, Belgaum. You will be given a copy of this form for your information and to keep for your records.

Statement of Consent:

To voluntarily agree to take part in this study I must sign on the line below. If I choose to take part in this study I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read or it has been read to me this entire consent form including the risks and benefits and had all my questions answered. I will be given a copy of this consent form.

Signature or left thumb print of participant or legally authorized representative.

Participant's Name: Participant's Signature or thumb print:

Experimenter's Name: Experimenter's Signature:

Witness' Name: Witness' Signature:

Guardian's Name: Guardian's Signature or thumb print:

Date: Place:

KEY TO MASTERCHART

S.No: Serial number.

IP/OP number: Inpatient/ Outpatient number.

M: Male

F: Female

Wt (kg): Weight in kilograms.

Waist (cm): Waist in centimeter.

BP (mm Hg): Blood pressure in millimeter of mercury.

FBG (mg/dl): Fasting blood glucose in milligram per deciliter.

S.Total chol (mg/dl): Serum total cholesterol in milligram per deciliter.

S.Tri (mg/dl): Serum triglycerides in milligram per deciliter.

S.HDL (mg/dl): Serum high density lipoprotein cholesterol in milligram per deciliter.

S.LDL (mg/dl): Serum low density lipoprotein cholesterol in milligram per deciliter.

MetS: Metabolic syndrome.

P: Present

MASTER CHART

S.No	IP/OP number	Age (years)	Sex	Wt (kg)	Waist (cm)	BP (mm Hg)	FBG (mg/dl)	S.Total chol (mg/dl)	S.Tri (mg/dl)	S.HDL (mg/dl)	S.LDL (mg/dl)	MetS
1	933567	19	M	67	79.5	118/70	93	173	149	40	103	
2	1003653	37	F	58	87.5	120/80	87	174	77	46	113	
3	806914	18	F	47	65	122/80	103	138	102	39	79	
4	1008697	24	F	46	74.5	110/70	118	141	234	42	52	P
5	1041722	35	M	71	92.5	146/110	86	155	97	44	92	P
6	630231	60	F	68	96	140/86	88	176	100	38	118	P
7	0307224	18	F	35	63	146/90	89	116	114	42	51	
8	793792	22	F	37	64.5	120/70	103	211	98	44	147	
9	975246	22	M	41	67.5	110/90	98	136	100	34	82	
10	1012189	27	M	73	87.5	120/76	109	211	160	37	142	P
11	586334	24	M	42	72.5	90/70	97	91	135	29	35	
12	998793	26	M	73	91	114/80	92	165	190	30	97	P
13	631611	38	M	80	96	120/80	91	204	305	32	111	P
14	711687	18	M	40	63	130/80	88	98	109	28	48	
15	0313032	18	M	45	64.5	120/80	71	145	329	37	42	
16	737510	29	F	54	76	100/70	87	135	110	35	78	
17	583917	18	F	59	73.5	110/70	83	115	114	35	57	
18	0321861	21	F	39	62.5	120/80	116	125	254	35	39	P
19	788531	50	M	65	100.5	140/100	127	172	154	41	100	P
20	590869	50	F	59	93.5	130/80	102	162	244	34	79	P
21	117620	50	F	60	85.5	106/80	89	159	100	42	97	
22	585625	36	F	72	93.5	150/100	90	160	114	36	101	P
23	1025556	29	M	69	86	130/70	104	84	169	28	22	P
24	1059360	47	M	53	89.5	120/80	95	257	310	45	150	

25	590311	35	F	37	63	110/70	89	128	98	21	87	
26	671662	24	F	40	57.5	114/80	89	124	92	37	69	
27	579166	25	F	60	75	110/70	87	107	68	37	56	
28	749442	68	M	48	72	140/88	117	149	102	35	94	P
29	1054437	18	F	58	76.5	120/80	106	113	202	31	42	P
30	0326230	32	F	75	90	130/84	106	194	140	44	122	P
31	592079	28	F	56	73.5	120/70	93	175	216	38	94	
32	608547	26	F	46	74.5	120/70	93	134	205	38	55	
33	1033269	26	M	46	75	130/70	94	101	97	37	54	
34	1032869	35	F	65	89.5	110/70	96	182	155	40	111	P
35	968465	38	F	58	72	120/80	89	197	125	40	132	
36	327235	18	F	50	65	114/70	87	198	117	34	141	
37	976650	19	F	60	78	140/90	89	177	112	39	116	
38	1080831	20	M	49	65	120/80	90	120	90	36	66	
39	749429	20	M	45	63.5	130/84	85	110	115	39	48	
40	757878	48	F	55	83.5	130/90	76	168	103	40	107	P
41	594650	32	M	56	81.5	130/80	71	164	165	34	97	P
42	734293	50	M	73	90	130/80	97	199	266	36	110	P
43	582120	35	M	60	84.5	110/90	83	197	159	38	127	P
44	1153251	25	M	100	110	150/100	100	220	164	40	147	P
45	858239	20	M	44	65	110/70	95	184	79	50	118	
46	583904	44	F	56	85	124/90	90	197	129	47	124	P
47	590938	31	F	70	87	130/90	117	108	72	40	54	P
48	115312	40	F	50	80	126/82	92	193	123	46	122	
49	820980	47	M	49	81.5	120/70	118	204	209	43	119	
50	608609	20	M	55	83	120/70	80	108	62	44	52	
51	333710	56	M	61	94.5	124/80	171	164	159	39	93	P
52	1122068	20	F	41.5	71.5	104/60	94	167	175	42	94	

53	890055	29	F	57	85	120/90	94	178	106	45	112	
54	341895	26	F	43	64.5	104/70	88	132	81	45	71	
55	1138879	32	M	61.5	81	110/70	95	233	204	41	151	
56	344363	40	M	53	81	130/80	83	176	165	40	103	
57	344987	42	M	48	85	104/70	90	181	95	50	112	
58	348930	22	M	70	95	120/80	89	211	211	43	126	
59	351352	46	M	63	80	140/90	93	188	135	48	113	
60	351565	46	F	60	87.5	120/80	107	105	74	32	58	P
61	354953	19	F	42	62	110/70	74	129	37	48	74	
62	352241	18	F	48	66.5	130/90	81	146	91	42	86	
63	352461	28	M	64	88	130/96	80	187	149	41	116	
64	353095	38	F	55	76	110/70	85	201	122	29	148	
65	352999	22	M	50	69	140/100	75	197	156	38	128	
66	353090	22	F	42	69.5	110/80	79	159	177	39	85	P
67	354642	47	M	42	67.5	110/70	102	147	134	41	79	
68	355618	22	M	52.5	72.5	90/60	89	192	261	39	101	
69	357313	28	M	52	69.5	120/80	81	114	125	35	54	
70	1218117	45	F	38	59	130/90	88	209	240	40	121	P
71	362608	29	M	67	82.5	110/60	90	127	159	28	67	
72	363050	26	M	53	72	120/80	100	75	71	28	33	
73	359060	40	F	32	55.5	116/70	91	165	116	51	91	
74	358474	30	F	40	63	100/76	81	148	87	67	64	
75	359615	46	F	40	61	120/80	76	195	256	37	107	
76	370209	38	F	50	66	126/80	44	149	119	49	76	
77	370592	34	F	32	57	110/80	86	137	87	38	82	
78	370650	33	F	70	89.5	120/86	89	181	278	41	85	P
79	372313	50	F	60	83	136/86	109	190	117	38	129	P
80	371808	22	M	60	76.5	120/80	89	153	103	40	92	

ETHICAL CLEARANCE CERTIFICATE

K.L.E.SOCIETY'S
JAWAHARLAL NEHRU MEDICAL COLLEGE,
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Date: 7/10/2008

To,

Dr.
Postgraduate student in
Department of Pharmacology,
J.N.Medical College,
Belgaum.

Dear Dr.

The JNMC – Institutional Ethics Committee on Human Subjects Research met on 6th October, 2008 to consider your application for approval of the research project "**PREVALENCE OF THE METABOLIC SYNDROME IN SCHIZOPHRENIC PATIENTS RECEIVING SECOND GENERATION ANTIPSYCHOTIC AGENTS-A CROSS SECTIONAL STUDY**".

After review of the documents submitted by you and satisfactory explanations provided to the members, the committee has provided approval date through October 5th, 2009 at which time the study will be reviewed by the committee.

If you have any questions concerning the above, please feel free to contact the committee office.

Sincerely,

(Dr.V.D.Patil)
Chairman,
JNMC Institutional Ethics Committee on
Human Subjects Research