ORIGINAL ARTICLE

# Metabolic Disturbances in Schizophrenia Patients With Positive, Negative and Cognitive Symptoms

**P. Uma Devi, S Murugam**

## Abstract

Elevated cholesterol, triglycerides and glucose are known independent risk factors for coronary heart disease. This study examines the status of cholesterol, triglycerides and glucose of schizophrenia patients with positive, negative and cognitive symptoms and to investigate the association between these levels and obesity. This was a prospective observational study involving samples of patients who met established criteria for schizophrenia and were admitted to the mental health care center, Coimbatore. Glucose, total cholesterol and triglycerides levels increased when schizophrenia patients are treated with anti-psychotic drugs. Although mean changes in glucose and cholesterol levels remained within clinically normal ranges, about one patient in eight studied developed abnormally high glucose, and also one in five patients assessed has abnormal cholesterol levels. The obesity and metabolic disorders observed in the patients were higher than the prevalence in the control group and confirms that there are deregulations of metabolic pathways in schizophrenic patients. The rate of obesity and metabolic disorders observed in this study were higher than the prevalence in the control group sugesting that more attention should be paid to the metabolic condition of psychiatric patients.

**Key Words**

Schizophrenia, Metabolic Disturbances, Lipid

## Introduction

Schizophrenia is a syndrome causing a major public health problem. It usually begins early in adult life, its prognosis is often poor and it causes excess morbidity and mortality, as well as extensive negative personal, familial, social, occupational and educational consequences. Life expectancy is approximately 20% shorter than that of the general population (1).The symptoms of schizophrenia fall into three broad categories: Positive, negative and cognitive symptoms (2). A metaanalysis concludes that 60% of the excess mortality in patients with schizophrenia is attributable to physical illness. The causes of death comprise a broad range of conditions, similar to the general population, but schizophrenic patients die at a younger age. Mortality from cardiovascular disease is increased in both men and women with schizophrenia. The greatest research need at the moment seems to be identification of specific risk factors for the excess mortality among schizophrenic patients (3). The rates of cardiovascular events and new onset diabetes are higher than expected in patients with schizophrenia. The major risk factors for cardiovascular disease include obesity, dyslipidemia, hypertension and hyperglycemia. These risk factors are key elements defining the metabolic syndrome (4).The heightened health risks associated with schizophrenia and the medications used in its treatment, together with the belief that the health needs of people with schizophrenia who take antipsychotic medications are typically not adequately addressed so far. So the present study was undertaken with the purpose to assess and compare the change in weight and glucose and lipid metabolism disturbances in schizophrenia patients.

## Materials and Methods

***Patient Groups:*** A total of 60 schizophrenic patients of age group 18-65 years of both sexes from good socioeconomic background were selected from Udhayam Mananala Kaapagam, a mental health care center in Coimbatore, Tamilnadu, India. The patients were divided

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into three groups with twenty patients in each group: schizophrenics with positive symptoms, schizophrenics with negative symptoms, and schizophrenics with cognitive symptoms. They all met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders-IV) criteria (American Psychiatric Association, 2000) (5) for schizophrenia. Patients with different symptoms have different medications based on their severity.Patients having an evidence of 1) organic brain damage, mental retardation, alcohol or drug abuse, 2) impairment of renal function, 3) hepatic dysfunction, 4) a history of pancreatitis, 4) suicide attempt in past year, 5) cataracts, 6) pregnant women or a woman who intends to become pregnant were excluded from the study.

***Reference Groups***: Sixty age and sex-matched healthy normal control subjects with no individual and familial history of mental illness or antipsychotic treatment were recruited to participate in this study. They included 30 males and 30 females with their ages ranged from 15 to 65 years. Both patients and controls were recruited during the same period from Coimbatore district. Matching between the patients and controls was done according to sex, age and patients are currently free of smoking, alcohol intake and have uniform dietary habits. The participants were asked to fast overnight before coming to clinical examination, where their weight, height, waist circumference and blood pressure were measured, Body Mass Index (BMI) was calculated and blood samples were taken. Fasting plasma glucose, cholesterol and triglyceride levels were estimated. BMI was also measured for the selected groups. Waist circumference was measured at the level midway between the lowest rib margin and the iliac crest. In men waist circumference 100 cm and under was defined as normal, over 100 cm as obese, and in women 90 cm was defined as cut-off point. The clinical charts prepared for patients and control subjects to know whether they are overweight or obese or not. Thus, it was known from the clinical charts that none of the subjects in the reference group was overweight or obese.

***Ethical Considerations***: The project was approved from the board of institutional review Committee. Informed and written consent was obtained from all subjects.

***Blood Sampling and Determination of Plasma Constituents***: Assessments for the present analyses included fasting blood samples for glucose, cholesterol and triglycerides. The metabolic fasting sample was drawn between 8 and 10 a.m. after at least 8 hours' fasting, before medication administration. Plasma glucose, cholesterol and triglyceride levels were determined by enzymatic procedure applying the Roche/Hitachi Modular D-P automated chemistry analyzer 112 and using the standard analytical system packs Glucose / God-pap, Cholesterol / CHOD cod-pap and Triglycerides / GPO-pap. Weight, height and BMI were determined. Body Mass Index was computed as body weight (kg) divided by the square of height ($m^2$). Height and weight for each patient in the study group were measured at the time of blood examination.

**Statistical Analysis**

Analysis of variance (ANOVA) were used to examine the differences among the treatment groups and reference groups in mean glycaemia and cholesterolaemia levels and to compare mean BMI levels among treatment groups. Since triglyceride levels were not normally distributed, median trigliceridaemia levels were compared among groups.

**Results**

Results in (*Table1* and *Figure1*) shows a significant increase in glucose, total cholesterol and triglycerides levels in all the study groups compared to the control group ($p<0.01$). Plasma glucose and triglycerides were increased more significantly in schizophrenics with cognitive type ($p<0.01$) when compared to positive and negative types. There is no statistically significant differences were found in glucose and cholesterol levels between schizophrenics with positive and negative symptoms. In the current study, the mean BMI values were over the clinical threshold of overweight in all groups and over the clinical threshold of obesity in the negative group were observed. BMI mean values differed among groups ($p = 0.001$) and results revealed that patients with negative symptoms had a significantly higher BMI (*Figure 2*). Since the risk of disturbances to both the glucose and the lipid metabolism and the risk of weight gain appear to be increased by all antipsychotic treatments and hard to differentiate among the various symptoms of schizophrenia, according to the international consensus conferences (6), and also based on the suggestions of Illaria *et al* (7), it is advisable that the periodical monitoring of weight, fasting plasma glucose cholesterol and triglyceride levels should be performed in routine clinical practice with all antipsychotics.

**Discussion**

Psychiatry is constantly faced with challenges related to the medical status of its patients and the co morbid effects of the pharmacologic treatment of psychiatric disorders (8) of the severe mental disorders, particularly schizophrenia results in incapacity to work, impairs the quality of life, and is associated with a substantially high

*Table 1. Levels of plasma Glucose, Total Cholesterol, Triglycerides & BMI in Schizophrenia patients & Healthy controls*

| Biochemical Constituents | Schizophrenia Patients | | | Control |
|---|---|---|---|---|
| | Positive Symptoms | Negative Symptoms | Cognitive Symptoms | |
| Glucose ( mg\dl ) | 118.28 ± 9.87d | 116.39 ± 10.07c | 123.86 ± 14.09b | 89.15 ± 6.49a |
| Total Cholesterol ( mg\dl ) | 241.95 ± 42.24dc | 243.21 ± 41.64c | 249.75 ± 41.64bc | 153.03 ± 9.94a |
| Triglycerides ( mg\dl ) | 162.15 ± 7.10dc | 166.90 ± 6.18c | 201.45 ± 11.89b | 136.20 ± 5.18a |
| BMI ($kg\backslash m^3$ ) | 23.14 ± 2.7a | 28.60 ± 1.9cb | 27.06 ± 2.3b | 23.83 ± 2.4a |

*Values are expressed by mean ± SD, n = 20*
*a ( statistical significance compared to control group)*
*b (statistical difference between positive and negative group)*
*c (statistical difference between positive and cognitive group)*
*d (statistical difference between negative and cognitive group)*

***Fig 1. Metabolic Profile of Schizophrenia Patients with Different Symptoms and Healthy Control Subjects***

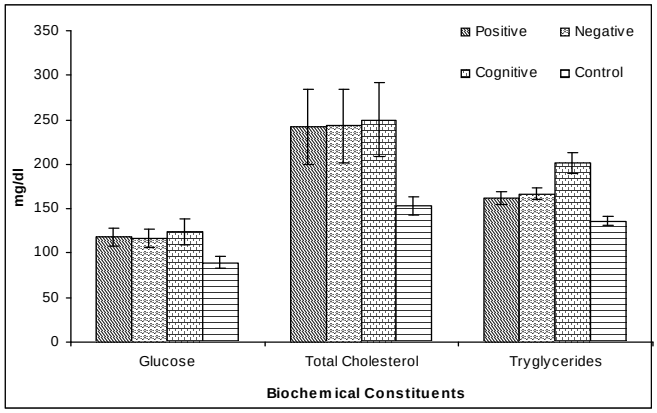
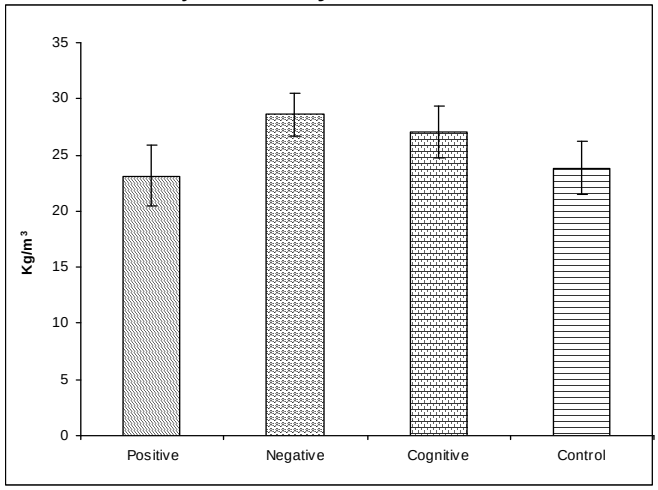



***Fig 2. BMI of Schizophrenia Patients with Different Symptoms and Healthy Control Subjects***




mortality rate from suicide even at a relatively young age (9). The primary findings of the present study are that all groups had a poorer metabolic profile – in particular, a significantly higher mean glycaemia than were noticed in all patient groups compared with the control groups. While intra - group comparison was made, no profound differences in mean glycaemia levels among the positive and negative groups were found, but persons with cognitive symptomology were showing statistically more significant increase in glucose levels. It was also observed from this study that 40 % percent of the studied patient population, without a previous history of diabetes, had newly diagnosed disturbances of glucose metabolism (IGT or type 2 diabetes). The prevalence of diabetes in schizophrenia patients was much higher than the prevalence of diabetes in the general population. In the current study, although fasting glucose concentrations did not differ between the study groups, there was a significant difference in glucose concentrations with the highest value demonstrated in patients with cognitive symptoms ($p<0.01$). Literature says that the patients with schizophrenia are more at risk for abnormal glucose than matched controls (10). In the present study, 40% of the schizophrenia patients or subjects had fasting glucose higher than or equal to 114 mg/dl. There are several theories for cognitive impairment in individuals with diabetes. Some pathways by which diabetes can affect cognition involve glucose or insulin metabolism or the formation of advanced glycation end products. Increases or decreases in glucose concentrations can affect cognitive function. Some studies have found an association between chronically elevated glucose levels and poor performance on cognitive tests. Higher fasting insulin levels in older adults with IGT and higher serum insulin concentrations after a 2-hour glucose challenge in women without diabetes were associated with poorer performance on the mini mental score evaluation (MMSE) (11).The mechanism for the elevation in lipid levels is somewhat obscure, but it has been previously attributed to weight gain associated with the use of antipsychotic medication. Accumulation of fat in the waist enhances the release of free fatty acids in the liver and accelerates liver triglyceride synthesis and very-low-density lipoprotein secretion. Increases in free fatty acid concentrations may also inhibit metabolism of glucose, especially in muscle tissue, resulting in impaired glucose tolerance and type-2 diabetes (National Heart, Lung and Blood Institute 2001) (11). It has been postulated that changes in lipid levels may be related to the 3-ring structure of the dibenzodiazepine-derived compounds.

This structure is conformationally similar to the phenothiazide nucleus, which has a known propensity to increase serum triglyceride levels (12). In order to study the lipid concentrations and the risk of hyperlipidemia in the study subjects using antipsychotic medication regularly, the levels of total cholesterol and triglycerides were assessed in this study. Hypercholesterolemia was determined as TC = 240 mg/dL, hypertriglyceridemia as TG = 200 mg/dl (13). Results of the present study in table 1 indicated that mean TC and TG were significantly higher in the schizophrenia group than in the comparison groups. The raised levels of triglycerides are statistically significant in patients with cognitive symptoms. The difference between the levels of triglycerides in positive and negative symptoms is not significant.Dyslipidemia, especially elevated triglyceride level has been associated with cognitive impairment in patients with or without diabetes (14). Hypertension, independent of diabetes, has been reported to be a predictor of poor cognitive test performance. This effect may in part be due to increased risk of cerebrovascular disease with hypertension (15). Since diabetes coexists with dyslipidemia, hyperinsulinemia, and hypertension, several of these mechanisms could be operating in concert to produce impaired cognition. Both the metabolism of glucose and lipids are interconnected. There is reason to believe that oxidation of low-density lipoprotein cholesterol (LDL-C) plays an important part in atherogenesis and CVD (16, 17).

A meta-analysis showed that a 10% change in the concentration of plasma TC is associated with a 10% decrease of the odds of death. The effect of high plasma TG concentration on atherosclerosis and its complications is more controversial, with some data supporting the role of plasma TG level as an independent risk factor. The higher total cholesterol level could mainly be due to higher LDL cholesterol. This is in accordance with the findings in many epidemiological studies. LDL cholesterol in turn may get increased by elevated glucose or impaired glucose levels (18). Koponen (19) recommended it for monitoring and documenting in patient charts the effects of antipsychotic medication on patient's weight and metabolism. Koponen also recommended monitoring weight and body mass index or waist circumference and blood pressure during every visit. He also recommended determination of blood glucose, triglyceride, cholesterol and prolactin levels once or twice a year, or more often (e.g. every three months) in high-risk patients. Furthermore, he recommended that the patient should keep a food record in case of weight gain of more than 4 kg since the beginning of treatment. In case of a weight increase of over 7% compared to the weight when starting treatment a consultation with a dietician or nutritionist, caloric restriction and more effective physical exercise should be carried out.

Abnormal metabolic levels and BMI were defined in our study on the basis of the National Cholesterol Education Program (NCEP) (20) and World Health Organization (WHO) (21) criteria. In the current study, it was found that the BMI of negative and cognitive patients are significantly high when compared with the control subjects. Among the selected patients, 38% of the patients are over weight and 12 percent of patients were obese.Individuals with schizophrenia are as obese as or more obese than individuals without schizophrenia. As described earlier, antipsychotics are associated with weight gain and elevated lipid and glucose values. Obesity and weight gain have been associated with type II diabetes (21), hypercholesterolemia and hypertriglyceridemia. Hypercholesterolemia is a well-known risk factor for coronary heart disease. The effect of high plasma TG concentration on atherosclerosis and its complications is more controversial than the effect of TC. However, a gradient of risk of ischemic heart disease is associated with increasing TG levels, also after controlling for the other major risk factors of ischemic heart disease (22).

Some interventions for managing weight gain associated with atypical antipsychotics have been studied (23), but further studies of interventions and their effectiveness are needed. There is currently very limited evidence available that behavioral interventions actually work in overweight patients treated with antipsycotics (24). The characteristics of schizophrenia sufferers mean that weight management will be even more difficult to achieve than in populations without mental health difficulties. The high prevalence of this syndrome in schizophrenia underscores the need to develop comprehensive efforts directed at controlling weight and improving physical activity as well as the importance of selecting antipsychotic medications with no or little capability to induce metabolic side effects. Based on the present findings, it was revealed that schizophrenia patients with cognitive symptomology are facing more metabolic disturbances. The rate of obesity and metabolic disorders observed in the current independent study was higher than the prevalence in our control group and in the general population as reported by epidemiological studies. Furthermore this result is consistent with the prevalence found in extensive studies of psychiatric samples. These findings implied *per se* that more attention should be paid

to the metabolic condition of the psychiatric patients. Particular efforts should be made to implement counselling about patients' lifestyles and behaviours, which could potentially limit the antipsychotic metabolic side effects as rightly pointed out by Faulkner *et al* (25).

## Conclusion

In a society in which cardiovascular disease continues to be a principal cause of morbidity and mortality, clinicians need to be aware of the metabolic risk factors when treating patients with schizophrenia.

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