Prevalence of diabetes, obesity, and metabolic syndrome in subjects with and without schizophrenia (CURES-104)

Subashini R, Deepa M, Padmavati R¹, Thara R¹, Mohan V

ABSTRACT

Background: There are some reports that diabetes and metabolic syndrome (MS) are more prevalent among schizophrenia patients. However, there are very few studies in India which have estimated the prevalence of diabetes and MS in schizophrenia patients. Aims: The aim of this study was to determine the prevalence of diabetes, obesity, and MS in subjects with and without schizophrenia. Settings and Design: This case control study comprised of “cases” i.e. subjects with schizophrenia recruited from a schizophrenia centre at Chennai and “controls” i.e. healthy age- and gender-matched subjects without psychiatric illness selected from an ongoing epidemiological study in Chennai in a 1:4 ratio of cases: Controls. Materials and Methods: Fasting plasma glucose and serum lipids were estimated for all subjects. Anthropometric measures including height, weight, and waist circumference were assessed. Diabetes and impaired fasting glucose (IFG) were defined using American Diabetes Association criteria. Statistical analysis: One-way ANOVA or student’s “t” test was used to compare continuous variables and Chi-square test to compare proportion between two groups. Results: The study group comprised of 655 subjects, 131 with schizophrenia and a control group of 524 subjects without schizophrenia. The prevalence of the diabetes, IFG, abdominal obesity and MS were significantly higher among subjects with schizophrenia compared to those without schizophrenia–diabetes (15.3% vs. 7.3%, (0.003), IFG (31.3% vs. 8.6%, (0.001), abdominal obesity (59.2% vs. 44.7%, (0.001), and MS (34.4% vs. 24%, (0.014). Conclusion: In subjects with schizophrenia, the prevalence of diabetes, IFG, abdominal obesity, and MS is significantly higher than in those without schizophrenia.

KEY WORDS: Impaired fasting glucose, metabolic syndrome, obesity, schizophrenia, south India, type 2 diabetes

Introduction

The prevalence of type 2 diabetes is rising globally and according to the International Diabetes Federation (IDF), in 2010, India had 50.8 million people with diabetes and this number is set to increase to 87 million by the year 2030 (Diabetes Atlas, 2009).¹ Earlier studies have reported that Asian Indians have certain unique clinical and biochemical characteristics that are collectively referred to as the “Asian Indian Phenotype” which confers an increased susceptibility to diabetes² and premature cardiovascular disease.³

Earlier studies have shown that schizophrenia subjects have higher rates of impaired glucose tolerance and diabetes than the general population.⁴ Some global studies have reported on the prevalence of MS in subjects with schizophrenia.⁶ However, there is only one study on the prevalence of MS among subjects with schizophrenia in the Indian population and a figure of 37.8% was quoted in that study.⁸ The prevalence of MS in schizophrenia subjects is reported to be two to four times higher than in the general population.⁹ Estimates of the prevalence of MS and diabetes among schizophrenia subjects could provide vital data for planning appropriate care services. Moreover, a recent study reports that subjects with schizophrenia have limited access to general health care and less opportunity for cardiovascular risk screening.¹⁰ Hence, the present study was undertaken with the objective of estimating the prevalence of diabetes, impaired fasting glucose, obesity, and MS among subjects with schizophrenia.
**Materials and Methods**

In this case control study, the cases are subjects with schizophrenia (aged ≥20 years) diagnosed as having schizophrenia as per ICD-10 diagnosis and recruited from a schizophrenia care center in Chennai. This is a non-governmental organization involved in the care and rehabilitation of persons with serious mental illnesses. All subjects were requested to be on at least 8 h overnight fast by the clinic nurse.

To match for the cases, age- and sex-matched healthy controls (adults aged ≥20 years) (without psychiatric illness) were recruited from the Chennai Urban Rural Epidemiology Study (CURES), one of the largest epidemiological studies on diabetes carried out in India. From a total of 155 Corporation wards in Chennai, 46 wards were randomly selected for CURES. The detailed study design is described in previous publications.[11-15]

Briefly, in Phase 1 of the urban component of CURES, 26,001 individuals were recruited based on a systematic sampling technique. Phase 2 of CURES deals with studies of the prevalence of microvascular and macrovascular complications of diabetes among those identified with diabetes in Phase 1. In Phase 3 of CURES, every tenth subject recruited in Phase 1 (n = 2,600) was invited to the centre for detailed anthropometric measurements and biochemical tests. Of these, 2,350 participated in the study (response rate: 90.4%). The control subjects, defined as those who had no history of psychiatric illness, were randomly selected from Phase 3 of CURES and were age and sex matched in the ratio, 1:4 (cases: Controls). The study was conducted between December 2004 and January 2005.

A structured questionnaire was administered to the subjects to collect information on medical history and anthropometric measurements, which included height, weight, waist, and hip circumferences were taken using standard techniques as described in the definition section.[11] Blood samples were collected between 7 and 8 am, after ensuring at least 8 h of overnight fasting, for estimating fasting plasma glucose and lipids. The samples were immediately transferred to the central laboratory where they were analyzed. Plasma glucose and serum lipids were estimated using a Hitachi 912 Auto analyser (Mannheim, Germany) utilizing kits supplied by Roche Diagnostics GmbH (Mannheim, Germany).

**Measurements and definitions**

Height was measured with a tape to the nearest 0.1 cm. Subjects were requested to stand upright without shoes with their back against the wall, heels together, and eyes directed forward. Weight was measured with a spring balance that was kept on a firm horizontal surface. Subjects wore light clothing, stood upright without shoes and weight was recorded to the nearest 0.5 kg. Body mass index (BMI) was calculated as body weight in kilogram divided by the height in meter (kg/m²).

Waist circumference was measured using a non-stretchable fiber measuring tape. The subjects were asked to stand erect in a relaxed position with both feet together on a flat surface. Waist circumference was measured as the smallest horizontal girth between the costal margins and the iliac crests. Two measurements were made and the mean of the two was taken as the waist circumference.

Hip circumference was taken as the greatest circumference at the level of greater trochanters (the widest portion of the hip) on both sides. Two measurements were made and the mean of the two was taken as the hip circumference.

Blood pressure was recorded in the sitting position in the right arm to the nearest 2 mmHg using the mercury sphygmomanometer (Diamond Deluxe BP apparatus, Pune, India). Two readings were taken 5 min apart and the mean of the two was taken as blood pressure.

**Diabetes**

American Diabetes Association guidelines[14] were used to establish the diagnosis of diabetes (Fasting glucose levels ≥126 mg/dl).

**Impaired fasting glucose**

Impaired fasting glucose (IFG) was diagnosed if fasting plasma glucose ≥100 mg/dl to 125 mg/dl based on ADA guidelines.[14]

**Metabolic syndrome**

MS was diagnosed using the IDF criteria.[15] Abdominal obesity plus two or more of the following risk factors: Waist circumference ≥90 cm in men and ≥80 cm in women; fasting plasma glucose (FPG) ≥100 mg/dl; blood pressure ≥130/85 mm/Hg; serum triglycerides ≥150 mg/dl, serum HDL cholesterol <40 mg/dl in men and, <50 mg/dl in women.

**Typical and atypical antipsychotic drugs**

Typical antipsychotics (sometimes referred to as conventional antipsychotics or conventional neuroleptics) are a class of antipsychotic drugs first developed in the 1950s and used to treat psychosis (in particular, schizophrenia), and are generally being replaced by atypical antipsychotic drugs. First generation antipsychotic (FGA) acts by blocking D2 receptors. This action in the mesolimbic receptors is responsible for the antipsychotic efficacy of this group of drugs. However, these drugs also block Dopamine receptors in mesocortical regions (causing worsening of negative and cognitive symptoms); nigrostriatal pathway (causing extrapyramidal side effects), and the tuberoinfundibular regions (causing prolactinemia). Examples of typical antipsychotics are haloperidol, trifluperazine, and chlorpromazine.

Atypical antipsychotics (also known as second generation antipsychotics) are a class of prescription medications used to treat psychiatric conditions. The atypicality of the second-generation antipsychotics (SGA) is attributed to the coupling of D2 antagonism with Serotonin 2A antagonism. All atypical antipsychotics are FDA approved for use in the treatment of schizophrenia. Examples of atypical antipsychotics are clozapine, rispridone, and olanzapine.
Statistical analysis
Statistical analysis was performed using SAS 9.2. One-way ANOVA or student’s “t” test was used to compare groups for continuous variables and Chi-square test was used to compare proportion between two groups. Values are expressed as mean±SD. P values of <0.05 were considered as the level of significance.

Ethical approval
Institutional ethical committee approval was obtained and written informed consent was also obtained from all study subjects prior to the study. Confidentiality of both subjects and physician-related information was ensured.

Results
One hundred and thirty-four schizophrenia subjects were recruited. Of these, three physically ill patients were excluded from the study as they were unable to participate. Thus, 131 subjects with schizophrenia (male n=68, female n=63) were finally included in this study. The controls comprised of 524 subjects (male n=272, female n=252) recruited from the CURES study.

Table 1 reports on the clinical characteristics of the two groups. The mean age of the study population was 44±12 years (range 20–80 years) and 51.9% were males. The BMI was significantly higher in subjects with schizophrenia as compared to those without schizophrenia (23.6±4.8 kg/m² vs. 23.0±3.7 kg/m², P=0.042). Subjects with schizophrenia also had higher waist circumference (males: 87.0±12.3 cm vs. 83.1±10.8 cm, P=0.015 and females: 88.8±11.7 cm vs. 82.8±11.0 cm, P<0.001), higher hip circumference (in females) (95.7±13.4 cm vs. 92.3±8.7 cm, P=0.018) and higher fasting plasma glucose (105±32 mg/dl vs. 92±31 mg/dl, P<0.001) compared to the respective subjects without schizophrenia.

The prevalence of diabetes and impaired fasting glucose among subjects with and without schizophrenia is presented in Table 2. The prevalence of impaired fasting glucose using ADA criteria was 31.3% in subjects with schizophrenia and 8.6% in subjects without schizophrenia (P<0.001). Self-reported diabetes was not significantly different between the groups. However, newly diagnosed diabetes (fasting ≥126 mg/dl) was 9.9% and 3.8% respectively among subjects with and without schizophrenia (P<0.001). The overall prevalence of diabetes was 15.3% among subjects with schizophrenia and 7.3% in those without schizophrenia (P=0.003). All schizophrenia subjects were receiving antipsychotic medications. This included 11.5% (n=15) who were on typical antipsychotics, 60% (n=78) on atypical antipsychotics and 28.5% (n=37) on both typical and atypical antipsychotics [Table 3]. The subjects on atypical antipsychotics showed a higher frequency of diabetes, impaired fasting glucose, abdominal obesity, and metabolic syndrome, compared to those who were receiving only typical antipsychotics or a combination of typical and atypical antipsychotics. The differences however did not reach statistical significance.

Figure 1 shows that the prevalence of abdominal obesity was higher among subjects with schizophrenia compared to those without (59.2% (n=74) vs. 44.7% (n=234), P<0.001).

The prevalence of metabolic syndrome in subjects with and without schizophrenia is shown in Figure 2. Among subjects with schizophrenia, the prevalence of MS was 34.4% (n=43), while among those without schizophrenia, it was 24.0% (n=126) (P=0.014).

Discussion
Very few studies have been conducted so far on Indian subjects with schizophrenia in relation to the prevalence of diabetes and MS. This study makes the following points: (i) the prevalence of diabetes and IFG, as well as abdominal obesity and MS are significantly higher in subjects with schizophrenia compared to those without; (ii) subjects with schizophrenia treated with atypical medications had relatively higher rates of cardio-metabolic risk factors when compared to those on typical medications although the differences did not reach statistical significance.

Screening for cardio-metabolic risk factors among subjects with schizophrenia poses several challenges. Earlier studies have observed that even when subjects with schizophrenia consent to participate in diabetes screening studies, many investigators struggle to successfully complete the oral glucose tolerance
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Testing or even to obtain fasting blood glucose levels. This can lead to high study drop-out rates, or use of less reliable indicators of diabetes such as non-fasting blood glucose levels. There is one study in a drug-naïve population that has used OGTT in 50 patients. In the present study, we could not perform OGTT due to unwillingness of the subjects with schizophrenia; hence, prevalence rates were estimated using the ADA fasting plasma glucose criteria.

According to the Chennai Urban Rural Epidemiology Study (CURES), the prevalence of diabetes (in the age group of the control group studied) in the general population of Chennai was 7.3%, while that of impaired fasting glucose was 8.6%. The prevalence of diabetes (15.3%) and impaired fasting glucose (31.3%) was higher among subjects with schizophrenia compared to the control subjects (CURES) which suggests that the prevalence of dysglycemia is much higher among schizophrenia patients.

A study from Singapore reported a diabetes prevalence of 30.9% while impaired glucose tolerance was reported in 16% among subjects with schizophrenia. The Patient Outcomes Research Team (PORT) study reported the diabetes prevalence of 14.9% among schizophrenia subjects. The prevalence of impaired fasting glucose (IFG) was reported to be 15% among Caucasian drug-naïve subjects with schizophrenia. Another study among middle-aged European subjects with schizophrenia, reported a prevalence rate of IFG of 8.5%.

In the present study, the prevalence of impaired fasting glucose (31.3%) among subjects with schizophrenia was much higher compared to the European studies. This may be a reflection of higher diabetes rates in India in general, which is attributed to the "Asian Indian Phenotype," associated with increased waist circumference and body fat (particularly visceral fat) leading to greater insulin resistance.

Abdominal obesity, another component of the Asian Indian Phenotype and a component of MS, is a well-established risk factor for a high prevalence of diabetes. The present study found that the prevalence of abdominal obesity was higher in subjects with schizophrenia compared to those without. Earlier studies have shown that women with schizophrenia were more frequently

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<th>Table 2: Prevalence of diabetes and impaired fasting glucose in subjects with and without schizophrenia</th>
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<td>Impaired fasting glucose</td>
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<td>Self-reported diabetes n (%)</td>
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FBS: Fasting blood sugar; ADA: American Diabetes Association; *Chi-square; P<0.05

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<th>Table 3: Antipsychotic medication utilization and its relation to risk factors among subjects with schizophrenia</th>
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<tr>
<td>Abdominal obesity (n=73)</td>
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<td>Metabolic syndrome (n=42)</td>
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<sup>a</sup>Trend Chi square
obese than men.\[23\] In the present study also, the prevalence of the abdominal obesity was higher among female subjects (80%) with schizophrenia compared to males (40%). A Chinese study on schizophrenia\[24\] however, found no significant gender difference in the prevalence of obesity (39.6% in females and 40% in males).

The term MS refers to a cluster of metabolic risk factors including central obesity, glucose intolerance, hyperinsulinemia, low HDL cholesterol, high triglycerides, and hypertension.\[25\] Several studies have reported on the prevalence of MS in the general population. In CURES, we reported that the prevalence of MS using IDF criteria, was 25.8%.\[26\] An earlier Indian study\[8\] revealed that subjects with schizophrenia had a 37.7% prevalence of MS using IDF criteria.\[26\] A study in Finland showed a fourfold risk of MS among young subjects with schizophrenia compared to the general population.\[7\] The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study in USA, reported 42.7% prevalence of MS using ATP III criteria.\[27\] Another study in a US population also reported a 38.6% prevalence of MS\[28\] while a study from Brazil showed a prevalence of MS of 29% using the same criteria.\[29\] The present study also confirms a higher prevalence of MS among subjects with schizophrenia (34.4%), using IDF criteria. However, differences in the criteria used to define MS could contribute to the differences in prevalence rates of MS within studies.

A number of recent studies have confirmed that the use of any anti-psychotic drugs was associated with an increase in newly diagnosed diabetes.\[30,31\] Antipsychotic medication in schizophrenia is known to induce weight gain and this is thought to be responsible for the excess weight among individuals with schizophrenia.\[32\] While weight gain may be a mechanism for the development of diabetes, a direct effect of these drugs on insulin action in muscle may also be an important contributor to diabetes.

Nowadays atypical antipsychotic drugs tend to be used more often to treat schizophrenia.\[33\] These drugs are shown to be associated with an increased risk for diabetes,\[14-36\] in addition to varying degrees of metabolic adverse effects, such as weight gain, dyslipidemia and in some cases, cardiovascular disease.\[37\] A published report on the consensus development conference on antipsychotic drugs and obesity also showed that subjects on atypical antipsychotics had a significantly greater risk of developing diabetes than those on typical antipsychotics.\[38\] The present study also shows that those under atypical medications relatively had higher rates of diabetes, abdominal obesity and metabolic syndrome as compared to subjects on typical medications although the difference was not statistically significant probably due to small study numbers.

The other risk factors in schizophrenia patients include depression, possibly due to the stress of hospitalization,\[39\] alcohol abuse, overeating, and physical inactivity, all of which could contribute to the increased prevalence of obesity, diabetes, and MS in these subjects.

This study has certain limitations. Firstly, OGTT, the gold standard method for screening diabetes has not been carried out and secondly, the duration of the psychiatric drugs, which is one of the major causes of increasing obesity in subjects with schizophrenia, has not been taken into account in this study. Finally, the cross-sectional nature of the study does not allow for cause-effect relationships to be established. However, one of the strengths of this study is that the controls were taken from an epidemiological study.

In conclusion, we report that prevalence of diabetes, impaired fasting glucose, obesity, and metabolic syndrome are higher in subjects with schizophrenia compared to those without schizophrenia. This underscores the need to screen schizophrenia subjects for diabetes and MS. Early detection of these disorders would enable us to take therapeutic measures, and thus delay the complications of diabetes. The first step in prevention of diabetes is to identify and screen these high risk groups. This can be done using a simple screening tool like the Indian Diabetes Risk Score (IDRS)\[40\] which could be used in subjects with schizophrenia to identify those who are likely to have diabetes or MS.\[41\]

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