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Original Research

Glucose Tolerance Testingin First Episode, Drug Naïve Patients with Schizophrenia

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Abstract

Background: Schizophrenia is ranked 8th leading cause of disability adjusted life years (DALY) in the age group between 15 to 44. The DALYs rate in India according to World Health organization was 268.903 per 100,000 residents. Previous studies conducted in antipsychotic naïve patients of schizophrenia suggest that these patients of schizophrenia are already predisposed for developing metabolic syndrome (MetS) and type 2 DM due to the disease itself

Aims and objectives: To assess occurrence of impaired glucose tolerance in drug naïve patients with schizophrenia in comparison to normal healthy individuals.

Materials and Methods: Thirty patients suffering from schizophrenia fulfilling DSM-5 criteria for diagnosis were studied and compared with age and sex matched 30 normal healthy controls and 30 normal healthy siblings of schizophrenic patients in the in the Department of Psychiatry, Peoples Hospital and Research Centre, Bhanpur, Bhopal. Details on age, gender, education, occupation, marital status, duration of illness, glucose tolerance test, blood pressure, pulse pressure, waist hip ratio, body mass index (BMI), and total score on brief psychiatric rating scale was recorded.

Results: The mean value of GTT at 0 hour was significantly higher in cases as compared to control ($p=0.014$), at 1 hour was significantly higher in cases as compared to control ($p<0.001$) and sibling ($P<0.001$) and at 2 hour was significantly higher in cases as compared to control ($p=0.01$) and sibling ($P=0.013$). Duration of illness was found to have significant positive correlation with GGT level at 0 hour ($r=-0.404;p=0.027$) however no significant correlation was obtained between duration of illness and GGT at 1 and 2 hour. BPRS Score did not show any significant correlation with the GGT levels at 0, 1 and 2 hour.

Conclusion: We found higher values of FPG and IGT in the drug naive patients of schizophrenia and their siblings; this support the apportionment of environment and genetic predisposition to impaired glucose metabolism. It is important to screen both the patients of schizophrenia and their relatives for Type 2 Diabetes Mellitus to prevent future complications.

Keywords: BPRS Score, glucose tolerance test, American diabetes association, schizophrenia

Introduction

Schizophrenia is a chronic illness that typically has its onset in young age and lasts a lifetime with only occasional recovery in a few patients.[1, 2] According to the World Health Organization estimate in year 2016, there are more than 21milion people suffering from schizophrenia worldwide.[3] It affects 3-6.6 persons per 1000 population, has a lifetime prevalence of 4.0 per 1000 persons and point prevalence ranges from 2.6 to 6.7 per 1000.[4] According to National Mental Health Survey of India 2015-16, the lifetime prevalence of Schizophrenia in India was 1.41% and current prevalence was 0.5%.[5]

In the past, most of the evidence indicating higher prevalence of metabolic syndrome and Type 2 diabetes mellitus in patients with schizophrenia comes from studies among patient receiving antipsychotic drugs, implicated in the pathogenesis of both metabolic syndrome and type 2 DM.[6] But recently, several studies conducted in antipsychotic naïve patients of schizophrenia suggest that these patients of schizophrenia are already predisposed for developing MetS and T2DM due to the disease itself. However negative studies have also been published and thus it is difficult to determine, if schizophrenia leads to the development of these abnormalities or vice versa.[7]

We compared the glucose metabolism in the patients with schizophrenia and their siblings with the control population. We hypothesized glucose intolerance to be an endophenotype, expected to be abnormal in the patients of schizophrenia and their siblings. The distinctive feature of our study is that we compared the glucose metabolism at the end of 1-hour and 2-hour periods to study the difference in the glucose load handling in the patients of schizophrenia, siblings of schizophrenic patients and the controls followed by the calculation of PG% using the scores of OGTT.

We also studied the parameters of lipid profile in our subjects. The previous studies done in the western countries and some Asian countries like China compared the metabolic abnormalities in the patients with Schizophrenia and healthy controls but none of them compared all the three i.e. patients of schizophrenia, their siblings and healthy controls all at once, making this

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study first of its kind. Abnormalities found in siblings of schizophrenia patients may unlock valuable information about the cause of the illness especially regarding the existence of predisposing factors and provide key insights into the illness pathway and treatment plans.

Materials and Methods

Present cross-sectional study was performed on 30 patients (14 male patients and 16 female) suffering from schizophrenia fulfilling DSM-5 [8] criteria for the diagnosis. Thirty normal healthy controls were selected comprising of 15 males and 15 females. 30 normal healthy siblings of schizophrenic patients (not necessarily sibling of the same drug naive schizophrenic patients) comprising of 11 males and 19 females.

Age, gender, education, occupation, marital status, duration of illness, glucose tolerance test, blood pressure, pulse pressure, waist hip ratio, body mass index (BMI), and total score on brief psychiatric rating scale was recorded.

Schizophrenia patients diagnosed as per DSM-5 without any history of antipsychotic medication intake in age group 18-30 yrs were included. Normal healthy individuals in age group 18-30 yrs for controls and siblings of patients of schizophrenia (not necessarily sibling of the same drug naive schizophrenic patients) in the age group 18-30 yrs of age were also included. Subjects not fulfilling age criteria mentioned in inclusion criteria, history of recognized cardiovascular disease, diabetes mellitus, malignancy, endocrine disease , history of medication known to affect glucose or lipid metabolism and patient taking any psychotropic medicationwere excluded.

We selected the patients from the OPD and IPD both. After a complete description of the study to the patients, healthy controls, and siblings of the patient of schizophrenia, written informed consent was obtained. All subjects fulfilling the inclusion criteria and exclusion criteria on the basis of detailed clinical examination and history were chosen. The subjects after being settled were explained regarding the nature of this study in the language suitable to them. Those subjects who gave written consent were then interviewed. Illness-related variables were rated with the Brief Psychiatric Rating Scale version 4.0 (BPRS) [9] at the time of first encounter. This was a one point, comparative study where we compared Glucose tolerance test at 0 hour, 1 hour and 2 hour in schizophrenia patients, healthy controls and siblings of patients of schizophrenia (not necessarily sibling of the same drug naive schizophrenic patients).

All subjects were given a 2 h, 75-g oral GTT, as endorsed by WHO and considered to be the gold standard for testing of risk of diabetes, which began between 8 and 9 AM after an overnight fast. Blood samples were obtained at three time points for the OGTT—at baseline (before the consumption of 75-g oral glucose), and at 1 hour and 2 hour after taking the glucose drink. Blood samples were collected in EDTA-containing tubes, via a venous catheter inserted into an antecubital vein. Plasma glucose were assessed for each of the time points. The diagnosis of impaired glucose tolerance were based on WHO guidelines, which are as follows: Fasting plasma glucose should be below 6.1mmol/L(110mg/dl).

Fasting levels between 6.1 and 7.0 mmol/L (110 and 125 mg/dl) are borderline(impaired fasting glycaemia) and fasting levels repeatedly at or above 7.0mmol/L (126mg/dl) are diagnostic of diabetes. A 1 hour GTT glucose level below 10mmol/L (180mg/dl) is considered normal .For a 2hour GTT , a glucose level 7.8mmol/L(140mg/dL) is normal, whereas higher glucose levels indicate hyperglycemia. Blood plasma glucose between 7.8mmol/L (140mg/dL) and 11.1 mmol/ L (200mg/dL) at 2 hours.

The data obtained was subjected to statistical analysis with the consult of a statistician. The data so obtained was compiled systematically. A master table was prepared and the total data was subdivided and distributed meaningfully and presented as individual tables along with graphs.

Statistical analysis was done using Statistical Package of Social Science (SPSS Version 20; Chicago Inc., USA). Data comparison was done by applying one way ANOVA and Tukey's post hoc analysis was performed to three group analysis. Quantitative variables were compared using mean values and qualitative variables using proportions. Significance level was fixed at $P \leq 0.05$.

Results

Rates of IFG amongst cases were significantly higher as compared to Control (p=0.001) and Sibling (p=0.002). Rates of IFG was similar among Control and sibling (p=0.658). Rates of subjects having mean plasma glucose level >155mg/dl at 1 hour was significantly higher in cases as compared to other groups. Rates of subjects having mean plasma glucose level >155mg/dl at 1 hour of GTT between Control and sibling was comparable (p=0.456). Rates of IGT at 2 hour were significantly higher in cases as compared to controls and siblings. Rates of IGT between controls and siblings were comparable (p=0.684).

Table 1: Comparing Demographic and baseline characteristics of study population

Socioeconomic data	Cases	Controls	Siblings	p Value
Age	24.17±3.88	24.30±3.73	23.67±3.84	>0.05
Gender (male/female)	14/16	15/15	11/19	0.557
Residence (rural/urban)	13/17	15/15	2/18	0.730
Education (P/S/M/HS/G/PG)	7/10/4/3/5/1	6/10/3/5/5/1	1/7/1/10/9/2	0.204
Occupation (S/US/UE)	5/15/7	5/16/6	11/13/3	0.471
BMI	24.25±4.32	23.42±3.89	24.67±3.52	0.422
Waist Hip Ratio	0.81±0.05	0.80±0.3	0.81±0.8	0.623

PG % (p=0.158), pulse pressure (p=0.748) and SBP (p=0.106) was equally distributed between all the three groups.

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Table 2: Comparing all laboratory investigations between groups

Variable	Cases	Controls	Siblings	p Value
GTT at 0 hour*	96.39±22.28	82.39±15.55	85.19±18.11	0.01
GTT at 1 hour**	145.22±29.41	08.76±20.79	120.13±21.44	<0.001
GTT at 2 hour***	136.65±61.21	97.39±16.01	107.16±25.02	<0.001
Systolic BP	131.27±15.51	123.60±12.70	126.53±13.47	0.106
Diastolic BP	87.33±8.24	80.40±5.15	81.27±5.36	<0.001
Pulse pressure	43.60±11.24	43.20±10.61	45.27±11.47	0.748

Post Hoc test was done using Tukey test, *p Value between case and control; 0.014, between Case and sibling; 0.062, between control and sibling; 0.834. ** p Value between case and control; <0.001, between Case and sibling; <0.001, between control and sibling; 0.169. *** p
Value between case and control; 0.01, between Case and sibling; 0.013, between control and sibling; 0.602.
On applying the Pearson Correlation, we found that Duration of illness was found to have significant positive correlation with GGT level at 0 hour (r=-0.404;p=0.027) however no significant correlation was obtained between duration of illness and GGT at 1 and 2 hour. BPRSScore did not show any significant correlation with the GGT levels at 0, 1 and 2 hour.

Table 3: Comparison of GTT within Cases as per sociodemographic profile

Parameters		GTT					
		0 hour	p Value	1 hour	P value	2 hour	P value
Gender	Male	93.25±18.58	0.480	146.07±28.73	0.885	126.52±60.24	0.406
	Female	99.14±25.96		144.48±30.93		145.51±62.61	
Residence	Rural	89.34±21.50	0.132	140.53±26.80	0.455	122.03±48.98	0.260
	Urban	101.78±21.94		148.81±31.60		147.82±68.45	
Education	Primary	106.47±13.75	0.183	156.25±8.43	0.370	169.52±73.41	0.204
	Middle	78.80±14.19		139.60±23.28		96.22±6.66	
	Higher secondary	117.93±31.86		154.96±45.80		190.96±79.99	
	Graduate	95.32±28.95		120.14±11.30		124.82±62.15	
	Post Graduate	96.40		134.50		98.80	
Occupation	Unemployed	108.48±28.82	0.467	170.91±29.03	0.039	195.87±70.00	0.035
	Skilled	89.50±16.67		140.76±35.04		103.36±28.73	
	Non skilled	92.80±21.17		134.72±19.39		120.81±49.97	

Discussion

One of the most intriguing topic and an academic controversy of the recent times is whether the drug naïve patients of schizophrenia have predilection for development of metabolic abnormalities such as abnormalities of glucose and lipid metabolism or not. There are different school of thoughts that exist on the matter. Therefore to resolve the conflict we decided to do a cross sectional study aimed to compare early derangements in glucose homeostasis between drug naïve patients with schizophrenia, healthy controls and siblings/first degree relatives. We measured the early derangements in glucose homeostasis (i.e. pre-diabetes) by applying oral glucose tolerance test, which is a more sensitive test to measure abnormalities in glucose metabolism than the fasting plasma glucose levels.[10] It is endorsed by WHO as the only tool to identify individuals with impaired glucose tolerance.

Our findings demonstrate that the patients with schizophrenia had higher mean fasting plasma glucose levels than siblings/first degree relatives (p=0.062) and healthy controls (p=0.014). About30% of the patients with schizophrenia had IFG compared to siblings/first degree relatives (6.67%)(p=0.002) and healthy controls (3.3%) (p=0.001). Studies [11-13] done in the past, which used fasting blood glucose as a tool to check glucose metabolism abnormalities, show divergent results. One pioneer study of Ryan et al[14] found that drug naive patients with schizophrenia had higher levels of fasting plasma glucose and about 15% of antipsychotic naive schizophrenia patients showed impaired fasting glucose. Chen et al [15] and Zhang et al[16] from China recently found out that drug naïve patients with schizophrenia had higher levels of fasting plasma glucose. However two studies from China found that fasting plasma glucose in drug naïve patients with schizophrenia did not differ from healthy controls of the study population.[12,15]

Because of these conflicting results, it was hard to consider FPG to be conclusive. We decided to use OGTT over American Diabetes Association approved FPG for the diagnosis of risk of diabetes because while FPG helps us in identifying subjects with IFG it does not help us identify the subjects with Impaired Glucose Tolerance (IGT). IGT is defined by a 2 hour post glucose load glycaemia (2hPG) of 140-199 mg/dl. OGTT is one such test which can help in identifying both IFG and IGT. A European epidemiological study[17] suggests that IGT is far ahead of IFG in diagnosing diabetes and considered IFG to be inconclusive. Schianca GP et al[18] found IFG to be indicative of insulin secretion while IGT to be indicative of insulin sensitivity. Based on all these observations they suggested that to effectively screen the patients with deranged glucose homeostasis there is no replacement of OGTT. Although few studies in the past used GTT to calculate glucose tolerance in drug naïve patients with schizophrenia but no such attempt has been made in India, making this study the first in India to use OGTT as standard measure to calculate glucose tolerance and insulin sensitivity.[7, 11]

Again our findings demonstrate that the patients with schizophrenia had significantly higher 2 hour plasma glucose (2hPG)

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levels than siblings (p=0.013) and healthy controls (p=0.01). IGT rates (30%) in our study among cases were higher in comparison to healthy controls than the rates reported in some of the previous studies such as the one by Spelman et al [7] (10.5% in first episode drug naïve patients and 18.2% in relatives), and Fernandez-Egea et al [11] (6% IGT in drug naïve patients with schizophrenia) but is very similar to the results of Chen et al[15] (24.5%) in ham Chinese population. Hu et al had reported that there exists huge diversity in diabetes prevalence and health expenditure throughout the world.[19] Also, Whiting et al found that the prevalence rate of diabetes is higher in developing world.[20] Hence our finding of a 30% IGT rate, higher than those reported in the Western countries is consistent with these epidemiological findings of a higher prevalence rate of diabetes in Asian countries or in developing countries likeIndia.

Again our findings demonstrate that the patients with schizophrenia had significantly higher 1 hour plasma glucose (1hPG) levels than siblings/first degree relatives($p<0.001$)and healthy controls($p<0.001$). To best of our knowledge, there are no earlier studies assessing the plasma glucose concentration at 1 hour of OGTT in patients with schizophrenia (both drug naïve and on antipsychotic medication) . Our study is the first of its kind to assess the drug naïve patients with schizophrenia for glucose metabolism abnormalities at one hour post glucose load. However, more studies are needed in this regard to establish the predictive power of the test and also to understand the validity of the test.

Bartoli et al[21] in their article documented another way of analyzing OGTT by calculating PG% which is a measure of insulin sensitivity (β cell function)- higher PG% corresponds to a fall in insulin sensitivity (or increase in insulin resistance) and a lower PG% corresponds to a rise in insulin sensitivity. This is very critical to know, since two patients who both have Normal Glucose Tolerance (NGT) but different PG% can have different risks of worsening glucose tolerance. Thus by using a single test of OGTT along with the glycemic measurements the simultaneous determinations of insulin sensitivity can be done. The previous studies, including the one at our center (using a different sample), have been done on insulin resistance with HOMA IR test using serum insulin which is a expensive procedure. So we evaluated insulin sensitivity (by measuring PG %) using the scores of OGTT, which is a key differentiator of our study and makes us the first to do so. When we analysed our data further and calculated the PG% in our study samples we could not find any statistical difference between all the three groups.($p= 0.158$).

Thus, at all the 4 points of analysis described above we obtained similar results with cases having significantly higher values as compared to the siblings and the controls on measures of glucose metabolism (mean plasma glucose at 0 hour i.e. FPG, 1 hour and 2 hour and rates of IFG and IGT and PG%). The values of the siblings were higher than that of the controls but the difference was not significant.

Thus, as we hypothesized the finding of our study was in concordance with the studies conducted in the past. Spelman et al[7] and Fernandez-Egea et al[11] reported that the rates of impaired glucose tolerance were higher in the relatives of the patients with schizophrenia, than that in the healthy matched control subjects. We also found higher frequencies of IFG and IGT in the siblings as compared to the controls, but the difference was not significant.

There were differences in the sampling of the studies, Spelman et al[7] took the first degree relatives of the schizophrenic patients in their study whereas our study comprised of the siblings/ first degree relatives of patients with schizophrenia not necessarily of the cases, still the results of our study were directionally same with those of Spelman et al but were of a different magnitude. Our study, however, differed from the study of Fernandez-Egea et al[11] as they reported a significantly higher 2 hour mean glucose concentration in the siblings than in controls. One probable reason of this difference could be that Fernandez Egea et al [11] only compared a small sample of the siblings of schizophrenic patients and healthy controls.

Our observation might be consistent with the multifactorial model of schizophrenia.[22, 23] Multifactorial model hypothesize that it's not a single gene or a single environmental factor that causes schizophrenia. Rather, it is the sum total of all the genes and environmental factors that leads to this disorder. Hence, there must be a graded genetic predisposition to the disorder in a way such that as the probability of developing schizophrenia (or showing related glucose homeostasis impairments) increases the degree of predisposition also. In other words, as the genetic load increases the chances of developing schizophrenia or the impairments related to it like glucose homeostasis disturbances also increases. Inadvertently, in our study the siblings might have been belonging to the families having low genetic load or they might have grown up in environment not predisposing them to the disorder or its abnormalities or in other words the genes and other factors that prevented the development of schizophrenia in these siblings of schizophrenic patients might have also prevented the development of glucose intolerance.

In the group of patient with schizophrenia we compared mean plasma glucose level at 0 hour (FBG), 1 hour(1hPG) and 2 hour (2hPG) as per their socio demographic profile. There was no statistical significant difference in mean plasma glucose levels at 0, 1 and 2 hour as per the distribution of gender, residence and education level but the mean plasma glucose at 1 hour ($p = 0.039$) and 2 hour ($p= 0.035$) were significantly higher in cases who were unemployed than skilled or non skilled workers. Goff et al[24] it has been documented that patients with schizophrenia show significantly higher rates of smoking, compared to the general population. It has also been observed that patients with schizophrenia have a sedentary lifestyle, have a diet higher in fat and low in fibre, and with less physical in activity.[25] These factors also play a crucial role in the development of diabetes mellitus.[26] Different life style factors, diet and physical activity level may also provide explanation of divergent results in our study. One limitation of our study is that we did not asses the different life style factors.

One of the major limitations of our study was that ours was a cross sectional study so we cannot comment on the actual risk of development of diabetes in the patients of schizophrenia. We did not use other methods to see insulin resistance in our study though in an earlier study conducted at our centre (in a different sample) in drug naïve patients with schizophrenia had significantly higher levels of fasting plasma glucose as compared to healthy controls using HOMA-IR. Another method that we could have used for the analysis of glucose metabolism abnormalities is the estimation of HbA1C. However, only the

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higher values of HbA1C are conclusive for diagnosing diabetes whereas none of its value predicts the risk of diabetes. We did not assess the lifestyle factors and other confounding factors like substance use, which could have affected results.

Conclusion

The higher values of FPG and IGT in the drug naive patients of schizophrenia and their siblings support the apportionment of environment and genetic predisposition to impaired glucose metabolism. It is ideal to screen both the patients of schizophrenia and their relatives for Type 2 Diabetes Mellitus to prevent future complications.

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