Original Article

Anthropometric parameters as indicators of metabolic derangements in schizophrenia patients stabilized on olanzapine in an Indian rural population

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ABSTRACT

Context: For any given body mass, Asian Indians have higher central obesity than Europeans. A periodic measurement of body mass index (BMI) and waist hip ratio (WHR) is practically more feasible than other parameters of metabolic syndrome by repeated blood collection. However, few studies are available on the relative importance of BMI and WHR as markers of dyslipidemia and insulin resistance in schizophrenia patients stabilized on second generation antipsychotics in Indian population. **Aim:** We conducted the present study on such patients to examine whether BMI or WHR can better predict dyslipidemia and insulin resistance in these patients in a rural area. **Settings and Design:** The study was a hospital based case control study under rural settings on 38 schizophrenia patients stabilized on olanzapine and 30 matched controls. **Materials and Methods:** Fasting concentrations of blood glucose, lipid parameters and serum insulin were assessed. Data for Homeostatic model for assessment of insulin resistance (HOMA-IR), BMI, and WHR were obtained to assess the insulin resistance, overall body fat distribution and abdominal fat dispensation respectively. **Statistical analysis used:** 't' test was performed to assay any difference in corresponding mean values between cases and controls. Dependence of HOMA-IR on key parameters was assessed by analysis of co-variance (ANCOVA) study. **Results:** Cases exhibited significantly higher values for HOMA-IR, serum triglyceride and low density lipoprotein cholesterol (LDLc) with a significantly lower high density lipoprotein cholesterol (HDLc) level. ANCOVA study reflected that irrespective of age and sex, HOMA-IR was dependent on serum triglyceride level and WHR (F=8.3 and 5.7 respectively, $P<0.05$), but not on BMI (F<0.001, $P=0.997$). **Conclusions:** Central obesity could be more closely associated with the pathogenesis of prediabetic state in our case group. So, WHR is a better anthropometric parameter than BMI for an early assessment of insulin resistance and dyslipidemia in schizophrenia patients stabilized on olanzapine in our region.

Key words: Schizophrenia, insulin resistance, dyslipidemia, waist hip ratio, body mass index

Introduction

People suffering from schizophrenia show higher rate of mortality in most regions of the world.[1-3] Increased risks for development of metabolic syndrome, lipid abnormalities and consequent cardiovascular deaths have been reported as important contributing factors.[4,5]

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Cardiovascular disease remains one of the primary causes of mortality among patients with severe mental illness, with standardized mortality ratios approximately two times greater than the general population.[6] Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness[7] and other large cohorts[8] have underscored the public health problem of high CHD risk and increased prevalence of prediabetic states, such as different features of metabolic syndrome, in patients with schizophrenia. In late 2005, the International Diabetes Federation modified the metabolic syndrome criteria previously elaborated by the National Cholesterol Education Program, with an emphasis on abdominal adiposity as a necessary condition to be met, in addition to a minimum of two of the other four criteria.[9] While

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this newer definition asserts the primacy of central obesity in the conceptualization of metabolic syndrome, it also fuelled an ongoing debate in the recent literature over the value of the metabolic syndrome concept.[10]

Thus, it seems that there are considerable arguments whether obesity or WHR is affected by olanzapine, and that different ethnic groups may have different reactions. However, obesity has been an important contributing factor for developing medical problems like type 2 diabetes mellitus and metabolic syndrome, which constitute important risk factors for cardiovascular deaths in the schizophrenia patients.[11] Goff *et al*,have suggested that clinicians treating schizophrenia patients with antipsychotics should properly monitor the cardiovascular risk factors, particularly for combating the metabolic syndrome, general obesity and abdominal obesity.[8] Weight gain is worse with clozapine and olanzapine; minimal with aripiprazole and ziprasidone; and intermediate with other antipsychotics, including low-potency first generation antipsychotics (FGAs).[12] Among the second generation antipsychotic drugs (SGA), olanzapine and clozapine are associated with excessive body weight gain, hyperglycemia, dyslipidemia and probably a pro-coagulant state.[13,14]Olanzapine, although associated with a lesser amount of extra-pyramidal side effects, was found to cause a significant weight gain in bipolar mood disorder patients also.[15]Obesity, particularly abdominal fat deposition indicated by a high waist hip ratio, has been a strong predictor of cardiovascular sequel such as coronary heart disease, myocardial infarction, or stroke.[16,17] Although, several earlier studies as well as recent ones have indicated an overall increase in body fat, as indicated by an increased BMI, in schizophrenia patients stabilized on olanzapine or clozapine,[18-20] some of them did not find any change in the waist hip ratio suggesting that the type of fat distribution was not affected by either of these drugs.[20] On the other hand, another large study undertaken in India reported a significantly higher increase in the waist circumference and serum triglyceride in olanzapine treated patients.[21] Kim *et al*,reported that the relationship between BMI and insulin resistance was similar between the SGA treated schizophrenia and the reference population.[22] Different results from different areas thus indicated that the physical indices vary from region to region based on their geographical distribution. Asian Indians have been a unique ethnic group in terms of body morphology and cardiovascular disease risk. In a recent large cross sectional study involving 933 European, Maori, Pacific Island and Asian Indian adult volunteers, Asian Indians were found to have more fat; both total and in the abdominal region, with less lean mass, skeletal muscle and bone mineral than all other ethnic groups. Furthermore, their abdominal fat was found to increase with advancing age with little changes in overall body fat.[23] In a South Indian population group Kaur *et al*.found WHR to be the best predictor for type 2 DM.[24] However, few studies are available regarding relative importance of the WHR and BMI as markers of dyslipidemia and insulin resistance in the schizophrenia patients stabilized on SGAs in the Indian population.

Keeping these factors in mind we hypothesized that dyslipidemia and insulin resistance could be better reflected and predicted by either overall body fat or abdominal adiposity in our region and hence, undertook the present study to evaluate it by assessing corresponding lipid parameters, physical indices of obesity and insulin resistance by homeostasis model assessment (HOMA) in such subjects.

Materials and Methods

Study design
The present study was designed as a hospital based case control study within the study period of November 2009 to December 2010. It was undertaken in the outpatient department (OPD) of Psychiatry and the department of Biochemistry of a government medical college and hospital in a rural district in West Bengal, India.

Selection of cases and controls
Cases were selected as sample of convenience from consecutive patients of schizophrenia of both sexes, receiving oral olanzapine treatment for at least six months from the Psychiatry outpatient department (OPD). Diagnosis of schizophrenia was done by Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria.[25] Patients were included provided they had no other DSM IV disorder that required antipsychotic treatment, had attained the age of 18 years and could give informed consent after understanding the objectives of the study. All selected cases were stable on an average dosage of 5-15 mg per day of olanzapine. Patients receiving benzodiazepines in requisite dosage in addition to olanzapine were also considered. Exclusion criteria were: 1) type 2 diabetes mellitus or a history of the disease among first degree relatives, 2) any somatic illness at the time of inclusion, neoplasm, metabolic or endocrine disorder or neurological diseases, 3) substantial use of alcohol or nicotine in any form within last 6 months or DSM IV criteria for alcohol dependence disorder, psychoactive substance abuse, or dependence disorder, 5) use of any antipsychotic medication other than olanzapine, and any other medication associated with insulin resistance (e.g.

glucocorticoids, hydrochlorothiazides, furosemides, beta blockers, phenytoin, nicotinic acid etc.). All these criteria were included in a semi structured interview schedule.

Control subjects were selected from persons accompanying the patients in OPD who were free from any metabolic or psychiatric disorders. Relatives of the patients were excluded during this selection. Overall exclusion criteria were same as those used for case selection procedure. Additional exclusion criteria for the control group were any lifetime diagnosis of schizophrenia and/or major depressive illness, or any current Axis-I disorder. All participants were from a large rural base of Eastern India having approximately similar ethnicity, socioeconomic status and dietary habits. Written consents were obtained from all participants or their legal guardians. 38 patients (14 females) fulfilling the above inclusion and exclusion criteria were finally selected as cases for the study. Similarly, 30 age and sex (12 females) matched healthy people were recruited in the control group. The study followed the guideline of Helsinki declaration 1975 and was approved by the institutional ethical committee of the concerned Medical College and Hospital.

Estimation of test parameters

All parameters were assayed from 12 hr fasting blood samples obtained from cases and controls. Fasting blood glucose (FBG), serum total cholesterol and serum triglyceride were assayed by glucose oxidase peroxidase method (GOD-POD), cholesterol oxidase phenylperoxidaseaminophenozonphenol (CHOD-PAP), and glycerol phosphate oxidase peroxidase (GPO-POD) method respectively. High density lipoprotein (HDL) cholesterol was measured by phosphotungstic acid precipitation method. We calculated low density lipoprotein (LDL) cholesterol according to the method of Friedewald and colleagues. The biochemical assays were done using the autoanalyzer ERBA XL 600. Internal quality control was performed for all parameters simultaneously. All test reagents were purchased from Ranbaxy RFCL, India and the quality control materials (Lyphochek, level 1 and 2) were purchased from Bio-Rad laboratories, USA.

Serum insulin was assayed by ELISA kit AccuBind from Monobind Inc. USA. This method has been reported to show a high degree of correlation (correlation coefficient 0.975) with reference radioimmunoassay method. No cross reactivity with C-peptide was detected. The serum was separated at 4°C and was stored at-20°C till assay was done. Assays were done within one week from the date of collection in fully automated ELISA reader and washer from TECAN, Austria.

As a widely validated clinical and epidemiological tool for estimating insulin resistance and β cell function, the homeostasis model assessment (HOMA) is derived from a mathematical assessment of the balance between hepatic glucose output and insulin secretion from fasting levels of glucose and insulin.[26,27] This model requires only a single measurement of insulin and glucose in the basal state and so, in some conditions, is a suitable alternative for large-scale epidemiologic studies to the sophisticated "gold standard" methods which usually require dynamic data via costly and invasive procedures. Previous cross-sectional studies have shown that high HOMA-IR was associated with increased prevalence of impaired glucose tolerance (IGT) and type 2 diabetes in several population.[28]

The HOMA-IR in our present study was calculated with the help of HOMA2 Calculator v2.2 obtained from the website http://www.dtu.ox.ac.uk/homa. Body mass index (BMI) was calculated from the formula of weight (kg)/height (m^2) for both cases and controls.

Statistical analysis

The two matched groups were compared for differences between means of different test parameters by unpaired t tests [Table 1]. Analysis of co-variance (ANCOVA) was performed [Table 2] to find out the dependence of insulin resistance on FBG, BMI, WHR and lipid parameters in the case group after controlling the effects of age and sex. Significance was considered as $P<0.05$ for all statistical tests. All statistical analyses were done using SPSS software version 16.0 for Windows.

Results

Mean (SD) age in years for the cases and controls were 31.76 (7.82) and 35.46 (9.02) respectively, the difference being statistically insignificant (t=-1.78, P=0.08, data not shown in Table). The male: Female ratios were 24:14 and 18:12 respectively in cases and controls. The distribution of males and females in both groups was found insignificant by Chi square test, the $\chi 2$ for males and females between both groups being 1.19 (P=0.274) and 0.154 (P=0.695) respectively (data not shown in Table).

The mean values for fasting serum insulin and insulin resistance indicator HOMA-IR showed a significant higher value ($P<0.001$) in the case group without revealing any such change in FBG (P=0.201) [Table 1]. Serum triglyceride level and LDL cholesterol levels were higher ($P<0.001$ and P=0.034 respectively) while the HDL cholesterol level was significantly lowered (P=0.016) in the olanzapine treated group. Furthermore, WHR an

Table 1: Distribution of descriptive measures in olanzapine treated case (N=38) and control (N=30) groups

	Cases mean (SD)	Controls mean (SD)	t value	*P* value
Fasting blood glucose (mg/dl)	101(18.03)	96.2(13)	1.2	0.201
Insulin (uIU/ml)	18.23(5.78)	10.26(3.96)	6.3	<0.001*
HOMA-IR	4.56((1.81)	2.39(1.00)	5.5	<0.001*
Serum cholesterol (mg/dl)	169.47(24.51)	154.31(37.93)	1.98	0.052
Serum triglyceride (mg/dl)	168.89(41.61)	133.06(44.92)	3.37	0.001*
Serum LDLc (mg/dl)	101.87(22.4)	87.37(32.19)	2.17	0.034*
Serum HDLc (mg/dl)	35.21(6.09)	39.37(7.75)	-2.4	0.016*
BMI	21.68(5.54)	20.92(3.12)	0.61	0.54
WHR	0.92(0.06)	0.88(0.05)	2.4	0.017*

*$P<0.05$

Table 2: ANCOVA analysis controlling the effect of age and sex to show the dependence of the Insulin resistance (HOMA-IR) on various metabolic and anthropometric parameters in the olanzapine treated schizophrenia patients (N=38)

Tests of between-subjects effects

Dependent variable: Homa-IR

Source	F	Sig.
Corrected model	1.694	0.192
Intercept	5.888	0.036*
Serum cholesterol (mg/dl)	0.014	0.907
Serum triglyceride (mg/dl)	8.309	0.016*
Serum LDLc (mg/dl)	0.001	0.982
Serum HDLc (mg/dl)	0.541	0.479
BMI	0.000	0.997
WHR	5.770	0.037*
Age (Years)	0.665	0.775
Sex	0.108	0.749

R Squared=0.821 (Adjusted R Squared=0.336), * $P<0.05$

indicator of abdominal obesity, showed a significant higher value (*P*=0.017) in the case population whereas, no such change was found in the BMI (*P*=0.54), an indicator of general obesity.

Analysis of co-variance revealed significant dependence of HOMA-IR on serum triglyceride (F=0.016, *P*=0.016) and WHR (F=5.7, *P*=0.037) [Table 2] only that indicated WHR to be a better anthropometric predictor than BMI for development of insulin resistance in the olanzapine treated case population.

Discussion

In our present study we found that schizophrenia cases stabilized on olanzapine therapy exhibited higher values for insulin resistance (HOMA-IR), serum triglyceride and LDL cholesterol along with a lower HDL cholesterol level, than did the matched control group. ANCOVA study revealed that the HOMA-IR in cases was dependent on the serum triglyceride level and WHR, but not on the BMI.

The impact of olanzapine on metabolic outcomes has been well documented,[29] and the association between insulin resistance, serum triglycerides and central adiposity were found to be particularly strong for many years.[30,31] Although, some studies have attributed more importance to the overall body fat deposition (as reflected by an increased BMI) than the type of fat distribution (as reflected by an increased WHR) in olanzapine treated patients,[20] abdominal fat deposition has been supposed to be a strong predictor of cardiovascular sequel such as coronary heart disease, myocardial infarction, or

stroke [16,17] as well as the metabolic and blood pressure variables.[32]

In our study, abnormalities in the lipid metabolism in the case group was reflected by a significantly increased WHR, which is well in track with some recent large studies undertaken in the United States [7] and India.[21] In a Korean study also, Jeong *et al*, reported WHR to be more consistently related to the dyslipidemic changes than BMI.[33] Furthermore, a significant dependence of the HOMA-IR on the serum triglyceride level and WHR, as observed in our study [Table 2], indicated a causal relationship between SGA induced dyslipidemia and insulin resistance. It has been suggested that an insulin resistant state accompanies the developmental process of schizophrenia [34-36] that is further complicated by SGA induced dyslipidemia and other biochemical abnormalities. Kluge *et al*, has described an association of increased BMI in olanzapine treated patients with raised levels of serum leptin and cytokines.[20] Reduced levels of adiponectin were suggested to play a role in inducing insulin resistance in olanzapine treated patients.[37] Some authors have reported relationships between serotonin receptors HTR 2C and HTR 2A haplotypes with increased BMI and C peptide levels in these patients.[38] Thus, although it is evident that within 3 months of exposure to olanzapine there is a significant increase in the proportion of subjects meeting the criteria of metabolic syndrome,[7] the exact mechanism of this drug induced abnormal glucose metabolism remains unclear.[39-41] This requires special mention for a need of monitoring the patients on long term olanzapine treatment to minimize the metabolic and cardiovascular consequences. Increased WHR and BMI have been strong predictors of increased body

fat and cardiovascular sequel.[17,20] Asian Indians are a unique ethnic group in terms of body morphology as for any given BMI they have higher central obesity and abdominal fat. Raji *et al*,reported that despite a similar BMI, an altered body composition with greater abdominal fat was associated with hyperinsulinemia, insulin resistance, and dyslipidemia in the Asian Indian population in comparison to their matched Caucasian counterparts.[42] In a South Indian population group, Kaur *et al*,found WHR to be the best predictor for type 2 DM.[24] In our study, the analysis of co-variance revealed that WHR predicted the HOMA-IR values more significantly (F=5.7, *P*=0.037) than did the BMI (F<0.001, *P*=0.0.997) in the case group irrespective of their age and sex. Our findings, thus, extend these views by advocating that SGA induces a predominant abdominal fat deposition that, for any given BMI, turns out to be a major predictive factor for development of insulin resistance and dyslipidemia in schizophrenia patients stabilized on olanzapine in our region. An underlying purpose behind the identification of individuals who develop insulin resistance or manifest the physical indices of obesity, is to prevent the conversion from prediabetes to overt DM, since type 2 DM is considered a predictor of future myocardial infarction risk equivalent to having a diagnosis of CHD.[43] However, early changes in the insulin resistance are not reflected by corresponding alterations in the FBG levels. It is not also practically feasible to measure insulin resistance periodically in all sections of patients in all setups. On the other hand, a periodic measurement of WHR is a much easier and more approachable protocol.

Moreover, our interpretation reiterates the dependence of these anthropometric markers on different cultural and ethnic backgrounds. Adult anthropometry has been recognized as a biomarker of 'early life'[33] and several factors including genetic polymorphism of PPARγ gene[44] and some candidate genes for obesity and metabolic-related traits[45] may influence the variable interpretations of the parameters like BMI and WHR depending on ethnicity and cultural background in different regions. Likewise, polymorphism in genes implicated in circadian regulation or its related downstream pathways have been recently found to play important roles in the regulation of antropomorphic parameters, metabolic profile and insulin resistance in patients with schizophrenia during long-term treatment with SGA.[46] These genetic polymorphisms stress on the fact that the obesity and dyslipidemia induced by the second generation antipsychotics depend largely on the allelic variations of several genes in the population. Our findings, hence, necessitate relevant research works in our region accordingly.

Limitations

A limitation of our study is that we did not perform any formal evaluation of the diet of the participant which might have influenced the FBG and insulin levels. However, as all participants were from a similar geographical area having similar ethnicity and socioeconomic status they had almost similar types of dietary habits. Hence, the dietary factors did not seem to influence the findings in this study, since body weight (as reflected by the BMI) between the case and control group did not show a significant difference.

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