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A CASE CONTROL STUDY TO DETERMINE THE METABOLIC SYNDROME ASSOCIATION WITH A TYPICAL ANTIPSYCHOTIC DRUG (OLANZAPINE) AS SHORT DURATION VS LONG DURATION USAGE

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Abstract:

Objective: *To determine the association of metabolic syndrome with atypical antipsychotic drug (olanzapine) short term versus long term use.****Study Design:*** *Case control study.****Place and Duration of Study:*** *Chemical pathology department Services hospital, Lahore from August, 2018 to July, 2019.****Material and Methods:*** *The study was carried out on 240 subjects, 120 cases and 120 controls. For the purpose of the study cases were divided into four groups A, B, C and D according to the duration of drug use. Group A patients included those who the last the drug olanzapine for the last three months. Group B patients included those who were using the drug olanzapine for the last six months. Group C and D included those who were using the drug for last 1 year and more than one year (2-5 years) respectively. By employing non probability convenience sampling technique the data was collected from patients having the diagnosis of psychosis as per DSM IV modified criteria through a proforma and fasting blood samples were drawn. These samples were tested for fasting serum lipid profile and fasting plasma glucose. The data obtained were analyzed using SPSS version 21. For quantitative data Mean and SD were calculated. For qualitative data frequency and percentages were calculated. Qualitative data was compared using chi square test whereas quantitative data was compared using independent sample t-test.****Results:*** *There was statistically no significant difference in fasting plasma glucose between group A and B and their controls whereas in group C and D these levels were significantly high as compared to controls. Triglyceride levels were significantly higher and HDL cholesterol levels were significantly lower in all four groups as compared to controls. Comparison of qualitative data which included waist circumference and blood pressure showed statistically no significant rise for group A whereas waist circumference showed insignificant rise and blood pressure showed statistically significant rise for group B. On the other hand both waist circumference and blood pressure were significantly higher for group C and D as compared to controls. Overall study revealed a graded increase in components of metabolic syndrome with duration of olanzapine use. Out of thirty patients in each group two patients in group A, 5 in group B, 7 in group C and 10 patients in group D developed metabolic syndrome as per NCEP ATP III modified criteria.****Conclusion:*** *Development of metabolic syndrome is strongly associated with long term use of atypical antipsychotic drug olanzapine.*

Keywords: *Atypical antipsychotic, Diabetes mellitus, Dyslipidemia, Metabolic syndrome, Olanzapine.*

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INTRODUCTION:

Metabolic syndrome (MS) is an important risk factor for cardiovascular disease and type 2 diabetes. It consists of a constellation of metabolic abnormalities that include insulin resistance, hypertension, dyslipidemia and central obesity. The exact cause is not known but may be multifactorial. Insulin resistance is central to the development of metabolic syndrome [1]. Abdominal obesity is associated with MS which has a direct relationship with atherogenesis and subsequent ischemic heart disease and increase in morbidity and mortality. MS has appeared as an epidemic worldwide in adults as well as in elderly. It has emerged as an important public health issue [2]. NCEP ATP III gave definition of metabolic syndrome in 2001, which included three or more of the following five attributes [3].

1. Central obesity: Waist circumference>102 cm (M), >88cm (F)
2. Hypertriglyceridemia: Triglycerides >150 mg/dl
3. Low HDL cholesterol <40mg/dl (M),<50 mg/dl (F)
4. Hypertension: BP >130/85 mmHg or on medication for hypertension.
5. Fasting plasma glucose >100mg/dl

Individuals with major mental illness are a high-risk group for cardiac and metabolic derangements due to genetic predisposition, developmental and environmental stressors and their life style. This risk is compounded when they receive antipsychotic medication [2]. Metabolic syndrome and cardiovascular disease are important causes of morbidity and mortality among patients with severe mental illnesses receiving atypical antipsychotic drugs. There is a need for formulation of guidelines for screening, monitoring and managing the patients on antipsychotics in general and atypical antipsychotics for potential metabolic problems. Many mechanisms related to various drugs lead to these problems which include effects on glucose, lipid metabolism and effects on food intake [4]. Schizophrenia, schizoaffective disorder, schizophreniform disorder, bipolar illness, depression with psychotic features are important examples of psychotic disorders in which atypical antipsychotic drugs are used. Such patients when treated with olanzapine, clozapine and other atypical antipsychotics have higher abdominal waist circumference values, higher frequency of abnormal glucose levels, and dyslipidemias [5]. Physician should be aware that that the treatment for schizophrenia and other major psychotic disorders involves the right balance for the patients in terms of adverse effects versus benefits [6].

Our study is based on this NCEP ATP III definition of metabolic syndrome. Metabolic syndrome is a growing global challenge having several modifiable risk factors including diet, exercise, sedentary life style, and obesity. and non-modifiable risk factors like age, race, gender, genetics. Focusing on modifiable risk factors is a way forward to address this growing problem [2].

MATERIAL AND METHODS:

This was a case control study conducted in chemical pathology department Army Medical College, Rawalpindi in collaboration with AFIMH Rawalpindi after approval by ethical review committee of AM college. The data collection was completed within 11 months from 11th November 2014 to 31st October 2015. Study participants were patients with the diagnosis of psychosis as per DSM 4 modified criteria whereas age matched controls without psychosis and any major illnesses were also included in this study as control group. Patients taking drugs affecting lipid metabolism (example lipid lowering drugs, oral contraceptives etc.) were excluded from the study. Patients with history of infection, inflammation or other systemic diseases effecting serum lipid levels and glucose levels were also excluded. Patients who did not give consent were also not included in the study. The total sample size taken was 240 (120 cases and 120 controls). Non probability convenience sampling was used. A questionnaire was designed to collect data from the participants.

Informed consent was taken from every study participant before taking the interview, drawing blood sample and recording waist circumference and blood pressure. The participants were interviewed by using the questionnaire. Fasting for glucose estimation sample was taken in tube containing sodium fluoride. For lipid profile sample was taken in plain tube. Samples were centrifuged and analyzed within two hours on fully automated chemistry analyzer selector (Merck).

Data were validated after double entry and then analysis was carried out using SPSS version 21. For the purpose of the study the patients were divided into four groups i.e. those using drug olanzapine for up to 3 months, those using drug for up to 6 months, those using drug (olanzapine) for up to 1 year and those using drug olanzapine for >1year (2-5 years). For quantitative data which included fasting plasma glucose, HDL cholesterol and triglycerides mean and SD were calculated and means were compared among cases and controls using independent samples t- test. For qualitative data which included blood pressure and

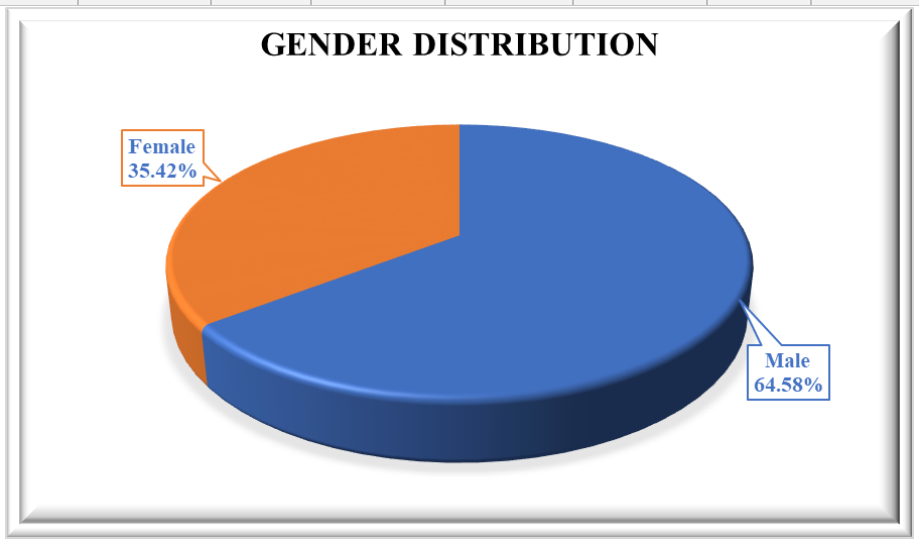
waist circumference, frequency and percentages were calculated and the data was compared among cases and controls using chi- square test.

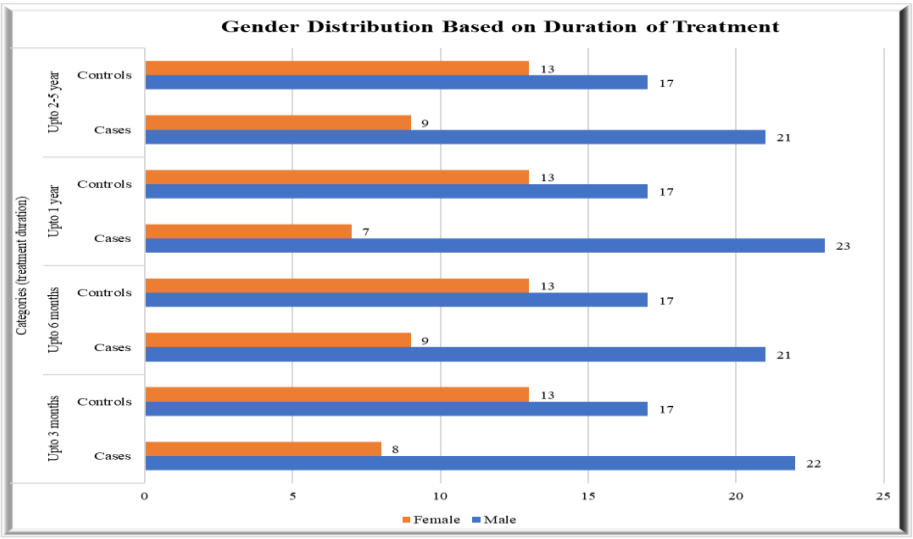
RESULTS:

Out of total 240 participants in the study 64.58% were males and 35.42% were females. The mean age was (mean ± SD) 35 ± 7 years for cases and 35 ± 9 years for controls. The age differences among cases and controls were not statistically significant. For the purpose of the study 120 patients were further divided into four categories, based on duration of olanzapine use. These categories included duration of olanzapine use for up to 3 months, up to 6 months, up to 1 year and more than 1 year (2-5 years) with each category containing 30 patients. For the diagnosis of metabolic syndrome NCEP ATP III modified criteria was used. The gender and patient distribution of cases and controls is shown in table-I.

Table No 01: Patient Distribution Based on Duration of Treatment

Gender	Categories (treatment duration)								Total
	Upto 3 months		Upto 6 months		Upto 1 year		Upto 2-5 year		
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls	
Male	22 (73.3%)	17 (56.7%)	21 (70%)	17 (56.7%)	23 (76.67%)	17 (56.7%)	21 (70%)	17 (56.7%)	155 (64.58%)
Female	8 (26.7%)	13 (43.3%)	9 (30%)	13 (43.3%)	7 (23.33%)	13 (43.3%)	9 (30%)	13 (43.3%)	85 (35.42%)
Total	30	30	30	30	30	30	30	30	240





Serum triglycerides were found to be significantly elevated whereas HDL-Cholesterol was significantly decreased in all four categories when difference of means was compared using independent samples t test as is shown in table-II. Fasting plasma glucose was found to be insignificantly raised, statistically, among the first two groups i.e. olanzapine use for up to 3 months and olanzapine use for up to 6 months where as it was found to be significantly raised among the last two groups i.e. olanzapine use for 1 year and more than 1 year (2-5 years). The difference of means among each of the four groups was compared by using independent samples t-test and p value was calculated. The mean ± SD and p-value for each of the four categories for triglycerides, HDL, and fasting plasma glucose are given in table-II.

Table No 02: Comparison of lipids and glucose levels among cases and controls

		Categories (treatment duration)			
		Upto 3 Months	**Upto 6 months**	**Upto 1 year**	**>1 year(2-5yrs)**
Triglyceride	Cases (Mean±SD)	1.552 ± 0.1918	1.44±.409	1.69 ± 0.288	1.80 ± .27006
	Controls (Mean±SD)	1.348 ± 0.083	1.27±0.092	1.3173 ± 0.136	1.36 ± .13323
P-value		0.001	0.029	0.001	0.001
HDL	Cases (Mean±SD)	1.15 ± 0.1264	1.131 ± 0.131	1.10 ± 0.1739	1.2060 ± 0.14335
	Controls (Mean±SD)	1.2437 ± 0.11684	1.26 ± 0.108	1.258 ± .0976	1.2393 ± .1121
P-value		0.005	0.000	0.000	0.045
Fasting Plasma Glucose	Cases (Mean±SD)	5.2603 ± 0.30439	5.42 ± 0.586	5.7 ± 0.9362	5.86 ± 1.10
	Controls (Mean±SD)	5.1833 ± 0.24925	5.31 ± 0.174	5.3 ± 0.17118	5.2470 ± .205
P-value		0.288	0.354	0.030	0.005

Comparison of qualitative data which include waist circumference and blood pressure in group A showed no statistically significant rise whereas blood pressure was significantly higher in group B. On the other hand, categorical variables i.e. blood pressure and waist circumference showed statistically significant rise for up to 1 year use i.e. group C and greater than 1 year (2-5 year) use i.e. group D. This is shown in tables-III and IV. Overall study revealed 2 out of 30 patients for group A, 5 out of 30 patients for group B, 7 out of 30 patients for group C and 10 out of 30 patients for group D who had developed metabolic syndrome as per NCEP ATP III modified criteria.

Table No 03: Comparison of Waist Circumference Among Cases and Controls

Categories			**Waist Circumference**				Total	Chi-square test
Duration of use of olanzapine			1 wc male >102cm	2 wc female >88cm	3 wc male normal<1 02cm	4 wc female normal<88cm		Asymp Sig. (2-sided)
<6 months (3 months)	Groups	1 Olepra	0	0	22	08	30	0.176
		2 Controls	0	0	17	13	30	
	Total		0	0	39	21	60	
6 months	Groups	1 Olepra	1	2	20	07	30	0.169
		2 Controls	0	0	17	13	30	
	Total		1	2	37	20	60	
1 year	Groups	1 Olepra	5	1	18	06	30	0.035
		2 Controls	0	0	17	13	30	
	Total		5	1	35	19	60	
>1 year (2-5 year)	Groups	1 Olepra	6	2	07	07	30	0.019
		2 Controls	0	0	13	13	30	
	Total		6	2	20	21	60	

Table No 04: Comparison of Blood Pressure Among Cases and Controls

Categories			BP.cat		Total	Chi-square test
Duration of use of olanzapine			1 normal (<130/85)	2 abnormal (>130/85)		Asymp. Sig.(2-sided)
Upto 3 months	Groups	1 Olepra	27	3	30	0.237
		2 Controls	30	0	30	
	Total		57	3	60	
Upto 6 months	Groups	1 Olepra	25	5	30	0.020
		2 Controls	30	0	30	
	Total		55	5	60	
Upto1 year	Groups	1 Olepra	18	12	30	0.000
		2 Controls	30	0	30	
	Total		48	12	60	
>1 year (2-5 years)	Groups	1 Olepra	18	12	30	0.000
		2 Controls	30	0	30	
	Total		48	12	60	

DISCUSSION:

Low HDL cholesterol levels have been associated with increased cardiovascular mortality and HDL levels below 50mg/dl in women and 40 mg/dl in men are considered hazardous to health. Dyslipidemia (decreased HDL cholesterol) is known to increase cardiovascular mortality and morbidity as well as health care cost5. Individuals exposed to olanzapine are at an increased risk for diabetes and dyslipidemia [6]. Newcomer et al. found significant weight loss, a marked drop in triglyceride and total cholesterol levels and a marked increase in HDL levels in obese patients 16 weeks after switching over to aripiprazole from olanzapine use [7]. The results of our study were consistent with literature [5,6,7,8] showing an increase in dyslipidemia with increase in duration of atypical antipsychotic use.

Clozapine and olanzapine use are associated with great weight gain, diabetes and dyslipidemia (increased triglycerides) [9]. Metabolic dysregulation manifesting initially as weight gain rapidly results in obesity with concurrent dyslipidemia, impaired glucose tolerance which is likely to contribute to cardiovascular disease in patients with severe mental illness on atypical antipsychotics [10]. Our results of increase in serum triglycerides with increase in duration of olanzapine use were consistent with literature and other studies [11,12].

A blood pressure of >130/85 mmHg is considered elevated as per NCEP ATP III modified criteria. The relationship between hypertension and insulin resistance is well established13. Incidence of hypertension increases with increase in duration of olanzapine use [13]. Our results were consistent with literature [13] showing an increase in incidence of olanzapine use up to one-year use whereas they were inconsistent for more than one-year (2-5 year) drug use showing no further increase from one-year use (similar results for one year and more than one-year drug use).

Many studies have suggested the role of second-generation antipsychotics in the occurrence of metabolic abnormalities including glucose dysregulation [7]. Some studies have provided evidence for an increased prevalence of glucose abnormalities such as impaired fasting glucose and insulin resistance in patients on antipsychotic drugs [14,15]. Our results showed minimal disruption of glucose at short term use and maximal disruption at long term use with increased incidence of diabetes and impaired fasting glucose with increase in durations of drug use. Our results were consistent with literature [7,14,15].

Weight gain especially intra-abdominal obesity is a known root cause of MS and insulin resistance. Obesity (increased waist circumference) in patients with severe mental disorders and on treatment with atypical antipsychotics is reported to be twice than that of general population [16]. In our study NCEP ATPIII criteria of increased waist circumference was followed. Our findings were consistent with literature [17,18,19] showing an increase in waist circumference with increase in duration of drug use.

CONCLUSION:

Development of metabolic syndrome is strongly associated with long term use of atypical antipsychotic drug olanzapine. It is recommended that olanzapine use should be limited to short term use only. For long term use other atypical antipsychotics with less known side effects such as ziprasidone or aripiprazole may be used. More research for development of newer, safer

and more effective atypical antipsychotics with less association with metabolic syndrome is required.

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