Research Article

Atypical Antipsychotics and Dyslipidemia- Experience at Psychiatry Hospital Hyderabad, Pakistan

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Abstract

Objective: To evaluate effects of atypical antipsychotics on the serum lipid contents of inpatients suffering from psychosis at Psychiatry Hospital Hyderabad, Pakistan.

Methods: Total 160 patients suffering from psychosis were randomly selected from psychiatry hospital Hyderabad, Sindh, Pakistan during October 2014 to September 2015 along with 188 control subjects and they were followed from baseline (drug naïve-first-episode psychosis (FEP) patients); on admission to 3rd month of their treatment with three different antipsychotic drugs (i.e. risperidone, olanzapine and clozapine). Blood samples were collected on admission and after completion of each month for analysis of serum lipid contents.

Results: Concentration of serum high-density lipoprotein cholesterol (HDL–C), total cholesterol (TC), triglycerides (TGs), very low-density lipoprotein cholesterol (VLDL–C) as well as total lipids (TL) were significantly reduced in baseline psychotic patients when compared with controls. When 2nd and 3rd months risperidone treated psychotic patients were compared with baseline psychotic patients, TC, TG, VLDL–C and TL were significantly increased. Serum lipid contents in Olanzapine and Clozapine treated psychotic patients were significantly increased in 2nd and 3rd months as compared to baseline psychotic patients, whereas, reverse was true for HDL–C. The low-density lipoprotein cholesterol (LDL–C)was increased in 2nd month treated psychotic patients as compared to baseline psychotic patients. When all three drugs were compared, clozapine was found highly associated with dyslipidemia.

Conclusion: Atypical Antipsychotics may play a role in developing dyslipidemia. Among three psychotic drugs Clozapine is the most significant in causing dyslipidemia to the psychotic patients in Pakistan.

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Introduction

Schizophrenia and other psychosis are prodigious psychological disorders among the young population at the onset of adulthood.[1] Atypical antipsychotics are commonly used as the first-line pharmacotherapy for psychotic disorders due to the extensive range of efficacy as compared to first

generation antipsychotics and are proven significant in the improvement of schizophrenia and other psychosis treatment.[2] Unfortunately, several metabolic disorders, like hypertriglyceridemia, dysregulation of glucose, obesity and higher levels of serum cholesterol are induced due to the commonly used drugs especially atypical antipsychotics.[3] Diseases of Cardiovascular system playa significant role to increase mortality and morbidity. In spite of the various medicines used for treating psychotic patients some other contributing factors are also causing metabolic syndrome, such as smoking, obesity, inactivity, and dietary risk of cardiovascular diseases.[1] More than 70% mortality rate of coronary heart diseases can be caused by conventional risk variables such as hyperlipidemia, hypertension, diabetes and smoking, with the last two profoundly common in patients with schizophrenia.[4] Recent evidence suggests that a variety of metabolic disturbances, including weight gain, hyperglycemia, diabetes, and hyperlipidemia, may be associated with exposure to certain new generation antipsychotics.[5] All these effects contribute to increased mortality among cardiovascular disease patients.[6] Inspite of these complications, Second generation antipsychotic drugs are broadly used due to their higher medicinal efficacy as compared to first generation antipsychotic drugs.[7] Various investigations demonstrate the elevated serum lipid contents in schizophrenia patients in contrast to healthy population.[5] This dyslipidemia has been regarded as a result of antipsychotic medication and lifestyle factors, but dyslipidemia has also been demonstrated in unmedicated schizophrenia patients.[8] The course as well as result of schizophrenia is viewed as heterogeneous. The way of the connection between serum lipid contents, metabolism of lipids and clinical features of psychosis is still unknown.[9] Hence, present study was aimed to evaluate the atypical antipsychotic drug effects on the serum lipids of psychotic in patientsat Psychiatry Hospital Hyderabad, Pakistan.

Patients and Methods

A total number of 160 patients suffering from psychosis (80=Risperidone, 40= Olanzapine, 40=Clozapine); all males, were randomly selected from Psychiatry Hospital Hyderabad, Sindh, Pakistan and they were followed from baseline (drug naïve-first-episode psychosis (FEP) patients); on admission to 3rd month of their treatment with three different antipsychotic drugs (i.e. risperidone, olanzapine and clozapine). All the patients belonged to low socio-economic status of mean age range 25.8 ± 3.4 to 40.3±6.1 years. They were mainly laborer or jobless with sedentary life style. A comparative group of 188 locality matched healthy individuals of same age and gender having negative personal or family history of psychotic disorders, obesity, diabetes and hypertension with normal BMI were also included in present study as controls from Hyderabad and adjoining areas. This study was carried out in October 2014 to September 2015. After obtaining a verbal consent, 5 ml fasting (10 to 12 hours) whole blood sample of all psychotic in-patients from baseline (on admission) as well as after completion of each month for 3 months antipsychotic treatment and controls were collected. Ethical approval was obtained from Institutional Ethics Committee, Institute of Biochemistry, University of Sindh, Jamshoro. Serum lipid contents such as TGs, TC, TL, LDL-C as well as HDL-Cwere analyzed on Merck Micro Lab 300 semiautoanlyser, whereas, VLDL-Cwas calculated as serum concentration of TGs divided by five.10-11Statistically whole data was analyzed using MS Excel, 2013. To compare serum lipid contents of control subjects with psychotic patients and baseline to one month, two months as well as three months treated psychotic patients, the student's t-test was applied. Single factor ANOVA was also used to observe the dyslipidemia form baseline to three months treated psychotic patients in all drugs individually and among group of three drugs. Values were evaluated using descriptive statistical methods (mean ± standard deviation [SD]) and findings were considered significant at $p<0.05$.

Results

Total 160 male psychotic patients with mean age range of 25.8±3.4-40.3±6.1 years on antipsychotic drugs for three months, and 188 healthy subjects with same gender and age were recruited for this study. All the serum lipid contents were significantly altered in psychotic patients from baseline to 3rdmonth treatment among all three drugs, except LDL–C in risperidone treated psychotic patients. Significantly decreased serum lipid contents except LDL–C were found in risperidone baseline psychotic patients when compared with controls. Olanzapine baseline psychotic patients revealed significantly low serum TC, HDL–C, TL when compared to controls. Serum TC, HDL–C were significantly decreased, whereas, TG and VLDL–C were found significantly increased in clozapine baseline psychotic patients as compared to controls (table. 1, 2, 3).

Concentration of serum HDL–C, TC, TG, VLDL–C as well as TL were observed significantly reduced in baseline psychotic inpatients when compared with controls. It was found that TC, TG, VLDL–C and TL were significantly increased in 2nd and 3rd months risperidone treated psychotic patients respectively as compared to baseline psychotic patients, whereas, reverse was true for HDL–C, while LDL–C was non-significant gradual increase in all three months when compared to baseline psychotic patients (Table.1).

Table 1: *Month Wise Comparison of Serum Lipid Contents in Psychotic Inpatients Treated with Risperidone*

Lipid contents (mg/dl)	Controls Mean ± SD	Patients with Psychosis				
		Baseline Mean ± SD	1 Month Mean ± SD	2 Month Mean ± SD	3 Month Mean ± SD	ANOVA p-value <0.01
TC	176.7±13.33	160.9±10.17[a]	159.55±8.56	174.9±11.14[*#]	184.2±19.06[**]	<0.001
TG	132.3±8.89	125.8±11.01[a]	137.45±25.81	153.45±12.58[*#]	158.8±9.13[**]	<0.001
HDL–C	46.7±8.09	41.45±4.35[a]	38.8±5.70	33.8±5.63[*#]	30.2±4.45[**]	<0.001
LDL–C	85.3±6.64	82.65±19.33	87.45±20.72	92.6±12.68	98.55±51.64	0.38
VLDL–C	26.46±1.77	25.1±2.20[a]	27.49±5.16	30.69±2.51[*#]	31.76±1.82[**]	<0.001
TL	591.15±16.76	560.8±23.45[a]	573.25±37.73	604.75±17.51[*#]	621.75±60.39[**]	<0.001

ap–value <0.05 when baseline to controls is compared, *p–value <0.05 when baseline to 1 month is compared, #p–value <0.05 when baseline to 2 months is compared, **p–value <0.05 when baseline to 3 months is compared. TC: total cholesterol, TG: triglyceride, HDL–C: high density lipoprotein cholesterol, LDL–C: low density lipoprotein cholesterol, VLDL–C: very low-density lipoprotein cholesterol, TL: total lipids

Table 2: *Month Wise Comparison of Serum Lipid Contents in Psychotic Inpatients Treated with Olanzapine*

Lipid contents (mg/dl)	Controls Mean ± SD	Patients with Psychosis				
		Baseline Mean ± SD	1 Month Mean ± SD	2 Month Mean ± SD	3 Month Mean ± SD	ANOVA p-value <0.01
TC	176.7±13.33	159.4±14.42[a]	168.4±9.82	174.6±7.36[*#]	203.9±8.56[**]	<0.001
TG	132.3±8.89	129.3±3.94	140.3±19.91	159±13.75[*#]	166.7±8.11[**]	<0.001
HDL–C	46.7±8.09	41.5±3.74[a]	39.2±2.48	36±4.24[*#]	28.1±5.40[**]	<0.001
LDL–C	85.3±6.64	85.9±13.93	88.7±11.43	97.8±20.92	105.3±13.49[**]	0.03
VLDL–C	26.46±1.77	25.86±0.78	28.06±3.98	31.8±2.75[*#]	33.34±1.62[**]	<0.001
TL	591.15±16.76	566.1±18.35[a]	586.6±24.29	617.4±21.55[*#]	654±22.15[**]	<0.001

p-value <0.05 when baseline to controls is compared, *p-value <0.05 when baseline to 1 month is compared, *#p-value <0.05 when baseline to 2 month is compared, **p-value <0.05 when baseline to 3 month is compared. TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, VLDL-C: very low density lipoprotein cholesterol, TL: total lipids

Table 3: *Month Wise Comparison of Serum Lipid Contents in Psychotic Inpatients Treated with Clozapine*

Lipid contents (mg/dl)	Controls Mean ± SD	Patients with Psychosis				
		Baseline Mean ± SD	1 Month Mean ± SD	2 Month Mean ± SD	3 Month Mean ± SD	ANOVA p-value <0.01
TC	176.7±13.33	160.1±7.65[a]	167.7±9.03	189.2±9.41[*#]	206±10.94[**]	<0.001
TG	132.3±8.89	140.6±7.27[a]	145.5±13.16	161.7±9.29[*#]	187±34.47[**]	<0.001
HDL-C	46.7±8.09	43.4±2.79[a]	41±2.94	34.7±3.05[*#]	23.4±5.89[**]	<0.001
LDL-C	85.3±6.64	86.9±10.22	89.3±8.09	92.4±6.2	108.4±7.62[**]	<0.001
VLDL-C	26.46±1.77	28.12±1.45[a]	29.1±2.63	32.34±1.86[*#]	37.4±6.89[**]	<0.001
TL	591.15±16.76	581±20.92	593.5±22.9	628±15.85[*#]	674.8±35.7[**]	<0.001

p – value <0.05 when baseline to controls is compared, *p – value <0.05 when baseline to 1 month is compared, *#p – value <0.05 when baseline to 2 month is compared, **p – value <0.05 when baseline to 3 month is compared. TC: total cholesterol, TG: triglyceride, HDL – C: high density lipoprotein cholesterol, LDL – C: low density lipoprotein cholesterol, VLDL – C: very low density lipoprotein cholesterol, TL: total lipids

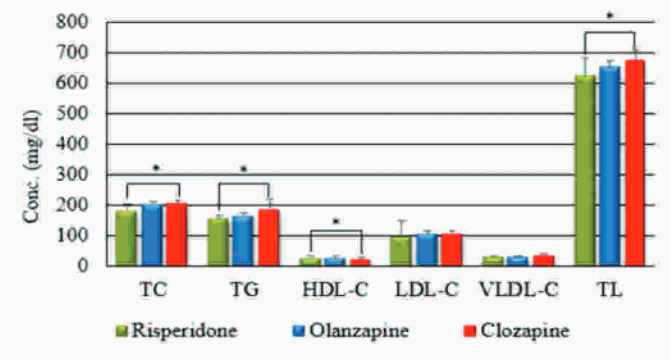
Table 4: *Correlation of Antipsychotics Treatment with Month Wise Serum Lipid Content Alterations from Baseline to Third Month Among All Three Drugs*

Lipid contents (mg/dl)	Risperidone			Olanzapine			Clozapine		
	1M	2M	3M	1M	2M	3M	1M	2M	3M
TC (BL)	0.11	0.61^{b*}	0.72^{c*}	0.37	0.69^{b*} 0.77^{d**}	0.81^{c**} 0.65^{f*}	0.41	0.61^{b*}	0.64^{c*} 0.76^{f*}
TG (BL)	0.21	0.78^{b*}	0.76^{c*}	0.27	0.86^{b**} 0.76^{d*}	0.88^{c**} 0.74^{f*}	0.43	0.67^{d*}	0.89^{f**}
HDL-C (BL)	0.09	-0.23	-0.59^{c*}	-0.18	-0.52	-0.68^{c*}	-0.14	-0.78^{b**} 0.65^{d*}	-0.86^{c**} 0.60^{f*}
LDL-C (BL)	0.33	0.14	0.36	0.24	0.41	0.82^{c**}	0.49	0.63^{d*}	0.50
VLDL-C (BL)	0.21	0.78^{b*}	0.76^{c*}	0.27	0.86^{b**} 0.76^{d*}	0.88^{c**} 0.74^{f*}	0.43	0.67^{d*}	0.89^{f**}
TL (BL)	0.41	0.69^{d*}	0.34	0.42	0.65^{b*}	0.70^{f*}	0.14	0.81^{d*}	0.73^{c*}

BL= baseline, M= month. Significant Correlation: *p-value <0.05, **p-value <0.01, a= significant correlation between BL & 1M, b= significant correlation between BL & 2M, c= significant correlation between BL & 3M, d= significant correlation between 1M & 2M, e= significant correlation between 1M & 3M, f= significant correlation between 2M & 3M.

Serum lipid contents in Olanzapine and Clozapine treated psychotics were significantly increased in 2nd and 3rd months treated psychotic patients, except LDL–C in 2nd month treated psychotic patients as compared to baseline psychotic patients, whereas, HDL–C was significantly decreased in 2ndand 3rdmonth treated psychotic patients as compared to baseline psychotic patients (Table. 2,3).

The serum TC, TG and TL were significantly highly increased in Clozapine drug treated psychotic patients followed by Olanzapine and Risperidone, whereas, reverse was found for HDL–C (Figure. 1).



*p <0.01, TC= Total cholesterol, TG= Triglycerides, HDL-C= High density lipoprotein cholesterol, LDL-C= Low density lipoprotein cholesterol, VLDL-C= Very low density lipoprotein cholesterol, TL= Total lipids

Figure.1 *Comparison of serum Lipid contents on completing 3 months with 3 different antipsychotic drugs*

In table 4,significantly positive correlation of serum TC, TG and VLDL-C in 2nd and 3rd month was found with baseline Risperidone and Olanzapine treated psychotic patients, serum TL was found significantly positively correlated in 2nd month with 1st month whereas, HDL–C in 3rd month was significantly negatively correlated with baseline at p-value <0.05. The serum levels of TC, TG and VLDL-C of Olanzapine treated psychotic patients were also significantly positively correlated in 1st month with 2nd month as well as 2nd month with 3rd month p-values <0.01 and <0.05.LDL–C was significantly positively correlated in 3rd month as compared to baseline at p-value <0.01 and TL in 2nd month with baseline and 3rd month at p-value <0.05. Serum TC of 2ndand 3rd months Clozapine treated psychotic patients was significantly positively correlated to baseline and 3rd month with 2nd month at p-value <0.05. Concentrations of serum VLDL-C and TG in 2nd month showed a significant positive correlation with 1st and 3rd month at p-value <0.05 and <0.01 respectively, 2nd month serum LDL–C was found significantly positively correlated with 1st month, whereas, 2nd month serum TL was significantly positively correlated with 1st month and of 3rd month with baseline at p-value <0.05. Serum levels of HDL-C in 2nd and 3rd months presented significant negative correlation with baseline psychotic patients at p-value <0.01. On other hand serum HDL-C of 2nd month described significant positive correlation to 1st and 3rd months at p-value <0.05.

Discussion

Novel antipsychotics may increase the possibility of hyperlipidemia, is evident from experimental studies as well as emergent clinical concern. In recent, it was suggested by Baptista et al, that antipsychotic drugs may possibly give rise to insulin resistance, speedy body weight expansion and enhance appetite which, thus, might be the cause of dyslipidemia in susceptible people.[12] Sengupta et al. in 2008 revealed that lipid metabolites of drug-naïve psychotic patients do not fluctuate in contrast to healthy controls, but Verma et al. in 2009 reported significantly elevated serum levels of TC and LDL-C in healthy controls as compared to drug naïve psychosis patients, whereas, Zaki et al. in 2014 reported the elevated levels of serum TC and TG in drug naive (baseline) psychotic patients when compared with healthy controls and reverse was found for HDL-C.[13-,15] In present study, dyslipidemia was also seen in baseline psychotic patients when compared to controls (table. 1, 2, 3), it may be due to unhealthy life style, because, primarily the patients were found with sedentary life style in present study. Psychiatric patients frequently exhibit unhealthy life style and do lesser daily exercise as compared to general population.

Clinical epidemiological investigations had provided another connection between antipsychotic treatment and expanded occurrence of hyperlipidemia[16]. DeHert et al. in 2011 performed a study in which he reported the highest risk of dyslipidemia in Clozapine and Olanzapine antipsychotic drugs, whereas, risperidone confers an intermediate risk of this metabolic abnormality.[17] These results also support our study findings mentioned in figure 2, in which we have also found the highest levels of dyslipidemia in clozapine treated psychotic patients rather than olanzapine and risperidone treated patients. Casey et al. performed a 4 week study and statistically reported a non-significant increase in serum concentration of total cholesterol in both risperidone as well as olanzapine along with divalproex treated patients, whereas, Lindenmayer et al. revealed significantly increased serum total cholesterol levels in a randomized two-fold visually impaired control trial.[18,19] In 2006 Olfson et al. conducted a planned 3 week random trial treatment by olanzapine and found the significantly increased serum levels of triglycerides in fasting.[16] In present study, we found significantly raised serum lipid contents in Olanzapine, Clozapine and also in Risperidone treated psychotic patients from baseline to 3rd month treated psychotic patients, except LDL–C (Table. 2,3). These results confirm the study of Casey et al.that mostly studies regarding dyslipidemia are linked to antipsychotic drugs.[20] Olanzapine as well as Clozapine drugs have the most grounded relationship with the most noteworthy increase of serum TG besides LDL–C and TClevels, whereas, decreased HDL–Clevels.[17]

In 2002 Koro et al. investigated the databases of greater than 18000 patients with schizophrenia and he found that dyslipidemia was five time greater in olanzapine treated patients as compared to controls.[20] Hyperlipidemia was reported in olanzapine treated patients within first few months in a small observational study done by Melkersson et al. in 2000.[21] Study of Correllet al. reported that risperidone has been associated with a low risk of adverse effects on serum lipids as repeated in present study (Table 1) especially on cholesterol and triglyceride levels.[22] In 2004 a study was conducted by Almeras et al.on patients treated with risperidone and olanzapine for 6 months. The results of Almeras et al. are comparable with present study, in which he found the higher levels of LDL–C, triglyceride and decreased levels of HDL–C in olanzapine treated patients as compared to risperidone treated patients or control group, whereas levels of HDL–C, LDL–C, TC as well as TG were also decreased in risperidone treated patients in contrast to control group.[23]

We are the first to explore the association of antipsychotic drugs (risperidone, olanzapine and clozapine) with serum lipid contents alteration in a three-month's follow-up of psychotic patients in present study through correlation (table 4) that clozapine followed by olanzapine alters the serum lipid contents namely serum TC, TG, HDL-C, VLDL-C and total lipids in three months of psychotic treatment.

Conclusion

Atypical Antipsychotics may play a role in developing dyslipidemia. Among three psychotic drugs Clozapine most significantly associated with dyslipidemias among the psychotic patients in Pakistan.

Limitations of study

In this study number of patients suffering from psychosis is not large enough, though ideally larger number of sample population is required and similar type of studies should be carried out for a long period on psychotic patients treated with all antipsychotic drugs that are available and are extensively used by

the hospitals to cure psychotic patients in Pakistan.

Ethical Approval: Given

Conflict of Interest: None

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