Metabolic Issues in Schizophrenic Patients Receiving Antipsychotic Treatment

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Received: 29 August 2013 / Accepted: 27 December 2013 / Published online: 23 January 2014
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Abstract Schizophrenia is a psychotic disorder with a complex pathophysiology and requires treatment that includes long term administration of antipsychotics that is said to be associated with metabolic syndrome. This study was designed to evaluate the impact of seven different antipsychotics prescribed to schizophrenic patients, on development of metabolic syndrome in the patients. A total of 210 patients with schizophrenia (30 patients in each drug therapy group) were recruited according to ICD-10 criteria and were assigned to receive the drug for 16 weeks. Measurement of anthropometric (body weight, waist circumference, blood pressure) and biochemical parameters (glucose, insulin, HOMA-IR, triglycerides, LDL, HDL) was done and the patients were subjected to ATP-III defined criteria for

metabolic syndrome. Patients undergoing treatment with olanzapine were more prone to metabolic syndrome as the drug induces weight gain after 16 weeks of treatment. It also induces dyslipidemia ($P < 0.001$) and hyperglycemia ($P < 0.01$). Clozapine was found to be second most potent drug in inducing metabolic syndrome as the weight in clozapine treated patients increased after 16 weeks, along with a significant increase in glycemic ($P < 0.001$) and lipid parameters ($P < 0.01$). Aripriazole and amisulphride are comparatively safer drugs as their role in inducing metabolic abnormalities in schizophrenic patients was insignificant, although the impact of long term administration of these drugs needs to be explored. It is clear from the study that antipsychotic treatment induces metabolic syndrome so, it becomes important that the metabolic and cardiovascular risk factors should be surveillance regularly in schizophrenic patients undergoing antipsychotic treatment.

Keywords Metabolic syndrome · Typical antipsychotics · Insulin resistance · HOMA-IR · ATP III · Atypical antipsychotics

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Introduction

Schizophrenia is a psychiatric disorder with a complex pathophysiology and a broad range of behavioral, neurodevelopmental, structural and biological abnormalities in the perception, that may affect all five senses manifesting mainly as auditory hallucinations, paranoid or bizarre delusions or disorganized speech and thinking with significant social or occupational dysfunction affecting 1.4–4.6/1,000 population [1]. Studies have indicated a higher prevalence of metabolic syndrome in persons with serious mental illness [2] which may be attributed to mood disorders, psychotic

disorders and certain lifestyle factors such as, sedentary habits and high fat and carbohydrate intake in diet.

Treatment of schizophrenia and other mental disorders include long term administration of antipsychotic agents, rehabilitation, family and community support and education [3]. Although the drugs used are highly effective and have become the cornerstone for the treatment of schizophrenia as they reduces positive symptoms, yet they are also associated with extra pyramidal symptoms, tardive dyskinesia and harsh side effects [4]. Antipsychotic drugs usually prescribed for the treatment of schizophrenia have recently been found to be associated with risk factors of metabolic syndrome such as hypertension, obesity, insulin resistance, low level of HDL and high levels of triglycerides [5–7]. The clustering of these factors may contribute in the development of diabetes mellitus and coronary artery disease [8]. The present study is an attempt to examine both conventional and atypical antipsychotics prescribed for the treatment of schizophrenia, for their role in inducing metabolic syndrome, diabetes and cardiovascular diseases.

Materials and Methods

The study was carried out on 210 subjects of both sexes selected from the IPD/OPD of Psychiatric Centre of SMS Medical College and attached hospitals. They were screened and classified as schizophrenics if they met the ICD-10 diagnostic criteria and were treatment naïve since last 3 months. The patients were further divided into seven groups of 30 each according to the treatment with antipsychotics including haloperidol as conventional drug and olanzapine, risperidone, quetiapine, clozapine, amisulphide, aripriazole as atypical antipsychotics in therapeutic flexible clinical dose regimen. The patients suffering from any chronic disorder like diabetes, hypertension, cirrhosis, neoblastic disorder, asthma, renal disease, hypo and hyperthyroidism were excluded from the study. These 210 patients, divided into seven groups of 30 patients each according to the type of antipsychotic given for 16 weeks and were observed for the changes in the anthropometric and biochemical parameters. The clinical and anthropometric specifications of the patients were recorded with the help of a questionnaire filled at the time of admission. Venous blood from each subject after an overnight fast was collected from anticubital vein in plain tubes and serum was separated by centrifugation at 2,000 rpm for 15 min and in the tubes with fluoride (for glucose estimation). Anthropometric assessment was done by measuring body weight (kg), waist circumference (cm), blood pressure (mm/Hg) while biochemical profile was assayed on a fully automated analyser (OLYMPUS AU400). Blood glucose was estimated by GOD-POD method [9], serum cholesterol

by CHOD-PAP method [10], serum triglycerides by GPO-PAP method [10], HDL and LDL cholesterol by direct homogeneous method [11], insulin by using chemiluminiscent assay [12] and HOMA-IR [13] by the formula fasting glucose (mmol/ml) = fasting insulin(μu/ml)/22.5.

Subjects after receiving antipsychotic treatment for 16 weeks were subjected to ATP-III defined criteria for metabolic syndrome, according to which metabolic syndrome sufferers were identified by, as having three or more of the following [14]:

- (a) Elevated waist circumference: men: ≥ 90 cm and women ≥ 80 cm.
- (b) Elevated triglycerides: ≥ 150 mg/dl.
- (c) Reduced HDL cholesterol: men: < 40 mg/dl and women: < 50 mg/dl.
- (d) Elevated blood pressure: 130/85 mmHg.
- (e) Elevated fasting glucose: ≥ 110 mg/dl.

Statistical analysis was done by Student's 't' test and results were expressed as $\pm$ SD while significance was evaluated by *P* value.

Results

The study population was divided into seven groups with 30 subjects each according to the antipsychotic treatment given. Patients were observed for changes in the anthropometrical and biochemical parameters after 16 weeks of drug treatment and the following results were interpreted.

On analysis of data, it was found that there was significant weight gain in patients receiving atypical antipsychotics i.e. Olanzapine, Clozapine, Quetiapine and Risperidone. However the atypical third generation drugs Aripriazole and Amisulphride have no significant effect on body weight. Similarly for waist circumference Olanzapine and Clozapine showed significant increase after 16 weeks of antipsychotic treatment. Haloperidol the conventional antipsychotic drug did not show any significant change in body weight and waist circumference of the patients receiving this medication for 16 weeks (Table 1).

Another anthropometric parameter studied was changes in blood pressure after 16 weeks of antipsychotic treatment it was observed that Olanzapine and Risperidone showed significant change in diastolic pressure without any change in systolic blood pressure. Haloperidol and Quetiapine were the only drug that affected both systolic and diastolic blood pressure (Table 2).

The biochemical parameters i.e. glycemic and lipid parameters were also studied in seven drug groups that predispose the subjects to an increased risk of metabolic syndrome. Blood glucose values significantly increased in all the subjects except the patients receiving Aripriazole and amisulphride.

Table 1 Changes in body weight and waist circumference after administration of antipsychotics

Drugs	Body weight (kg)			Waist circumference (cm)		
	Base line	After 16 weeks	<i>P</i> value	Base line	After 16 weeks	<i>P</i> value
Olanzapine	65.5 ± 4.72	68.53 ± 4.79	<0.001	89.46 ± 5.27	92.72 ± 5.51	<0.01
Haloperidol	66.1 ± 3.30	67.16 ± 3.62	>0.05	88.7 ± 5.85	89.29 ± 5.92	>0.05
Clozapine	65.03 ± 3.18	67.83 ± 3.53	<0.01	88.61 ± 7.24	93.15 ± 9.14	<0.05
Quetiapine	64.46 ± 3.14	66.36 ± 3.35	<0.05	88.26 ± 6.46	89.4 ± 6.85	>0.05
Risperidone	64.46 ± 3.14	66.26 ± 3.45	<0.05	88.26 ± 6.46	89.64 ± 6.85	>0.05
Amisulphride	66.13 ± 3.36	67.11 ± 3.63	>0.05	88.73 ± 5.90	89.22 ± 5.87	>0.05
Aripriazole	66.13 ± 3.36	67.11 ± 3.63	>0.05	88.73 ± 5.90	89.22 ± 5.87	>0.05

Significant change: *P* < 0.01; *P* < 0.05; *P* < 0.001**Table 2** Changes in blood pressure after administration of antipsychotics

Drugs	Blood pressure (mmHg)					
	Systolic			Diastolic		
	Base line	After 16 weeks	<i>P</i> value	Base line	After 16 weeks	<i>P</i> value
Olanzapine	119.83 ± 7.58	123.6 ± 7.58	>0.05	78.53 ± 4.55	81.9 ± 3.82	<0.05
Haloperidol	117.76 ± 4.76	120.86 ± 5.24	<0.05	77.1 ± 4.70	80 ± 5.03	<0.05
Clozapine	125.66 ± 12.20	129.56 ± 13.0	>0.05	81.2 ± 6.33	84.23 ± 6.04	>0.05
Quetiapine	118 ± 4.80	120.6 ± 5.29	<0.05	77.23 ± 4.55	80 ± 5.0	<0.05
Risperidone	118. ± 4.80	120.6 ± 5.29	>0.05	77.23 ± 4.55	80 ± 5.03	<0.05
Amisulphride	122.03 ± 8.13	123.2 ± 8.19	>0.05	80.7 ± 7.88	81.9 ± 7.92	>0.05
Aripriazole	122.26 ± 8.12	123.1 ± 8.06	>0.05	80.8 ± 7.93	81.8 ± 7.9	>0.05

Significant change: *P* < 0.01; *P* < 0.05; *P* < 0.001**Table 3** Changes in blood glucose, insulin levels and HOMA-IR after administration of antipsychotics

Drugs	Blood glucose (mg)			Insulin (μu/ml)			HOMA-IR		
	Base line	After 16 weeks	<i>P</i> value	Base line	After 16 weeks	<i>P</i> value	Base line	After 16 weeks	<i>P</i> value
Olanzapine	82.73 ± 8.27	103.17 ± 12.18	<0.001	13.48 ± 5.89	20.75 ± 11.41	<0.01	2.81 ± 1.41	5.51 ± 3.64	<0.001
Haloperidol	80.36 ± 7.67	88.13 ± 7.83	<0.001	12.75 ± 5.65	14.91 ± 5.98	>0.05	2.57 ± 1.30	3.28 ± 1.50	>0.05
Clozapine	84.5 ± 7.93	100.87 ± 12.17	<0.001	13.53 ± 4.83	20.21 ± 7.71	<0.001	2.83 ± 1.09	5.17 ± 2.54	<0.001
Quetiapine	83.43 ± 7.76	94.73 ± 10.9	<0.001	14.44 ± 6.01	18.46 ± 6.25	<0.05	3.01 ± 1.41	4.40 ± 1.91	<0.01
Risperidone	84.17 ± 7.90	95.52 ± 11.52	<0.001	14.73 ± 5.51	18.85 ± 6.56	>0.05	3.12 ± 1.37	4.57 ± 2.11	>0.05
Amisulphride	83.63 ± 9.09	89.4 ± 9.75	>0.05	13.16 ± 6.08	14.09 ± 6.27	>0.05	2.17 ± 1.32	3.07 ± 1.35	>0.05
Aripriazole	85.16 ± 9.13	88.9 ± 10.12	>0.05	13.13 ± 6.01	13.16 ± 5.93	>0.05	2.74 ± 1.30	2.86 ± 1.31	>0.05

Significant change: *P* < 0.01; *P* < 0.05; *P* < 0.001

Serum insulin and HOMA IR (to assess insulin resistance) showed significant increase in patients receiving Olanzapine, Clozapine and Quetiapine for 16 weeks (Table 3).

On assessing lipid parameters it was found that triglyceride, LDL cholesterol and HDL cholesterol shows significant alterations in patients receiving Olanzapine, Quetiapine and Risperidone. Third generation drugs Amisulphride and

Aripriazole however did not show any significant change in patients receiving this medication for 16 weeks (Table 4).

Overall assessment shows that Olanzapine is the drug which has maximum potential to cause metabolic syndrome followed by Clozapine, Risperidone and Quetiapine. Haloperidol has also similar effects on metabolic parameters but their propensity to cause metabolic syndrome is

Table 4 Level of lipid parameters before and after antipsychotic treatment

Drugs	Triglycerides			LDL cholesterol			HDL cholesterol		
	Base line	After 16 weeks	P value	Base line	After 16 weeks	P value	Base line	After 16 weeks	P value
Olanzapine	122.83 ± 21.97	147.83 ± 19.61	<0.001	94.50 ± 16.94	111.19 ± 18.40	<0.001	43.56 ± 2.76	39.24 ± 3.91	<0.001
Haloperidol	113.2 ± 19.29	120.93 ± 19.43	>0.05	110.75 ± 23.11	116.99 ± 25.71	>0.05	41.67 ± 2.52	39.95 ± 2.44	<0.05
Clozapine	123.83 ± 22.25	138.96 ± 21.13	<0.01	99.09 ± 19.68	114.90 ± 23.30	<0.01	41.81 ± 4.04	37.33 ± 4.98	<0.001
Quetiapine	120.6 ± 19.6	131.96 ± 19.60	<0.05	100.37 ± 17.35	110.22 ± 18.09	<0.05	41.41 ± 2.35	39.78 ± 2.53	<0.05
Risperidone	120.76 ± 19.72	131.16 ± 20.44	<0.05	100.33 ± 17.37	109.72 ± 18.65	<0.05	41.41 ± 2.35	39.85 ± 2.54	<0.05
Amisulphride	115.5 ± 17.61	123.06 ± 16.13	>0.05	109.18 ± 24.91	115.78 ± 26.11	>0.05	42.71 ± 3.31	41.17 ± 3.00	>0.05
Aripriazole	116.9 ± 16.21	122.76 ± 16.18	>0.05	112.42 ± 25.69	115.84 ± 26.80	>0.05	41.76 ± 3.81	40.63 ± 3.75	>0.05

Significant change: $P < 0.01$; $P < 0.05$; $P < 0.001$

less than Olanzapine and Clozapine. Aripriazole and Amisulphride are relatively safer drugs (Fig. 1).

Discussion

Schizophrenia, a devastating mental illness which has a wide prevalence and is associated with high rate of morbidity and mortality [15]. The increase in morbidity and mortality has also been associated with increased prevalence of metabolic syndrome which is characterized by a constellation of risk factors including obesity, dislipidemia, hyperglycemia, hypertension [16].

In this study the association between different antipsychotic medication used in the treatment of schizophrenia and metabolic syndrome has been explored. The metabolic effects of typical and atypical antipsychotic were studied in drug naïve patient suffering from schizophrenia that were not having any significant illness before the commencement of the drug treatment. These drugs effectively reduce psychotic symptoms [17] however they too are associated with severe side effects like weight gain and disruption of glucose metabolism that may lead to diabetes. As per our study all drugs were involved in the induction of weight gain in the subjects excluding the subjects under aripriazole and amisulphride treatment.

In most cases weight gain and central adiposity are major players in the pathophysiology of antipsychotic-induced metabolic syndrome. It has been found that appetite stimulating effects, genetic factors, sedentary lifestyle and impaired metabolic regulation are the key players in inducing weight gain after antipsychotic treatment.

The pathophysiology of weight gain is mediated through monoaminergic, cholinergic and histaminergic neurotransmission [18]. Accordingly greater weight gain seen in the case of clozapine and olanzapine is explained by differential affinities for serotonin 5-HT_{2C} and H₁ receptors.

In this study an increase in blood glucose and insulin level that induces increased risk of metabolic syndrome which is in accordance with other studies. It has been found that the metabolic disturbances associated with the use of atypical antipsychotics is a direct consequence of alteration of insulin sensitivity. Impaired parasympathetic regulation of β -cell activity mediated by blockade of histaminergic and muscarinic receptors may contribute to an increased metabolic risk [19]. Development of type 2 diabetes mellitus is a direct consequence of the antipsychotic mediated impairment of glucose transporter function via alteration in the insulin signaling pathway resulting in elevated circulating glucose levels, compensatory insulin hyper secretion and reduced insulin sensitivity [20].

Elevated fasting plasma triglycerides level are an important indicator of insulin resistance and thus serve as a valuable

Fig. 1 Number of patients developing metabolic syndrome

marker for evaluating a patients potential risk of metabolic syndrome [21]. A direct correlation between increased adiposity and increased LDL-cholesterol and decreased HDL-cholesterol level has been found in the present study.

It has been attributed from our study that antipsychotic induced weight gain and dysregulation of other metabolic parameters predispose patients with mental illness to an increased risk of cardiovascular mortality and morbidity. Treatment with atypical antipsychotics impose new standards for patients educations, informed consent and risk benefit analysis in the selection of pharmacotherapy. Monitoring guidelines suggest the consideration of switching to an atypical antipsychotic with less weight gain ability if a person with schizophrenia gains more than 5 % of his baseline weight or if dyslipidemia or hyperglycemia worsens.

Conclusion

Since antipsychotic drugs cause metabolic abnormalities therefore it's recommended that regular monitoring of metabolic and cardiovascular risk factors should be done. Monitoring should be individually tailored together with an emphasis on modification of lifestyle factor such as diet and exercise. The long term effects for the third generation drugs i.e. Aripriazole and Amisulphride needs to be explored.

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