Metabolic dysfunction related to typical and atypical antipsychotics in drug-naive patients with nonaffective psychosis: a prospective comparative study

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Background
Metabolic syndrome induced by antipsychotic (AP) drugs is commonly encountered in patients with nonaffective psychosis. Epidemiological studies report that 52% of patients with severe mental illness such as schizophrenia, schizoaffective disorder, bipolar disorder, and depression have metabolic syndrome compared with only 23–25% of the general population and thus have a markedly decreased life expectancy.

Aim
The study aimed to compare the effect of typical and atypical APs on different metabolic parameters in newly diagnosed drug-naive patients with psychotic disorders for a period of 12 weeks, which were divided into three follow-up visits, and clarify the associated risk factors.

Patients and methods
A convenient sample of 80 patients 18–50 years of age, of both sexes, from both inpatient and outpatient departments of the Institute of Psychiatry were screened for possible inclusion in the study. All patients were interviewed using SCID-I. Patients fulfilling the DSM-IV diagnostic criteria for schizophrenia, delusional disorder, brief psychotic disorder, and/or schizophreniform disorder, who had never been treated with psychotropic medication, and who had no comorbid medical conditions were included. Using computerized randomization, patients were assigned to two groups: group I received typical APs and group II received atypical APs. Demographic and clinical data were collected and anthropometric measurements were taken. Finally, laboratory analysis was performed for assessment of fasting blood glucose and lipid profile.

Results
The mean age of the patients was 26.03 ± 6.53 years in group I and 28.48 ± 6.29 years in group II. Group I patients were prescribed haloperidol, trifluoperazine, and flupenthixol, whereas group II patients were prescribed risperidone, olanzapine, and quetiapine. With regard to weight gain, patients in both groups were found to gain weight; however, it was more evident in patients given atypical APs, with a statistically significant difference across visits. Fasting blood glucose level increased significantly across visits in each group, but a comparison between the two groups did not show statistical significance. With regard to lipid profiles, cholesterol levels increased across visits and showed a statistically significant difference in visit 3; serum triglycerides and low-density lipoprotein increased as well but with no statistical significance; high-density lipoprotein decreased across visits but with no statistical significance.

Conclusion
AP medications, although providing a tremendous change in the lives of patients and giving them a better future, have imposed more of a burden on their metabolic profiles. This is especially true of atypical compounds.

Keywords:
atypical anti-psychotic, drug- naive patients,
metabolic dysfunction, non-affective psychosis, typical anti-psychotic

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Introduction

Metabolic syndrome (MetS) is the new epidemic of the 21st century [1] with high mortality rates [2]. Epidemiological studies have shown that 52% of patients with severe mental illness such as schizophrenia, schizoaffective disorder, bipolar disorder, and depression have MetS, compared with only 23–25% of the general population, markedly decreasing their life expectancy [3–7]. By far, the largest sample of patients with schizophrenia reported to have MetS is 42.7% out of 689 patients according to the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [8]. MetS is associated

with a four-time relative risk of developing diabetes and approximately twice the risk for coronary heart disease, stroke, and premature mortality [9].

The higher prevalence of MetS in schizophrenic patients is due to several reasons; some are biological and some are environmental. These patients have the unhealthiest lifestyle, an unhealthy diet, heavy smoking, and limited physical activity [6]. In addition, they have increased baseline risk for glucoregulatory disturbances and development of diabetes mellitus irrespective of the use of any medications, as well as higher baseline body weight and visceral fat distribution [10]. Moreover, there is laboratory evidence for the presence of impaired glucose and lipid metabolism in drug-naive patients [11]. One suggested explanation is the dysfunction of the hypothalamic–pituitary–adrenal axis due to stress with the prolonged high level of steroids conferring higher risks on patients' metabolic profiles and leading to insulin resistance [6]. Other explanations given are the unhealthy lifestyle led by those patients with an unbalanced diet and a lack of physical activity [12].

Patients with schizophrenia are believed to have 'illness-related' vulnerability to metabolic problems that could be attributed to several environmental and biological factors [6,13–15]. In fact, data from participants ($n = 1460$) recruited into the CATIE schizophrenia study showed that 30.2% of patients who had diabetes, 62.4% of those who had hypertension, and 88.0% of those with dyslipidemia were not receiving any treatment [8].

Nevertheless, antipsychotic (AP) medications are associated with similar metabolic dysregulations due to induced weight gain (mainly abdominal/visceral), with a consequent increase in fasting blood glucose (FBG) and dyslipidemia [6,16]. The mechanism of such adverse events is complex and involves an interplay between various genetic, neurochemical, and hormonal systems [7]. Hasnain *et al.* [6] suggested the following possible explanations: an increase in appetite may be due to antagonism of histamine and serotonin receptors; an allele polymorphism of leptin gene with increased leptin secretion may lead to a disturbance of insulin secretion and diabetes mellitus; dopamine antagonism is proposed as dopamine normally stimulates insulin secretion through an adrenergic-mediated pathway.

It is worth mentioning that these metabolic adversities related to APs are heterogeneous and variable even within the same class of APs [16,17].

Rationale

Studying the profile of metabolic dysfunction associated with the use of both typical and atypical APs in psychotic patients and the analysis of the possible risk factors related to such dysfunction is mandatory to be able to individualize interventional management and apply a prevention plan.

Aim

This study aimed to compare the effect of typical and atypical APs on different metabolic parameters in newly diagnosed drug-naive patients with psychotic disorders over a 12-week period, and clarify the associated risk factors.

Patients and methods

This prospective comparative study was approved by the Ethical Committee of Ain Shams University. A convenient sample of 102 patients from both the inpatient and outpatient departments of the Institute of Psychiatry were screened for possible inclusion in the study. Patients were enrolled if they met the following criteria:

(1) fulfilled the DSM-IV diagnostic criteria for schizophrenia, delusional disorder, brief psychotic disorder, and/or schizophreniform disorder;
(2) were from 18 to 50 years of age;
(3) had never been treated with psychotropic medication;
(4) had no comorbid medical conditions (according to the clinical examination of a consultant physician);
(5) were not receiving any other medications that could influence their weight, blood sugar, or blood lipids; and
(6) agreed to participate in the study and signed an informed consent form.

According to a computer-generated randomization drawn up by statisticians, patients were randomly assigned to receive typical APs (e.g. trifluoperazine, haloperidol, flupenthixol) or atypical APs (e.g. risperidone, olanzapine, quetiapine).

The mean dose in both groups was adjusted to a chlorpromazine equivalent ranging from 280 to 300, as calculated using the standardized conversion formula [18–20].

Concomitant medication was not allowed, with the exception of anticholinergic medications or benzodiazepines. Eight patients withdrew their consent, nine did not show up in the follow-up period, and an additional five had their medication changed by their consultants. In all, 22 of the 102 patients were excluded, leaving us with 80 patients (46 men and 34 women) who completed the study. The patients were divided into two groups: group I, 40 patients who received typical APs; and group II, 40 patients who received atypical APs.

Assessment

(1) Demographic and clinical data were collected.
(2) The Structured Clinical Interview for DSM-IV (SCID-I) [21] was used by a senior clinical psychiatrist to confirm the diagnosis. We used the Arabic version of the SCID-I [22].
(3) Anthropometric measurements such as patient height, weight, and BMI were assessed at baseline, and then at 6 and 12 weeks.
(4) Laboratory analysis was carried out at the Institute of Psychiatry Laboratory under the supervision of a consultant clinical pathologist.

The following parameters were assessed at baseline and then at 6 and 12 weeks: FBG level, total cholesterol (TC), high-density lipoprotein (HDL), and triglyceride (TG) level.

For each patient, 5 ml of venous blood was drawn and collected in a plain vacutainer tube after 8 h fasting to measure the FBG level, and then 6 h later (a total of 14 h fasting) another 5 ml of venous blood was collected to

assess the lipid profile. Blood samples were processed immediately after collection. All assays were performed using an automated chemistry analyzer (Diruics T240; DIRUI Industrial Co., Ltd, China) with the exception of low-density lipoprotein (LDL)-cholesterol, for which the Friedewald formula was used if the serum TG level was less than 400 mg/dl; if the TG level was more than or equal to 400 mg/dl, LDL-cholesterol was measured directly.

Interpretation of results: hypercholesterolemia was defined as a TC of at least 240 mg/dl; hypertriglyceridemia was defined as TG level of at least 200 mg/dl; and high LDL-cholesterol was defined as LDL of at least 160 mg/dl. An HDL-cholesterol level below 40 mg/dl for men and 50 mg/dl for women is known to be low, with an increased risk for cardiovascular disease.

Statistical analyses

The results of the study were analyzed using the statistical package for the social sciences (SPSS, electronic version 19th ed., 2010, SPSS for Windows; SPSS Inc., Chicago, Illinois, USA). SPSS (IBM Corp., Armonk, New York, USA) is a comprehensive and flexible statistical analysis and data management system. Data were extrapolated at baseline, and after 3 and 6 months, and were tabulated and analyzed using the following:

(1) Descriptive statistics
   (a) Mean $(\overline{X})$ and SD (for quantitative data).
   (b) Frequency with percentage (for qualitative data).
(2) Student's *t*-test: This was used to test for the significance of an independent variable in experiments in which there are only two levels of the variable (to compare between two independent means).
(3) χ^2-Test: This was used to test the significance of the difference between the frequencies of the different observations (i.e. qualitative data).
(4) One-way analysis of variance test (*F*): This was used when comparing several means to evaluate how several independent variables interact with each other and what effects these interactions have on a dependent variable.
(5) Multiple regression analysis: This is a powerful technique used for predicting the unknown value of a variable from the known value of two or more variables (also called the predictors). The variable we want to predict is called the dependent variable.
(6) *P*-value: This was used to indicate the level of significance: *P*-values less than 0.05 were considered significant.

Results

Baseline assessment

Table 1 shows that the mean age of group I patients was 26.03 ± 6.53 years and that of group II patients was 28.48 ± 6.29 years, with no statistical differences between them. Male was the predominant sex in both groups (60% in group I and 55% in group II).

The majority of patients were diagnosed with schizophrenia (65% in group I vs. 57.5% in group II), followed by schizophreniform disorder (15% in group I vs. 25.5% in group II), delusional disorder, and brief psychotic episode (10% for both diagnoses in both groups).

Haloperidol was prescribed extensively for group I patients (42.5%), followed by trifluoperazine (37.5%) and flupenthixol (20%).

Risperidone was frequently prescribed for group II patients (40%), followed by olanzapine (32.5%) and quetiapine (27.5%).

Ninety percent of patients in group I used anticholinergic medications compared with only 25% in group II ($P < 0.001$). A family history of diabetes was encountered equally in both groups.

Comparison between the two groups with regard to high-density lipoprotein, low-density lipoprotein, cholesterol, and triglycerides

Table 2 illustrates that both groups showed changes in the blood concentration of HDL from visit to visit.

For the typical APs group I, the mean was 58.43 ± 7.61 at the initial visit, decreasing to 56.58 ± 7.37 at 6 weeks ($P_1 < 0.001$) and further decreasing to 54.85 ± 7.88 at 12 weeks ($P_2 < 0.001$) from the initial visit.

For the atypical APs group II, the mean was 55.52 ± 7.70 at the initial visit, decreasing to 53.58 ± 7.47 ($P_1 < 0.001$) at 6 weeks and further decreasing to 51.50 ± 7.53 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Changes were statistically significant in both groups from visit to visit, but the head-to-head comparison between visits between the two groups was statistically nonsignificant ($P_3 = 0.094$, 0.075, and 0.056 for visits 1, 2, and 3, respectively).

Both groups showed changes in the blood concentration of LDL from visit to visit. For the typical APs, the mean was 126.30 ± 17.85 at the initial visit, increasing to 133.25 ± 17.45 ($P_1 < 0.001$) at 6 weeks and further increasing to 142.20 ± 17.33 ($P_2 < 0.001$) at 12 weeks from the initial visit.

In group II patients who received atypical APs, the mean was 128.83 ± 20.70 at the initial visit, increasing to 135.87 ± 21.01 ($P_1 < 0.001$) at 6 weeks and further increasing to 146.63 ± 22.11 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Changes were statistically significant in both groups from visit to visit, but the comparison between head-to-head visits between the two groups was statistically nonsignificant ($P_3 = 0.561$, 0.545, and 0.322 for visits 1, 2, and 3, respectively).

Thus, our results showed that HDL estimation in both groups reduced across visits and LDL levels increased across visits, with no statistical differences between the two groups in the three visits.

Table 1 Baseline assessment

	Group I: typical antipsychotics [*N* (%)]	Group II: atypical antipsychotics [*N* (%)]	Test of significance (*P*)
Sex			
Male	24 (60.0)	22 (55.0)	0.651
Female	16 (40.0)	18 (45.0)	
Age			
Range	18.0–49.0	19.0–44.0	0.091
Mean ± SD	26.03 ± 6.53	28.48 ± 6.29	
Median	25.50	28.0	
Diagnosis			
Schizophrenia	26 (65.0)	23 (57.5)	0.850
Delusional disorder	4 (10.0)	4 (10.0)	
Brief psychotic episode	4 (10.0)	4 (10.0)	
Schizophreniform disorder	6 (15.0)	9 (25.5)	
Use of anticholinergics			
No	4 (10.0)	30 (75.0)	<0.001*
Yes	36 (90.0)	10 (25.0)	
Family history for diabetes			
No	34 (85.0)	34 (85.0)	1.000
Yes	6 (15.0)	6 (15.0)	
Drugs used			
Haloperidol	17 (42.5)	–	
Trifluoperazine	15 (37.5)	–	
Flupenthixol	8 (20)	–	
Risperidone	–	16 (40)	
Olanzapine	–	13 (32.5)	
Quetiapine	–	11 (27.5)	

*Statistically significant at $P \leq 0.05$.

Table 2 Comparison between patients receiving typical antipsychotics (group I) and patients receiving atypical antipsychotics (group II) regarding high-density lipoprotein and low-density lipoprotein parameters across visits

	Initial visit	6 weeks	12 weeks	*F* (*P*)
HDL				
Typical antipsychotics				
Minimum–maximum	34.0–73.0	33.0–71.0	31.0–79.0	60.460* (<0.001)
Mean ± SD	58.43 ± 7.61	56.58 ± 7.37	54.85 ± 7.88	
Mean difference (P_1)		1.850* (<0.001)	3.575* (<0.001)	
Mean difference (P_2)		1.725* (<0.001)		
Atypical antipsychotics				
Minimum–maximum	35.0–77.0	35.0–75.0	34.0–72.0	78.407* (<0.001)
Mean ± SD	55.52 ± 7.70	53.58 ± 7.47	51.50 ± 7.53	
Mean difference (P_1)		1.950* (<0.001)	4.025* (<0.001)	
Mean difference (P_2)		2.075* (<0.001)		
P_3	0.094	0.075	0.056	
LDL				
Typical antipsychotics				
Minimum–maximum	98.0–159.0	103.0–160.0	114.0–172.0	274.889* (<0.001)
Mean ± SD	126.30 ± 17.85	133.25 ± 17.45	142.20 ± 17.33	
Mean difference (P_1)		6.950* (<0.001)	15.900* (<0.001)	
Mean difference (P_2)		8.950* (<0.001)		
Atypical antipsychotics				
Minimum–maximum	69.0–155.0	76.0–166.0	83.0–179.0	389.318* (<0.001)
Mean ± SD	128.83 ± 20.70	135.87 ± 21.01	146.63 ± 22.11	
Mean difference (P_1)		7.050* (<0.001)	17.800* (<0.001)	
Mean difference (P_2)		10.750* (<0.001)		
P_3	0.561	0.545	0.322	

F, *F* value for analysis of variance (ANOVA) with repeated measures test; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
P, *P*-value for ANOVA with repeated measures for comparing different periods.
P_1, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between initial visit and that at 6 and 12 weeks.
P_2, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between visits at 6 and 12 weeks.
P_3, *P*-value for Student's *t*-test comparing between typical antipsychotics and atypical antipsychotics.
*Statistically significant at $P \leq 0.05$.

For the typical APs, the mean cholesterol level was 180.35 ± 18.86 at the initial visit, increasing to 185.30 ± 22.82 at 6 weeks and further increasing to 196.60 ± 20.24 at 12 weeks from the initial visit, which was statistically significant ($P_1 < 0.001$).

For the atypical APs, the mean cholesterol level was 188.13 ± 18.50 at the initial visit, increasing nonsignificantly to 191.75 ± 33.21 at 6 weeks ($P_1 = 1.00$) and further increasing to 207.58 ± 21.30 ($P_2 = 0.014$) at 12 weeks from the initial visit (Table 3).

The comparison between groups I and II revealed a significant elevation in the cholesterol level in visit 3 in group II ($P_3 = 0.021$), whereas there was no significant increase in visits 1 or 2 (Table 3).

Measures of TGs for group I receiving typical APs showed that the mean was 159.55 ± 34.97 at the initial visit,

Table 3 Comparison between patients receiving typical antipsychotics (group I) and patients receiving atypical antipsychotics (group II) regarding cholesterol and triglycerides across visits

	Initial visit	6 weeks	12 weeks	*F* (*P*)
Cholesterol				
Typical antipsychotics				
Minimum–maximum	138.0–211.0	106.0–218.0	153.0–229.0	29.576* (<0.001)
Mean ± SD	180.35 ± 18.86	185.30 ± 22.82	196.60 ± 20.24	
Median	184.0	191.50	200.0	
Mean difference (P_1)		4.950 (0.194)	16.250* (<0.001)	
Mean difference (P_2)		11.300* (<0.001)		
Atypical antipsychotics				
Minimum–maximum	139.0–218.0	22.0–230.0	165.0–250.0	11.795* (<0.001)
Mean ± SD	188.13 ± 18.50	191.75 ± 33.21	207.58 ± 21.30	
Median	189.50	197.0	210.0	
Mean difference (P_1)		3.625 (1.000)	19.450* (<0.001)	
Mean difference (P_2)		15.825* (0.014)		
P_3	0.066	0.314	0.021*	
Triglycerides				
Typical antipsychotics				
Minimum–maximum	87.0–200.0	92.0–203.0	98.0–222.0	22.006* (<0.001)
Mean ± SD	159.55 ± 34.97	163.88 ± 34.55	172.70 ± 34.28	
Median	175.0	179.50	187.0	
Mean difference (P_1)		4.325* (<0.001)	13.150* (<0.001)	
Mean difference (P_2)		8.825* (0.003)		
Atypical antipsychotics				
Minimum–maximum	87.0–203.0	96.0–227.0	109.0–245.0	82.015* (<0.001)
Mean ± SD	159.93 ± 35.09	170.65 ± 34.0	183.93 ± 35.50	
Median	175.0	180.50	188.50	
Mean difference (P_1)		10.725* (<0.001)	24.000* (<0.001)	
Mean difference (P_2)		13.275* (<0.001)		
P_3	0.962	0.379	0.152	

F, *F* value for analysis of variance (ANOVA) with repeated measures test.
P, *P*-value for ANOVA with repeated measures for comparing between different period.
P_1, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between initial visit and that after 6 and 12 weeks.
P_2, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between visits at 6 and 12 weeks.
P_3, *P*-value for Student's *t*-test for comparing typical antipsychotics with atypical antipsychotics.
*Statistically significant at $P \leq 0.05$.

increasing to 163.88 ± 34.55 ($P_1 < 0.001$) at 6 weeks and further increasing to 172.70 ± 34.28 ($P_2 = 0.003$) at 12 weeks from the initial visit.

For group II patients treated with atypical APs, the mean was 159.93 ± 35.09 at the initial visit, increasing to 170.65 ± 34.0 ($P_1 < 0.001$) at 6 weeks and further increasing to 183.93 ± 35.50 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Comparison between the two groups across visits showed nonsignificant differences between them as regards TG levels ($P_3 = 0.962$, 0.379, and 0.152 for visits 1, 2, and 3, respectively) (Table 3).

Comparison between the groups with regard to level of fasting blood glucose

In the typical APs group I, the mean fasting blood glucose level was 84.68 ± 6.58 at the initial visit, increasing to 90.53 ± 6.43 ($P_1 < 0.001$) at 6 weeks and further increasing to 97.45 ± 7.20 ($P_2 < 0.001$) at 12 weeks from the initial visit (Table 4).

In the atypical APs group II, the mean fasting blood glucose level was 86.03 ± 9.09 at the initial visit, increasing to 91.83 ± 10.14 ($P_1 < 0.001$) at 6 weeks and further increasing to 100.92 ± 12.37 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Changes were statistically significant in both groups from visit to visit, but the comparison between the two groups showed statistically nonsignificant differences ($P_3 = 0.449$, 0.496, and 0.130 for visits 1, 2, and 3, respectively).

Comparison between the groups regarding body weight and body mass index

Table 4 also shows the mean body weight in group I as 69.52 ± 8.88 at the initial visit, increasing to 70.78 ± 8.62 ($P_1 < 0.001$) at 6 weeks and further increasing to 72.39 ± 8.44 ($P_2 < 0.001$) at 12 weeks from the initial visit.

For the atypical APs, the mean was 75.94 ± 8.59 at the initial visit, increasing to 77.43 ± 8.48 ($P_1 < 0.001$) at 6 weeks and further increasing to 79.49 ± 8.41 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Comparing the two groups revealed statistically significant differences across visits ($P_3 = 0.002$, 0.001, 0.001 for visits 1, 2, and 3, respectively).

BMI at the initial visit was 23.44 ± 2.42, increasing to 23.79 ± 2.38 ($P_1 < 0.001$) at 6 weeks and further increasing to 24.26 ± 2.41 ($P_2 < 0.001$) at 12 weeks from the initial visit.

For the atypical APs the mean was 25.70 ± 2.08 at the initial visit, increasing to 26.18 ± 2.07 ($P_1 < 0.001$) at 6 weeks and further increasing to 26.87 ± 2.08 ($P_2 < 0.001$) at 12 weeks from the initial visit.

Comparison of the changes in BMI in group I versus group II indicates that there is a significant increase in

Table 4 Comparison between patients receiving typical antipsychotics (group I) and patients receiving atypical antipsychotics (group II) regarding fasting blood glucose, body weight, and body mass index

	Initial visit	6 weeks	12 weeks	*F* (*P*)
FBG				
Typical antipsychotics				
Minimum–maximum	73.0–101.0	79.0–105.0	84.0–112.0	325.267* (<0.001)
Mean ± SD	84.68 ± 6.58	90.53 ± 6.43	97.45 ± 7.20	
Mean difference (P_1)		5.850* (<0.001)	12.775* (<0.001)	
Mean difference (P_2)		6.925* (<0.001)		
Atypical antipsychotics				
Minimum–maximum	72.0–103.0	75.0–114.0	79.0–126.0	161.982* (<0.001)
Mean ± SD	86.03 ± 9.09	91.83 ± 10.14	100.92 ± 12.37	
Mean difference (P_1)		5.800* (<0.001)	14.900* (<0.001)	
Mean difference (P_2)		19.100* (<0.001)		
P_3	0.449	0.496	0.130	
Body weight (kg)				
Typical antipsychotics				
Minimum–maximum	53.0–92.50	55.50–93.0	56.50–94.0	108.149* (<0.001)
Mean ± SD	69.52 ± 8.88	70.78 ± 8.62	72.39 ± 8.44	
Mean difference (P_1)		1.250* (<0.001)	2.862* (<0.001)	
Mean difference (P_2)		1.612 (<0.001*)		
Atypical antipsychotics				
Minimum–maximum	56.50–93.0	58.0–93.50	60.0–96.0	177.877* (<0.001)
Mean ± SD	75.94 ± 8.59	77.43 ± 8.48	79.49 ± 8.41	
Mean difference (P_1)		1.48/7* (<0.001)	3.55* (<0.001)	
Mean difference (P_2)		2.063* (<0.001)		
P_3	0.002*	0.001*	<0.001*	
BMI				
Typical antipsychotics				
Minimum–maximum	19.0–30.10	19.90–30.30	20.40–30.70	42.978* (<0.001)
Mean ± SD	23.44 ± 2.42	23.79 ± 2.38	24.26 ± 2.41	
Median	22.75	23.20	23.90	
Mean difference (P_1)		0.352* (<0.001)	0.827* (<0.001)	
Mean difference (P_2)		0.475* (<0.001)		
Atypical antipsychotics				
Minimum–maximum	21.50–31.50	22.10–32.40	22.90–33.20	142.036* (<0.001)
Mean ± SD	25.70 ± 2.08	26.18 ± 2.07	26.87 ± 2.08	
Median	25.80	26.15	26.85	
Mean difference (P_1)		0.475* (<0.001)	1.170* (<0.001)	
Mean difference (P_2)		0.695* (<0.001)		
P_3	<0.001*	<0.001*	<0.001*	

F, *F* value for analysis of variance (ANOVA) with repeated measures test; FBG, fasting blood glucose.
P, *P*-value for ANOVA with repeated measures for comparing between different periods.
P_1, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between initial visit and that after 6 and 12 weeks.
P_2, adjusted Bonferroni's *P*-value for ANOVA with repeated measures for comparison between visits at 6 weeks and 12 weeks.
P_3, *P*-value for Student's *t*-test for comparing between typical antipsychotics and atypical antipsychotics.
*Statistically significant at $P \leq 0.05$.

group II measures compared with those in their group I counterparts across the three visits ($P \leq 0.05$).

In an attempt to study the risk factors associated with the development of metabolic dysfunction, we performed multiple logistic regression analyses.

Predictive factors for metabolic dysfunction related to antipsychotics

Table 5 and 6 shows that a high level of cholesterol is associated with the use of atypical APs, whereas family history of diabetes is a risk factor for higher FBG, regardless of the type of AP. In contrast, the use of atypical APs is found to be predictive for higher BMI, whereas atypical APs and female sex are risk factors for increased body weight.

Discussion

Metabolic dysfunction in patients receiving APs is among the most serious side effects encountered in this large category of patients, and it is more prevalent in those patients than in the general population, thus lowering their life expectancy by almost 20 years. MetS is diagnosed when a cluster of modifiable risk factors co-occur. This cluster includes obesity (mainly abdominal), diabetes mellitus type 2, physical inactivity, hypertension, dyslipidemia, elevated LDL, low HDL, elevated TGs, glucose intolerance, smoking [1,6], and increased levels of prothrombotic proteins and proinflammatory states. The core features are obesity and atherogenic dyslipidemia [6,23].

In this study, a prospective comparison was carried out between two groups of drug-naive, newly diagnosed psychotic patients regarding the effect of typical and atypical APs on different metabolic parameters over a period of 12 weeks and to clarify the associated risk factors. One group was receiving typical APs (haloperidol, trifluoperazine, and flupenthixole) and the other group was prescribed atypical APs (risperidone, olanzapine, and quetiapine).

Weight gain and body mass index

Both groups showed significant changes in mean body weight and BMI from visit to visit. Their mean body weight, as well as their BMI, increased significantly from

Table 5 Multiple logistic regressions for different measures

	R^2	β	Significance
Logistic regression test of predictive factors of LDL level			
Type of antipsychotic	0.054	−0.89	0.441
Age	–	0.115	0.329
Sex	–	−0.30	0.793
Family history of diabetes	–	0.172	0.132
Logistic regression test of predictive factors of HDL level			
Type of antipsychotic	0.095	0.177	0.119
Age	–	0.184	0.112
Sex	–	0.066	0.557
Family history of diabetes	–	0.101	0.363
Logistic regression test of predictive factors of cholesterol level			
Type of antipsychotic	0.080	−0.251	0.029*
Age	–	0.019	0.870
Sex	–	−0.084	0.464
Family history of diabetes	–	0.080	0.474
Logistic regression test of predictive factors of triglycerides level			
Type of antipsychotic	0.037	−1.315	0.192
Age	–	0.220	0.827
Sex	–	−0.791	0.431
Family history of diabetes	–	0.272	0.786
Logistic regression test of predictive factors of fasting blood glucose level			
Type of antipsychotic	0.114	−0.167	0.135
Age	–	0.070	0.538
Sex	–	0.187	0.097
Family history of diabetes	–	0.213	0.045*
Logistic regression test of predictive factors of BMI			
Type of antipsychotic	0.260	−0.497	0.000*
Age	–	0.050	0.634
Sex	–	0.006	0.951
Family history of diabetes	–	−0.26	0.791
Logistic regression test of predictive factors of body weight			
Type of antipsychotic	0.346	−0.381	0.000*
Age	–	0.177	0.73
Sex	–	0.441	0.000*
Family history of diabetes	–	−0.037	0.692

HDL, high-density lipoprotein; LDL, low-density lipoprotein.
*Statistically significant at $P \leq 0.05$.

Table 6 Summary of predictive factors for different measures

Metabolic measures	Predictive factor	Significance
Cholesterol level	Type of antipsychotic	0.029*
Fasting blood glucose	Family history of diabetes	0.045*
Body weight	Type of antipsychotic	0.000*
Family history of diabetes	Type of antipsychotic & sex	0.000*

*Statistically significant at $P \leq 0.05$.

visit 1 to visit 2 (6 weeks) and further on visit 3 (12 weeks). Moreover, the comparison of head-to-head visits between the two groups was statistically significant and showed higher levels with atypical APs. This finding was evident in multivariate analysis, as the type of AP and sex of the patient were the main predictors of weight gain. APs induced weight gain, which initiated a disruption in the lipid and sugar metabolisms with serious drawbacks [24] [i.e. induced obesity, mainly visceral (abdominal)], presenting an important determinant influencing the individual's health through facilitating the release of free fatty acids, peptides, and cytokines, which can adversely affect insulin action [7,25]. Yet, these side effects are modifiable and could be prevented by rigorous watchful monitoring of the early metabolic changes followed by early management [7,24].

Our results mirror data presented by a wealth of literature concerned with the adverse events of APs [26–28]. Most of those studies comparing the impact of each of the typical and atypical APs on body weight and BMI have also shown that all APs are associated with weight gain, but atypical APs induce more weight gain compared with typical APs [28–31].

Blood sugar

Patients of each of the two groups, whether treated with typical or with atypical APs, have shown an increase in their FBG levels from visit to visit in a statistically significant manner. However, comparison between visits head to head between the two groups was not statistically significant. The increase in FBG was predicted in multivariate analysis by the positive family history of diabetes mellitus, which was proved by Hasnain *et al.* [6] and Ray and Khess [10], who noticed that hyperglycemia and diabetes are detected in patients' first-degree relatives at a higher rate than in the general population, suggesting genetic vulnerability. This result should draw our attention to the importance of collecting information about family medical history before making the choice of which AP to prescribe.

It was long established that patients with schizophrenia have a higher risk of developing diabetes mellitus than the general population, even before any medicational side effects [6,7,15,32]. However, as shown in our study data, the risk is magnified when those patients receive AP treatment [14,16,33]. Yet, many comparative studies regarding the dysglycemic side effect of typical versus atypical APs have clarified that atypical APs are by far more hazardous in that aspect [7,12,34–36], which was not the case in this study. In 2016, Ray and Khess [10] studied 120 patients with schizophrenia and compared patients receiving typical APs, atypical APs, and those who were untreated for 3 months before the study. They found that there was a nonsignificant difference between the three groups regarding their FBG levels. Yet, there were significant differences in the serum insulin level between the three groups as well as in the Homeostasis Model of Assessment of Insulin Resistance (HOMA-IR), denoting insulin resistance. In other words, their study drew attention to the actual and more sensitive parameter when following up with AP-treated patients. Clinicians should look for insulin resistance and not serum glucose levels when monitoring their treated schizophrenic patients. Insulin resistance is the earliest step before hyperglycemia and, later, diabetes mellitus type 2 develop. Thus, AP treatment is suggested to cause insulin resistance rather than causing a primary defect in insulin secretion [37,38].

Lipid profile

In this study, both groups showed a significant increase in serum levels of LDL from visit to visit, a significant increase in each of TC and TGs, and a significant decrease in serum levels of HDL. However, the comparison between changes in visits head to head in both groups was statistically nonsignificant, except for TC whose changes were statistically nonsignificant from visit 1 to visit 2 in both groups, and only statistically

significant from visit 2 to visit 3. This superiority of atypical APs over typical APs in their dyslipidemic effect has long been established in numerous studies [17,23,39–41]. In their study Perez-Iglesias *et al.* [42] found a significant increase in TG levels with atypical APs (mainly olanzapine) when compared with haloperidol and risperidone; however, no significant changes were found with regard to cholesterol and LDL levels between their studied groups.

An increase in cholesterol levels was found in multivariate analysis to be affected by the type of AP and was higher with atypical APs. This is consistent with previous studies that ranked APs according to their dyslipidemic effects, in which olanzapine and clozapine ranked highest, followed by the others [43,44]. However, it is vastly argued that schizophrenic patients are genetically prone to hyperlipidemia, irrespective of any medication insult [45]. Interestingly, Mitchell *et al.* [32] compared two groups of treated and untreated patients with a first episode of schizophrenia and found that serum TG level was elevated in 16.9% of the untreated patients versus 19.6% of treated patients, whereas serum HDL was low in 20.4% in the untreated group versus only 21.9% in the treated group (irrespective of type of AP medication).

Conclusion and recommendations

Psychiatric patients usually encounter medical hazards because of their unhealthy lifestyle, unhealthy diets, low range of physical activity, disparities in healthcare, poor access to healthcare services, and quality of healthcare provision. AP medications, although bringing a tremendous change in their lives and giving patients a much better future, have imposed more of a burden on patients' metabolic profiles, especially atypical APs.

Patients with severe mental illnesses need more attention from their treating psychiatrists regarding their medical conditions, and the inclusion of a physician with the mental health team could provide better physical and mental health outcomes. Moreover, weight management guidelines should be an integral part of patient management. Tailoring treatment strategies and choosing the type of APs according to the patient's sex, weight, and basic metabolic profile at the initiation of treatment and inquiring about family history of diabetes, hyperlipidemia, and cardiovascular diseases are mandatory. Regular monitoring of weight, lipid profile, and insulin resistance should a part of workup during patient follow-up.

Strength and limitations

To our knowledge, this is the first Egyptian study following up and comparing the metabolic profile of patients under treatment with first-generation and second-generation AP medications. Although the researchers evaluated the patients at three points (0, 6, and 12 weeks), this study needs to be replicated on a larger number of patients and with follow-up of the metabolic profile over a longer period of time, taking into consideration the cultural impact on individual lifestyles. A different study design is also recommended (i.e. a case–control study to compare the metabolic effect of APs with healthy control). Correlation of laboratory findings with regular blood pressure monitoring, waist circumference, and weight will allow more accurate diagnosis of MetS.

The limitations of this study include a lack of differentiation between different APs; this would have allowed us to have a clearer perspective of each AP's individual effect, taking into account the fact that the wealth of studies come from western countries, but we needed this differential study to observe the ethnic impact of each medication's effect. We depended only on FBG in assessing the glycemic dysregulation; however, it is not the earliest indicator. In hindsight, perhaps we should have measured either the HbA1C or the insulin level in order to have an indication of the occurrence of insulin resistance, which is the initial feature of glycemic dysregulation, followed by elevated blood sugar levels. Recording a blood pressure measurement and a waist circumference would also have been of importance in this study.

Conflicts of interest

There are no conflicts of interest.

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