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Antipsychotic-induced Changes in Blood Levels of Leptin and Ghrelin in Schizophrenia: A Short-term Prospective Study

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Abstract

Background: Schizophrenia (SZ) is a psychotic disorder with a complex pathophysiology. It requires long term treatment with antipsychotics (APs) which are associated with metabolic syndrome.

Aim of the study: To assess the effect of three widely-used APs, namely olanzapine (OLZ), quetiapine (QUET), and risperidone (RIS) on body weight, and its relation with appetite hormones, metabolic markers, and oxidative stress, in SZ AP-naïve men.

Subjects and Methods: 25 Patients were recruited and investigated in a functional follow-up analysis for 8 weeks. Critical changes in body weight as well as in leptin, ghrelin, glucose, lipid profile and oxidative stress markers were examined as a function of duration of AP exposure. Fifteen healthy men were included as controls.

Results: At baseline, there were no major differences between SZ patients and controls. Treatment with APs caused a significant increase in body weight, leptin, glucose, cholesterol, triglycerides, LDL, VLDL, and malondialdehyde, which were negatively correlated with ghrelin, HDL, and catalase. These changes were more profound in the OLZ group, but negligible in the RIS one. However, not all patients in each treatment group were affected equally.

Conclusion: The role of leptin in AP-induced weight gain is supported. However, not all patients respond to an AP similarly. Tailored SZ medications and thorough biochemical markers assessment must be incorporated in clinical treatments. Further studies with larger number of patients and longer periods of follow-up are recommended.

Keywords: Critical differences; Olanzapine; Quetiapine; Risperidone; Oxidative stress; Antipsychotic-induced weight gain; Treatment outcome

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Introduction

Schizophrenia (SZ) is a chronic, severe mental disorder that affects how a person thinks, feels, and behaves. It can cause hallucinations, delusions, and other mental problems that make it seem like a person has lost touch with reality. It affects about 1 in 100 people, and tends to run in families [1]. Recent studies have identified genetic factors that confer an increased risk of SZ and participate in the disease etiopathogenesis [2].

Atypical antipsychotics, an effective treatment for schizophrenia, have a range of pharmacologic properties leading to differences in tolerability as well as heterogeneity in treatment response [3]. Antipsychotic-induced Weight Gain (AIWG) is a serious side-effect of AP medication leading to metabolic syndrome and increased cardiovascular morbidity, which contributes to poor treatment adherence and significant morbidity [4]. Unfortunately, the mechanisms responsible for these complications are not completely understood. According to various studies, leptin has been associated with AIWG [5,6].

Leptin is considered one of the best markers of total body fat in animals and humans. It is secreted by adipose tissue and regulates energy homeostasis, neuroendocrine function, metabolism, immune function and other systems through its effects on the central nervous system and peripheral tissues. A hyperleptinemic state has been observed in obese subjects, which appears to indicate a loss of leptin's ability to stop overeating behavior (leptin resistance) [5]. Thus far, results on the relation between leptin and AIWG have been mixed such that some studies reported increased leptin levels [7,8] while others reported no change [6,8]. This inconsistency could be due an impact of genetic variation in the genes encoding leptin and leptin receptor, but results have not been conclusive [3,9]. Consequently, individual patient characteristics must be considered when making treatment choices, especially from an adverse event or tolerability perspective.

Accordingly, the aim of the present work was to assess individual changes in body weight and BMI after the start of a specific AP (during 8 weeks of treatment). Also, to correlate these changes with the critical changes (clinical relevant changes) in different metabolic markers.

Methodology

Study design and population

This is a prospective cohort study. It included 25 male drug-naïve schizophrenic patients, aged between 18 and 47 years (27.8 ± 8.3). The patients were selected among inpatients in the institute of psychiatry-neuropsychiatry department, Ain Shams University Hospitals in Cairo, Egypt, who were medically indicated for initiation of treatment with olanzapine (10mg/day), quetiapine (600 mg/day), or risperidone (6 mg/day). The diagnosis of schizophrenia was performed following the criteria of the International Classification of Diseases-10 (*ICD-10).* All patients received electroconvulsive therapy (ECT) (6–8 sessions). Fifteen healthy males without current or past psychiatric disorders were included and served as controls. Blood samples were collected, and body weights recorded before the commencement of treatments (baseline, all subjects), and repeated after 2, 4 and 8 weeks for all patients. The study protocol was approved by the ethics committee of Faculty of Medicine, Ain Shams University. A written informed consent was obtained from the patients and control groups involved in the study. It was taken in a private setting after full discussion of the study rational. Participants in the study were informed that the study is totally free and voluntary, and that it does not imply a direct benefit for him/her, although data obtained could be used for the benefit of other patients. They also were told that they have the right to withdraw from the study at any time without giving any justification.

Exclusion criteria:

1) Patients who had a substance-related disorder or other physical illness, including hypertension or hyperlipidemia that might affect their appetite or glucose metabolism;

2) Significant weight loss/gain ± 1 kg in the past 8 weeks.

Blood collection and assessment

Venous blood was collected in the morning after 12 hours of fasting, into two tubes: A part of the blood was taken on sodium fluoride for the determination of plasma glucose (10). Another part was left to coagulate to obtain serum after centrifugation at 1000 g for 15 minutes. The serum was then stored at -20°C to be thawed only once on demand for the remaining analysis.

Routine laboratory investigations were carried using commercial kits (Spectrum diagnostics, Egypt). These included: Fasting blood glucose (FBS) [11], total cholesterol [12], triglycerides (TG) [13], LDL- cholesterol [14], HDL- cholesterol [15], and VLDL- cholesterol [16].

Serum leptin was measured using double-antibody enzyme immunoassay method of [17] using an ELISA kit (BioVendo, Czech Republic). Serum ghrelin was determined by the double-antibody enzyme immunoassay method [18] using an active ghrelin ELISA kit, according to the manufacturer's instructions (BioVendo, Czech Republic). Both lipid peroxidation as malondialdehyde (MDA) and catalase enzyme activity were measured using commercial assay kits (Biodiagnostics, Egypt) according to the colorimetric methods described by Sinha AK [19] and Yoshioka T, et al. [20] respectively.

Statistical analysis

Statistical analysis was performed using SPSS/PC software program (version 21; IBM SPSS statistics, USA). Data were tested for normal distribution using the Kolmogorov–Smirnov test, and were found to be normally distributed at baseline, hence represented as mean ± standard deviation. The study design and complex aim call for different ways of statistical analysis that allow to compare not only effects of APs, but also to compare these effects with respect to the baseline of each subject individually, stratifying for duration of AP use.

The corresponding parameters in the groups at baseline (healthy and SZ patients) were compared by means of independent-samples T-test. Results after 8 weeks of treatment were compared with their own baseline values (paired-sample *t*-tests). Correlations between the changes (as percentage) in the different parameters with body weight were carried by Pearson correlation coefficient analysis. The level of statistical significance was set at $P < 0.05$.

Critical differences: To assess the significance of differences (true change) between consecutive results obtained in each patient, the reference change value (RCV) was calculated. RCV is defined as the critical differences that must be exceeded between two sequential results for a significant (or true) change to occur [21]. The RCV is calculated as percentage change from the median value of each marker according to Ricos C, et al. [22] and Westgard QC [23], and does not depend on the method of measurement used. In schizophrenic drug-naïve patients a 7% change in body weight was considered clinically relevant weight gain [8] RCV values for leptin, ghrelin, MDA and catalase were determined by the sample quartiles (percent change of highest quartile from lowest quartile). The results were computed by the crosstabs procedure in two-way tables, and presented in stacked column charts, in which columns represent percent of patients who achieved marked differences (critical differences) **(Figure**

1). The legend under each column represents RCV value for each analyte.

Results

Baseline characteristics of the patients and controls are shown in **Table 1**. Cases were similar to controls with regard to baseline characteristics, with the following exceptions cholesterol; LDL and catalase were lower in patients group.

The changes in each AP treated group after 2, 4, and 8 weeks of treatment presented as percent change from baseline are illustrated in **Figures 2a and 2b**. In both the olanzapine (OLZ) and quetiapine (QUET) treated groups the degree of change amplified by time, reaching maximum after 8 weeks. The changes were more pronounced in the OLZ treated patients compared to those receiving QUET. Patients treated with risperidone (RIS) showed little or no changes through the treatment period. Results revealed an increase in body weight, glucose, leptin, cholesterol, triglycerides, LDL, VLDL, and MDA, while a decrease in ghrelin, HDL, and catalase was observed.

To test the significance of changes after 8 weeks of treatment compared to baseline, paired-sample *t*-test was applied on all the parameters for each AP treatment **(Table 2)**.

In the OLZ group all the studied parameters were significantly ($p<0.01 - p<0.001$) altered, except catalase enzyme, which showed non-significant change. QUET treatment caused less significant changes than the OLZ group ($p<0.05 - p<0.01$), showing that the decrease in HDL was not significant. None of the parameters was significantly changed in the RIS treated group.

Correlations between the changes (as percentage) in the different parameters with body weight for all patients through the follow-up period were carried by Pearson correlation coefficient analysis **(Table 3)**. Changes in body weight were significantly correlated with the changes in all the studied parameters. The strongest correlations were those with leptin and total cholesterol ($r=0.874$ and 0.819 respectively). The changes in leptin were positively correlated with total cholesterol, LDL, VLDL, and MDA in a descending order, while an inverted correlation was observed between the changes in leptin with ghrelin, HDL, and catalase.

The number of patients who showed marked adverse effects (critical differences) after treatment with the different APs (within-individual change) were calculated from the reference change value (RCV) by cross-tabulation analysis. Results revealed that body weight increased clinically, i.e., more than 7% from the baseline level (RCV=7) in 90% of patients treated with OLZ, 100% of the patients receiving QUET, and only 11% in the RIS treated group. Leptin was elevated (RCV= 6.7) in 100%, 83%, and 11% of patients treated with OLZ, QUET, and RIS respectively, these changes paralleled with 60%, 83%, and 44% of patients with a critical decrease in ghrelin (RCV= 6.8). Fasting blood sugar (FBS) was clinically elevated (RCV= 5.6) in 70%, 67%, and 22% of patients receiving OLZ, QUET, and RIS respectively. Total cholesterol (RCV=5.95) and triglycerides (RCV=19.9) increased in both the OLZ (100% & 80%) and QUET (67% & 67%) groups respectively, but none of the RIS treated group showed altered levels. The decrease in HDL (RCV=7.3) and increase in LDL (RCV=7.8) and

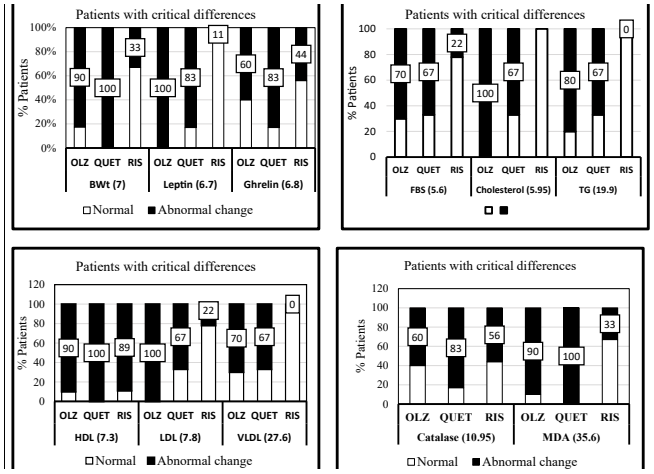

Figure 1 Stacked column charts: Segments present percent within treatment. Within-individual changes (no change, or abnormal change) after 8 weeks of treatment with different APs, calculated from the reference change value (RCV). Each segment represent the percentage of patients in each category.

Table 1 Descriptive characteristics of schizophrenia cases and controls at baseline (Independent-Samples T Test).

Variables	Control (n=15)	Patients (n=25)	P
	Mean ± SD	Mean ± SD	
Body weight	71.5 ± 9.41	68.0 ± 8.6	NS
BMI	23.9 ± 4.2	22.7 ± 3.1	NS
Leptin ng/mL	2.99 ± 0.22	3.05 ± 0.22	NS
Ghrelin pg/mL	44.9 ± 2.3	44.5 ± 2.1	NS
FBS mg/dL	79.8 ± 9.4	79.5 ± 9.2	NS
Cholesterol mg/dL	170.7 ± 10.6	163.0 ± 9.8	0.05
Triglycerides mg/dL	80.7 ± 15.7	76.0 ± 9.1	NS
HDL mg/dL	56.7 ± 4.7	58.9 ± 5.8	NS
LDL mg/dL	98.1 ± 10.9	88.9 ± 11.3	0.01
VLDL mg/dL	16.1 ± 3.2	15.2 ± 1.8	NS
Catalase U/L	468.1 ± 125.5	387.1 ± 148.8	0.05
MDA nmol/mL	3.68 ± 1.7	3.53 ± 1.5	NS

VLDL (RCV=27.6), were recorded in 90%, 100%, and 70% of the OLZ group, in 100%. 67%, and 67% in the QUET group, and in 89%, 22% and zero % in the RIS group respectively. A decrease in catalase (RCV= 10.95) and an increase in MDA (RCV=35.6) were recorded in 60% and 90% of the OLZ group, 83% and 100% of the QUET group, and in 56% and 33% of the RIS group respectively.

Discussion

It is now well known that use of the atypical antipsychotics is perhaps the most effective treatment we currently have for schizophrenia and other serious mental illnesses. Unfortunately due to their associated risk for metabolic syndrome, use of these medications may be placing these individuals at greater risk for several comorbidities, resulting in an accumulation of life years lost due to cardiovascular disease [3,24].

The present study assessed absolute changes in body weight

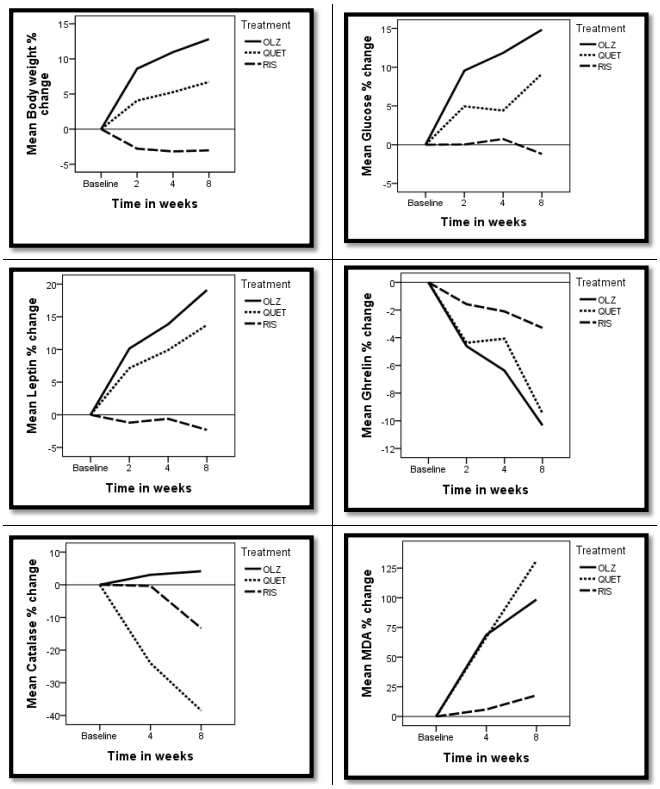

Figure 2a Changes (as percent) from baseline after 2, 4, and 8 weeks of treatments.

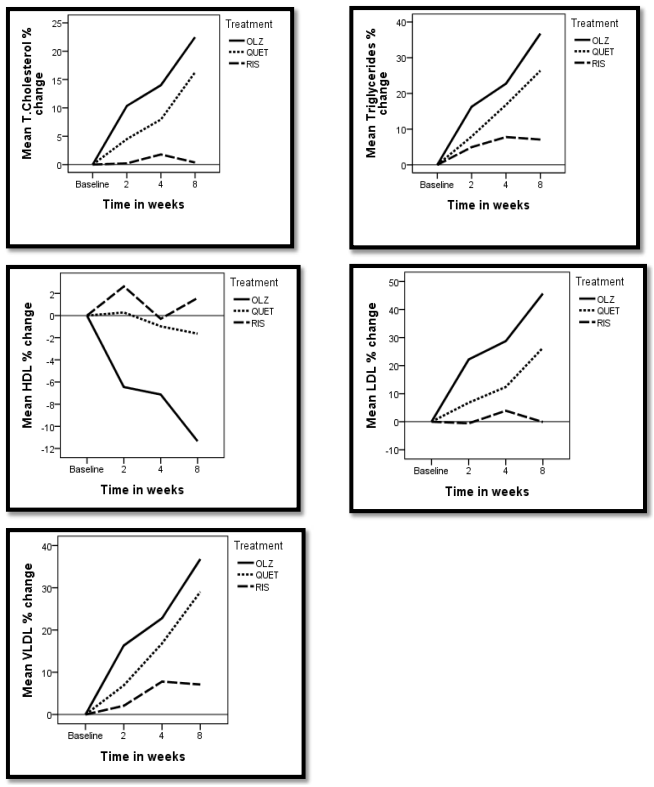

Figure 2b Changes (as percent) from baseline after 2, 4, and 8 weeks of treatments.

and BMI as well as the proportion of subjects with more than 7% increase in body weight (or clinically relevant weight gain) after the start of three APs, namely olanzapine (10 mg/day), quetiapine (600 mg/day), and risperidone (6 mg/day), in APs naïve patients. We aimed also to discover whether metabolic complications of schizophrenia (SZ) are present in before treatment, and to what extend these complications are intensified during treatment. These changes were followed for 8 weeks, allowing for assessment of possible progress with duration of AP treatment.

The present study presents several outcomes:

(1) At baseline SZ patients' characteristics did not differ significantly from controls.

(2) OLZ and QUET caused increase in body weight and BMI with increased duration of AP use, which was not observed in the RIS treated patients.

(3) The changes in body weight were strongly correlated with increase in leptin.

(4) Hyperleptinemia was accompanied by an increase in the risk of metabolic syndrome (increase in FBS, cholesterol, triglycerides, LDL, VLDL, and MDA, and a decrease in HDL, catalase, and ghrelin levels).

(5) The above changes differed among patients in each treated group. Hence, individual patient characteristics must be considered when making treatment choices, especially from an adverse event or tolerability perspective.

Weight gain is a major side effect of antipsychotics (APs), which contributes to poor treatment adherence and significant morbidity. The mechanisms involved in AP-induced weight gain are incompletely understood. Studies in drug-naïve patients are more informative than switch studies, as weight outcomes are not influenced by the level of overweight due to a previous AP, thus allowing for assessment of an effect that can be attributed to a specific AP [8]. At baseline the body weight and BMI of SZ patients did not differ from controls. After treatment with OLZ and QUET both showed a significant increase, which correlated with duration of treatment, and the proportion of patients gaining more than 7% weight (or clinically relevant weight gain) expanded with duration of AP. Many reports have suggested that olanzapine and quetiapine induce weight gain [5,6,8,9,25-27]. However, the mechanism behind this weight gain remains unclear [6]. Eating disorders was one of the suggested causes [28].

Appetite and body weight are controlled by complex hypothalamic neurocircuitry, in which leptin and ghrelin are crucial elements of this control system [9]. Both leptin and ghrelin were within the normal ranges before treatment, this is in line with previous studies [29], conversely others suggested that schizophrenia is associated with increased blood leptin [30]. During treatment with OLZ and QUET, we found a significant increase in leptin, which was negatively correlated with ghrelin level, while patients receiving RIS showed normal leptin and ghrelin levels, which is supported by previous reports [9,31]. It was suggested that hyperleptinemia in schizophrenia is likely to represent a secondary effect related to AP-induced weight gain, signifying that leptin acts as a negative

Table 2 Changes after 8 weeks of treatment compared to baseline (Paired-Sample t-test).

	Treatment (n=number of patients)					
	OLZ (n=10)		QUET (n=6)		RIS (n=9)	
Weeks	0	8	0	8	0	8
Body weight Kg	65.8 ± 9.9	73.9 ± 9.3	67 ± 4.6	71.5 ± 5.8	71.2 ± 8.3	69 ± 8.5
p	0.001		0.010		NS	
BMI	22.0 ± 3.7	24.7 ± 3.4	22.34 ± 1.9	23.8 ± 2.3	23.6 ± 3.2	22.9 ± 3.0
p	0.001		0.012		NS	
Leptin ng/mL	3.06 ± 0.2	3.64 ± 0.2	3.05 ± 0.1	3.5 ± 0.3	3.03 ± 0.3	2.96 ± 0.3
p	0.001		0.020		NS	
Ghrelin pg/mL	45.0 ± 2.2	40.3 ± 2.4	44.1 ± 2.3	40.0 ± 3.3	44.2 ± 2.1	42.7 ± 2.1
p	0.001		0.004		NS	
FBS mg/dL	77.0 ± 8.4	87.6 ± 4.6	81.1 ± 8.4	88.0 ± 4.8	81.1 ± 10.9	79.2 ± 6.4
p	0.004		0.010		NS	
Cholesterol mg/dL	162.0 ± 11.2	198.2 ± 16.2	162.2 ± 9.0	188.5 ± 18.8	164.7 ± 9.5	164.9 ± 3.6
p	0.001		0.010		NS	
TG mg/dL	75.5 ± 8.0	103.0 ± 14.8	82.2 ± 10.4	103.6 ± 17.0	72.5 ± 8.0	77.2 ± 6.3
p	0.001		0.010		NS	
HDL mg/dL	62.4 ± 5.5	55.0 ± 3.9	55.5 ± 2.9	54.4 ± 3.5	57.3 ± 6.0	57.7 ± 3.9
p	0.002		NS		NS	
LDL mg/dL	84.5 ± 10.4	122.6 ± 15.8	90.3 ± 8.6	113.5 ± 18.1	93.0 ± 12.9	91.7 ± 5.9
p	0.001		0.030		NS	
VLDL mg/dL	15.1 ± 1.6	20.6 ± 3.0	16.4 ± 2.1	21.1 ± 3.8	14.5 ± 1.6	15.4 ± 1.3
p	0.001		0.020		NS	
Catalase U/L	364.9 ± 165	291.2 ± 124	467.0 ± 172	271.8 ± 89	358.5 ± 106	299.0 ± 149
p	NS		0.024		NS	
MDA nmol/mL	4.11 ± 1.8	7.18 ± 1.9	2.16 ± 0.6	5.03 ± 2.0	3.81 ± 0.9	4.34 ± 1.3
p	0.010		0.010		NS	

Table 3 Pearson correlation coefficients (r) relating strength of correlations between the changes (percentage) in the studied parameters for all patients through the 8 weeks of follow-up.

	Glucose	Leptin	Ghrelin	Catalase	MDA	Chol.	TG	HDL	LDL	VLDL
B.wt	0.587	0.874	-0.519	-0.343	0.654	0.819	0.599	-0.436	0.761	0.615
Glucose	-	0.476	-0.414	-0.341	0.499	0.613	0.360	NS	0.515	0.328
Leptin	-	-	-0.616	-0.310	0.577	0.778	0.701	-0.487	0.745	0.706
Ghrelin	-	-	-	0.382	-0.552	-0.542	-0.534	0.383	-0.500	-0.519
Catalase	-	-	-	-	-0.599	-0.343	-0.287	0.465	-0.363	-0.290
MDA	-	-	-	-	-	0.660	0.582	-0.290	0.612	0.587
Chol.	-	-	-	-	-	-	0.742	-0.365	0.918	0.730
TG	-	-	-	-	-	-	-	NS	0.602	0.985
HDL	-	-	-	-	-	-	-	-	-0.585	NS
LDL	-	-	-	-	-	-	-	-	-	0.586

All correlations were highly significant (p<0.001). Shaded squares: significant (p< 0.05).
NS: Not significant

feedback signal in the event of fat increase [9]. Leptin resistance is characterized by decreased availability of leptin to the brain despite normal or even higher plasma levels. Mechanisms of leptin resistance are complex including genetic mutation of leptin receptor, failure of self-regulation of hypothalamic centers, limited transport of leptin through blood-brain barrier, and intracellular molecular mechanisms [32]. Consequently, it was projected that ghrelin may be downregulated as a consequence of body weight gain induced by APs, showing a normalizing effect on energy homeostasis and metabolic change induced by b the antipsychotics [2,25].

Within-individual changes in leptin revealed that all OLZ treated patients had clinical increase in their leptin levels (an increase >6.7% from base line), corresponding to 83% of the QUET treated group. None of the patients treated with RIS showed abnormal leptin level. Ghrelin decreased critically (RCV=6.8) in 60%, 83%, and 44% of the patients treated with OLZ, QUET, and RIS respectively. To our knowledge this is the first study on the critical differences of leptin and ghrelin in APs treated patients.

The etiology of the cardiometabolic disorders in schizophrenia is multifactorial and includes oxidative stress [2,28,33], conventional risk factors such as genetic and lifestyle factors, and

drug side effects [2,34]. In addition, as in the general population, eating behaviors and eating disorders are crucial in determining the etiology of cardiometabolic disorders in patients with schizophrenia [28]. In the present work at baseline fasting blood sugar was within normal range, but increased significantly after 8 weeks of treatment with OLZ and QUET (paired-sample t-test). Results on the pre-treatment glucose levels have been mixed such that some studies report increased levels [35], while others report no change [36]. Recent genetic studies have provided suggestive support for the involvement of glucose metabolism cascades in the genetic risk of SZ, which could explain these diversities. The present results concur with this conclusion, since critical difference analysis showed that glucose was not altered equally in patients treated with a specific APs. In the OLZ group 72% of the patients developed hyperglycemia (RCV=5.6), corresponding to 67% in the QUET group, and 22% in the RIS group. Thus, genetic factors modulate these changes [2].

At baseline total cholesterol and LDL levels were lower in patients compared to controls. After 8 weeks of treatment, body weight gain and increased leptin levels were positively correlated with dyslipidemia (elevation in cholesterol, triglycerides, LDL, and VLDL, with a decrease in HDL). The severity of the metabolic disturbances were maximum in patients treated with OLZ, followed by those treated with QUET. Patients treated with RIS showed minimum changes. Critical analysis confirmed these results, which concur with the conclusions presented by Potvin S, et al. [9], that some APs such as olanzapine and quetiapine (less so) are associated with significant metabolic side effects, while others, such as risperidone have mild adverse effects. The effect of APs on metabolic markers was previously studied in SZ patients under different conditions, as reported in recent reviews [2,9,37,38]. Antipsychotics have been shown to disrupt lipid homeostasis, they inhibit cholesterol biosynthesis and impair the intracellular cholesterol trafficking, leading to lipid accumulation in the late endosome/lysosome compartment. These effects could underlie some of the metabolic adverse effects induced by prolonged treatment with antipsychotic [38], however, the mechanisms responsible for metabolic side effects associated with APs are not completely understood.

Catalase and malondialdehyde were studied as parameters of oxidative stress. Before treatment catalase activity was lower in patients compared to control, but MDA showed no significant difference, which is in line with previous meta-analysis [39,40]. After treatment for 8 weeks catalase was reduced only in the QUET treated group (paired sample t-test). These results do not represent the true effect of APs on catalase, as seen from the critical difference analysis, which revealed that catalase was reduced clinically (RCV=10.95) in 60%, 83% and 56% of patients treated with OLZ, QUET, and RIS respectively. Thus we recommend that within-individual variations should be taken into consideration when following the effect of drugs on patients [3,4]. This would aid in the effort to personalize mental illness pharmacotherapy and optimize treatment. We did not find similar analysis in the literature, nonetheless our results concur with previous studies on the important role of genetic factors on patient's outcome [41].

Lipid peroxidation marker MDA was elevated significantly ($p<0.01$) after treatment with both OLZ and QUET, and was inversely correlated with the catalase level. This could be expected, since the decreased catalase would shunt the conversion of hydrogen peroxide from water and oxygen toward hydroxyl radical production. Increase hydroxyl radicals would result in increased lipid peroxidation and consequently increase MDA [40,42].

Conclusion

In summary, metabolic cascades are altered in SZ patients treated with APs, which include changes in the levels of leptin, ghrelin, glucose, and lipid profile. Genetic factors are known to modulate these changes, but it remains elusive whether and how a genetic predisposition to metabolic disturbance has a primary role in SZ pathology**.** Clinicians should focus on preventing initial cardiometabolic risk because subsequent reduction in this risk is more difficult to achieve, either through behavioral or pharmacologic. In order to prevent well studied long-term consequences of the metabolic risk factors a careful individual decision for an antipsychotic, a close monitoring for metabolic side effects of the chosen antipsychotic, switching the antipsychotic therapy if appropriate and focusing on how to improve physical activity of the individual patient are essential.

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