Insulin Resistance and Increased Leptin Concentrations in Noncompliant Schizophrenia Patients but Not in Antipsychotic-Naive First-Episode Schizophrenia Patients

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Background: The onset of diabetes and impaired glucose metabolism among schizophrenic patients has been the topic of numerous recently published articles, with research implicating weight gain, the use of antipsychotic medication, history of diabetes mellitus in family members, and the diagnosis of schizophrenia itself as risk factors. Therefore, it was the aim of this study to determine the glucose metabolism parameters in noncompliant unmedicated schizophrenic patients (antipsychotic-free) and first-episode antipsychotic-naive schizophrenic patients to investigate whether there is a preexisting impairment of glucose metabolism in never-medicated schizophrenic patients.

Method: Plasma glucose, insulin, C-peptide, and leptin concentrations were determined in 50 antipsychotic-free and 50 antipsychotic-naive DSM-IV schizophrenia patients and 50 healthy control subjects. Insulin resistance was calculated through the homeostatic model assessment (HOMA). The General Linear Model (univariate) procedure was used to perform analysis of covariance. Patients were recruited from July 2001 to December 2002.

Results: Antipsychotic-free patients showed significantly increased insulin ($p = .001$) and C-peptide ($p = .02$) concentrations and a significantly higher degree of insulin resistance ($p = .003$), as measured with the HOMA index, in comparison with the antipsychotic-naive patients and the control group. Significantly increased leptin concentrations ($p = .000$) were also noted in the antipsychotic-free patients and were attributed to the effects of body mass index ($p = .000$) and sex ($p = .000$).

Conclusions: The results reported in this study suggest the effect of previous antipsychotic treatment on glucose metabolism parameters and weight-related hormones such as leptin, while ruling out a preexisting impairment of glucose metabolism in never-medicated first-episode schizophrenic patients.

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The onset of diabetes and impaired glucose metabolism among schizophrenic patients has been the topic of numerous recently published articles,[1–9] with research implicating weight gain, the use of antipsychotic medication, history of diabetes mellitus in family members, and the diagnosis of schizophrenia itself as risk factors.[1] Most evidence indicating the link between type 2 diabetes mellitus and schizophrenia has come from cross-sectional and retrospective studies performed with patients on treatment with atypical antipsychotics, such as olanzapine, risperidone, and quetiapine,[2–7] although conventional antipsychotics such as phenothiazines and, to a lesser extent, butyrophenones have also been implicated in this side effect.[8] However, several studies have also suggested that patients with schizophrenia show an increased risk of developing diabetes mellitus regardless of antipsychotic medication,[9] with a rate of between 18% and 30% for schizophrenia patients with type 2 diabetes mellitus in their family members[10] as compared with a rate of 1.2% to 6.0% in the general population.

Weight gain associated with atypical antipsychotic treatment can also contribute to abnormalities in glucose metabolism or new-onset diabetes mellitus, as obesity is

known to increase the risk of diabetes by 28-fold through a decreased insulin sensitivity.[11] Treatment compliance may also be adversely affected by weight gain, with obese psychiatric patients being 13 times more likely than nonobese patients to request discontinuation of their antipsychotic medications and 3 times more likely to be noncompliant.[12] There have been reports, however, of new-onset insulin-resistant diabetes in schizophrenic patients on atypical antipsychotic treatment experiencing minimal or no weight gain.[6]

The role of leptin in antipsychotic-induced weight gain merits investigation, as antipsychotics result in elevated leptin levels, probably in relation to weight gain,[13–16] and both insulin and leptin are hormones involved in the regulation of body weight. Leptin is a hormone synthesized in the adipose tissue that plays a role in the regulation of appetite, food intake, and body weight. Leptin is believed to be a messenger from the adipocyte that signals the brain about the extent of body fat through a negative feedback regulatory mechanism.[17] It has been proposed that obesity is accompanied by a "leptin resistance" due to decreased transport of the peptide through the blood-brain barrier and to postreceptor abnormalities, with increased leptin concentrations in overweight humans.[18] Recent studies have shown increased leptin concentrations in schizophrenic patients treated with clozapine,[19] conventional antipsychotics,[14,19] and olanzapine[3] and in patients taking olanzapine and clozapine in comparison with those taking haloperidol[20] after adjusting for body mass index (BMI) and sex, although other reports have failed to note any difference between the antipsychotics administered.[16]

While most of the reported studies have focused on the effect of both conventional and atypical antipsychotics on glucose metabolism and weight gain,[2,4–7] to our knowledge, there have been no studies comparing the glucose homeostasis, insulin resistance, and leptin concentrations between schizophrenic patients previously exposed to antipsychotic drugs and those never exposed. Therefore, it was the aim of this study to compare the glucose metabolism parameters in these 2 patient groups—noncompliant unmedicated schizophrenics (antipsychotic-free) and first-episode never-medicated (antipsychotic-naive) schizophrenics—to investigate whether there is a preexisting impairment of glucose metabolism in never-medicated schizophrenic patients and to determine the liability of previous antipsychotic treatment to affect the glucose metabolism.

METHOD

Patients

Patients were included in the study after being consecutively admitted to an acute psychiatric unit during the years 2001 and 2002 due to psychotic symptoms. Patients were recruited from July 2001 to December 2002. They were divided into 2 groups: antipsychotic-free and antipsychotic-naive patients. All patients gave written informed consent to the procedures of the study, which consisted of a blood collection before onset of antipsychotic treatment. All patients were hospitalized at the time of the blood sampling, so fasting conditions were met in all cases. Patients with a comorbid DSM-IV diagnosis of substance abuse or dependence, any physical illness, or active treatment that could influence glucose homeostasis were excluded from the study. BMI and family history of type 2 diabetes mellitus were not exclusion criteria in either of the patient groups or the control group and were used as covariates in the statistical comparisons in order to assess their influence on the dependent variable. As BMI is related to a higher probability of developing type 2 diabetes mellitus due to the reported link between obesity and insulin resistance,[11] exclusion of patients with higher BMI would have led to a methodological bias. BMI was calculated as the quotient of body weight (kg) divided by the square of height (m). BMI normal values range from 18.5 to 24.9 kg/m^2.[21] Information about type 2 diabetes mellitus in first-degree relatives up to 2 generations was recorded from all patients through family interviews and from healthy controls by direct open questioning.

Results of urine tests for illicit drug (cocaine, opiates, amphetamines, and cannabis) use were negative. Routine blood test (including hemogram and cell count, liver function, and protein, sodium, and potassium levels) results were within normal limits. This study was approved by the local ethics committee.

The antipsychotic-free group consisted of 50 patients (mean ± SEM age = 35.4 ± 1.2 years) with a confirmed DSM-IV diagnosis of paranoid schizophrenia. Age at onset of symptomatology was 24.5 ± 0.9 years, and age at first treatment was 26.2 ± 0.9 years. At the time of the study, patients had been taking several antipsychotic drugs for 10.1 ± 9.6 years during different time lengths, combining periods on active treatment with those without compliance. So, retrospective information concerning type and dosage of antipsychotic and treatment duration was not reliable. Patients had been off psychotropic (antipsychotic, antidepressant, or mood stabilizer) medication for 17.8 ± 2.8 months because of noncompliance, and were included in the study after hospitalization due to exacerbation of psychotic symptoms. Information about compliance with antipsychotic treatment based on patients' self-reports and family interviews was obtained from medical records supplied by the patient's psychiatrist. Antipsychotic noncompliance in these patients was not in any case related to weight gain.

The antipsychotic-naive group included 50 patients with a first psychotic episode, in which the diagnosis of schizophrenia was confirmed after 6 months according to the DSM-IV criteria. None had ever taken an antipsychotic, antidepressant, or mood stabilizer.

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Table 1. Demographic and Clinical Data of the Studied Groups of Schizophrenia Patients and Healthy Controls[a]

Variable	Antipsychotic-Free (N = 50)	Antipsychotic-Naive (N = 50)	Controls (N = 50)	Statistic	p Value
Age, y					
Mean ± SEM	35.4 ± 1.2	25.2 ± 0.6	29.8 ± 0.7	F = 34.3	.000*
Range	18–65	14–46	21–45		
Age at onset, mean ± SEM, y	24.5 ± 0.9	NA	NA	NA	NA
Age at first treatment, mean ± SEM, y	26.2 ± 0.9	NA	NA	NA	NA
Time off medication, mean ± SEM, mo	17.8 ± 2.8	NA	NA	NA	NA
Gender, male/female, N	32/18	33/17	31/19	$\chi^2 = 0.04$	.84
Body mass index, mean ± SEM, kg/m^2	24.5 ± 0.9	22.2 ± 0.3	22.1 ± 9.3	F = 6.4	.002*

[a]Comparisons between continuous variables were assessed through the analysis-of-variance test; comparisons between dichotomous variables were assessed through the χ^2 test.
*Statistical significance between the antipsychotic-free group and both the antipsychotic-naive and control groups (Bonferroni test).
Abbreviation: NA = not applicable.

The control group included 50 individuals (31 men and 19 women) recruited from the hospital staff. None were taking any psychotropic drug or medication that could interfere with the glucose homeostasis parameters or showed abuse of or dependence on illicit drugs.

Analytical Methods

Ethylenediaminetetraacetic acid (EDTA) tubes were used to collect 20 mL of blood from each patient in fasting conditions and before onset of antipsychotic treatment. After centrifugation of each blood sample at 1000 g for 30 minutes at 4ºC, 1-mL aliquots were frozen at –80ºC until analysis.

Plasma glucose concentrations were determined enzymatically by an automatized glucose oxidase method. Plasma leptin concentrations were determined by a radioimmunoassay (RIA) method (Linco Research, Inc., St. Charles, Mo.) using rabbit antihuman leptin serum and according to the procedure described elsewhere.[22] The within-assay and between-assay coefficients of variations (CVs) were 5.0% and 4.5%, respectively, with a detection limit of 0.5 ng/mL and a 100% specificity toward human leptin. Plasma insulin concentrations were determined by an immunoradiometric assay (IRMA) method using an antibody adsorbed in solid phase (coated tube) and the other antibody labeled with ^{125}I (Radim, Rome, Italy). The within-assay and between-assay CVs were 3.0% and 8.4%, respectively. The detection limit was 39 pmol/L. Plasma C-peptide concentrations were determined by an IRMA method (Diagnostic Products Corporation, DPC, Los Angeles, Calif.). The within-assay and between-assay CVs were 3.9% and 6.3%, respectively. The detection limit was 0.03 pmol/L.

The reference values corresponding to our laboratory and using the above-mentioned analytical techniques were the following: leptin = 4.2 ± 2.9 ng/mL in men and 9.1 ± 3.0 ng/mL in women; glucose = 4.2 ± 0.7 mmol/L; insulin = 80.8 ± 20.0 pmol/L; and C-peptide = 0.64 ± 0.2 pmol/L. No differences between sexes were noted in glucose, C-peptide, and insulin.

Insulin resistance was calculated through the homeostatic model assessment (HOMA)[23] according to the formula modified for the units used in the present study: glucose (mmol/L) × insulin (pmol/L)/156.

Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Chicago, Ill.) version 11.0. Since leptin concentrations did not follow a normal distribution, a log transformation was applied in order to perform statistical analyses. The main objective of the analyses was to compare demographic and biochemical parameters between both patient groups and the control group. Therefore, factorial analysis of variance (ANOVA) tests with the diagnosis (naive, free, and control groups) as the independent variable and age and BMI as dependent variables were used. The General Linear Model (univariate) procedure was used to perform analysis of covariance (ANCOVA) to control for the effect of age, BMI, familial history of type 2 diabetes mellitus, and sex (covariates) on the dependent variable (biochemical parameters), with diagnosis (naive, free, and control groups) as the fixed-effect factor. Bonferroni tests were used for post hoc comparisons between groups. Comparisons between both sexes were performed through the Student t test unpaired, 2-tailed. Comparisons between dichotomic variables were assessed through the χ^2 test. Pearson correlation coefficients were determined to assess the relationship between quantitative variables. The overall significance level was set at p = .05.

RESULTS

Overall Sample Description

As expected, antipsychotic-free patients were significantly older than both the antipsychotic-naive patients and the control group (mean ± SEM = 35.4 ± 1.2 vs. 25.2 ± 0.6 and 29.8 ± 0.7 years, respectively; F = 34.3, p = .000) (Table 1). However, age at onset of symptoms (24.5 ± 0.9 years) and age at first treatment (26.2 ± 0.9

Table 2. Biochemical Variables in Antipsychotic-Free Schizophrenia Patients According to Sex[a]

Variable	Men (N = 32)	Women (N = 18)	Statistic	p Value
Age, y	32.4 ± 1.3	41.5 ± 2.4	t = –3.5	.001
BMI, kg/m^2	23.0 ± 1.1	26.6 ± 1.4	t = –2.3	.05
Leptin, ng/mL	1.10 ± 0.14	2.91 ± 0.18	t = –7.7	.000
Glucose, mmol/L	4.3 ± 0.1	4.6 ± 0.1	t = –1.43	.15
C-peptide, pmol/L	0.66 ± 0.07	0.69 ± 0.06	t = –0.27	.79
Insulin, pmol/L	97.4 ± 13.6	90.1 ± 5.7	t = 0.39	.69

[a]Values are mean ± SEM except for leptin concentrations, which are expressed as geometrical means after performing logarithmic transformation; comparisons were assessed through the Student t test, 2-tailed, unpaired.
Abbreviation: BMI = body mass index.

Table 3. Biochemical Variables in Antipsychotic-Naive Schizophrenia Patients According to Sex[a]

Variable	Men (N = 33)	Women (N = 17)	Statistic	p Value
Age, y	23.7 ± 0.7	27.6 ± 1.4	t = –2.7	.007
BMI, kg/m^2	21.2 ± 0.7	22.4 ± 0.3	t = 2.01	.05
Leptin, ng/mL	0.83 ± 0.07	1.99 ± 0.11	t = –8.4	.000
Glucose, mmol/L	4.3 ± 0.1	4.3 ± 0.1	t = 0.39	.69
C-peptide, pmol/L	0.51 ± 0.02	0.55 ± 0.04	t = –0.94	.79
Insulin, pmol/L	63.6 ± 2.6	67.3 ± 4.7	t = –0.65	.51

[a]Values are mean ± SEM except for leptin concentrations, which are expressed as geometrical means after performing logarithmic transformation; comparisons were assessed through the Student t test, 2-tailed, unpaired.
Abbreviation: BMI = body mass index.

years) in the antipsychotic-free patients coincided with the age reported in the antipsychotic-naive group. Antipsychotic-free patients also showed a significantly increased BMI (24.5 ± 0.9 vs. 22.2 ± 0.3 kg/m^2; F = 6.4, p = .002). Sex distribution was not different between the studied groups (χ^2 = 0.04, p = .84). Family history of type 2 diabetes mellitus was present in 36% (N = 18) of the antipsychotic-free patients, 34% (N = 17) of the antipsychotic-naive patients, and in 10% (N = 5) of the control subjects. Therefore, all statistical comparisons between the studied groups were performed using age, sex, BMI, and family history of diabetes as covariates.

Differences Between Sexes

When patients were divided according to sex, women were significantly older than men, showed a statistically significantly increased BMI, and had statistically significantly higher plasma leptin concentrations both in the antipsychotic-free and in the antipsychotic-naive subgroups (Tables 2 and 3). Higher increased leptin concentrations were noted in the antipsychotic-free than in the antipsychotic-naive women (2.91 ± 0.18 vs. 1.99 ± 0.11 ng/mL). Glucose, C-peptide, and insulin concentrations were not significantly different between sexes in the studied groups.

In the control group, no differences between sexes were noted for age, BMI, glucose, insulin, and C-peptide

Table 4. Significant Correlations in Antipsychotic-Free Schizophrenia Patients[a]

Variable	Glucose	Insulin	C-Peptide	Leptin	BMI	HOMA	Age
Glucose							
r Value		0.32	0.29			0.47	
p Value		.02	.03	NS	NS	.000	NS
Insulin							
r Value			0.89			0.98	
p Value			.000	NS	NS	.000	NS
C-peptide							
r Value						0.87	
p Value				NS	NS	.000	NS
Leptin							
r Value					0.57		0.53
p Value					.001	NS	.000
BMI							
r Value							0.40
p Value						NS	.01

[a]Calculated using the Pearson correlation coefficient; r values for nonsignificant correlations not shown.
Abbreviations: BMI = body mass index, HOMA = homeostatic model assessment, NS = nonsignificant.

Table 5. Significant Correlations in Antipsychotic-Naive Schizophrenia Patients[a]

Variable	Glucose	Insulin	C-Peptide	Leptin	BMI	HOMA	Age
Glucose							
r Value		0.31	0.23			0.58	
p Value		.002	.02	NS	NS	.000	NS
Insulin							
r Value			0.59	0.22	0.24	0.94	
p Value			.000	.008	.04	.000	NS
C-peptide							
r Value				0.21	0.20	0.68	
p Value				.01	.02	.000	NS
Leptin							
r Value					0.42	0.22	0.31
p Value					.000	.02	.000

[a]Calculated using the Pearson correlation coefficient; r values for nonsignificant correlations not shown.
Abbreviations: BMI = body mass index, HOMA = homeostatic model assessment, NS = nonsignificant.

(data not shown). However, women showed significantly increased leptin concentrations compared with men (9.0 ± 0.4 vs. 4.4 ± 0.5 ng/mL; t = –5.9, p = .000).

Correlations Between Variables

A different pattern of significant correlations was noted in the antipsychotic-free (Table 4) as compared with the antipsychotic-naive (Table 5) patients. In summary, glucose, insulin, and C-peptide showed the same pattern of correlation in both groups (see Tables 4 and 5). However, leptin concentrations from the antipsychotic-naive patients were significantly correlated with insulin, C-peptide, BMI, and age, while a loss of the significant correlation between leptin and both insulin and C-peptide was noted in the antipsychotic-free patients. With regard to the HOMA index, significant correlations were noted with insulin, glucose, and C-peptide both in the antipsychotic-free and antipsychotic-naive groups,

Table 6. Comparison of the Biochemical Parameters Associated With Glucose Metabolism and Weight Gain in Both Groups of Schizophrenia Patients and Healthy Controls[a]

Parameter	Antipsychotic-Free Patients (N = 50)	Antipsychotic-Naive Patients (N = 50)	Controls (N = 50)	Corrected Model			Fixed Effect Factor[b] (diagnosis)		Covariates[b]							
									Age		BMI		Sex		Family history of diabetes	
				F Value	df	p Value	F Value	p Value	F Value	p Value	F Value	p Value	F Value	p Value	F Value	p Value
Glucose, mmol/L	4.47 ± 0.08	4.33 ± 0.05	4.22 ± 0.08	1.2	6	.30	1.5	.21	2.5	.11	0.27	.60	2.09	.15	0.05	.81
C-peptide, pmol/L	0.67 ± 0.05	0.52 ± 0.02	0.60 ± 0.02	2.4	6	.02*	3.9	.02	0.01	.92	0.88	.35	0.40	.52	1.5	.21
Insulin, pmol/L	95.7 ± 8.3	64.6 ± 2.3	74.4 ± 2.1	3.9	6	.001*	10.7	.000	1.8	.17	0.06	.79	0.18	.67	0.09	.76
Leptin, ng/mL	1.81 ± 1.10	1.13 ± 0.91	1.80 ± 0.63	42.9	6	.000*	4.6	.01	2.5	.11	66.9	.000	114.8	.000	3.7	.06
HOMA	2.79 ± 0.31	1.82 ± 0.07	2.01 ± 1.87	3.4	6	.003*	9.2	.000	0.28	.59	0.07	.78	0.05	.94	0.19	.66

[a]All values are mean ± SEM except for leptin concentrations, which are expressed as geometrical means (log leptin).
[b]The General Linear Model (univariate) procedure was used to perform analysis of covariance to control for the effect of age, BMI, family history of type 2 diabetes mellitus, and sex (covariates) on the dependent variable, with diagnosis as the fixed-effect factor.
*Statistical significances between antipsychotic-free and both antipsychotic-naive and controls using the post hoc Bonferroni test.
Abbreviations: BMI = body mass index, HOMA = homeostatic model assessment.

but the significant correlation between HOMA index and leptin concentrations that was noted in the naive patients was missing in the antipsychotic-free patients. All statistically significant correlation coefficients are shown in Tables 4 and 5.

Comparisons Between Groups

Glucose concentrations were not significantly different between antipsychotic-free and antipsychotic-naive patients and the control group, nor was there a significant effect of the patient's age, sex, family history of diabetes, or BMI on this biochemical variable (Table 6). However, antipsychotic-free patients showed significantly increased insulin (F = 3.9, p = .001) and C-peptide (F = 2.4, p = .02) concentrations in comparison with the antipsychotic-naive patients and the control group after using age, BMI, family history of diabetes, and sex as covariates, with the main effect on the statistical significance of the corrected model being the diagnoses. Antipsychotic-free patients also showed a significantly higher degree of insulin resistance, as measured with the HOMA index (2.79 ± 0.31), in comparison with the antipsychotic-naive patients (1.82 ± 0.07) and the control group (2.01 ± 1.87; F = 3.4, p = .003), with a lack of significant effect of any of the covariates tested. With regard to leptin, the significantly increased concentrations noted in the antipsychotic-free patients (1.81 ± 1.10 ng/mL vs. 1.13 ± 0.91 ng/mL and 1.80 ± 0.63 ng/mL in the naive patients and control subjects, respectively) were attributed, to a higher extent, to the effect of BMI (F = 66.9, p = .000) and sex (F = 114.8, p = .000), with the effect of the diagnosis being smaller (F = 4.6, p = .01). Age and family history of diabetes had no significant effect on any of the tested variables (Table 6).

DISCUSSION

To our knowledge, this is the first study comparing glucose metabolism and concentrations of weight-related hormones between schizophrenic patients off medication for several months and first-episode never-medicated patients. Most studies published so far have assessed glucose homeostasis parameters in actively treated schizophrenic patients.[2–7,24] However, some of those studies present several limitations concerning the sample size, the random glucose determinations, the nonfasting blood collection, or the lack of basal values prior to treatment. Furthermore, most of these studies have compared the effect of several antipsychotics on glucose homeostasis parameters showing a significant variation in treatment duration and type between the treatment groups.[4] The only study published so far on first-episode never-medicated patients is the one from Ryan and coworkers[25] performed in 26 drug-naive patients.

Schizophrenia has been related to abnormal glucose metabolism, independently of previous antipsychotic treatment,[26] with rates of 0% in those patients below 50 years of age and of 12.9% in those between 50 and 59 years of age. These rates are in agreement with the finding that glucose, leptin, insulin, and C-peptide concentrations and HOMA index in our antipsychotic-naive patients were not statistically significantly different from those values obtained in the control group. However, it is likely that with an older sample of patients, a higher incidence of glucose abnormalities would be

Table 7. Biochemical Parameters Associated With Glucose Homeostasis in the Natural History of Type 2 Diabetes Mellitus[a]

Stage	Glucose	Insulin	C-Peptide
1 Pre–insulin resistance	Normal	Increased	Increased
2 Insulin resistance "metabolic syndrome"	Normal or increased	Increased +	Increased +
3 Diabetes mellitus type 2	Increased	Decreased	Decreased

[a]Data from Weyer et al.[30] and Lebovitz.[37]
Symbol: + = greater than in Stage 1.

found. In fact, the 15% impaired fasting glucose tolerance and increased glucose and insulin concentrations reported in the study by Ryan et al.[25] in their 26 first-episode patients could be attributed to their patients being significantly older than our studied group (33 ± 13 years vs. 25 ± 0.6 years).

Previous studies performed with schizophrenic patients have shown elevated fasting blood glucose concentrations together with hyperinsulinemia after active antipsychotic treatment.[3,26,27] However, the design of these studies is not comparable to ours. In the study by Melkersson et al.,[3] the patient sample consisted of 14 patients on active treatment with olanzapine for 0.2 to 1.4 years, with a mean age of 44 years (range, 30–60 years) and a duration of the disease ranging from 1.5 to 34.0 years. In their study, there were no laboratory measures prior to antipsychotic initiation, and the included patients were not antipsychotic-free at the time of admission. Lindenmayer et al.[27] included 108 non–antipsychotic-free schizophrenic patients who were randomly assigned to 3 atypicals and 1 conventional antipsychotic. Seven of the initial group of patients had baseline elevated glucose concentrations and were excluded from the study.

In the study by Meyer,[28] performed retrospectively in 47 patients treated with olanzapine and 47 patients with risperidone, glucose levels were available within 3 months prior to drug initiation and at 1 year of treatment, with the olanzapine cohort showing increased glucose concentrations from baseline in comparison with the risperidone patients. In this study, no other glucose homeostatic parameters were determined, and the patients' mean age was 44 years.

In the only study published in first-episode naive patients,[25] the authors found impaired fasting glucose tolerance in 4 subjects, together with increased plasma insulin and glucose concentrations and higher HOMA index in the first-episode naive patients. However, the statistical power of this study, calculated from the sample size and the mean and SD corresponding to each variable, ranges from 36% to 48%, which increases the possibility of a type II error and thus the rejection of the null hypothesis.[29]

In our group of antipsychotic-free patients, the finding of a significant hyperinsulinemia without elevated fasting glucose concentrations rules out the existence of an insulin resistance (hyperinsulinemia accompanied by hyperglycemia), although significantly higher HOMA index was noted in these patients. These normal glucose levels support the hypothesis that chronic antipsychotic administration may induce a pre–insulin resistance state with increased insulin secretion (Table 7). Furthermore, in contrast to our naive patients, the lack of a significant correlation between BMI and both insulin and C-peptide in the antipsychotic-free patients further supports that this hyperinsulinemia can not be attributed to an increased BMI or to overweight but to the effect of prior antipsychotic treatment, as previously reported by Baptista et al.[14] in 26 women undergoing chronic antipsychotic treatment.

One of the limitations of the present study concerns the lack of information about previous exposure to antipsychotics in the group of antipsychotic-free patients. At the time of the study, our patients had been taking several antipsychotic drugs for 10.1 ± 9.6 years during different time lengths, combining periods on active treatment with periods without compliance. For this reason, retrospective information concerning antipsychotic type and dosage and treatment duration was not reliable, although it might be assumed that these patients initiated antipsychotic treatment with a conventional antipsychotic and that in most cases the last antipsychotic administered was an atypical. However, it can be hypothesized that a cumulative effect of type and length of antipsychotic treatment might play a role in the development of insulin resistance.

In our study, the young age of our antipsychotic-free patients (35.4 ± 1.2 years) may prevent this primary hyperinsulinemia from causing a secondary hyperglycemia due to insulin resistance. In fact, hyperinsulinemia, insulin resistance, and normal blood glucose levels may be present for long periods in the absence of diabetes mellitus.[30] These results are in agreement with those reported by Melkersson et al.[3] and Meyer[28] showing the existence of insulin resistance and not type 2 diabetes mellitus in schizophrenic patients during active treatment with antipsychotics. It is not known whether active or previous antipsychotic treatment causes hyperinsulinemia by inducing a direct peripheral insulin resistance on the pancreatic beta cells in vitro,[31] by having a direct effect on the lipid metabolism as a response to increased glucose concentrations, or by a direct effect of the drug on insulin release. Increased insulin secretion may also play a role in the antipsychotic pharmacologic action, since insulin stimulates serotonin reuptake through specific receptors, which suggests that insulin may have neuromodulatory functions in the central nervous system.[32]

Obesity is a well-recognized risk factor for the development of diabetes, and the mechanisms of weight gain associated with antipsychotic treatment are not well understood. Antipsychotics may reduce the feedback sensitivity of the central nervous system to the leptin signal, thus leading to a cascade of increased appetite, leptin se-

cretion, and weight gain.[33] So far, several studies have reported increased leptin concentrations after antipsychotic treatment. In the study by Melkersson et al.,[3] increased leptin concentrations were noted in 57% of the patients taking olanzapine, independent of elevated BMI, together with a significant positive correlation between leptin and insulin. In their study, 10 out of 14 patients had signs of the metabolic syndrome, with insulin resistance and/or overweight. However, the authors could not exclude the possibility that this syndrome was present before olanzapine treatment as there were no records of values for pretreatment variables and the initial body weight was obtained from the patients' self-reports and not from an objective record. Kraus et al.[20] reported increased leptin concentrations, weight, and BMI in patients receiving olanzapine (N = 8) or clozapine (N = 11) in comparison with those taking haloperidol (N = 13) during 4 weeks. In a recent study[16] performed in 59 schizophrenic patients on active treatment with both atypical and conventional antipsychotics, leptin concentrations did not differ from healthy control values, although differences among the antipsychotics administered were noted.

In the present study, a significant increase in plasma leptin concentrations was noted in the antipsychotic-free as compared with the antipsychotic-naive patients after adjusting for age, BMI, HOMA, family history of type 2 diabetes mellitus, and sex. Furthermore, women showed significantly higher leptin concentrations in both schizophrenic groups, although this increase was higher in the antipsychotic-free group. So far, several studies have indicated the existence of a positive relationship between leptin and both BMI and insulin,[13,15,20,34] as insulin is known to stimulate leptin production in adipocytes.[35,36] These findings are in agreement with those reported in our drug-naive patients, with significant positive correlations between leptin and insulin, C-peptide, BMI, HOMA index, and age, and between BMI and insulin. However, in our antipsychotic-free patients, the leptin system seems to be altered, as evidenced by the loss of the positive correlation between leptin and insulin, HOMA index, and C-peptide, a finding probably attributed to previous antipsychotic treatment.

In summary, the results reported in this study suggest an effect of previous antipsychotic treatment on glucose metabolism parameters and weight-related hormones such as leptin, while ruling out a preexisting impairment of the glucose metabolism in never-medicated first-episode schizophrenic patients.

Drug names: clozapine (Fazaclo, Clozaril, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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