Elevated Levels of Insulin, Leptin, and Blood Lipids in Olanzapine-Treated Patients With Schizophrenia or Related Psychoses

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Background: The aim of this study was to investigate the influence of the antipsychotic agent olanzapine on glucose-insulin homeostasis to explain possible mechanisms behind olanzapine-associated weight gain.

Method: Fourteen patients on treatment with olanzapine (all meeting DSM-IV criteria for schizophrenia or related psychoses) were studied. Fasting blood samples for glucose, insulin, the growth hormone (GH)-dependent insulin-like growth factor 1, and the insulin-dependent insulin-like growth factor binding protein-1 (IGFBP-1) were analyzed, as well as GH, leptin, and blood lipid levels and the serum concentrations of olanzapine and its metabolite *N*-desmethylolanzapine. In addition, body mass index (BMI) was calculated. Moreover, weight change during olanzapine treatment was determined.

Results: Twelve of the 14 patients reported weight gain between 1 and 10 kg during a median olanzapine treatment time of 5 months, whereas data were not available for the other 2 patients. Eight patients (57%) had BMI above the normal limit. Eleven patients were normoglycemic, and 3 showed increased blood glucose values. Most patients (10/14; 71%) had elevated insulin levels (i.e., above the normal limit). Accordingly, the median value of IGFBP-1 was significantly lower for the patients in comparison with healthy subjects. Moreover, 8 (57%) of 14 patients had hyperleptinemia, 62% (8/13) had hypertriglyceridemia, and 85% (11/13) hypercholesterolemia. Weight change correlated positively to blood glucose levels and inversely to the serum concentration level of *N*-desmethylolanzapine. Additionally, the levels of blood glucose, triglycerides, and cholesterol correlated inversely to the serum concentration of *N*-desmethylolanzapine.

Conclusion: Olanzapine treatment was associated with weight gain and elevated levels of insulin, leptin, and blood lipids as well as insulin resistance, with 3 patients diagnosed to have diabetes mellitus. Both increased insulin secretion and hyperleptinemia may be mechanisms behind olanzapine-induced weight gain. Moreover, it is suggested that the metabolite *N*-desmethylolanzapine, but not olanzapine, has a normalizing effect on the metabolic abnormalities.

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Olanzapine is a new antipsychotic drug that has been shown to be effective in treatment of patients with schizophrenia or related psychoses.[1,2] Moreover, significantly fewer adverse movement disorders such as akathisia, dystonia, and parkinsonian symptoms have been associated with olanzapine compared with classical antipsychotics, and neither agranulocytosis (as occurs with clozapine) nor any other hemotoxicity has been reported during olanzapine therapy.[1,3,4] However, increased appetite and weight gain are more frequently recorded with olanzapine than with classical agents.[1,3,5–7] The mechanisms behind olanzapine-associated weight gain are poorly understood, and since weight gain contributes to noncompliance with treatment and may lead to medical morbidity,[8,9] it is important to clarify the mechanisms behind this side effect.

Treatment with the atypical antipsychotic agent clozapine can also be associated with marked weight gain,[10–14] and 2 earlier studies[15,16] have found that clozapine may, in addition, enhance insulin secretion. Furthermore, previous case studies[17–26] have described 16 patients who developed diabetes mellitus, diabetic ketoacidosis, diabetic coma, or impaired glycemic control of already diagnosed diabetes after beginning clozapine therapy. Olanzapine, which is a thienobenzodiazepine derivate, resembles clozapine in structure[27] (Figure 1). Therefore, olanzapine can also be expected to influence glucose-insulin homeostasis. Additionally, recent case studies[24,28–32] have described 13 patients with psychoses who developed diabetes mellitus, diabetic ketoacidosis, or impaired glycemic control of already diagnosed diabetes after they started treatment with olanzapine.

Insulin, which stimulates cellular glucose uptake and is an antilipolytic hormone, may cause weight gain through

a direct effect on adipose tissue and through affecting appetite via hypoglycemia.[33] In addition to insulin, the hormone insulin-like growth factor I (IGF-I) induces glucose uptake, and amino acid uptake with protein synthesis in muscles, but has no direct effect on adipose tissue.[34] The majority of IGF-I (99%), however, circulates bound to binding proteins, insulin-like growth factor binding proteins (IGFBPs) 1–6.[35] IGFBP-1 is supposed to regulate the availability and bioactivity of IGF-I,[35] and its production in the liver is insulin regulated.[36,37] Since insulin inhibits the hepatic production of IGFBP-1, the diurnal rhythm of IGFBP-1 shows a pattern with highest levels when insulin concentrations are low. Therefore, measurement of fasting IGFBP-1 concentrations can be used as an indirect parameter of insulin secretion.[36,37] Circulating IGF-I, which is produced mainly in the liver, is in turn particularly growth hormone (GH) dependent, as well as nutrition and insulin dependent.[34] Thus, low IGF-I levels are a marker of GH deficiency, which is known to cause weight gain.[38] The hormone leptin also plays a role in the regulation of appetite, food intake, and body weight.[33] This hormone is synthesized by adipocytes[39] and has its major site of action at the leptin receptors in the hypothalamus.[33] Insulin is known to stimulate leptin production in adipocytes,[40] and, conversely, leptin may influence insulin release from the pancreatic beta cells.[41]

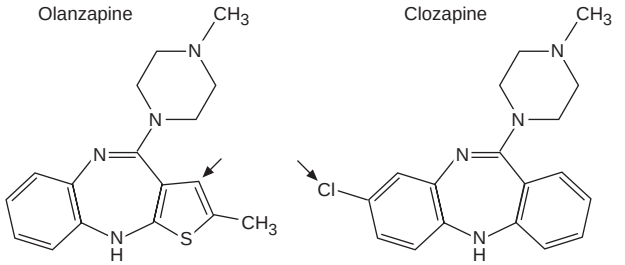
The aim of this study was to investigate the influence of olanzapine on hormones involved in glucose-insulin homeostasis to explain possible mechanisms behind olanzapine-associated weight gain. We analyzed blood glucose, insulin, IGF-I, IGFBP-1, GH, leptin, and blood lipid levels in 14 olanzapine-treated patients and investigated these parameters in relation to the patients' body mass index (BMI) and weight change during treatment, as well as to the dose and serum concentration of olanzapine and its metabolite *N*-desmethylolanzapine.

METHOD

Patients

Consecutive outpatients on treatment with olanzapine at the Department of Psychiatry, St. Görans Hospital, Stockholm, Sweden, were asked to participate in the study. Patients who had a substance-related disorder, known diabetes mellitus, or other physical illness that could influence glucose-insulin homeostasis were excluded. The present study included 14 patients, 7 men and 7 women, diagnosed with either schizophrenia or schizophreniform or schizoaffective disorder according to DSM-IV criteria[42] (Table 1). The median age of the patients was 44 years (range, 30–60 years), and the duration of disease ranged from 1.5 to 34 years (median = 10.8 years). Six of the 14 patients had a family history of type 2 diabetes mellitus (patients 3, 8, 9, 10, 11, 12 in Table 1).

Figure 1. Chemical Structure of Olanzapine and Clozapine[a]



[a]From Budavari et al.[27] The chemical structure of olanzapine resembles that of clozapine apart from the fact that the olanzapine molecule includes a thieno ring (arrow) in place of the benzo ring of clozapine and that the clozapine structure is halogenated with a chlorine atom (arrow) while olanzapine is not.

All patients received monotherapy consisting of the antipsychotic agent olanzapine, and the only concomitant medications used were orphenadrine hydrochloride and/or benzodiazepine derivates. The daily dose of olanzapine ranged from 5 to 20 mg (median = 12.5 mg/day), and the patients received the antipsychotic medication once or twice daily. At assessment, the patients had been on treatment with olanzapine for at least 0.2 years, with a median treatment period of 0.4 years (range, 0.2–1.4 years). Before being treated with olanzapine, 8 patients were treated with classical antipsychotics, 3 patients were treated with clozapine (patients 2, 3, 6 in Table 1), and 3 patients had no psychopharmacologic treatment (patients 1, 8, 12 in Table 1).

The laboratory investigation included measurement of fasting blood glucose levels and fasting serum concentrations of insulin, IGF-I, IGFBP-1, GH, leptin, blood lipids, and olanzapine and its metabolite *N*-desmethylolanzapine. Given that the subjects were outpatients also at the time of assessment, an agreement between the psychiatrist and the patients well-known to her was made, which assured fasting status. In addition, BMI was calculated, and the changes in weight and BMI during treatment were estimated (as explained below). The median BMI (kg/m^2) prior to olanzapine treatment was determined to be 24 in both men and women (range, 21–28 for the men and 20–27 for the women).

The study was approved by the Ethics Committee of the Karolinska Hospital, Stockholm, and the Medical Products Agency of Sweden. The patients participated after giving informed consent.

Analysis of Blood Samples

All blood samples were collected in the morning, prior to breakfast and medication.

Blood glucose was determined by a glucose oxidase method, using the 950 Immunologic-Rate-Colorimetric system (Johnson & Johnson Clinical Diagnostics, Inc.,

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Table 1. Clinical Characteristics and Laboratory Findings of 14 Patients Treated With the Antipsychotic Agent Olanzapine[a]

Patient	Sex	Diagnosis (DSM-IV)	Age, y	Duration of Olanzapine Treatment, y	Change in weight, kg	Change in BMI	BMI (recommended levels: M ≤ 27, F ≤ 25)	Blood Glucose Level, mmol/L (mg/dL) (reference range 3–6 [54–108])	Insulin, pmol/L (reference range < 144)	GH, µg/L (reference range < 14)	IGF-I (reference range ± 2 SD)	IGFBP-1, µg/L (reference range M 5–93, F 9–101)	Leptin, µg/L	Triglycerides, mmol/L (reference range ≤ 2.0)	Cholesterol, mmol/L (reference range < 5.0)
1	M	Schizophrenia, paranoid type	30	0.8	...	...	35[b]	5.1 (91.9)	330[b]	0.01	0.60	4[b]	25.2[b]	3.46[b]	5.15[b]
2	M	Schizophrenia, undifferentiated type	36	0.7	5	2	30[b]	4.9 (88.3)	359[b]	0.01	–2.10[b]	3[b]	23.1[b]	...	...
3	M	Schizophrenia, paranoid type	39	0.3	8	2	23	5.0 (90.1)	79	0.03	–0.38	24	6.7	1.83	4.65
4	M	Schizophrenia, paranoid type	42	1.4	...	...	29[b]	5.3 (95.5)	194[b]	0.05	–0.07	8	21.2[b]	2.08[b]	8.79[b]
5	M	Schizophrenia, undifferentiated type	49	0.3	6	2	26	5.9 (106.3)	230[b]	0.03	1.03	6	26.1[b]	2.44[b]	5.48[b]
6	M	Schizophrenia, paranoid type	49	0.4	10	2	29[b]	7.0 (126.1)[b]	301[b]	0.01	–1.20	18	29.4[b]	11.23[b]	10.16[b]
7	M	Schizophrenia, paranoid type	60	0.8	2	0	23	5.1 (91.9)	287[b]	0.21	1.15	23	7.9	2.50[b]	6.31[b]
8	F	Schizoaffective disorder	30	1.3	4	2	26[b]	5.4 (97.3)	136	0.21	–0.64	13	16.0	1.27	5.48[b]
9	F	Schizophrenia, paranoid type	31	0.3	3	1	23	4.6 (82.9)	266[b]	0.23	0.41	14	26.9[b]	1.79	5.70[b]
10	F	Schizophreniform disorder	35	0.9	10	4	24	5.2 (93.7)	93	1.94	2.17[b]	29	15.6	0.64	4.40
11	F	Schizophreniform disorder	45	0.4	5	2	25	5.6 (100.9)	222[b]	1.33	–0.04	16	31.8[b]	3.51[b]	9.26[b]
12	F	Schizophreniform disorder	46	0.3	1	1	26[b]	4.8 (86.5)	86	6.74	1.31	17	22.6	1.11	5.07[b]
13	F	Schizophrenia, disorganized type	53	0.2	5	2	29[b]	6.6 (118.9)[b]	373[b]	0.24	–0.23	20	39.5[b]	4.22[b]	8.29[b]
14	F	Schizophrenia, paranoid type	57	0.3	10	4	30[b]	6.9 (124.3)[b]	237[b]	1.91	0.51	11	29.3	4.08[b]	7.80[b]
Median			44	0.4	5	2	M = 29, F = 26	5.3 (95.5)	234	0.21	0.19	M = 8, F = 16	M = 23.1, F = 26.9	2.44	5.70
Mean ± SD			43 ± 10	0.6 ± 0.4	5.8 ± 3.1	2 ± 1	M = 28 ± 4, F = 26 ± 3	5.5 ± 0.8 (99.1 ± 14.4)	228 ± 100	0.93 ± 1.82	0.18 ± 1.10	M = 12 ± 9, F = 17 ± 6	M = 19.9 ± 9.0, F = 26.0 ± 8.6	3.09 ± 2.69	6.66 ± 1.94

[a]Abbreviations: BMI = body mass index (kg/m^2), GH = growth hormone, IGF-I = insulin-like growth factor I, IGFBP-1 = insulin-like growth factor binding protein-1, SD = standard deviation. Symbol: ... = data missing or not reported. Fasting blood levels of glucose, hormones, IGF-I, and lipids are shown.
[b]Levels above or below normal reference limits.

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New York, N.Y.). Insulin was measured in serum by a radioimmunoassay (RIA) method, using guinea pig antiserum and charcoal addition to separate bound and free insulin.[43] The intra-assay coefficient of variation (CV) was 5% and the interassay CV, 10%. The detection limit was 56 pmol/L. Insulin-like growth factor I was measured by an RIA method designed by Bang et al.[44] and expressed as age-correlated standard deviation scores based on samples from healthy men and women.[45] The detection limit was 8 μg/L. Including the extraction step, the intra-assay and interassay CVs were 4% and 11%, respectively. Concentrations of IGFBP-1 were determined according to the RIA method of Povoa et al.,[46] slightly modified with a lower detection limit of 1.6 μg/L. The intra-assay and interassay CVs were 3% and 10%, respectively. To determine serum levels of GH, a commercial kit consisting of a 2-site fluoroimmunometric GH assay based on 2 monoclonal antibodies was used (DELFIA hGH, Wallac, Inc., Turku, Finland). Leptin was measured in serum by an RIA method designed by Ma et al.,[47] using a commercial RIA kit (Linco Research, Inc., St. Louis, Mo.). Elevated leptin levels were determined after individual comparison to normal values adjusted for BMI and sex.[47]

Triglyceride concentrations were measured by an enzymatic method as described by Spayd et al.[48] and cholesterol by an enzymatic method similar to that proposed by Allain et al.[49] According to recommendations by the European Atherosclerosis Society, the European Society of Cardiology, and the European Society of Hypertension, fasting triglycerides should be ≤ 2.0 mmol/L and total cholesterol, < 5.0 mmol/L.[50]

The serum concentration of olanzapine was analyzed by a high-performance liquid chromatography method with electrochemical detection.[51] To determine the serum concentration of the metabolite *N*-desmethylolanzapine, the same method[51] with minor modifications was used.

BMI was calculated according to the formula BMI = kg/m^2, where kg = the body weight in kilograms and m = the height in meters.[52] The changes in weight and BMI during olanzapine treatment were calculated from the patients' self-reports of preolanzapine weight and of present weight and height in the study.

Statistical Methods

The results are given as median and range. Because the different variables were assumed not to be normally distributed, the nonparametric Mann-Whitney test was used in the statistical analyses. In addition, the strength of the linear relationship between 2 parameters was calculated by the Spearman rank correlation coefficient (r_s), a nonparametric measure of correlation. A p value of less than .05 was considered statistically significant (not corrected according to Bonferroni). The Mann-Whitney test was performed using Sigma Stat for Windows (Jandel Scientific GmbH, Erkarth, Germany), and r_s was calculated using Statistica for Windows (Statsoft, Inc., Tulsa, Okla.).

RESULTS

Weight Change and BMI

Data on the patients are given in Table 1. Twelve (86%) of 14 patients reported weight gain and increased BMI during olanzapine treatment, whereas data were not available for the other 2 patients. The median change in weight was 5 kg (range, 1–10 kg), and median change in BMI was 2 (range, 0–4), with no differences found between the sexes.

Irrespective of sex, BMI was over recommended levels in 8 (57%) of the patients (recommended levels are ≤ 27 in men and ≤ 25 in women). In addition, the median BMI was 29 (range, 23–35) for the men and 26 (range, 23–30) for the women (see Table 1).

Blood Glucose, Hormone, and Lipid Levels

Three patients had elevated fasting blood glucose levels (> 6.0 mmol/L [> 108.1 mg/dL]), and the other 11 patients were normoglycemic. The median level of blood glucose was 5.3 mmol/L (range, 4.6–7.0 mmol/L [95.5 mg/dL; range, 82.9–126.1 mg/dL]) (see Table 1).

Ten (71%) of 14 patients had elevated insulin levels. Additionally, the median value of insulin for the patients was elevated compared with the upper normal limit: median = 234 pmol/L (range, 79–373 pmol/L; reference in a normal population < 144 pmol/L) (see Table 1).

Twelve patients had IGF-I levels within normal limits (± 2 SD), whereas 2 patients had slightly deviated IGF-I values. The median level of IGF-I (expressed as age-correlated SD) was 0.19 (range, –2.10 to 2.17). In addition, GH values were below the upper reference limit (< 14 μg/L) in all patients (see Table 1).

The median level of IGFBP-1 was 15 μg/L (range, 3–29 μg/L) for all patients, 8 and 16 μg/L for men and women, respectively (see Table 1). Compared with healthy subjects, the patients treated with olanzapine had a significantly lower median value of IGFBP-1, 15 versus 27 μg/L ($p < .05$; data not shown).

Leptin levels were elevated in 5 men and 3 women (57% of the patients) when individually compared with normal values adjusted for BMI and sex[47] (see Table 1). The median level of leptin was 24.2 μg/L (range, 6.7–39.5 μg/L) for all patients, 23.1 and 26.9 μg/L for men and women, respectively.

Eight (62%) of 13 patients had elevated triglyceride levels (> 2.0 mmol/L).[50] Additionally, 11 (85%) of 13 patients showed increased cholesterol values (≥ 5.0 mmol/L).[50] The median level of triglycerides was 2.44 mmol/L (range, 0.64–11.23 mmol/L) and that of cholesterol was 5.70 mmol/L (range, 4.40–10.16 mmol/L) (N = 13) (see Table 1).

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Olanzapine and *N*-desmethylolanzapine

The median serum concentration of olanzapine was 116 nmol/L (range, 61–280 nmol/L) and that of *N*-desmethylolanzapine was 11 nmol/L (range, 5–42 nmol/L). In addition, serum *N*-desmethylolanzapine concentrations correlated to the concentrations of olanzapine (N = 13; r_s = 0.70, p = .008).

Relationship Between Clinical and Laboratory Findings

Hormone levels. There was no correlation found between IGFBP-1 and insulin levels (r_s = –0.34, p = .23). Leptin concentrations correlated to the insulin levels (r_s = 0.57, p = .03), whereas no correlation was found between leptin and IGFBP-1 levels.

Lipids and blood glucose or hormone levels. The triglyceride levels correlated to blood glucose and insulin levels (r_s = 0.70, p = .007 and r_s = 0.75, p = .003, respectively), but not to IGFBP-1. In addition, cholesterol levels correlated to blood glucose levels (r_s = 0.62, p = .02), whereas there was only a tendency toward a correlation between cholesterol and insulin levels (r_s = 0.54, p = .06) and no correlation found between levels of cholesterol and IGFBP-1.

Blood glucose, hormones, and BMI. No correlation was found between blood glucose levels and BMI, whereas there was a tendency toward a correlation between insulin levels and BMI (r_s = 0.52, p = .06). In addition, levels of IGFBP-1 were inversely correlated to BMI (r_s = –0.66, p = .01). Irrespective of sex, no correlation was found between leptin and BMI (r_s = 0.43, p = .13).

Blood glucose, hormones, or lipids and weight change. A positive correlation was found between blood glucose levels and weight change (N = 12; r_s = 0.63, p = .03), whereas no correlations were found between hormone or lipid levels and weight change.

Weight change, blood glucose, hormones, or lipids and treatment time. There was a tendency toward an inverse correlation between leptin and the duration of treatment with olanzapine (r_s = –0.50, p = .07). However, no correlations were found between weight change, blood glucose, insulin, IGFBP-1, or lipids and the treatment time.

Weight change, blood glucose, hormones, or lipids and olanzapine. The weight change was inversely correlated to the serum concentration of *N*-desmethylolanzapine (N = 12; r_s = –0.59, p = .04), whereas no correlation was found between weight change and serum olanzapine concentration. Levels of blood glucose, triglycerides, and cholesterol also correlated inversely to the concentration of the metabolite (r_s = –0.77, p = .002; r_s = –0.61, p = .03; and r_s = –0.65, p = .02, respectively), but not to the serum olanzapine levels. There was a tendency toward an inverse correlation between leptin and the concentration levels of *N*-desmethylolanzapine (r_s = –0.55, p = .05), but not between leptin and olanzapine. No correlations were found between insulin or IGFBP-1 levels and the serum concentration levels of olanzapine or *N*-desmethylolanzapine.

DISCUSSION

In this study, 57% of the patients (4 men and 4 women) exhibited elevated BMI after a median of 5 months of treatment with olanzapine, which is a greater rate than expected in a healthy population.[53] Weight gain during treatment with olanzapine, as has been described in other studies,[1,3,5–7] was reported by 12 of 14 patients in the study independent of pretreatment weight. Three patients became overweight during the olanzapine treatment, and 3 other patients, who were overweight before they started with olanzapine, gained additional weight during treatment.

One fifth (3/14; 21%) of the patients had elevated fasting blood glucose values, indicating diabetes mellitus. The median blood glucose level was relatively high in spite of hyperinsulinemia, which is the diagnostic criterion of insulin resistance.[54] This was seen in the patients with both normal and increased BMI, suggesting causative factors of the insulin resistance other than overweight.

Most of the patients had hyperinsulinemia as well as hyperlipidemia. In addition, the patients' triglyceride concentrations were correlated with blood glucose and insulin levels, and the cholesterol levels were correlated with blood glucose levels. Since hyperlipidemia and especially hypertriglyceridemia may be connected with insulin resistance,[54] these findings further support the theory that enhanced insulin secretion in our patients may be secondary to insulin resistance. At the same time, the increased concentrations of triglycerides and cholesterol cannot be excluded from being a direct effect of the treatment. To compare, an earlier study[55] has shown that olanzapine use was associated with an increase in triglyceride levels, and 3 other studies[56–58] concerning clozapine have reported higher serum triglyceride levels in patients treated with clozapine compared with patients taking classical antipsychotics.

Hyperinsulinemia was verified by low IGFBP-1 levels,[36,37] also suggesting that there was no insulin resistance at the hepatic level. Moreover, insulin levels had a tendency to correlate to BMI. In accordance, levels of IGFBP-1 were inversely correlated to BMI. Taken together, these correlations may also be related to the development of insulin resistance.

The finding that blood glucose levels were positively correlated to weight change points to a relationship between the patients' weight gain during treatment and the development of insulin resistance. Moreover, findings that weight change as well as levels of blood glucose and blood lipids were inversely correlated to serum concentration levels of *N*-desmethylolanzapine, but not to serum

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olanzapine levels, may suggest that higher serum concentrations of the metabolite *N*-desmethylolanzapine are connected to a less-prominent weight gain, insulin resistance, and hyperlipidemia than are low-to-moderate concentrations. Accordingly, these inverse correlations would seem to suggest that *N*-desmethylolanzapine, but not olanzapine, has a normalizing effect on these metabolic abnormalities. In comparison, the results of the North American olanzapine trial[5] showed that more patients in the groups with low-to-moderate doses of olanzapine gained weight than those in the group with higher doses.

It is, however, not known whether the olanzapine treatment caused hyperinsulinemia by inducing direct peripheral insulin resistance at the cellular level or by having a direct effect on the lipid metabolism with secondary insulin resistance and hyperinsulinemia. Since the antipsychotic drug chlorpromazine has been shown to have a direct effect on the pancreatic beta cells in vitro,[59] it can not be ruled out that olanzapine also exerts a direct influence on the beta cells and insulin secretion.

In contrast to what normally is seen in healthy subjects,[37,60] we did not find an inverse correlation between IGFBP-1 levels and insulin in the patients receiving olanzapine. This lack of correlation was also found in patients on therapy with clozapine in our previous study.[16] Similar to those patients receiving clozapine, the patients receiving olanzapine showed low IGFBP-1 levels also at fasting insulin levels within normal limits, which can be explained by a higher diurnal insulin secretion in these patients, since IGFBP-1 levels reflect the integrated diurnal insulin secretion better than fasting morning insulin levels do.[60,61] If olanzapine exerts a direct or indirect effect on the beta cells and influences insulin secretion during the whole 24 hours, the diurnal insulin level will be higher than the morning insulin level and better reflected by the IGFBP-1 level.

Leptin levels are usually high in overweight humans.[62] Independent of elevated BMI, however, 57% of our patients receiving olanzapine had increased leptin levels, and in contrast to healthy overweight people,[62] no correlation between leptin and BMI was found in the patients. The gender difference that normally exists, in that women have higher circulating leptin levels than men,[63] was also lacking in our patients. We found, however, a positive correlation between leptin and insulin levels. Since insulin is known to stimulate leptin production in adipocytes,[40] and insulin resistance with hyperinsulinemia has been associated with increased leptin levels,[62,64] the elevated leptin levels in our patients may be due to their increased insulin levels and insulin resistance. However, it cannot be excluded that the olanzapine treatment had a direct effect on the leptin production, with elevated leptin levels as a consequence. Conversely, leptin is known to affect pancreatic beta cell function, where both inhibitory and stimulatory effects on insulin secretion have been reported.[41,65] To compare, in a study by Kraus et al.,[66] a significant increase in leptin levels was found in patients receiving olanzapine or clozapine compared with patients on haloperidol or no pharmacologic treatment and in another study,[67] serum leptin levels were found to increase rapidly after initiation of clozapine therapy. However, in those 2 studies,[66,67] insulin levels were not measured.

Since the GH-dependent IGF-I levels were normal and none of our patients had undetectable GH levels, GH secretion seems to be normal in patients receiving olanzapine. Thus, olanzapine-induced weight gain is probably not caused by GH deficiency. In contrast, the result in our previous study,[16] in which a significantly lower median level of IGF-I in patients taking clozapine compared with patients taking classical antipsychotics was found, pointed to lower GH secretion in the clozapine group.

It is to be observed that the majority of patients (10/14) had signs of the metabolic syndrome[68] with insulin resistance, hyperlipidemia, and/or overweight. Although we cannot exclude that this syndrome also was present before the onset of treatment, we recommend weight as well as fasting levels of blood glucose and blood lipids to be tested before and during olanzapine treatment. The metabolic syndrome increases the risk of cardiovascular disease[68] and should therefore be treated.

Since insulin is known to stimulate appetite through hypoglycemia as well as growth of adipose tissue,[33] increased insulin secretion may be a mechanism behind weight gain during olanzapine treatment. Considering that leptin is also involved in the regulation of body weight homeostasis,[33] BMI-independent hyperleptinemia may well be associated with olanzapine-induced weight gain.

Moreover, we cannot exclude that the probable ability of olanzapine to influence insulin secretion also may play a role in the agent's antipsychotic action, since specific receptors for insulin are known to be present throughout the human brain,[69] and in neuronal cells, insulin inhibits [^{3}H] norepinephrine uptake and stimulates [^{3}H] serotonin uptake, which suggests that insulin may have neuromodulatory functions in the central nervous system.[70,71]

It is, however, to be noted that the present study is limited by a small sample size with a total of 14 patients included and by the absence of a suitable control group. In the absence of laboratory values prior to olanzapine initiation, we cannot rule out whether some of our patients also had metabolic abnormalities before the olanzapine treatment.

In conclusion, in this study with a limited number of consecutive patients with psychotic disorders, olanzapine treatment was associated with weight gain, hyperinsulinemia, hyperlipidemia, and insulin resistance. Three patients were also diagnosed with diabetes mellitus. Independent of the patients' elevated BMI, the leptin levels were increased and were correlated to insulin. Both the increased insulin secretion and the hyperleptinemia may be mecha-

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nisms behind olanzapine-induced weight gain. Moreover, it is to be noted that less prominent weight gain, hyperglycemia, and hyperlipidemia were found at higher serum concentration levels of the metabolite *N*-desmethylolanzapine, which would seem to suggest that the metabolite, but not olanzapine itself, has a normalizing effect on the metabolic abnormalities. Finally, considering that 71% of the patients had signs of the metabolic syndrome, it is suggested that weight as well as fasting levels of blood glucose and blood lipids should be tested before and during olanzapine treatment. Olanzapine, like clozapine, seems to increase insulin secretion, which may be interesting regarding the mechanisms behind these agents' antipsychotic action as well as their side effects.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), orphenadrine (Norflex and others).

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